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CONVENTIONAL THERAPEUTIC INTERVENTIONS FOR SARS-COV-2: A REVIEW

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ABSTRACT
The origin of the SARS-CoV-2, a β-coronavirus is not yet identified. The pandemic action of the virus has been intimidating peoples across the world. The spike proteins of the virus portray a crown-like configuration that binds with Angiotensin-converting enzyme 2 receptors via its six amino acids. The binding of the spike proteins and Angiotensin-converting enzyme 2 receptors results in the host transmission. We have investigated the different therapeutics for the management of COVID-19. A systematic literature survey has been carried out using research databases to understand the underlying mechanism and evaluate the drugs for prevention and treatment of COVID-19. The therapeutic interventions for COVID-19 can be categorized into two categories: virus-specific therapy and host-specific therapy. Researchers have been functioning on the repurposing of available pharmacological agents, including Antimalarials, Monoclonal antibodies, Convalescent plasma therapy, Protease inhibitors, Immunomodulators, Vaccines, Stem cell therapy as potential therapeutics to treat COVID-19. Potent immunomodulatory 'Rasayana' plants possess phytoconstituents that may exhibit synergistic action could provide protection against SARS-CoV-2. Although, many existing drugs have been tried for the treatment of COVID-19, no drug alone or in combination has shown groundbreaking result. However, efforts are going on to develop the drug as well as vaccines. This development process is a time requiring process; until vaccines or new drugs become operational, repurposing of existing drugs is indispensable.

KEYWORDS: Coronavirus, Angiotensin, Spike protein, Main protease, Rasayana, Vaccines.

1. INTRODUCTION
A novel human coronavirus has originated in Wuhan, China, in December month in 2019. It has become a severe health threat to the world. The virus causes severe acute respiratory syndrome (SARS). It has shown similarities to SARS related other coronaviruses.[1–3] Due to the similarities with SARS coronavirus (SARS-CoV), the virus is named as SARS-CoV-2 by International Committee of Taxonomy of viruses.[4] SARS-CoV-2 has infected more than millions of people worldwide and the death of more than 200000 of people.[5] This virus has spread rapidly coronavirus.[8] The origin of SARS-CoV-2 is yetunconfirmed and is being discussed from different pAoints of view by different people. It remains a matter of debate in the scientific and political world. The Spike protein (S protein) is the most crucial part of the virus for interaction with the crossing the regional boundaries and caused a pandemic situation. The disease is considered as a global threat for humanity and evolving rapidly in the world scenario.[6,7] The disease is termed as Coronavirus disease-2019 (COVID-19) by the World Health Organization. This virus is a β-coronavirus and it is reported as the seventh human host cell. It determines the infectivity and the host selection. S protein of SARS coronaviruses is a glycoprotein and mediates the entry of the virus into the host cells. The S protein of the virus forms a homotrimeric structure to interact with the host cell. S protein of SARS-CoV-2 consists of two functional regions S1 and S2. These two regions exist in the perfusion conformation through non-covalent binding.[9–11] The S1 region functions as the receptor-binding domain (RBD) and stabilizes the perfusion conformation, whereas the S2 region functions as fusion protein.[11–14] The homotrimer of S1 appears to exist in partially opened states in highly infectious human coronaviruses. However, it remains close in mildly infectious other human coronaviruses. SARS-CoV-2 S protein has shown different distinct conformational form at the apex of the homotrimer. These observations suggest that the multiple conformations of S protein play a significant role in pathogenicity and transmissibility of the novel virus, SARS-CoV-2. The opening of the RBD of the S1 region appears to be crucial for interaction with Angiotensin-converting enzyme 2 receptor (ACE2), followed by

initiation and conformational changes. The process leads to cleavage and fusion of the virus with the host cell membrane, followed by entry into the cells.[14] Sequence analysis demonstrated 76.04%, 73.33% and 50.00% similarities for S protein, RBD and receptor binding motif (RBM) between SARS-CoV-2 and SARS-CoV.[15] Full-length genomic sequence analysis has demonstrated 79.6% similarities between SARS-CoV and SARS-CoV-2. More interestingly, the same study has demonstrated 96% similarity for the whole genome of RaTG13 bat coronavirus.[3] Zhang *et al*. reported that Pangolin-CoV has more similarities with SARS-CoV-2 than RaTG13 bat coronavirus. They reported 91.02% and 90.55% similarities with SARS-CoV-2 for Pangolin CoV and RaTG13 bat coronavirus. We have observed a difference for similarities between SARS-CoV-2 and RaTG13 bat coronavirus. It is necessary to evaluate whether the variation exists in SARS-CoV-2 or RaTG13 bat coronavirus.[16] The RBD of S protein has six amino acids important for the infectivity of the virus as they play a critical role in binding with ACE2 receptors.[15] The RBD region of SARS-CoV-2 appears to have a higher affinity to ACE2 of human as compared to other SARS related viruses.[3,14–16] There is a functional furin cleavage site between S1 and S2 subunits of the S protein of SARS-CoV-2. This is a unique feature of SARS-CoV-2. The polybasic furin cleavage site is due to the presence of four amino acid residues in the S protein of SARS-CoV-2.[14] Furin and other proteases cleave the junction between S1 and S2 at this point. In other SARS related viruses and β-coronaviruses, this unique cleavage site has not been observed.[8] SARS-CoV and related other coronaviruses have a monobasic cleavage site between S1 and S2 region of the S protein.[9,10,17,18] In the current situation, it is necessary to develop an effective therapeutic intervention to prevent and control the disease. As we know that new drug development is a time consuming process, researchers have been working on repurposing available pharmacological agents to control and prevent the disease. This work is carried out to review the ongoing therapeutic interventions and other possible potential therapeutics to control COVID-19.

2. TRANSMISSION

The airborne droplets produced by the infected patient are considered as the major route of transmission for SARS-CoV-2. Close contact with an infected patient is strictly prohibited without personal protective equipment to prevent the transmission of the disease. Detection of the virus in the gastrointestinal tract indicates the possibility of saliva and stool as a route of transmission.[19–21] Transmission of the virus through the oral-faecal route should be considered carefully and necessary preventive measures should be taken by health authorities. A study analysed 38 pregnant women infected with SARS-CoV-2 in China. The author reported there was no maternal death as well as no transmission of the virus from mothers to newborn baby when tested after delivery of baby.[22] Chen *et al.* reported no intrauterine transmission of SARS-CoV-2 virus from mother to child in nine patients.[23] Although it appears to be no intrauterine transmission of the virus from the reported data, precautionary measures should be taken to avoid the intrauterine transmission. The incubation period of SARS-CoV-2 is on an average of 5 to 6 days. It may be up to 14 days in some cases. The transmission from the infected patient can occur in the pre-symptomatic condition. This transmission of the virus is termed as pre-symptomatic transmission. The shedding of the virus is highest on the upper respiratory tract within 3 days of symptomatic condition. The infected patient becomes symptomatic if the patient shows signs and symptoms of COVID-19. Personal protective equipment (PPE) is necessary to prevent symptomatic transmission of the virus. In many countries, laboratory-confirmed patients with COVID-19 are found to be asymptomatic. There are no signs and symptoms of COVID-19 in those patients. There are high possibilities of virus transmission from person to person in those asymptomatic cases.[5]

3. MUTATIONS OF SARS-CoV-2

The phylogenetic network analysis demonstrated three variants of SARS-CoV-2. The study analysed 160 genomes of SARS-CoV-2. The three variants have been classified as A, B and C type and identified by a change in amino acids. Type B is located in East Asia whereas Type A and C are significantly located in Europe and America. Immunology and environmental resistance are two key factors of mutations. The mutations of the virus form lineages of the virus.[24] However, no such report has been found and hence, it is necessary to locate regions of mutations and their significance in viral virulence. Mutations in conserved regions of the virus must be evaluated carefully. These data are crucial in the rational vaccine development program.

4. VIRUS-SPECIFIC POTENTIAL THERAPEUTIC INTERVENTIONS

4.1 Viral entry inhibition or fusion inhibition

Chloroquine phosphate

Chloroquine is an anti-malarial **drug,** primarily used to prevent and treat malaria. Chloroquine is additionally used for amoebiasis that occurs outside the intestines, rheumatoid arthritis and lupus erythematosus. Currently, it is exhibiting potential for the treatment of SARS-CoV-2. It has exhibited *in vitro* activity against various viruses, including coronaviruses.[25–28] It has exhibited *in vitro* activity in various cell lines against and Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV with EC_{50} values of 3.0 µM and 1–8.8 µM respectively.[26,29] It exhibited significant antiviral activity against SARS-CoV-2 in Vero E6 cells. It exhibited potent activity with an EC_{50} value of 1.13 µM.[25] Chloroquine, at a dose of 500 mg BD by mouth is supported by the outcomes of these reports. Multiple clinical trials have been initiated using various dosages in patients with COVID-19 in China and other countries.[30–32] Reports of possible clinical benefits of Chloroquine phosphate have been accumulating,

including a decrease in duration of sickness and viral titre. Currently, available data for chloroquine phosphate concerning COVID-19 treatment is insufficient to support the therapeutic benefits in patients with SARS-CoV-2 infection.[30,32,33] For patients weighing 50 kg or more, the therapy can be initiated as 1 g on the 1st day of the therapy. It is followed by 500 mg OD for 4 to 7 days based on clinical evaluation of the patient conditions.[34] Results from a study consisting of more than 100 patients demonstrated chloroquine phosphate was therapeutically more effective than the control treatment for inhibition of the exacerbation of pneumonia, improvement of lung conditions, promoting viral clearance from the body and minimizing the duration of illness. Severe adverse reactions to chloroquine phosphate were not noted in the patients.[32] In 2006, a study reported that chloroquine had approximately 5-fold higher potency than hydroxychloroquine. The EC_{50} value of chloroquine was 6.5 ± 3.2 µM whereas the EC_{50} value of hydroxychloroquine was 34 ± 5 µM.[35] However, the potency of hydroxychloroquine (EC_{50} of 0.72 µM) was found to be greater than the potency of chloroquine (EC_{50} of 5.47 µM) against SARS-CoV-2 in Vero cells. The authors have suggested two dosage regimens for the use of hydroxychloroquine in COVID-19 based on physiologically based pharmacokinetic (PBPK) modelling. The first regimen was the administration of a loading dose of 1200 mg (divided into 800 mg and 400 mg) on 1st day, followed by 400 mg OD through oral route. The second regimen was the administration of the loading dose of 400 mg BD on 1st day, followed by 200 mg BD. The author suggested the use of a lower dosage regimen for the treatment of patients with COVID-19.[36] The use of chloroquine for treatment or prevention of SARS-CoV-2 is at the preliminary stage and not established yet. Due to the potential adverse effects of chloroquine phosphate, the investigators must be cautious while designing the trial protocol. Multicenter trials and statistically validated data are necessary to determine the clinical efficacy of chloroquine phosphate for the treatment or prevention of SARS-CoV-2.

Hydroxychloroquine

It is an anti-malarial drug used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. It has exhibited potential anti-viral activity against coronaviruses *in vitro*.[33,36,37] The *in vitro* study of hydroxychloroquine exhibited anti-viral activity against SARS-CoV-2 in infected Vero E6 cells; data suggesting it may be more potent than chloroquine *in vitro*.[36,37] It possesses immunomodulatory activity that could contribute to the management of inflammatory response in patients with viral infections.[36,38,39] Multiple clinical trials have been initiated using various dosages in patients infected with SARS-CoV-2 in China and other countries.[31] Outcomes from clinical trial in patients with SARS-CoV-2 infection are increasing, but the data is insufficient to establish the safety of the drug for treatment of COVID-19.[40,41] Gautret *et al.* recently published a preliminary report of an ongoing trial in hospitalized patients with SARS-CoV-2 infection to evaluate the efficiency of hydroxychloroquine as a single dosage form or in combination with azithromycin. Those patients who were untreated were considered as negative controls. The authors have reported on 36 infected patients, including 20 patients in hydroxychloroquine treated group and 16 patients in the control group. 14 patients were treated with hydroxychloroquine at a dose of 200 mg 8 hourly for 10 days. Six patients were treated with a combination of hydroxychloroquine and azithromycin. The dose of azithromycin was 500 mg on 1st day, followed by 250 mg OD on 2nd to 5th days. The primary endpoint of the trial was negative as per polymerase chain reaction (PCR) results for SARS-CoV-2 in nasopharyngeal samples on day 6. At day 6, 8 patients were found PCR negative in the hydroxychloroquine group (57%). In the combination group, all 6 patients (100%) were found PCR negative at day 6. Only 2 out of 16 patients were found PCR negative at day 6 (12.5%) in the control grouping. A patient was reported as negative on day 6. But he was found positive at day 8 on being treated with both drugs after a test has been carried out in PCR. Investigators have found 100% viral eradication in the combined treatment group (all 6 patients of the group) compared to viral eradication in 57% of patients taking hydroxychloroquine alone (8 out of 14). The result suggested that hydroxychloroquine could be a therapeutic option for clearance of SARS-CoV-2 from the nasopharynx. Although the results from the trial are promising, we have to consider certain limitations of these data. The author did not mention the clinical outcomes in these patients regarding the viral eradication as the endpoint. Six patients in the treatment group received hydroxychloroquine plus azithromycin, not hydroxychloroquine alone. From the given data, we cannot reliably identify which patients they were. Treated patients were older on an average than control patients. Hydroxychloroquine immunotherapy patients with CT values < 23 were separated from those patients with CT values > 23. In the supplementary table, some PCR results are stated in terms of the number of replications required to make the diagnosis, while others are merely labelled "POSITIVE". It is unclear whether the viral PCR tests were all carried out at one centre, or whether those testing the samples were unaware of treatment allocation. Either of these factors could have introduced bias facts. It is not stated whether hydroxychloroquine was present in bodily fluids in concentrations that might influence the PCR results, although this seems unlikely. Eight controls were labelled positive on day 0, but no quantitative data on PCR were given, and in two controls the test was not done. It is not, therefore, possible to describe whether viral loads differed at baseline between the two groups. The virus tests were negative in one patient in the control group and three patients in the treatment group at one time-point, but became positive subsequently, casting doubt on the choice of a single (previously unspecified) day on which to assess viral clearance.[40] In a small trial,

30 patients were randomized into 1:1 ratio. Treatment group patients were treated with hydroxychloroquine sulfate at a dose of 400 mg OD for 5 days in combination with conventional treatment. The control group was treated with conventional treatment alone. The primary endpoint of the study was negative PCR in pharyngeal swabs of the patients on day 7. 13 patients were PCR negative on day 7 treated with hydroxychloroquine (86.7%) and 14 patients were PCR negative from the control (93.3%). The reported data were unclear for the remaining 3 patients from both groups. The median duration from hospitalization to negative PCR and temperature normalization was found to be similar in the hydroxychloroquine group and the control group. All patients exhibited improvement of lung conditions at follow-up studies.[41] Most of the studies have been evaluating the efficacy of hydroxychloroquine based on negative PCR conversion in nasopharyngeal samples on day 6 or 7.[40,41] The reverse transcription-polymerase chain reaction (RT-PCR) tests are recommended for diagnosis of COVID-19 using upper and lower respiratory samples.[42,43] Chen *et al.* carried out a randomized clinical trial to evaluate the efficacy of hydroxychloroquine. The trial was registered with the Chinese clinical trial registry (ChiCTR2000029559). The participants of the trial were placed in a parallel-group trial. Out of 62 patients, 46.8% (29 of 62) were male and 53.2% (33 of 62) were female, the mean age was 44.7 years. The study reported the duration of clinical recovery, the body temperature recovery time and the cough remission time were significantly shortened in the hydroxychloroquine treatment group. They also reported a larger proportion of patients with improved pneumonia in the hydroxychloroquine group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31). Although the report demonstrated good results, there are many limitations of the study. There might be selection bias as the pre-specified exclusion criterion does not define what "other conditions", it would make an individual "unsuitable to participate". There is no explanation of the shortfall in patient numbers, comparing 300 patients originally specified and 62 patients actually recruited. The patients in the study were 18 years old or older, while the protocol specified patients aged 30 to 65 years. While the mean ages and standard deviations (SD) of the patients in each group are reported, the proportion of each group in different deciles of age is not reported. The standard treatment included antiviral agents, antibacterial agents, and immunoglobulin with or without corticosteroids. The antiviral and antibacterial agents were unspecified, and the proportions of individuals in each group who received any agent were not reported. The trial was supposed to be a double-blind trial, and the protocol stated that starch pills were to be used in the control group. But, there is no mention of the administration of a dummy treatment in the report. An additional analysis was carried out for the chest computed tomography (CT) scans taken on day 0 and day 6. It demonstrated improvement in 25 patients out of 31 hydroxychloroquine-treated patients and 17 patients out of 31 control patients. These results are not quite significant at the 0.05 level. It is unclear whether those reading the radiographs were blind to the treatment allocation. Cough and fever were absent in 25 out of 31 hydroxychloroquine-treated patients and 23 out of 61 control patients at the baseline respectively. The absence of typical symptoms of SARS-CoV-2 infection may, therefore, mean that the patients were unrepresentative. Although the outcomes are described as being statistically significant, it is not clear that they were clinically significant.[44] Mahevas *et al.* reported no evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for SARS-CoV-2-positive hypoxic pneumonia using routinely collected data to emulate a target trial. The data were presented in the study by using real-world data collected from the routine care of 181 patients hospitalized with hypoxemic pneumonia due to COVID-19. 84 patients were given hydroxychloroquine 600 mg OD within 48 h of admission in addition to standard care; 97 patients were not. The outcome includes many parameters. The patients' death with 7 days or transferred to ICU were 20.2% for hydroxychloroquine group and 22.1% for the group without hydroxychloroquine. The patients died within 7 days were 2.8% for hydroxychloroquine group and 4.6% for the group without hydroxychloroquine. The acute respiratory distress syndrome (ARDS) within 7 days in patients was 27.4% for the hydroxychloroquine group and 24.1% for the group without hydroxychloroquine. The QT interval prolongation needing discontinuation was observed in eight patients from the hydroxychloroquine group.[45] Molina *et al.* reported no evidence on instant viral consent or clinical welfare utilizing the blending of hydroxychloroquine and azithromycin in patients with severe SARS-CoV-2 infection. They described the treatment of 11 consecutive patients under their care using a combination of hydroxychloroquine and azithromycin. One patient died within 5 days. Another patient was withdrawn from the study after 4 days because of prolongation of the QT interval. In eight patients, repeated nasopharyngeal swabs were still positive for SARS-CoV-2 RNA at 5–6 days after the start of treatment. As the study represents a small observational study, it is difficult to derive any significant conclusion from the study.[46] Although the results are conflicting, recently a large-scale trial demonstrated a promising result with hydroxychloroquine. A cohort study reported the virological cure in 91.7% within 10 days. A cohort of 1061 infected patients treated with at least 3 days with hydroxychloroquine and azithromycin combination and a follow up of at least 9 days was investigated. 47 patients (4.4%) exhibited prolonged viral carriage at completion of treatment, but the viral culture was negative at day 10. A poor clinical outcome was observed in 46 patients (4.3%). Out of 46 patients, 5 patients died (0.47%), 10 patients were transferred to ICU and 31 patients required more than 10 days of hospitalization. The poor clinical outcome was found to be associated with older age,

initial higher severity and low hydroxychloroquine serum concentration.[47] Efficacy and safety of hydroxychloroquine for treatment or prevention of SARS-CoV-2 infection have not been established yet.[31,48] Food and drug administration (FDA) authorized the dosage of hydroxychloroquine as 800 mg on 1st day. It is followed by 400 mg OD for 4th to 7th days of total treatment based on clinical status for SARS-CoV-2 infected hospitalized adults and adolescents weighing 50 kg or more.[34]

Umifenovir

It is an anti-viral treatment for influenza infection. It inhibits membrane fusion.[49] The fusion between the viral envelope (surrounding the viral capsid) and the cell membrane of the target cell is inhibited, thereby prevents viral entry to the target cell.[50] Umifenovir exhibited more activity against RNA viruses than DNA viruses.[51] It stimulates a humoral immune response, induces interferon-production and stimulates the phagocytic function of macrophages.[52] Umifenovir has been studied for the treatment of hepatitis C.[53] A multicenter randomized trial was carried out in China to evaluate the efficacy and safety of conventional therapy with favipiravir and umifenovir in moderate SARS-CoV-2 infected patients. The primary outcome was clinical recovery rate of day 7. Duration of fever, cough relief time and auxiliary oxygen therapy or noninvasive mechanical ventilation rate represented the secondary outcomes. 120 patients were assigned to favipiravir group (116 assessed) and 120 to umifenovir group (120 assessed). For patients with moderate SARS-CoV-2 infection, the clinical recovery rate on day 7 was 55.86% in the umifenovir group and 71.43% in the favipiravir group. The latency to fever reduction and cough relief in favipiravir group was found to be significantly shorter than that in umifenovir group for moderately ill patients. The similar result was observed in patients with hypertension and diabetes. The most frequently observed treatment-associated adverse events were abnormal liver function (LFT), psychiatric symptom reactions, digestive tract reactions and raised serum uric acid (3 [2.50%] in umifenovir group versus 16 [13.79%] in favipiravir group, P <0.0001).[54] There were many limitations to the study. Subgroup analysis was not predefined in the protocol. Details of randomization procedure were not mentioned and no allocation concealment. There was no blinding in the study including data analysis with sub-optimal statistical tests.[55]

Camostat mesylate

It is an orally active protease inhibitor, increases exocrine pancreatic secretion and pancreatic weight in rats, reduces amylase release from pancreatic acini. For chronic pancreatitis, the conventional dose is 600 mg daily. For postoperative reflux esophagitis, it is taken as a dose of 300 mg. The daily doses are taken 8 hourly after each meal. The oral administration of camostat mesylate inhibits inflammation, cytokine expression and fibrosis in the pancreas.[56] The fusion of host cells and the virus depends on the host cell factors ACE2 and type II transmembrane serine proteases, TMPRSS2. S protein of SARS-CoV-2 is primed by TMPRSS2. Priming of S proteins by host cell proteases is essential for viral entry into cells and encompasses S protein cleavage at the junction between S1/S2. The S1/S2 cleavage site of SARS-CoV-2 S protein harbours several arginine residues which indicate high cleavability.[57] Many other coronaviruses depend on TMPRSS2. TMPRSS2 and HAT cleave the HCoV-229E S-protein (229E-S) and augment 229E-S-driven cell-cell fusion.[58] The S proteins of SARS-CoV can use endosomal cysteine proteases CatB/L for S protein priming in TMPRSS2- cells.[59] Instead of CatB/L, S protein priming by TMPRSS2 is essential for viral entry into primary target cells and viral spread in the infected host.[60–62] Camostat mesylate treatment significantly reduced Calu-3 cell infection with authentic SARS-CoV-2. Camostat mesylate treatment inhibited SARS-CoV S protein and SARS-CoV-2 S protein driven entry into primary human lung cells.[57] The data suggests the mechanism of action of camostat mesylate could be due to the inhibition of TMPRSS2. Based on the present data, camostat mesylate can be evaluated for the treatment of SARS-CoV-2 infected patients. Furthermore, the development of potential inhibitors of TMPRSS2 can be explored.

Bromhexine hydrochloride

It is used as a mucolytic drug in the treatment of respiratory disorders associated with productive cough. It could be a potential molecule for the treatment of SARS-CoV infections as an inhibitor of TMPRSS2.[63] An interventional randomized study is being carried out to evaluate the effectiveness of bromhexine hydrochloride in combination with standard therapy in patients with mild SARS-CoV-2 infection.[64]

Griffithsin

It is a red-alga-derived lectin, that binds to oligosaccharides on the surface of various viral glycoproteins, including HIV glycoprotein 120 and SARS-CoV spike glycoprotein.[65] Griffithsin was administered intranasally against SARS-CoV infected mice and found that the levels of cytokines decreased compared with those infected with SARS-CoV alone.[66] Griffithsin exhibited anti-viral activity against SARS-CoV_{Urbani}, SARS-CoV_{Tor-II}, SARS-CoV_{CuHK}, SARS-CoV_{Frank}, SARS-$CoV_{200300592}$ in Vero 76 cells with EC_{50} value of 48 nM, 48 nM, 61 nM, 94 nM and 280 nM respectively.[66,67] Three molecules of griffithsin are capable of binding S protein in a dose-dependent manner with very high affinity. Interestingly, such interaction does not inhibit the binding of the SARS-CoV S protein to the host cell human ACE2 receptor. Studies on mouse-adapted MA15 SARS-CoV demonstrated that mice received daily doses of intranasally administered griffithsin had 100% survival rate. There was no loss in weight, improved lung histopathology scores, and reduction of lung tissue virus titers in the treatment group. In contrast, the control group experienced weight

loss and had only a 30% survival rate.[66] Griffithsin could be a potential molecule against SARS-CoV-2 based on the findings.

Angiotensin II Receptor Blockers (ARB inhibitors)

ARB inhibitors may possess defensive effect against lung damage in coronavirus infection. The possible mechanisms of action involve inhibition of the virus binding to host cells.[68,69] A clinical trial is being carried out to find the efficacy of ACE inhibitors in the treatment of SARS-CoV-2 infected patients. The study uses losartan in adult patients with SARS-CoV-2 infection requiring hospitalization. The primary outcome measures are sequential organ failure assessment (SOFA), the respiratory score.[70] There are potential risks associated with the use of Angiotensin II Receptor Blockers for the treatment of SARS-CoV-2 infection. They may lead to an increase in the expression of ACE2 receptor.[68,71] Increased expression of ACE2 may potentially facilitate SARS-CoV-2 infections.[68]

Promazine

It is an anti-psychotic drug, found to exhibit antiviral activity against SARS-CoV virus.[72] It exhibited potent inhibition of binding of the S protein of SARS-CoV to ACE2.[73] As an approved drug, promazine can be repurposed for SARS-CoV-2 infection.

Nicotianamine

It is a metal-ligand found in soybean and other plant sources.[74] It is found to be a novel ACE2 inhibitor. It can be evaluated for combating SARS-CoV-2 infection.[75]

Monoclonal antibodies (mAbs)

Polyclonal antibodies from recovered patients have been used to treat SARS-CoV-2 infection.[76] Since the S-protein of SARS-CoV-2 is closely related to SARS-CoV, researchers have been investigating SARS-CoV mAbs with potential cross-reactivity and/or cross-neutralizing activity against SARS-CoV-2 infection.[3] Researchers reported a SARS-CoV specific human neutralizing mAb, CR3022 from the blood of a convalescent SARS patient. It could bind SARS-CoV-2 RBD with high affinity. The epitope of CR3022 on the RBD did not overlap with the ACE2-binding site.[77,78] It followed a fast-on (k_{on} of 1.84×10^5 Ms^{-1}) and slow-off (k_{off} of 1.16×10^{-3} s^{-1}) binding kinetics, resulting in a K_D of 6.3 nM. SARS-CoV-specific neutralizing antibodies m396, CR3014 exhibited potent interfering activity against the receptor binding site of SARS-CoV but these antibodies failed to bind to the S protein of SARS-CoV-2. It indicates the necessity to develop mAbs for SARS-CoV-2.[78] Bao L *et al.* demonstrated antibodies could protect SARS-CoV-2 infected rhesus macaques from reinfection.[79] Identification of potential antibodies from previously infected patients and their evaluation could be a potential intervention in the treatment of infected patients. REGN3048 and REGN3051 are the wholly human neutralizing monoclonal antibodies. When the animals were treated with monoclonal antibodies against MERS-CoV one day before challenge; respiratory disease was less severe. The animals were treated with both REGN3048 and REGN3051; viral loads in the lungs were reduced. Therapeutic treatment on day 1 after challenge was less efficacious as it did not prevent the development of severe respiratory disease and all treated animals developed bronchointerstitial pneumonia of similar severity as the control animals.[80]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) contains the pooled immunoglobulin G (IgG) from the plasma of approximately 1000 to 15000 donors per batch.[81] It is a choice of treatment in patients with antibody deficiencies. IVIGs typically contain more than 95 % unmodified IgG, which has intact Fc-dependent effector functions and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M (IgM).[82] IVIG is used in different clinical specialities including neurology, haematology, immunology, nephrology, rheumatology and dermatology. IVIG is used at a high dose (2 g / kg) for diseases in neurology, haematology, rheumatology, dermatology and others while replacement doses are comparatively low (0.4 g / kg). The mechanisms of action of therapeutic immunoglobulin are complex and depend on the dose and pathogenesis of disease under consideration. IVIG exhibits immunomodulatory functions including suppressing inflammatory cell proliferation, inhibiting phagocytosis and interfering antibody-dependent cytotoxicity.[83] A case-control study demonstrated patients with community-acquired pneumonia had significantly lower levels of IgG (especially IgG2 subclass) and IgA in comparison with a control group of healthy patients without pneumonia.[84] Another study confirmed that severe viral infection due to H1N1 was associated with lower levels of the IgG2 subclass.[85] A meta-analysis reported a reduction in mortality rate (approximately 21 %) in adult patients with sepsis and septic shock after receiving polyclonal immunoglobulins. The effect was more evident in the subgroup receiving IgM-enriched immunoglobulin.[86] A randomized, single-centre trial is being carried out to evaluate the efficacy of Intravenous Immunoglobulin Therapy in patients with SARS-CoV-2 infection. The interventions of the study are IVIG at a dose of 0.5 g/kg/d for 5 days with standard care for the experimental group and standard care for the control group. The primary outcome of the study includes clinical improvement based on the 7-point scale and lower Murray lung injury score.[87]

Convalescent plasma therapy

Convalescent plasma (CP) therapy is adaptive immunotherapy, applied for the prevention and treatment of infectious diseases. It has been used successfully in the treatment of SARS, MERS, and H1N1 pandemic with efficacy and safety.[88–91] A meta-analytical survey was carried out for 32 studies of SARS-CoV infection that illustrated a statistical significance of reduced

mortality after CP therapy, compared with placebo or no therapy.[92] The neutralizing activity of CP against SARS-CoV-2 was evaluated by a classical plaque reduction test using a recently isolated viral strain.[3] In a pilot-scale study, 10 severe patients with SARS-CoV-2 infection were treated with one dose (200 ml) of CP. The median time from onset of symptoms to hospital admission and CP transfusion was 6 days and 16.5 days respectively. The clinical symptoms disappeared or largely improved within 1 day to 3 days upon CP transfusion. Reduction of pulmonary lesions on chest CT examinations was observed. The neutralizing antibody titers of five patients increased and four patients remained at the same level after CP transfusion excluding on patients. Before treatment with CP, SARS-CoV-2 RNA was assayed by RT-PCR. It was positive in seven patients and negative in three cases before CP transfusion. After CP transfusion, SARS-CoV-2 RNA was decreased to an undetectable level in three patients on day 2, three patients on day 3, and one patient on day 6. One patient showed an evanescent facial red spot.[88] Zhang *et al.* reported case studies of convalescent plasma treatment in four critically ill patients with SARS-CoV-2 infection, including a pregnant woman. The duration between the hospital admission to initiation of CP transfusion ranged from 11 days to 18 days. The duration between CP transfusions to negative RT-PCR test results ranged from 3 days to 22 days. The level of neutralizing antibodies in CP could be important for the effectiveness of CP transfusion.[93] Patients who survived severe SARS-CoV-2 infection might mount higher antibody responses, which can persist for longer periods as compared with those with the non-severe disease.[94] Other interventions might influence the level of neutralizing antibodies.[95] Furthermore, well-designed trials should be carried out to establish the safety and efficacy of CP transfusion.

4.2 Proteolysis inhibition

Lopinavir and ritonavir

Lopinavir is an antiretroviral of the protease inhibitor class. It is used against the human immunodeficiency virus (HIV) infections as a fixed-dose combination with another protease inhibitor, ritonavir. Ritonavir strongly inhibits lopinavir metabolism; co-administration of lopinavir and ritonavir in healthy volunteers increases the area under lopinavir plasma concentration-time curve by > 100 fold. Diarrhoea and nausea are the most frequently reported adverse effects in patients receiving lopinavir/ritonavir based dosage regimens. Lopinavir has an approximate, 10-fold higher *in vitro* activity against both wild-type and mutant HIV-1 proteases than ritonavir. However, its activity is greatly attenuated by a high first-pass hepatic metabolism i*n vivo*. The low dose of ritonavir co-administered with lopinavir inhibits metabolic inactivation of lopinavir and acts only as its pharmacokinetic enhancer.[96] It has demonstrated *in vitro* potency against MERS-CoV and SARS-CoV. There are some substantiations of benefit in animal studies for the treatment of MERS-CoV.[97–99] In 2004, Chu *et al.* evaluated a series of anti-viral agents for anti-viral activity against SARS-CoV. They have reported that lopinavir (4 µg/ml) and ribavirin (50 µg/ml) inhibited SARS-CoV after 48 h of incubation and that the agents were synergistic when used together. Because of the promising *in vitro* results, they used combination therapy including lopinavir/ritonavir, ribavirin, and corticosteroids for SARS-CoV infected patient without ARDS in SARS-CoV infection. A total of 41 patients was treated with lopinavir/ritonavir combination therapy were compared to 111 patients receiving ribavirin plus corticosteroids in previous cases. It was observed from the comparison that there was a significant reduction in the development of ARDS or death of patients at 21 days of the therapy (2.4% versus 28.8%, $P < 0.001$). This data was further supported by a case-control matched study from the same centre.[97] A significant reduction in pulse steroid use, intubation and mortality among patients were observed in patients receiving lopinavir/ritonavir combination in comparison to without lopinavir/ritonavir as initial treatment.[100] de Wilde *et al.* later described the antiviral activity of lopinavir against SARS-CoV and demonstrated an EC_{50} value of 17.1 ± 1 µM in Vero E6 cells.[101] Sheahan *et al.* evaluated efficacy of lopinavir/ritonavir in combination with interferon beta (INF-β) against MERS-CoV *in vitro*. The addition of lopinavir/ritonavir did not significantly enhance the anti-viral activity of INF-β alone (EC_{50} = 160 IU/ml versus 175 IU/ml, respectively). The EC_{50} value of lopinavir/ritonavir and lopinavir alone were 8.5 µM and 11.6 µM, suggesting similar activity to that described for SARS-CoV. Despite *in vitro* activity against MERS-CoV, therapeutic doses of lopinavir/ritonavir + INF-β in mice models failed to reduce virus titre and exacerbated lung disease.[102] A randomized trial was carried out to evaluate the efficacy of lopinavir/ritonavir in combination with standard therapy in patients diagnosed with COVID-19. The primary outcome of the study was the duration of clinical development at two points on a seven-category ordinal level or release from the hospital. The study reported that there was no difference in both groups in terms of clinical improvement as the median time to clinical improvement was 16 days in both groups. The study reported lower 28th-day mortality rate in the lopinavir/ritonavir group as compared to the standard group. It was suggested that the initiation of lopinavir/ritonavir treatment within 12 days of onset of symptoms was associated with shorter time to clinical improvement. The study illustrated insignificant differentiation in a reduction of viral RNA titre, the extent of the infection, the time length of oxygen therapy, the time length of hospitalization, or period from randomization to death**.** The study also reported adverse effects in 13 patients because of which lopinavir/ritonavir treatment was terminated early in those patients. The dosage regimen was 400 mg of lopinavir and 100 mg of ritonavir BD orally for 14 days.[103] A small retrospective trial evaluated the use of lopinavir/ritonavir with or without umifenovir in patients diagnosed with COVID-19. The primary outcome of the trial was the negative result for the virus and clinical

improvement or deterioration of the health condition. The virus was undetectable in 6 out of 17 patients treated with lopinavir/ritonavir alone; compared to 12 out of 16 patients treated with both drugs in nasopharyngeal samples. At 14th day, the virus was undetectable in 9 out of 17 patients as compared to 15 out of 16 patients. The dosage regimen was 400 mg of lopinavir and 100 mg of ritonavir BD orally with or without umifenovir (200 mg every 8 h) for up to 21 days.[104] For the treatment of SARS-CoV-2 infected patients as per National Health Commission, China has fixed the dosage regimen as lopinavir 400 mg/ritonavir 100 mg orally in combination or without interferon (5 million units of interferon-α or correspondent two times each day as particular in 2 ml of sterile water by nebulization) and in combination or without ribavirin for up to 10 days.[105,106] Although it exhibited potent activity against SARS-CoV, the researcher must consider low activity in mouse models against MERS-CoV. *In vitro* studies, it exhibited lower activity as compared to remdesivir and chloroquine for SARS-CoV. If lopinavir/ritonavir combination is used for the treatment of patients diagnosed with COVID-19, the possible drug interactions must be examined and observation should be done for hepatotoxicity. Patients with elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) should be eliminated.

Protease inhibitor

Papain like protease (PL_{PRO}) and main protease (M^{PRO}) have essential functions in virus replication of SARS-CoV and inhibition of host immune response.[107] Cinaserin inhibited the replication of SARS-CoV and the mechanism of action of the drug could be inhibition of M^{PRO}.[108] M^{PRO} is found to be encoded in SARS-CoV-2, therefore it can be evaluated against SARS-CoV-2.[109] Jo *et al.* suggested herbacetin, rhoifolin and pectolin exhibited anti-viral activity against human coronavirus due to inhibitory action on M^{PRO}.[110] Ryu *et al.* reported biflavonoids from *Torreya nucifera* inhibited SARS-CoV M^{PRO}.[111] PL_{PRO} is a deubiquitinase encoded by a human coronavirus. It is an interferon (IFN) antagonist and inhibits host immune response against coronavirus. Diarylheptanoids were found to inhibit PL_{PRO} in SARS-CoV. It is extracted from the stem bark of *Alnus japonica.*[107] *In silico* and *in vitro* studies have been carried against SARS-CoV-2 M^{PRO} in the search of potential molecules. *In silico* studies demonstrated that andrographolide from *Andrographis paniculata* potentially inhibited the main protease of SARS-COV-2 (M^{PRO}). The study suggested that andrographolide possessed good solubility and targeting efficiency.[112] Natural compounds, including hypericin, baicalin, glabridin, cyanidin 3-glucoside exhibited potent inhibitory action against M^{PRO} *in silico.*[113] *In silico* screening of natural compounds discovered natural molecules having the capability to interact with M^{PRO}, ACE2 and RNA dependent RNA polymerase (RdRp). Viniferin, myricitrin, biorobin, hesperidin, phyllaemblicin B, nympholide A and afzelin were reported to be strongly bound to M^{PRO}.[114] The computational study of molecules from marine sources resulted in many promising inhibitors of M^{PRO}. These compounds are isolated from *Sargassum spinuligerum* brown algae. These compounds belong to a class of molecules known as phlorotannins, oligomers of phloroglucinol. These algae are used widely in traditional Chinese medicine.[115] Flavonoid compounds including apigenin-7-*O*-neohesperidoside, luteolin-7-rutinoside, and resinoside were also identified as potent inhibitors of M^{PRO} inhibitors.[116] Based on *in silico* data, Liu *et al.* reported telcagepant, vidupiprant, poziotinib, and fostamatinib as a potent drug against M^{PRO}. As clinical data are available for these drugs, they can be directly evaluated against SARS-CoV-2.[117] Kandeel *et al.* suggested use of a combination of ribavirin, telbivudine, vitamin B12 and nicotinamide against COVID-19 targeting M^{PRO} based on in silico studies.[118] Zhang *et al.* reported the development of a modified α-ketoamide having potential activity against M^{PRO} of SARS-CoV-2. The compound inhibited purified recombinant M^{PRO} with an IC_{50} value of 0.67 ± 0.18 μM. The compound exhibited anti-viral activity against SARS-CoV-2 with an EC_{50} value of 4-5 μM in human Calu3 cells.[119] Molecules from natural sources have been investigated for activity against M^{PRO}. Oolonghomobisflavan-A is a natural molecule isolated from the Tea plant. Oolonghomobisflavan-A exhibited hydrogen bonding with M^{PRO} and higher MM-PBSA binding energy than synthetic protease inhibitors including lopinavir in molecular dynamics and MM-PBSA studies.[120] Umesh *et al.* reported that M^{PRO} inhibitors from Indian spices including arjunglucoside-I, rosmanol, carnosol using computational approaches.[121] Peptide molecules have been investigated for inhibitory activity against M^{PRO} of SARS-CoV. Gan *et al.* reported on the anti-viral activity of AVLQSGFR octapeptide against SARS-CoV with EC_{50} of 2.7×10^{-2}. The peptide had shown the lowest EC_{50} value and higher selectivity index among ribavirin, mycophenolic acid, glycyrrhizin, 6–azauridine and pyrazofurin.[122]

4.3 Viral replication or synthesis inhibition

Favipiravir

It is a board spectrum inhibitor of the viral RNA polymerase. It is a selective and potent inhibitor of influenza viral RNA polymerase.[123] Favipiravir exhibited anti-viral activities against other RNA viruses.[124] Favipiravir inhibited the replication of the viral genome. In the presence of purine nucleosides or purine bases, favipiravir competes with purine nucleosides rather than pyrimidine nucleosides.[125] Chen *et. al.* conducted a prospective, randomized, controlled, open-label multicenter trial to evaluate favipiravir versus arbidol for COVID-19. 240 patients were randomized in a 1:1 ratio to receive conventional therapy plus arbidol (200 mg 8 hourly a day) or favipiravir (1600 mg BD for the first day followed by 600 mg BD for 10 days). The primary outcome of the trial was the clinical recovery rate on day 7. Latency to relief for pyrexia and cough, the rate of auxiliary oxygen therapy (AOT) or

noninvasive mechanical ventilation (NMV) were the secondary outcomes of the trial. The study reported a clinical recovery rate on day 7 did not significantly differ between the favipiravir group (71/116) and the arbidol group (62/120). Favipiravir significantly improved the latency to relief for pyrexia and cough. Clinical recovery was defined in the protocol as continuous (>72 h) recovery of body temperature, respiratory rate, oxygen saturation and cough relief after treatment, with following quantitative criteria: axillary temperature ≤36.6°C; respiratory frequency ≤24 times/min; oxygen saturation ≥98% without oxygen inhalation; mild or no cough. There are many limitations to the study. The control arm was not included in the study. No virological endpoint was mentioned in the protocol. The number of patients in the different age group was varied. The observation time frame was limited. In the trial, only 46.55% of patients in the favipiravir group and 38.33% in Arbidol group were nucleic-acid-positive at enrollment.[54] A randomized, double-blinded, multi-centred, three-armed, controlled study is being carried out to evaluate favipiravir in combination with chloroquine phosphate against pneumonia with SARS-CoV-2 infection. The three arms of the study are favipiravir tablets plus chloroquine phosphate tablet group (combined group), favipiravir tablet group and placebo treatment group (control group). The total enrollment for the study is 150 patients. The combined group will receive favipiravir 1600 mg BD on 1st day; followed by 600 mg BD from 2nd day to the 10th day of the treatment and chloroquine phosphate tablets: 1000 mg BD on 1st day; followed by 500 mg OD from 2nd to 3rd day; from 4th to 10th day, 250 mg OD. The favipiravir group will receive favipiravir 1600 mg BD on 1st day; followed by 600 mg BD from 2nd day to the 10th day of the treatment. The placebo treatment group will receive the placebo for favipiravir tablets and chloroquine phosphate.[126]

Remdesivir

Remdesivir is a novel nucleotide analogue having anti-viral activity. It is an investigational anti-viral monophosphoramidate formulated by Gilead Sciences, Inc. for treatment of Ebola. It is of an adenosine analogue-based prodrug. Active triphosphate nucleoside form of remdesivir binds to RNA-dependent RNA polymerase. The mechanism of action of remdesivir involves termination of RNA chain. Remdesivir exhibited significant antiviral activity against SARS-CoV-2 (EC_{50} = 0.77 µM) in Vero E6 cells at 48 h.[25] Remdesivir also exhibited antiviral activity against other coronaviruses including SARS-CoV and MERS-CoV.*[102,127–129]* It has exhibited potent selectivity for viral polymerases. Sheahan *et al.* showed that remdesivir possessed board therapeutic index in a human airway epithelial cell model.[127] Currently, remdesivir is being evaluated in clinical trials to establish the effectiveness and safety aspects for infected patients with COVID-19.[130] Remdesivir-treatment in COVID-19 was first reported from the United States in a 35-year-old male patient. The patient received remdesivir on 7th day of hospital admission due to existing pneumonia and fever. The health condition of the patient improved and the oropharyngeal swab was tested negative, but nasopharyngeal swab was tested positive on 8th day of hospital admission.[131] Four clinical trials of remdesivir are being carried out in the US. Two clinical trials are enrolling patients for treatment with remdesivir in China, one trial for the severe condition of the disease and one for the mild-moderate condition of disease.[132] A Phase 3 randomized trial is being carried out by Gilead Inc. to evaluate the effectiveness of 5- and 10-day regimens of remdesivir for severely ill patients. The dosage regimen for one group is 200 mg IV on 1st day, followed by 100 mg OD IV on 2nd to 5th day. For another group, the dosage regimen is 200 mg IV on 1st day, followed by 100 mg OD IV on 2nd to 10th day. Target enrollment of participants for the study is 600. The primary outcome is the proportion of patients with improvement of fever and oxygen saturation by day 14.[133] A randomized Phase II trial is initiated by NIAID to evaluate the effectiveness of remdesivir in hospitalized infected patients. The dosage of NIAID study protocol includes 200 mg IV on 1st day of treatment, followed by 100 mg OD IV for the duration of hospitalization to 10 days.[134]

Galidesivir

It is a broad spectrum of anti-viral activity developed by Biocryst Pharma. It has been used in Ebola and other hemorrhagic fever virus infections. The mechanism of action of galidesivir involves inhibition of RNA polymerase. It has exhibited broad-spectrum anti-viral effectiveness against a range of other RNA virus families including bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses, flaviviruses and phleboviruses.[135] Studies have demonstrated the potential of galidesivir to protect against both Ebola and Marburg viruses in both rodents and monkeys, even when administered up to 48 h after infection.[136] It exhibited activity against Zika virus in a mouse model.[137] Galidesivir has been investigated against SARS-COV-2.[138]

Niclosamide

Niclosamide is a medication used to treat tapeworm infestations. It includes diphyllobothriasis, hymenolepiasis and taeniasis.[139] Niclosamide is a proton carrier. It targets the acidic endosomes with broad anti-viral effects. It inhibits infection with pH-dependent human rhinoviruses (HRV) and influenza virus. The anti-viral activity of niclosamide is host targeted.[140] It exhibited anti-viral activity against SARS-CoV and MERS-CoV *in vitro* studies. The mechanism of action niclosamide was associated with inhibition of viral replication and antigen synthesis of SARS-CoV.[141,142]

Nitazoxanide

Nitazoxanide is a drug that is used in medicine for the treatment of various helminthic, protozoal and viral infections.[143] Structurally, it is similar to

niclosamide.[142] Tizoxanide, an active metabolite of nitazoxanide in humans also acts as a potent inhibitor of hepatitis B virus and hepatitis C virus replication.[145] Nitazoxanide inhibits the replication of RNA and DNA viruses including respiratory syncytial virus, parainfluenza, coronavirus, rotavirus, dengue, norovirus, yellow fever, Japanese encephalitis, human immune deficiency virus in cell culture assays. It has inhibitory effect on a broad range of influenza virus subtypes. It exhibited efficacy against influenza viruses that are resistant to neuraminidase inhibitors like oseltamivir.[142,143] Nitazoxanide is under investigation for the treatment of SARS-CoV-2. It exhibited anti-viral activity against MERS-CoV. In the treatment of influenza and influenza-like illness or other viral infections, the doses of Nitazoxanide are being investigated as 500 or 600 mg BD orally for 5 days.[31]

IndomethacinIt is a nonsteroidal anti-inflammatory agent. It exhibited potent antiviral activity against SARS-CoV by interfering the synthesis of viral RNA. *In vitro* and *in vivo* studies should be carried out to find out the potential of the drug against SARS-CoV-2.

4.4 Viral release inhibition

Oseltamivir

Oseltamivir is an antiviral medication used to treat and prevent influenza A and influenza B. It inhibits the neuraminidase enzyme, expressed on the viral surface. The neuraminidase enzyme promotes virus release from infected cells and facilitates viral movement within the respiratory tract. In a retrospective study, 99 patients with SARS-CoV-2 infection were diagnosed and treated at a single centre in Wuhan. 75 patients received oseltamivir (75 mg BD, oral route), ganciclovir (0·25 g BD, IV route), and lopinavir and ritonavir tablets (500 mg BD, oral route). Many patients also received antibiotic therapy, including single antibiotic therapy for 25 patients and combination therapy for 45 patients. At the time of evaluation, 57 patients remained in hospitalization, 31 patients had been discharged, and 11 patients had died.[150] While oseltamivir has been used for patients with SARS-CoV-2 infection in hospitals in China; significant data is not available to support the effectiveness of oseltamivir in the treatment of SARS-CoV-2 infection. Three trials have started with oseltamivir for SARS-CoV-2 infected patients. The dosages of oseltamivir for treatment of COVID-19 comprise of 300 mg OD, 75 mg OD or BD or 4-6 mg/kg OD (with a frequency not being specific) in different trials.[31] Although Oseltamivir was tried for SARS-CoV-2, it had not exhibited inhibitory anti-viral activity against SARS-CoV *in vitro* cell lines.

The research data for prevention and treatment of COVID-19 is rapidly emerging because of continuous research effort and collaboration across the globe. Repurposing of drugs and the vaccine development process has achieved a rapid pace in the search for drug discovery against SARS-CoV-2. Many clinical trials have been going on for repurposing drugs and develop vaccines. Although few drugs are showing good results in trials, the data are limited to ensure the safety and efficacy of those drugs. Structural analysis of protein molecules of the virus is providing crucial data for selection of target molecules. The S protein and the main protease of the virus are identified as crucial target sites to prevent the entry and replication of the virus. New candidate molecules may exhibit good activity, but researchers should carefully evaluate the risk of mutagenicity, teratogenicity, carcinogenicity, drug-induced diseases associated with the molecule. Currently, remdesivir and convalescent plasma therapy are emerging as potential medications for the treatment of COVID-19 based on the results from recent publications. Antimalarial drugs like chloroquine or hydroxychloroquine have been included in many national guidelines for the treatment of COVID-19. However, few studies reported no beneficial effect of hydroxychloroquine treatment over standard treatment. The use of hydroxychloroquine remains a matter of debate in the scientific community due to serious side effects. At current stage, personalised medicine should be implemented with adherence to the national and international guidelines based on the risk-benefit ratio. Concurrently, comparative study of symptomatic and asymptomatic cases is essential to understand the pathogenesis of the disease at the molecular level. It will help us to understand the body's defence mechanism against coronaviruses to develop potential therapeutics as well as to prevent a probable pandemic situation in future. Because of rapid responses from government agencies, many countries have been able to control the infection to a certain extent through precautionary measures, including sanitisations, social distancing, wearing masks and awareness programs. However, development of a universal vaccine for coronaviruses is the most urgent need of the mankind because of the recurrent waves of coronaviruses in the 21st Century.

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Conflict of interest

The authors declare no conflict of interest.

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Author contributions

Nayanmoni Boruah has contributed significantly to the design, literature survey, data analysis, editing of the work. Dr. Hemanta Kumar Sharma has contributed to the design, data analysis and review of the work. Dr. Sudarshana Borah has contributed to the design, literature survey and editing of the work. Kamallochan Barman, Aditya Bora, Bhanita Das and Jayita Das has also contributed to the literature survey and editing of the works.

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REFERENCES

1. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB (2020) Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA, 323(18): 1824-1836.
2. Wang L, Wang Y, Ye D, Liu Q (2020) Review of the 2019 novel coronavirus (SARS-CoV-2) based on current evidence. Int J Antimicrob Agents 105948. https://doi.org/10.1016/j.ijantimicag.2020.105948
3. Zhou P, Yang XL, Wang XG, *et al.*(2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798): 270–3.
4. Gorbalenya AE, Baker SC, Baric RS, *et al.*(2020) The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol, 5(4): 536–44.
5. WHO (2020) Coronavirus disease 2019 (COVID-19) Situation Report – 73. https://apps.who.int/iris/handle/10665/331686. Accessed 10 June 2020.
6. Sharma HK (2019) COVID-19: Fighting with Virus. Curr Trends Pharm Res., 6(2): 1–2.
7. WHO (2020) Country and Technical guidance – Coronavirus 2019 (COVID-19) – Naming the coronavirus disease (COVID-19). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. Accessed 10 May 2020.
8. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF (2020) The proximal origin of SARS-CoV-2. Nature medicine, 26(4): 450-452.
9. Belouzard S, Chu VC, Whittaker GR (2009) Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A, 106(14): 5871–6.
10. Millet JK, Whittaker GR (2014) Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein. Proc Natl Acad Sci U S A, 111(42): 15214–9.
11. Kirchdoerfer RN, Cottrell CA, Wang N, *et al.*(2016) Pre-fusion structure of a human coronavirus spike protein. Nature, 531(7592): 118–21.
12. Song W, Gui M, Wang X, Xiang Y (2020) Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog, 14(8): e1007236. https://doi.org/10.1371/journal.ppat.1007236
13. Gui M, Liu X, Guo D, *et al.*(2017) Electron microscopy studies of the coronavirus ribonucleoprotein complex. Protein cell, 8(3): 219-224.
14. Walls AC, Park YJ, Tortorici MA, *et al.*(2020) Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell, 181(2): 281-292.e1-e4. https://doi.org/10.1016/j.cell.2020.02.058
15. Wan Y, Shang J, Graham R, Baric RS, Li F (2020) Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol, 94(7): e00127-20. doi: 10.1128/JVI.00127-20.
16. Zhang T, Wu Q, Zhang Z (2020) Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. Curr Biol, 30(7): 1346-1351. https:/doi.org/10.1016/j.cub.2020.03.022
17. Bosch BJ, Bartelink W, Rottier PJM (2008) Cathepsin L functionally cleaves the severe acute respiratory syndrome coronavirus class I fusion protein upstream of rather than adjacent to the fusion peptide. J Virol, 82(17): 8887–90.
18. Glowacka I, Bertram S, Müller MA, *et al.*(2011) Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol, 85(9): 4122–34.
19. Wu Y, Guo C, Tang L, *et al.*(2020) Prolonged presence of SARS-CoV-2 viral RNA in faecal samples.Lancet Gastroenterol Hepatol, 5(5): 434–5.
20. Zhang W, Du RH, Li B, *et al.*(2020) Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect, 9(1): 386–9.
21. Liu J, Xiao Y, Shen Y, *et al.*(2020) Detection of SARS-CoV-2 by RT-PCR in anal from patients who have recovered from coronavirus disease 2019. J Med Virol. https://doi.org/10.1002/jmv.25875
22. Schwartz DA (2020) An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. https://doi.org/10.5858/arpa.2020-0901-SA
23. Chen H, Guo J, Wang C, *et al.*(2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet, 395(10226): 809–15.
24. Forster P, Forster L, Renfrew C, Forster M (2020) Phylogenetic network analysis of SARS-CoV-2 genomes. Proc Natl Acad Sci U S A, 117(17): 9241–3.
25. Wang M, Cao R, Zhang L, *et al.*(2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Vol. 30, Cell Res, 30(3): 269-271. https://doi.org/10.1038/s41422-020-0282-0
26. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M (2004) In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun, 323(1): 264–8.
27. Devaux CA, Rolain JM, Colson P, Raoult D (2020) New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents 105938. https://doi.org/10.1016/j.ijantimicag.2020.105938

28. Barber B (2018) Chloroquine and Hydroxychloroquine. In: Grayson ML (ed) The use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic, and antiviral drugs, 7th edn. CRC PRESS, 3030–48.
29. Vincent MJ, Bergeron E, Benjannet S, *et al.*(2005) Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J., 2: 69. https://doi.org/10.1186/1743-422X-2-69
30. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S (2020) A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care, 57: 279-283. https://doi.org/10.1016/j.jcrc.2020.03.005
31. ClinicalTrials.gov. COVID-19. https://clinicaltrials.gov. Accessed 5 May 2020
32. Gao J, Tian Z, Yang X (2020) Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends, 14(1): 72–3.
33. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D (2020) Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents, 55(4): 105932. https://doi.org/10.1016/j.ijantimicag.2020.105932
34. US FDA (2020) Fact sheet for health care providers emergency use authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of covid-19 in certain hospitalized patients. https://www.fda.gov/media/136537/download (Accessed 11 May 2020)
35. Biot C, Daher W, Chavain N, *et al.*(2006) Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. J Med Chem, 49(9): 2845–9.
36. Yao X, Ye F, Zhang M, *et al.*(2020) In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis an Off Publ Infect Dis Soc Am. ciaa237. https://doi.org/10.1093/cid/ciaa237
37. Liu J, Cao R, Xu M, *et al.*(2020) Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov, 6: 16. https://doi.org/10.1038/s41421-020-0156-0
38. Sahraei Z, Shabani M, Shokouhi S, Saffaei A (2020) Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. Int J Antimicrob Agents, 55(4): 105945. https://doi.org/10.1016/j.ijantimicag.2020.105945
39. Zhou D, Dai SM, Tong Q (2020) COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother https://doi.org/10.1093/jac/dkaa169
40. Gautret P, Lagier JC, Parola P, *et al.*(2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949
41. Chen J, Liu D, Liu L, *et al.*(2020) A Pilot Study of Hydroxychloroquine in treatment of Patients With Moderate COVID-19. *Zhejiang Da Xue Xue Bao Yi Xue Ban*, 49(2): 215-219.
42. US FDA (2020) CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. https://www.fda.gov/media/134922/download (Accessed 12 May 2020)
43. CDC (2020) Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19). https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html (Accessed 12 May 2020)
44. Chen Z, Hu J, Zhang Z, *et al.*(2020) Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv. https://doi.org/10.1101/2020.03.22.20040758
45. Mahevas M, Tran VT, Roumier M, *et al.*(2020) No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv. https://doi.org/10.1101/2020.04.10.20060699
46. Molina JM, Delaugerre C, Le Goff J, *et al.*(2020) No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Medecine et maladies infectieuses. Med Mal Infect, 50(4): 384. https://doi.org/10.1016/j.medmal.2020.03.006
47. Million M, Lagier JC, Gautret P, *et al.*(2020) Full-length title: Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis, 101738. https://doi.org/10.1016/j.tmaid.2020.101738
48. US FDA (2020) Letter of authorization: Emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 Coronavirus disease. 2020. https://www.fda.gov/media/136534/download. (Accessed 12 May 2020)
49. Leneva IA, Russell RJ, Boriskin YS, Hay AJ (2009) Characteristics of arbidol-resistant mutants of influenza virus: implications for the mechanism of anti-influenza action of arbidol. Antiviral Res., 81(2): 132–40.
50. Boriskin YS, Pécheur EI, Polyak SJ (2006) Arbidol: a broad-spectrum antiviral that inhibits acute and chronic HCV infection. Virol J., 3: 56.
51. Shi L, Xiong H, He J, *et al.*(2007) Antiviral activity of arbidol against influenza A virus, respiratory syncytial virus, rhinovirus, coxsackie virus and

adenovirus in vitro and in vivo. Arch Virol, 152(8): 1447–55.
52. Glushkov RG, Gus'kova TA, Krylova LI, Nikolaeva IS (1999) Mechanisms of arbidole's immunomodulating action. Vestn Ross Akad meditsinskikh Nauk, (3): 36–40.
53. Pécheur EI, Lavillette D, Alcaras F, *et al.*(2007) Biochemical mechanism of hepatitis C virus inhibition by the broad-spectrum antiviral arbidol. Biochemistry, 46(20): 6050–9.
54. Chen C, Zhang Y, Huang J, *et al.*(2020) Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. https://doi.org/10.1101/2020.03.17.20037432
55. Wilkinson J, Dahly D (2020) Statistical review of Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial (Version 1.0). Zenodo. https://zenodo.org/record/3734198#.XsZmAGgzbI
56. Gibo J, Ito T, Kawabe K, *et al.*(2005) Camostat mesilate attenuates pancreatic fibrosis via inhibition of monocytes and pancreatic stellate cells activity. Lab Invest, 85(1): 75–89.
57. Hoffmann M, Kleine-Weber H, Schroeder S, *et al.*(2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell, 181(2): 271-280.e8.
58. Bertram S, Dijkman R, Habjan M, *et al.*(2013) TMPRSS2 activates the human coronavirus 229E for cathepsin-independent host cell entry and is expressed in viral target cells in the respiratory epithelium. J Virol, 87(11): 6150–60.
59. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P (2005) Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Natl Acad Sci U S A, 102(33): 11876–81.
60. Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N (2019) TMPRSS2 Contributes to Virus Spread and Immunopathology in the Airways of Murine Models after Coronavirus Infection. J Virol, 93(6): e01815-18. doi: 10.1128/JVI.01815-18
61. Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S (2012) Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J Virol, 86(12): 6537–45.
62. Zhou Y, Vedantham P, Lu K, *et al.*(2015) Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res., 116: 76–84.
63. Lucas JM, Heinlein C, Kim T, *et al.*(2014) The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov, 4(11): 1310–25.
64. ClinicalTrials.gov (2020) Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19). https://clinicaltrials.gov/ct2/show/NCT04273763 (Accessed 15 May 2020)
65. Lusvarghi S, Bewley CA (2016) Griffithsin: An Antiviral Lectin with Outstanding Therapeutic Potential. Viruses, 8(10): 296.
66. O'Keefe BR, Giomarelli B, Barnard DL, *et al.*(2010) Broad-spectrum in vitro activity and in vivo efficacy of the antiviral protein griffithsin against emerging viruses of the family Coronaviridae. J Virol, 84(5): 2511–21.
67. Ziółkowska NE, O'Keefe BR, Mori T, *et al.*(2006) Domain-swapped structure of the potent antiviral protein griffithsin and its mode of carbohydrate binding. Structure, 14(7): 1127–35.
68. Fang L, Karakiulakis G, Roth M (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med, 8(4): e21. https://doi.org/10.1016/ S2213-2600(20)30116-8
69. Gurwitz D (2020) Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 10.1002/ddr.21656. https://doi.org/10.1002/ddr.21656
70. ClinicalTrials.gov (2020) Losartan for Patients With COVID-19 Requiring Hospitalization. https://clinicaltrials.gov/ct2/show/NCT04312009 (Accessed 15 May 2020)
71. Zheng YY, Ma YT, Zhang JY, Xie X (2020) COVID-19 and the cardiovascular system. Nat Rev Cardiol, 17(5): 259–60.
72. Zhang XW, Yap YL (2004) Old drugs as lead compounds for a new disease? Binding analysis of SARS coronavirus main proteinase with HIV, psychotic and parasite drugs. Bioorg Med Chem., 12(10): 2517–21.
73. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY (2007) Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Res., 74(2): 92–101.
74. Trampczynska A, Böttcher C, Clemens S (2006) The transition metal chelator nicotianamine is synthesized by filamentous fungi. FEBS Lett, 580(13): 3173–8.
75. Takahashi S, Yoshiya T, Yoshizawa-Kumagaye K, Sugiyama T (2015) Nicotianamine is a novel angiotensin-converting enzyme 2 inhibitor in soybean. Biomed Res., 36(3): 219–24.
76. Jiang S, Hillyer C, Du L (2020) Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. Trends Immunol, 41(5): 355–9.
77. ter Meulen J, van den Brink EN, Poon LLM, *et al.*(2006) Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants. PLoS Med, 3(7): e237. https://doi.org/10.1371/journal.pmed.0030237
78. Tian X, Li C, Huang A, *et al.*(2020) Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect, 9(1): 382-385.

79. Bao L, Deng W, Gao H, *et al.*(2020) Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. bioRxiv. https://doi.org/10.1101/2020.03.13.990226 (Accessed 15 May 2020)
80. de Wit E, Feldmann F, Okumura A, *et al.*(2018) Prophylactic and therapeutic efficacy of mAb treatment against MERS-CoV in common marmosets. Antiviral Res., 156: 64–71.
81. Imbach P, Barandun S, d'Apuzzo V, *et al.*(1981) High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet, 1(8232): 1228–31.
82. Rütter A, Luger TA (2001) High-dose intravenous immunoglobulins: an approach to treat severe immune-mediated and autoimmune diseases of the skin. J Am Acad Dermatol, 44(6): 1010–24.
83. Jolles S, Sewell WAC, Misbah SA (2005) Clinical uses of intravenous immunoglobulin. Clin Exp Immunol, 142(1): 1–11.
84. de la Torre MC, Bolíbar I, Vendrell M, *et al.*(2013) Serum immunoglobulins in the infected and convalescent phases in community-acquired pneumonia. Respir Med, 107(12): 2038–45.
85. Gordon CL, Langan K, Charles PGP, *et al.*(2011) Pooled human immunoglobulin therapy in critically Ill patients with pandemic 2009 influenza A(H1N1) pneumonitis and immunoglobulin G2 subclass (IgG2) deficiency. Clin Infect Dis., 52(3): 422-6.
86. Kreymann KG, de Heer G, Nierhaus A, Kluge S (2007) Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. Crit Care Med., 35(12): 2677–85.
87. ClinicalTrials.gov (2020) The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia. https://clinicaltrials.gov/ct2/show/NCT04261426 (Accessed 15 May 2020)
88. Duan K, Liu B, Li C, *et al.*(2020) Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A, 117(17): 9490–6.
89. Cheng Y, Wong R, Soo YOY, *et al.*(2005) Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol, 24(1): 44–6.
90. Hung IF, To KK, Lee CK, *et al.*(2009) Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis an Off Publ Infect Dis Soc Am, 52(4): 447–56.
91. Ko JH, Seok H, Cho SY, *et al.*(2018) Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther, 23(7): 617–22.
92. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, *et al.*(2015) The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis., 211(1): 80–90.
93. Zhang B, Liu S, Tan T, *et al.*(2020) Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest. https://doi.org/10.1016/j.chest.2020.03.039
94. Chen J, Zhu H, Horby PW, *et al.*(2020) Specificity, kinetics and longevity of antibody responses to avian influenza A(H7N9) virus infection in humans. J Infect, 80(3): 310–9.
95. Luke TC, Kilbane EM, Jackson JL, Hoffman SL (2006) Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med, 145(8): 599–609.
96. Cvetkovic RS, Goa KL (2003) Lopinavir/ritonavir: a review of its use in the management of HIV infection. Drugs, 63(8): 769–802.
97. Chu CM, Cheng VCC, Hung IFN, *et al.*(2004) Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax, 59(3): 252–6.
98. Chen F, Chan KH, Jiang Y, *et al.*(2004) In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol Off Publ Pan Am Soc Clin Virol, 31(1): 69–75.
99. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ (2020) A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol, 92(6): 556-563.
100. Chan KS, Lai ST, Chu CM, *et al.*(2003) Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J, 9(6): 399-406.
101. de Wilde AH, Jochmans D, Posthuma CC, *et al.*(2014) Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother, 58(8): 4875–84.
102. Sheahan TP, Sims AC, Leist SR, *et al.*(2020) Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun, 11(1): 222. https://doi.org/10.1038/s41467-019-13940-6
103. Cao B, Wang Y, Wen D, *et al.*(2020) A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 382(19):1787–99.
104. Deng L, Li C, Zeng Q, *et al.*(2020) Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J Infect S0163-4453(20)30113-4. doi: 10.1016/j.jinf.2020.03.002
105. Liu F, Xu A, Zhang Y, *et al.*(2020) 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 95:183–91.
106. National Health Commission & National

Administration of Traditional Chinese Medicine (2020) Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl) 133(9):1087-1095. doi:10.1097/CM9.0000000000000819

107. Park JY, Jeong HJ, Kim JH, *et al.*(2012) Diarylheptanoids from Alnus japonica inhibit papain-like protease of severe acute respiratory syndrome coronavirus. Biol Pharm Bull 35(11):2036–42.
108. Chen L, Gui C, Luo X, *et al.*(2005) Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication in vitro. J Virol 79(11):7095–103.
109. Chen Y, Liu Q, Guo D (2020) Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol 92(4):418–23.
110. Jo S, Kim S, Shin DH, Kim MS (2020) Inhibition of SARS-CoV 3CL protease by flavonoids. J Enzyme Inhib Med Chem 35(1):145–51.
111. Ryu YB, Jeong HJ, Kim JH, *et al.*(2010) Biflavonoids from Torreya nucifera displaying SARS-CoV 3CL(pro) inhibition. Bioorg Med Chem 18(22):7940–7.
112. Enmozhi SK, Raja K, Sebastine I, Joseph J (2020) Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. J Biomol Struct Dyn 1–7. doi: 10.1080/07391102.2020.1760136
113. Islam R, Parves MR, Paul AS, *et al.*(2020) A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2. J Biomol Struct Dyn 1–12. doi: 10.1080/07391102.2020.1761883
114. Joshi RS, Jagdale SS, Bansode SB, *et al.*(2020) Discovery of potential multi-target-directed ligands by targeting host-specific SARS-CoV-2 structurally conserved main protease. J Biomol Struct Dyn 1–16. doi: 10.1080/07391102.2020.1760137
115. Liu L, Heinrich M, Myers S, Dworjanyn SA (2012) Towards a better understanding of medicinal uses of the brown seaweed Sargassum in Traditional Chinese Medicine: a phytochemical and pharmacological review. J Ethnopharmacol, 142(3): 591–619.
116. Gentile D, Patamia V, Scala A, *et. al.* (2020) Putative Inhibitors of SARS-CoV-2 Main Protease from A Library of Marine Natural Products: A Virtual Screening and Molecular Modeling Study. Mar Drugs, 18(4): E225. https://doi.org/10.3390/md18040225
117. Liu S, Zheng Q, Wang Z (2020) Potential covalent drugs targeting the main protease of the SARS-CoV-2 coronavirus. Bioinformatics, 36(11): 3295-3298. https://doi.org/10.1093/bioinformatics/btaa224
118. Kandeel M, Al-Nazawi M (2020) Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. Life Sci., 251: 117627.
119. Zhang L, Lin D, Sun X, *et al.*(2020) Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science, 368(6489): 409–12.
120. Bhardwaj VK, Singh R, Sharma J, *et al.*(2020) Identification of bioactive molecules from Tea plant as SARS-CoV-2 main protease inhibitors. J Biomol Struct Dyn 1–10. Available from: doi:10.1080/07391102.2020.1766572.
121. Umesh, Kundu D, Selvaraj C, Singh SK, Dubey VK (2020) Identification of new anti-nCoV drug chemical compounds from Indian spices exploiting SARS-CoV-2 main protease as target. J Biomol Struct Dyn 1–9. Available from: doi:10.1080/07391102.2020.1763202
122. Gan YR, Huang H, Huang YD, *et al.*(2006) Synthesis and activity of an octapeptide inhibitor designed for SARS coronavirus main proteinase. Peptides, 27(4): 622–5.
123. Furuta Y, Komeno T, Nakamura T (2017) Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci., 93(7): 449–63.
124. Furuta Y, Gowen BB, Takahashi K, *et al.*(2013) Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Res., 100(2): 446–54.
125. Furuta Y, Takahashi K, Kuno-Maekawa M, *et al.*(2005) Mechanism of action of T-705 against influenza virus. Antimicrob Agents Chemother, 49(3): 981–6.
126. ClinicalTrials.gov (2020) Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia. https://clinicaltrials.gov/ct2/show/NCT04319900. Accessed on 15 May 2020
127. Sheahan TP, Sims AC, Graham RL, *et al.*(2017) Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med, 9(396): eaal3653. doi: 10.1126/scitranslmed.aal3653
128. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M (2020) The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem, 295(15): 4773–9.
129. Agostini ML, Andres EL, Sims AC, *et al.*(2018) Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. MBio, 9(2): e00221-18.
130. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents, 55(3): 105924.
131. Holshue ML, DeBolt C, Lindquist S, *et al.*(2020) First Case of 2019 Novel Coronavirus in the United States. N Engl J Med, 382(10): 929–36.
132. Rosa SGV, Santos WC (2020) Clinical trials on drug repositioning for COVID-19 treatment. Rev Panam

Salud Publica, 44: e40. doi: 10.26633/RPSP.2020.40
133. ClinicalTrials.gov (2020) Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19). https://clinicaltrials.gov/ct2/show/NCT04292899. Accesssed 15 May 2020.
134. ClinicalTrials.gov (2020) Adaptive COVID-19 Treatment Trial (ACTT) [Internet]. Bethesda (MD): National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04280705. Accessed 15 May 2020.
135. Westover JB, Mathis A, Taylor R, *et al.*(2018) Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters. Antiviral Res, 156: 38–45.
136. Warren TK, Wells J, Panchal RG, *et al.*(2014) Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature, 508(7496): 402–5.
137. Julander JG, Siddharthan V, Evans J, *et al.*(2017) Efficacy of the broad-spectrum antiviral compound BCX4430 against Zika virus in cell culture and in a mouse model. Antiviral Res., 137: 14–22.
138. Elfiky AA (2020) Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. Life Sci., 253: 117592.
139. Chen W, Mook RAJ, Premont RT, Wang J (2018) Niclosamide: Beyond an antihelminthic drug. Cell Signal, 41: 89–96.
140. Jurgeit A, McDowell R, Moese S, *et al.*(2012) Niclosamide is a proton carrier and targets acidic endosomes with broad antiviral effects. PLoS Pathog, 8(10): e1002976.
141. Wu CJ, Jan JT, Chen CM, *et al.*(2004) Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob Agents Chemother, 48(7): 2693–6.
142. Xu J, Shi PY, Li H, Zhou J (2020) Broad Spectrum Antiviral Agent Niclosamide and Its Therapeutic Potential. ACS Infect Dis., 6(5): 909–15.
143. Rossignol JF (2014) Nitazoxanide: a first-in-class broad-spectrum antiviral agent. Antiviral Res., 110: 94–103.