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MINIREVIEW

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An update on emerging therapeutics to combat COVID-19

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Abstract

Background: The COVID-19 pandemic has demanded effective therapeutic protocol from researchers and clinicians across the world. Currently, a large amount of primary data have been generated from several preclinical studies. At least 300 clinical trials are underway for drug repurposing against COVID-19; the clinician needs objective evidence-based medication to treat COVID-19.

Observations: Single-stranded RNA viral genome of SARS-CoV-2 encodes structural proteins (spike protein), non-structural enzymatic proteins (RNA-dependent RNA polymerase, helicase, papain-like protease, 3-chymotrypsin-like protease) and other accessory proteins. These four enzymatic proteins on spike protein are rate-limiting steps in viral replications and, therefore, an attractive target for drug development against SARS-CoV-2. In silico and in vitro studies have identified various potential epitomes as candidate sequences for vaccine development. These studies have also revealed potential targets for drug development and drug repurposing against COVID-19. Clinical trials utilizing antiviral drugs and other drugs have given inconclusive results regarding their clinical efficacy and side effects. The need for angiotensin-converting enzyme (ACE-2) inhibitors/angiotensin receptor blockers and corticosteroids has been recommended. Western countries have adopted telemedicine as an alternative to prevent transmission of infection in the population. Currently, no proven, evidence-based therapeutic regimen exists for COVID-19.

Conclusion: The COVID-19 pandemic has put tremendous pressure on researchers to evaluate and approve drugs effective against the disease. Well-controlled randomized trials should assess medicines that are not marketed with substantial evidence of safety and efficacy and more emphasis on time tested approaches for drug evaluation.

KEYWORDS
coronavirus, COVID-19, drug repurposing, in vitro, in vivo and in silico

1 | INTRODUCTION

The global epidemic of novel coronavirus (nCoV) began in Wuhan, China, reporting the first case on 31 December 2019.[1-5] Within four months, the disease was reported from more than 180 countries affecting 36 million and causing the death of 3.6 million humans globally.[2,6] Owing to the disease characteristics of global presence and transmission rate, WHO declared the infection as a pandemic.[6,7] Subsequently, WHO named the new coronavirus entity "2019-nCoV," which stands for "2019 novel coronavirus" and disease caused by it as COVID-19, an acronym that stands for coronavirus disease-2019. This novel *Betacoronavirus* has been proposed to have animal origin from Wuhan's seafood market,[8] resulting in human infection of animal origin.[9] The phylogenetic analysis virus is proposed to have originated from bats through an unknown mammalian host to humans.[3] Furthermore, phylogenetic analysis indicates nCoV is related to SARS-CoV-1,[5,10,11] which led the International Virus Classification Commission (ICTV) to name it "SARS-CoV-2".[5,9] Clinically, the disease spectrum ranges from mild respiratory tract illness (self-limiting), severe pneumonia, organ failure and death.[7]

1.1 | SARS-CoV-2 virology

The virus belongs to the genus betacoronavirus [12] and has been reported from mammals, birds, and humans.[13] Based on serological cross-reactivity and phylogenetic analysis, betacoronavirus is divided into three subgroups. Group I and Group II are responsible for causing disease in domestic animals, and group III for avian species. Studies in China have identified Group I and group II coronavirus from the upper respiratory tract of humans suffering from "atypical pneumonia".[14-16] Structurally, coronavirus is a group of positive sense-single stranded enveloped RNA viruses composed of the spike (S), envelope (E), membrane (M) and nucleocapsid (N) protein.[17,18] Coronaviruses show variable severity in their hosts and have been found to infect respiratory, enteric, hepatic and nervous systems.[19] Most infections caused by coronavirus are relatively mild but newly emerged strains of nCoV have shown a high degree of pathogenicity and change in cell tropism.[20] The high affinity/avidity of COVID-19 to ACE-2 receptor compared with SARS Cov-1 and other coronaviruses causes great threat to humans.[21] Preclinical and clinical studies have postulated acute respiratory distress syndrome (ADRs) as the cause of death in COVID-19.[22] ADRs' common mechanism in SARS-CoV-2, SARS-CoV, and MERS-CoV infection involves a deadly uncontrolled cytokine storm.[23] Cytokine storm involves the uncontrolled release of pro-inflammatory cytokines and chemokines from immune cells of COVID-19 patients, resulting in an unwanted inflammatory response and, subsequently, extensive tissue damage.[24] Furthermore, clinical evaluations have proposed pro-inflammatory cytokines and chemokines that cause the proliferation of specific cells and inhibit specific cells and release of acute-phase proteins.[3] Thus, the pathogenesis of COVID-19 leads to the cytokine release syndrome (CRS), which is an acute systemic inflammatory response characterized by multiple organ dysfunction.

1.2 | Earlier epidemics

Throughout human civilization, influenza epidemics occur periodically, and some of them are converted into pandemics.[25] The Spanish flu of 1918-1919, considered the mother of all plagues, affected one third of the global population and caused almost 50 million deaths worldwide.[26] The Spanish flu occurred in three distinct waves; the first wave began in spring 1918 from a Kansas military farm and spread to the entire America and Europe.[27] The second wave occurred spontaneously in august 1918 from several locations widely separated, and the scientists warned that this deadlier plague can wipe out more than half of the world population. By 1919, the third wave of an epidemic caused heavy mortality in America and Europe.[28] The most sticking feature of Spanish flu was the *"W"* pattern of the mortality curve, which means a disease caused higher mortality in young people, the geriatric population, as well as the middle age group.[29] Researchers found that the key to flattening the Spanish flu curve in 1919 was herd immunity, social distancing and quarantine of infected and suspected individuals.[30] 1956-1957 witnessed the advent of Asian flu as a potential epidemic when influenza A (H2N2) subtype was isolated from patients showing ARDS.[31] The 1956 epidemic resulted in 60,000 deaths in the USA, followed by the emergence of the influenza A (H3N2) subtype in 1968-1969 named the Hong Kong flu, which passed almost unnoticed due to spontaneous waxing in the autumn of 1969.[32] An alarming observation of the Hong Kong flu was the co-circulation of H1N1 subtype and H3N1 subtype, which led the scientific community to speculate about mixing two subtypes and henceforth emergence of novel influenza virus.[33] Fortunately, an epidemic was contained in 7 months from the date of its earliest occurrence using cutting-edge biological methods and other prophylactic measures.[34] The 21st century witnessed the second influenza epidemic of influenza A (H1N1) in May 2009, which affected northern hemisphere countries in two waves.[35] This epidemic of 2009 showed higher mortality in the age group of 5-20 years, while the least mortality was observed in the senior age group due to some residual immunity (>50 years). CDC attributed more than 30% of deaths in the 2009 epidemic to secondary bacterial infection.[36] Earlier, pandemics/epidemics were controlled by travel restrictions, proper quarantine measures[37] and supportive treatment to clinically ill patients.

1.3 | Earlier coronavirus epidemics

Coronavirus has been isolated from birds and mammals, causing pulmonary, enteric, neurological and hepatic diseases.[38] Due to the widespread presence of viruses from diverse genera and species, there are greater chances of genomic recombination. It is likely to emerge novel strains of the coronavirus that spill over to humans because of the increased human-animal interface.[39] Six species of coronavirus cause disease in humans; four species (229E, OC43, NL63 and HKU1) cause mild disease resembling common cold and resolves without any particular medication.[40] Two other strains include severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[41] These two strains are of zoonotic origin and cause severe fatal diseases in humans.[39] In 2003, SARS-CoV-1 was reported from Guangdong Province of China, which spread in 32 countries, causing almost 9000 cases and 1000 deaths.[34] SARS-CoV-1 was proposed to have emerged from some unknown animal source; viral genome isolated from Nasal civet cavity was found to be 99.8% homologous to human SARS-CoV-1 isolate.[42] MERS-CoV was responsible for an outbreak of the disease in the Middle East during 2012.[20] The MERS-CoV was found to have evolved from bats through camel as an intermediate host, with 1700 cases reported from 27 countries.[43] Presently, MERS-CoV is endemic in Middle Eastern countries as there are recurrent reports of positive serological patients from these countries.[44] Earlier, Cov epidemics, including SARS-CoV-1 and MERS-CoV, were treated by broad-spectrum antiviral ribavirin and lopinavir-ritonavir, corticosteroids and immune modulators. Still, none of these were explicitly effective against Cov in controlled, randomized clinical trials.[45]

2 | METHODS

An extensive literature survey was conducted through electronic search such as science direct, PubMed, Scopus, Web of science, J Gate and Google scholar.[46] Search terms used were COVID-19, SARS-CoV-2, 2019 and coronavirus. The names COVID-19, SARS-CoV-2 and coronavirus were combined with In silico, In vitro, clinical trial, treatment and vaccine. Search terms COVID-19, SARS-CoV-2 and coronavirus [46] resulted in more than 300 clinical trials to find evidence-based medicine against COVID-19 on 5 May 2020. Table 1 provides detailed clinical trial information in different stages, including clinical trials (completed, active, recruiting and not yet recruiting) and the number of patients in the experimental and placebo group. The literature cited in a present review dated from 1918 to 2020 and was limited to English. Furthermore, the study contains data obtained from clinical trials in different phases of evaluation. The final data collected were then compiled, evaluated, compared and conclusions drawn accordingly.

2.1 | Search for COVID-19 therapeutic/prophylactic agents

Presently, there are no effective approved therapeutics (specific antiviral agents) or prophylactics (vaccines) available against COVID-19, which could treat clinically ill patients and reduce virus shedding and hence inhibit transmission of disease.[6] Globally, there are reports which suggest a number of drugs that could serve as potential candidates against COVID-19, but the clinical efficacy of these drugs remains yet to be evaluated. Owing to the non-availability of effective medicines for COVID-19, currently, researchers are working on a three-pronged strategy to develop effective drugs against COVID-19; these include (a) in-silico/in-vitro studies, (b) drug repurposing and (c) denovo drug discovery against COVID-19. Remdesivir, a potent viral polymerase inhibitor, can be effective against COVID-19. A recently completed clinical trial has offered encouraging result of using remdesivir in COVID-19 patients, which led the FDA to grant emergency use authorization to remdesvir.[47] Contrary to this, lopinavir and ritonavir, an antiviral drug combination used against HIV, have completely failed to offer a significant advantage in COVID-19 patients.[47] In the present review, an attempt has been made to summarize major therapeutic and prophylactic interventions against COVID-19 with their clinical outcomes and shortcomings.

3 | COVID-19 AND POTENTIAL DRUG TARGETS ON THE PATHOGENETIC PATHWAY

A SARS-CoV-2 virus is akin to SARS-CoV, and MERS-CoV and spike (S) protein of SARS-CoV-2 virus consist of an S1 and S2 subunit; cellular interaction involves the binding of the S1 subunit of the virus with ACE-2 receptor of the host cell.[48] This interaction and subsequent endosome formation for cellular internalization are facilitated by host type 2 transmembrane serine protease, TMPRSS2 (Figure 1).[49] On cellular translocation, viral RNA is translated on host cellular machinery to synthesize viral polypeptides. The synthesis of viral RNA follows this by RNA-dependent RNA polymerase enzyme [49like3-chymotrypsin-like protease ($3CL^{pro}$)] enzyme that plays a crucial role in processing the viral RNA. Further, followed by the packaging of viral RNA and viral structural proteins to form viral particles released from the cell exocytosis against COVID-19 patients. The mechanism of action of this drug combination in

TABLE 1 Summary of clinical trials using antiviral agents against COVID-19

S. No	Registration No (phase)	Title of study	Interventions/outcome/conclusion of study
1.	ChiCTR2000029600	Clinical study on safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19)	Group A (n = 30) alpha-interferon atomization Group B (n = 30) Lopinavir and Ritonavir +alpha-interferon atomization Group C (n = 30) Favipiravir +alpha-interferon atomization Completed with results available on http://www.chictr.org.cn/searchprojen.aspx?ishtml=recruitmentstatuspr&type=statuspr&recruitmentstatus=1004004&createyear=
2.	NCT04333550	Application of Iron Chelator (Desferal) to Reduce the Severity of COVID-19 Manifestations	Group A (N = 25) Deferoxamine addition to standard treatment Intervention Group B (N = 25) standard treatment Recruiting Last Update Posted: 4 May 2020
3.	NCT04336904	A Multi-centre, Randomized, Double-blind, Placebo-controlled, Phase III Clinical Study Evaluating the Efficacy and Safety of Favipiravir in the Treatment of Patients With COVID-19-Moderate Type	Group A (N = 50) Favipiravir addition to standard treatment Intervention Group B (N = 50) standard treatment Active, not recruiting Last Update Posted: 8 April 2020
4.	NCT04343183	Hyperbaric Oxygen Therapy (HBOT) as a Treatment for COVID-19 (COVID-19) Infection	Group A (N = 24) hyperbaric oxygen therapy addition to standard treatment Intervention Group B (N = 24) standard treatment Not yet recruiting Last Update Posted: 13 April 2020
5.	NCT04336462	Hydrogen-Oxygen Generator With Nebulizer in the Improvement of Symptoms in Patients Infected With COVID-19	Group A (N = 50) Hydrogen/oxygen mixed gas inhaled (proportion 2:1), 3 L/min. 6 h a day. Group A (N = 50) Oxygen inhaled, 3 L/min. 6 h a day. Recruiting Last Update Posted: 7 April 2020
6.	NCT04324489	DAS181 for Severe COVID-19: Compassionate Use	Group (n = 8) Patient receives nebulized DAS181 (4.5 mg BID/day for 10 d). Completed with no results posted Last Update Posted: 5 May 2020
7.	NCT04323228	Anti-inflammatory/Antioxidant Oral Nutrition Supplementation on the Cytokine Storm and Progression of COVID-19: A Randomized Controlled Trial	Group A (N = 15) oral nutrition supplement (ONS) enriched in eicosapentaenoic acid, Gamma-linolenic acid and antioxidants. Group A (N = 15) Dietary Supplement: isocaloric/isonitrogenous ONS Recruiting Last Update Posted: 22 September 2020
8.	NCT04335123(Phase I)	An Open-Label Phase 1 Trial of Losartan for Worsening Respiratory Illness in COVID-19	Group (n = 50) 25 mg QD from day 0 to day 3. Dose escalation to 50 mg QD until study completion Completed with no results posted Last Update Posted: 3 November 2020
9.	NCT04333420 (Phase II/III)	Open-label, Randomized Study of IFX-1 in Patients With Severe COVID-19 Pneumonia (PANAMO)	Group A (65) Best supportive care (BSC) + IFX-1Drug (Phase-II) Group B (65) Best supportive care only (Phase-III) Recruiting Last Update Posted: 26 April 2021
10.	NCT04339660 (Phase I/II)	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	Group A (15) 1*10E6 UC-MSCs /kg body weight suspended in 100 mL saline (Phase -I) Group A (15) 100 mL saline intravenously (Phase -II) Recruiting Last Update Posted: 9 April 2020

(Continues)

TABLE 1 (Continued)

S. No	Registration No (phase)	Title of study	Interventions/outcome/conclusion of study
11.	NCT04343755 (Phase II)	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	Group (n = 55) Convalescent Plasma Fresh plasma will be infused one time to hospitalized patients with COVID-19 infection Active, not recruiting Last Update Posted: 1 December 2020
12.	NCT04324996 (Phase I)	A Phase I/II Study of Universal Off-the-shelf NKG2D-ACE2 CAR-NK Cells Secreting IL15 Superagonist and GM-CSF-neutralizing scFv for Therapy of COVID-19	Group (n = 90) the efficacy of NKG2D-ACE2 CAR-NK cells in treating severe and critical 2019 new coronavirus (COVID-19) pneumonia Recruiting Last Update Posted: 17 November 2020
13.	NCT04329832 (Phase II)	Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19 (HAHPS)	Group A (150) Hydroxychloroquine Group B (150) Azithromycin Active, not recruiting Last Update Posted: 2 September 2020
14.	NCT04317092 (Phase II)	Multi-centre Study on the Efficacy and Tolerability of Tocilizumab in the Treatment of Patients With COVID-19 Pneumonia	(N = 400) Patients enrolled are treated with tocilizumab Active, not recruiting Last Update Posted: 3 March 2021
15.	NCT04328285 (Phase III)	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers (COVIDAXIS)	Participants: 1200 Group A: Hydroxychloroquine Group B: Placebo of Hydroxychloroquine Group C: Lopinavir and ritonavir Group D:Placebo of LPV/r Tablet Active, not recruiting Last Update Posted: 28 December 2020
16.	NCT04315298 (Phase II/III)	Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	Participants: 400 Group A: Sarilumab Group B: Placebo Completed with no results posted Last Update Posted: 1 October 2020
17.	NCT04330638 (Phase III)	Treatment of COVID-19 Patients With Anti-interleukin Drugs (COV-AID)	Participants: 342 Group A: Usual Care Group B: Anakinra Group C: Siltuximab Group D: Tocilizumab Active, not recruiting Last Update Posted: 2 March 2021
18.	NCT04304313 (Phase III)	A Pilot Study of Sildenafil in COVID-19	Participants: 10 Sildenafil citrate tablets Recruiting Last Update Posted: 17 March 2020
19.	NCT04326920 (Phase IV)	Sargramostim in Patients With Acute Hypoxic Respiratory Failure Due to COVID-19 (SARPAC) (SARPAC)	Participants: 80 Group A: Sargramostim Group B: Control Completed with no results posted Last Update Posted: 2 March 2021
20.	NCT04338347 (Phase IV)	CAP-1002 in Severe COVID-19 Disease	Participants: 80 (CAP-1002) containing 150 million allogeneic Cardiosphere-Derived Cells (CDCs). No longer available Last Update Posted: 1 December 2020

(Continues)

TABLE 1 (Continued)

S. No	Registration No (phase)	Title of study	Interventions/outcome/conclusion of study
21.	NCT04334512 (Phase II)	A Study of Quintuple Therapy to Treat COVID-19 Infection (HAZDpaC)	Participants: 600 Quintuple therapy (Hydroxychloroquine, Azithromycin, Vitamin C, Vitamin D, and Zinc) Recruiting Last Update Posted: 8 April 2021
22.	NCT04329923 (Phase II)	The PATCH Trial (Prevention And Treatment of COVID-19 With Hydroxychloroquine) (PATCH)	Participants: 400 Group A: Hydroxychloroquine Sulphate 400 mg Group B: Hydroxychloroquine Sulphate 600 mg Group C: Hydroxychloroquine Sulphate 600 mg Group D: Placebo oral tablet Terminated (Cohort 1: slow accrual Cohort 2: Other studies showed no benefit Cohort 3: Study met pre-specified futility analysis at planned second interim analysis) Last Update Posted: 10 December 2020
23.	NCT04330690 (Phase II)	Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO)	Participants: 400 Group A: Standard treatment Group B: lopinavir/ritonavir plus standard of care Recruiting Last Update Posted: 5 March 2021
24.	NCT04304053 (Phase III)	Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention (HCQ4COV19)	Participants: 3040 Group A: Antiviral treatment and prophylaxis Group B: Standard Public Health measures Completed with no results posted Last Update Posted: 30 June 2020
25.	NCT04334382 (Phase III)	Hydroxychloroquine vs Azithromycin for Outpatients in Utah With COVID-19 (HyAzOUT)	Participants: 1550 Group A: Hydroxychloroquine Group B: Azithromycin Recruiting Last Update Posted: 9 April 2020
26.	NCT04331795 (Phase II)	Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE)	Participants: 50 Group A: Tocilizumab (beginning dose of 200 mg) Group B: Tocilizumab (beginning dose 80 mg) Completed with results available at https://clinicaltrials.gov/ct2/show/NCT04331795 and returned after quality control review Last Update Posted: 9 March 2021
27.	NCT04333225 (Phase II)	Hydroxychloroquine in the Prevention of COVID-19 Infection in Healthcare Workers	Participants: 360 Group A: standard treatment Group B: Hydroxychloroquine Completed with no results posted Last Update Posted: 26 January 2021
28.	NCT04313023 (Phase II)	The Use PUL-042 Inhalation Solution to Prevent COVID-19 in Adults Exposed to SARS-CoV-2	Participants: 200 Group A: PUL-042 Inhalation Solution Group B: Placebo Recruiting Last Update Posted: 17 March 2021
29.	NCT04307693 (Phase II)	Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	Participants: 150 Group A: Lopinavir/ritonavir Group B: Hydroxychloroquine sulfate Terminated (terminated early because no patients were further enrolled since mid-Apr 2020) Last Update Posted: 27 May 2020

(Continues)

TABLE 1 (Continued)

S. No	Registration No (phase)	Title of study	Interventions/outcome/conclusion of study
30.	NCT04323631 (Phase I)	Hydroxychloroquine for the Treatment of Patients With Mild to Moderate COVID-19 to Prevent Progression to Severe Infection or Death	Participants: 1116 Group A: Hydroxychloroquine Group B: The control group will not receive hydroxychloroquine Withdrawn (trial not started due to accumulating evidence against HCQ for COVID) Last Update Posted: 30 June 2020
31.	NCT04336254 (Phase I)	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	Participants: 20 Group A: Routine treatment + Intravenous injection of human dental pulp stem cells Group B: Routine treatment + Intravenous saline injection (Placebo) Recruiting Last Update Posted: 10 March 2021
32.	NCT04332094 (Phase II)	Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19 (TOCOVID)	Participants: 20 Group A:Tocilizumab + Azithromycin +Hydroxychloroquine Group B:Azithromycin + Hydroxychloroquine Recruiting Last Update Posted: 7 April 2020
33.	NCT04292899 (Phase III)	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	Participants: 2440 Group A: Remdesivir Administered as an intravenous infusion Group B: Standard of Care Treatment for COVID-19 Infection Completed with results posted on https://clinicaltrials.gov/ct2/show/results/NCT04292899
34.	NCT04329650 (Phase II)	Efficacy and Safety of Siltuximab vs Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia	Participants: 100 Group A: Experimental: Siltuximab Group B: Active Comparator: Methylprednisolone Recruiting Last Update Posted: 17 April 2020
35.	NCT04331470 (Phase II/III)	Evaluation of Efficacy of Levamisole and Formoterol+ Budesonide in Treatment of COVID-19	Participants: 30 Group A: Experimental: Levamisole Pill + Budesonide+Formoterol inhaler + Standard care. Group B: Active Comparator: Lopinavir/Ritonavir + hydroxychloroquine Recruiting Last Update Posted: 13 April 2020
36.	NCT04313322 (Phase I)	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Participants: 5 IV doses of WJ-MSCs Recruiting Last Update Posted: 18 March 2020
37.	NCT04320615 (Phase III)	A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)	Participants: 330 Group A: Tocilizumab (TCZ) Group B: Placebo Completed with no results posted Last Update Posted: 25 September 2020
38.	NCT04273581 (Phase II)	The Efficacy and Safety of Thalidomide Combined With Low-dose Hormones in the Treatment of Severe COVID-19	Participants: 40 Group A: Thalidomide Group B: Placebo Not yet recruiting Last Update Posted: 21 February 2020

(Continues)

TABLE 1 (Continued)

S. No	Registration No (phase)	Title of study	Interventions/outcome/conclusion of study
39.	NCT04338074 (Phase II)	TXA and coronavirus 2019 (COVID-19) in Outpatients (TCOutpatient)	Participants: 40 Group A: Tranexamic acid Group B: Placebo Recruiting Last Update Posted: 16 February 2021
40.	NCT04317040 (Phase III)	CD24Fc as a Non-antiviral Immunomodulator in COVID-19 Treatment (SAC-COVID)	Participants: 230 Group A: CD24Fc Treatment Group B: Placebo Completed with no results posted Last Update Posted: 26 March 2021
41.	NCT04334005 (Not Applicable)	Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19)	Not yet recruiting Last Update Posted: 7 April 2020
Summary of clinical trials using Chinese medicine against COVID-19			
42.	NCT04323332[&] (Phase-III)	A Retrospective Cohort Study to Evaluate the Efficacy and Safety of Traditional Chinese Medicine as an Adjuvant Treatment for Patients With Severe COVID-19	Participants: 50 Group A: Traditional Chinese Medicine Group B: Conventional Medicine Not yet recruiting Last Update Posted: 26 March 2020
43.	NCT04278963[#] (Phase-II/III)	Yinhu Qingwen Decoction for the Treatment of Mild / Common COVID-19	Participants: 300 Group A (Experimental): Yin Hu Qing Wen Decoction Group B (Placebo Comparator): Yinhu Qingwen Decoction low-dose group Group C (Active Comparator): Integrated Chinese and Western Medicine group Suspended (there were no eligible patients with COVID-19 in the participating centres) Last Update Posted: 11 May 2020
44.	NCT04310865[&] (Phase-II/III)	Yinhu Qingwen Granula for the Treatment of Severe COVID-19	Participants: 116 Group A (Experimental): Yinhu Qingwen Granula + Standard medical treatment Group B (Placebo Comparator): Yin Hu Qing Wen Granula (low does) + Standard medical treatment Suspended (there were no eligible patients with COVID-19 in the participating centres) Last Update Posted: 11 May 2020
45.	NCT04251871[$] (Not Applicable)	Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection	Participants: 150 Group A (Experimental): Conventional medicines and TCMs granules Group B (Active Comparator): Conventional Medicines Recruiting Last Update Posted: 5 May 2020
46.	NCT04306497[$] (Phase-II/III)	Clinical Trial on Regularity of TCM Syndrome and Differentiation Treatment of COVID-19. (CTOROTSADTOC)	Participants: 340 Group A: Cohort of western medicine Group B:Cohort of integrated TCM and western medicine Completed and no results posted Last Update Posted: 4 June 2020
47.	NCT04285190[&] (Not Applicable)	The Effect of T89 on Improving Oxygen Saturation and Clinical Symptoms in Patients With COVID-19	Participants: 120 Experimental: The T89 treatment group No Intervention: The blank control group Withdrawn (the COVID-19 epidemic in China has ended completely) Last Update Posted: 16 June 2020

(Continues)

TABLE 1 (Continued)

S. No	Registration No (phase)	Title of study	Interventions/outcome/conclusion of study
48.	NCT04279197[$] (Phase-II)	Treatment of Pulmonary Fibrosis Due to 2019-nCoV Pneumonia With Fuzheng Huayu	Participants: 136 Experimental: Basic Treatment + Fuzheng Huayu Tablet Placebo Comparator: Basic Treatment + Placebo Recruiting Last Update Posted: 23 September 2020
Summary of clinical trials using Corticosteroids against COVID-19			
49.	NCT04344288 (Phase-II)	Corticosteroids During COVI-19 Viral Pneumonia Related to SARS-Cov-2 Infection	Participants: 304 Experimental: Prednisone group control group: standard care Terminated (competent authority decision) Last Update Posted: 26 October 2020
50.	NCT04345445 (Phase-III)	Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalized COVID-19 Patients With High Risk of Progression	Participants: 310 Experimental: Tocilizumab Active Comparator: Methylprednisolone Not yet recruiting Last Update Posted: 14 April 2020
51.	NCT04329650 (Phase-II)	Efficacy and Safety of Siltuximab vs Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia	Participants: 100 Experimental: Siltuximab 11 mg/Kg Active Comparator: Methylprednisolone 250 mg/24 h Recruiting Last Update Posted: 17 April 2020
52.	NCT04273321 (Not Applicable)	Efficacy and Safety of Corticosteroids in COVID-19	Participants 400 Experimental: Methylprednisolone group control group: standard care Completed with no results posted Last Update Posted: 11 May 2020
53.	NCT04327401 (Phase-III)	COVID-19-associated ARDS Treated With Dexamethasone: Alliance Covid-19 Brasil III (CoDEX)	Participants 290 Experimental: Methylprednisolone +Standard Care control group: standard care Terminated Last updated: 22 March 2021
54.	NCT04344730 (Not Applicable)	Dexamethasone and Oxygen Support Strategies in ICU Patients With COVID-19 Pneumonia (COVIDICUS)	Participants 290 Placebo Comparator: Standard oxygen + placebo Experimental: Standard oxygen + Dexamethasone Active, not recruiting Last updated: 9 February 2021
55.	NCT04325061 (Phase-IV)	Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19 (DEXA-COVID19)	Participants 400 Active Comparator: Standard intensive+ dexamethasone Control group: standard intensive care Terminated (Lack of enrolment) Last Update Posted: 3 February 2021
56.	NCT04343729 (Phase-III)	Methylprednisolone in the Treatment of Patients With Signs of Severe Acute Respiratory Syndrome in COVI-19 (MetCOVID)	Participants: 420 Placebo Comparator: Saline solution Active Comparator: Methylprednisolone Completed with no results posted Last Update Posted: 9 March 2021
Summary of clinical trials using telemedicine against COVID-19.			
57.	NCT04337788 (Not Applicable)	Gerontological Telemonitoring of Older Adults Living in Nursing Homes With COVID-19 Disease (COVIDeHPAD)	Participants: 300 Experimental: gerontological telemonitoring action No Intervention: routine care without gerontological telemonitoring Not yet recruiting Last Update Posted: 1 June 2020

(Continues)

TABLE 1 (Continued)

S. No	Registration No (phase)	Title of study	Interventions/outcome/conclusion of study
58.	NCT04331600 (Phase-IV)	ChloroQUine As antiviRal treAtmeNT In coroNavirus infEction 2020 (QUARANTINE2020)	Participants: 400 Experimental: Standard of care + chloroquine phosphate + telemedical approach. Control Group: Standard of care + telemedical approach. Completed with no results posted Last Update Posted: 11 February 2021

COVID-19 remains yet to be identified, but it has been confirmed that main viral proteases of SARS-CoV-2 are not inhibited by this drug combination. Recently, a study has identified boceprevir, calpain/cathepsin inhibitors as potent chemotypes that inhibits the enzymatic activity of SARS-CoV-2, hence inhibit assembly of viral particles (Figure 2).[47,50,51]

3.1 | In-Silico studies for identification of potential drugs against COVID-19

The in-silico strategy uses molecular databases and bioinformatics tools to screen molecules/drugs for their effectiveness. It offers the advantage of high-throughput screening, elucidation of new functions of drug molecules.[52] In silico strategies provide requisite preliminary information on the efficacy of compounds for further validation in in vitro and in vivo studies.

Coronavirus binds via S protein with ACE-2 receptor located on host cell followed by receptor (TMPRSS2) mediated endocytosis for cellular invasion.[53,54] Based on molecular databases[55] analysed all possible proteins of SARS-CoV-2 identified 2 human targets ACE2 and TMPRSS2 enzymes. Both are potential targets to inhibit entry of the virus into cells.[56] They constructed surface glycoprotein sequence of SARS-CoV 2 and found spike glycoproteins dock with human ACE-2 receptor to further support these propositions. Spike proteins of SARS-CoV-2 have 10-20 times more affinity for ACE-2 receptor than SARS-CoV, which may be one of the possible reasons for the increased infectivity of SARS-CoV-2.[57] Furthermore, in silico studies found AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (CGK) enhance binding of viral S protein with host ACE-2 receptor and attributed increased susceptibility of lung tissue to the presence of AAK1 and CGK on lung alveolar epithelial cells.[58] Consequently,[59] found that baricitinib effectively blocks AAK1 and CGK and suggested clinical evaluation of baricitinib against SARS-CoV-2. The docking score of the N-terminal receptor binding domain of S protein revealed methyl Tanshinonate as a potential candidate for blocking S protein binding with ACE-2.[60,61] A battery of neutralizing monoclonal antibodies (mAbs) was constructed via protein database against MERS-CoV spike (S) protein of the virus, and a majority of these antibodies (mAbs) was found to bind to the N-terminal domain (NTD) of the S1 subunit of MERS-CoV.[62] Duan et al[63] constructed a phage-display library from B cells of SARS CoV convalescent patients for designing and neutralizing antibodies targeting epitope of spike protein on the S2 subunit.

Analysis of viral proteinase of SARS-CoV-2 using bioinformatics tools (ZINC drug database) identified papain-like protease (PL^{pro}), RNA-dependent RNA polymerase (RdRp) and 3-chymotrypsin-like protease as rate-limiting steps in the life cycle of SARS-CoV-2 and proposed drug designing against these enzymes.[64] An earlier study has determined the three-dimensional MERS-CoV papain-like protease (PLpro) by X-ray crystallography and found that it comprises two domains, an ubiquitin- and a catalytic domain. They proposed that pharmaceutical entities having the potential to cause mutagenesis of the deficient oxyanion hole of PLpro will cause unfolding of PLpro, hence subsequent loss of enzymatic activity PLpro can help drug designing against SARS-CoV-2.[56,58] In silico, evaluation of eucalyptol indicated absolute binding of eucalyptol to COVID-19 PL^{pro}.[65] Molecular analysis studies of SARS-CoV, MERS-CoV and SARS-CoV-2 found RNA-dependent RNA polymerase (RdRp) highly conserved, suggesting clinical evaluation of RdRp inhibitors for the treatment of SARS-CoV-2.[66]

3.2 | In silico studies for identification of candidate molecules for vaccine development

A novel approach of vaccine development using computational techniques, including immunogenomics, immunogenetics and bioinformatics, is called vaccinomics.[67] In 2004, study utilized bioinformatics and structural analysis to design proteins corresponding to the S1 surface regions of SARS-CoV and immunized them in rabbit and monkey. Antiserum collected was found to elicit specific antibodies to SARS-CoV, which strongly supports synthetic-peptide-based approaches for generating a vaccine against coronavirus.[67] Multiple

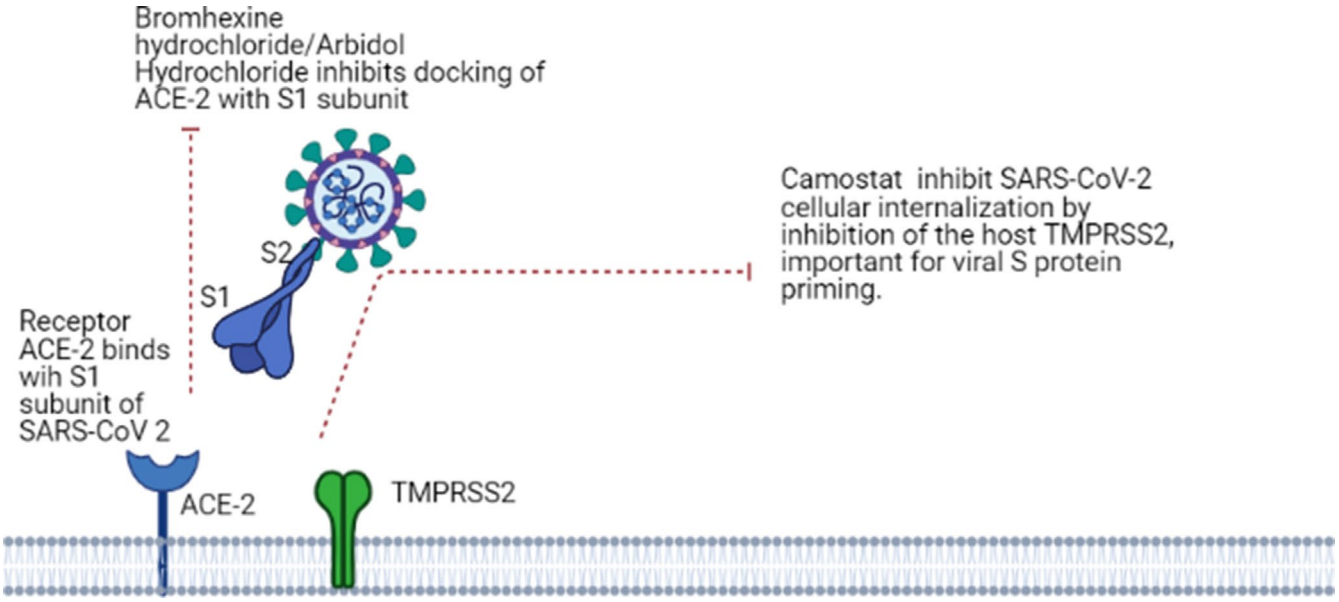


FIGURE 1 Inhibition of viral spike protein binding with cellular receptors. Bromhexine hydrochloride and arbidol hydrochloride inhibit docking of ACE-2 with S1 subunit hence inhibits viral phagocytosis (cellular internalization). Camostat inhibits TMPRSS2 cellular receptor, which is needed for priming of S protein and facilitation of docking between S1 and ACE-2

sequence alignment (MSA) found RdRp protein highly conserved in all human coronavirus strains and identified sequence WDYPKCDRA as highly immunogenic and accessible to the host immune system. Therefore, the study concluded that the target sequence could develop a universal vaccine against human coronavirus.[68] Novel nucleoside analogue designed by flex-base modification of the fleximers was combined with acyclic sugar moiety of acyclovir was found to inhibit replication of several human coronavirus strains.[69] Furthermore, Epitope Database and Analysis Resource of SARS-CoV, MERS-CoV, and other coronaviruses were used to identify candidate immune targets against SARS-CoV-2. This led to the identification of an array of regions in SARS-CoV-2, which have a high degree of homology with SARS-CoV and MERS-CoV and hence can serve as possible candidates for vaccine development against COVID-19.[70]

4 | IN VITRO STUDIES FOR IDENTIFICATION OF POTENTIAL THERAPEUTIC AGENTS AGAINST COVID-19

Driven by predictive information, in vitro studies offer an advantage to gear discovery of drug candidates. Molecular studies on virus-cellular receptor interaction found TMPRSS2 as cellular host factor critical for the spread of clinically relevant viruses, including coronaviruses and influenza A viruses.[71] An in vitro study by Ref. 72 evaluated postulates of in-silico studies in a human cell line (293T) and found the entry of the virus into the host cell is facilitated by S1 subunit of spike (S) protein which binds with angiotensin-converting enzyme 2 (ACE2). This is further supported by findings showing that serum from a COVID-19-recovered subject inhibits virus entry into cells of a human alveolar cell line and on Calu-3 cell line(pulmonary and intestinal). Moreover, camostat mesylate, a clinically approved serine protease inhibitor of TMPRSS2, partially inhibits SARS-CoV-2 entry into Caco2 and VeroE6/TMPRSS2-expressing cells, 2 reinforcing the applicability of cell culture models for drug discovery.[73,74] Patients who recovered from COVID-19 have a high concentration of neutralizing antibodies against viral S1 protein.[75] Based on these results, a study using serum from convalescent patients in cell line sera was found to significantly reduce SARS-2-Spike driven entry in host cell.[76] Based on these study results, it may be proposed that antibody response against S1 subunit may partially protect during infection.

Earlier in vitro studies have reported antiviral activity of ivermectin against dengue virus,[77] human immunodeficiency virus[77] and simian SV40 virus.[78,79] Ivermectin (antiparasitic drug) exhibited antiviral activity on Vero-hSLAM cell line infected with SARS-CoV-2. It resulted in a 5000-fold reduction in viral RNA after 48 hours in the Ivermectin group compared with the control group.[80] Remdesivir, a C-adenosine nucleoside triphosphate analogue, has shown activity against various RNA viruses (Coronavirus, Ebola virus and Flavivirus) by entering viral RNA chain and inhibiting RNA synthesis (Figure 3). Presently, in vitro and laboratory animal studies using remdesivir have shown promising results against SARS-COV-2.[81] These studies reported the effectiveness of

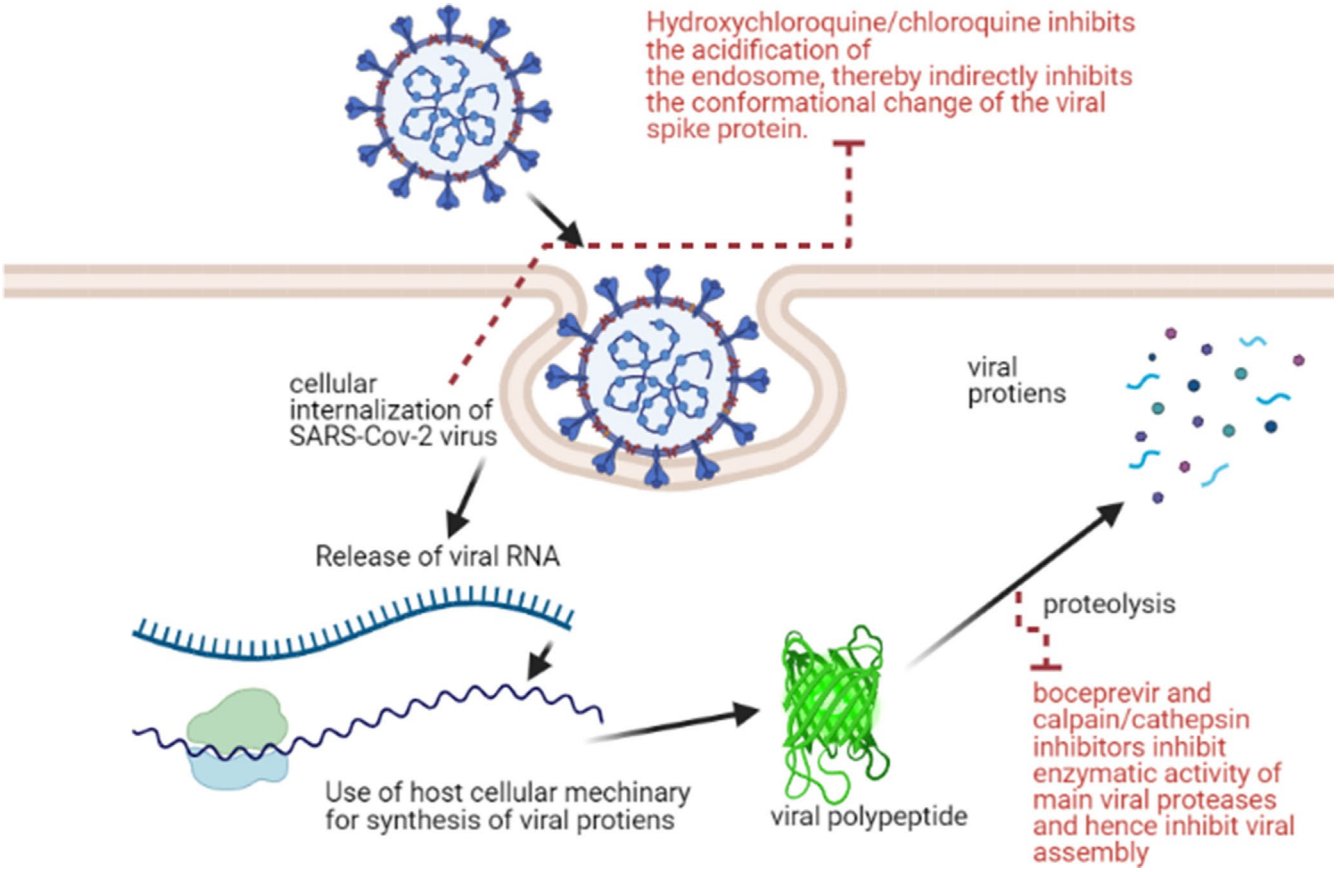


FIGURE 2 Inhibition of viral receptor-mediated viral phagocytosis. Hydroxychloroquine/Chloroquine Inhibits acidification of viral endosome hence inhibits viral phagocytosis (cellular internalization). Main SARS-CoV-2 protease inhibitors cause inhibition of viral protease and hence inhibit generation of viral proteins

remdesivir in viral replication, reduction in viral load and early resumption of symptoms in experimentally infected rats.[82]

In vitro studies have found chloroquine effective against HIV,[83] influenza,[84] H5N1 virus,[85] Chikungunya virus,[86] Zika virus,[87] Crimean-Congo haemorrhagic fever virus [88] and herpes simplex virus.[89] Studies using chloroquine on epithelial lung cell cultures were found to inhibit SARS-CoV replication.[90] Studies on the Vero cell line found that chloroquine causes deficit glycosylation in S protein receptors of viruses required for binding with angiotensin-converting enzyme 2 (ACE2).[91] In vitro studies using Vero E6 cell line have proposed chloroquine as an effective drug in reducing viral replication at a dosage achievable in lungs.[92] Chinese researchers who studied chloroquine's effect on SARS-CoV-2-infected cell line found the drug highly effective in reducing viral replication at a dosage achievable in the lung due to its effective penetration in lung tissues.[93-96] Furthermore, studies found that hydroxychloroquine (HCQ) more effectively inhibits SARS-CoV-2 replication than chloroquine.[97] The mechanism proposed for antiviral activity involves inhibition of essential steps in the viral life cycle, including glycosylation of cellular receptor, reductase-2 cathepsins MAP-kinase that inhibits viral assembly of SARS-CoV-2 and retard viral infection.[7,98,99] HCQ, when used in combination with other drugs, has been found to have potent activity against COVID-19.[96] An in vitro study has recently found synergistic action of combinational therapy of remdesivir (antiviral drug) and chloroquine against SARS-CoV-2.[99]

In vitro studies have suggested antiviral activity of HIV protease inhibitors (lopinavir/ritonavir) against SARS-CoV-2.[100] However, their efficacy is questionable against SARS-CoV-2 as coronavirus proteases do not contain a C2-symmetric pocket, which targets HIV protease inhibitors.[82,101] An in vitro study found ribavirin effective against SARS-CoV-2 at higher concentrations than required to inhibit other types of viruses.[99] A recent study on mouse models found more substantial evidence for anti-MERS-CoV activity of antiviral remdesivir than HIV protease inhibitors (Lopinavir/Ritonavir).[82] Ivermectin has been reported to limit infection caused by Venezuelan equine encephalitis virus (VEEV), West Nile virus and influenza virus.[102-105] Lv et al[106] reported ivermectin's antiviral activity in both in vitro and in vivo against pseudorabies virus (PRV).

The main protease M^{pro} of SARS-CoV-2 is involved in cleavage of viral polypeptides, and an earlier study has successfully treated feline infectious peritonitis using GC376,

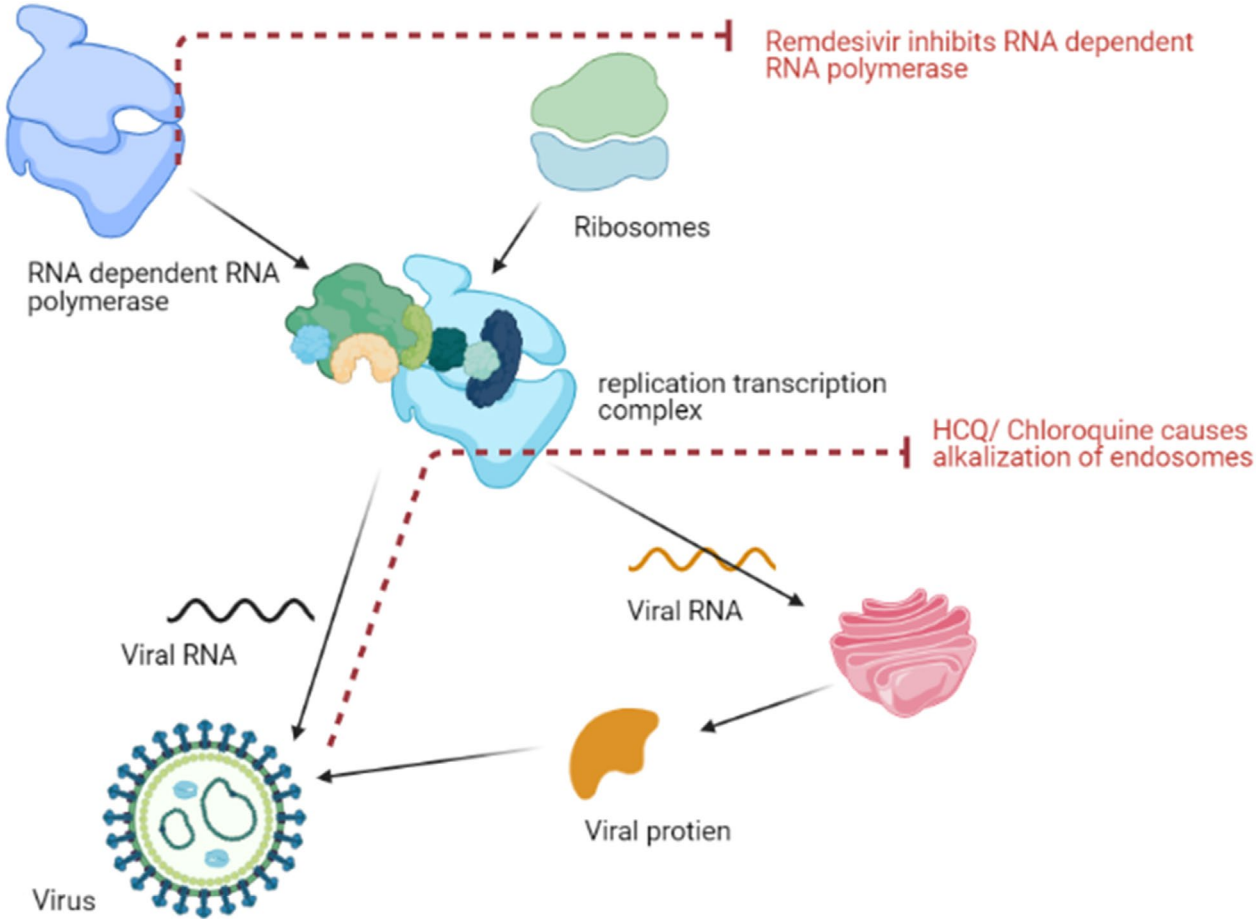


FIGURE 3 Inhibition of RNA-dependent RNA polymerase and viral assembly. Remdesivir inhibits RNA-dependent RNA polymerase hence inhibits viral RNA synthesis, while HCQ/ Chloroquine causes alkalization of endosomes hence inhibits viral particle assembly

a dipeptide-based protease inhibitor.[107] They found inhibitory action of GC376 against SARS-CoV-2 in cell culture. Hence, they proposed use of GC376 in clinical trials for development of a therapeutic regimen against COVID-19. To identify potent inhibitors of SARS-CoV-2 main protease, Ma et al[47] conducted a study using enzyme kinetic studies; mass spectrometry, thermal shift binding and fluorescence resonance energy transfer enzymatic assay and found that boceprevir and calpain inhibitors II and XII have a significant inhibitory activity against SARS-CoV-2 main protease. Furthermore, they found that these compounds inhibit SARS-CoV-2 replication in cell culture. They proposed use of these compounds in clinical trials for development of an effective therapeutic regimen against SARS-CoV-2. While, majority of the M^{pro} inhibitors of SARS-CoV-2 have γ lactam glutamine surrogate at the P1 position, and caplian inhibitor II and XII have hydrophobic moiety at P1 position. X-ray crystallographic studies have found that this hydrophobic moiety occupies the S1 pocket in an inverted binding pose, and hence, they can provide a new direction for development of an effective therapeutic regimen against SARS-CoV-2.[108] Papain-like proteases PLpro of SARS-CoV-2 are essential for posttranslational modifications of viral polypeptides and generation of functional replicase complex hence play important role in viral transmission.[109] Recently, a study found that inhibition of SCoV2-PLpro with GRL-0617 reduces viral replication.[110] Based on these findings, it is an urgent need to understand molecular rules governing PLpro substrate specificity, which can be helpful in designing effective drugs for COVID-19.[111]

5 | REVIEW OF SELECTED REPURPOSED DRUGS

Drugs used earlier against SARS-Cov and MERS are eligible candidates to develop a therapeutic regimen against COVID-19. Clinically investigated repurposed drugs that have shown promise in clinical trials against COVID-19 are summarized in Table 2. These drugs offer advantages as medicines have proven harmless, pharmacokinetics is well understood, and optimal dosages are standardized.[92] Recently after an outbreak of COVID-19, Ref. 129 has summarized almost 31 broad-spectrum antiviral agents (BSAA) as potential candidates for drug re-profiling against COVID-19. Clinical trials identified at Clinicaltrials.gov related to drug

repositioning for COVID-19 treatment are summarized and discussed below.

5.1 | SARS-CoV-2 membrane fusion inhibitors

A pilot clinical study (open-label, randomized and controlled) was conducted to evaluate the efficacy of Recombinant human angiotensin-converting enzyme 2 (rhACE2) against COVID-19. The study could not yield any encouraging result and was withdrawn after 7 days.[46] Recently, Tian et al[130] found that SARS-CoV-specific human monoclonal antibody CR3022 binds with receptor-binding domain (RBD) of COVID-19 and blocks the viral receptor (ACE-2) of cells and inhibit cellular infection.[130] Epitope of CR3022 and ACE2 binding site in COVID-19 RBD did not overlap. Therefore, the other potent specific neutralizing antibodies, such as m396 and CR3014, targeting the ACE2 binding site of SARS-CoV could not bind to COVID-19 S protein. Thus, CR3022 is a potential therapeutic choice for COVID-19 infection, alone or combined with other neutralizing antibodies. A study conducted on cell culture and laboratory animals found that the pan-coronavirus fusion inhibitor, EK1 peptide, was effective in reducing viral load. Both the EK1 and peptide HR2 domain could effectively block the transmission of the COVID-19 virus.[131] Furthermore, a lipopeptide EK1C4 generated from EK1 was found to be a more potent fusion inhibitor against S1 subunit of spike protein of SARS-CoV-2 compared with EK1.[131]

5.2 | Lopinavir-Ritonavir

A clinical trial against the Middle East respiratory syndrome (MERS) used lopinavir (HIV type 1 aspartate protease inhibitor) in combination with ritonavir (inhibitor of cytochrome P450). The synergistic action of combinational drug preparation was attributed to increased bioavailability of lopinavir in the presence of ritonavir.[83] An open-label, randomized clinical trial was conducted in Wuhan, China, to evaluate the efficacy of lopinavir-ritonavir in clinical cases.[116] Patients (n = 199) with confirmed COVID-19 infection were stratified as per the severity of disease as vindicated by ventilator support. Patients were divided into two groups; one group received standard care (n = 100) and the other group (n = 99) was treated with standard therapy in addition to lopinavir-ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days. Unfortunately, results were not encouraging as no improvement was observed in clinical improvement, viral load (detectable viral RNA) at different intervals. Although based on intention-to-treat analysis, the median time for recovery in the lopinavir-ritonavir group was one day lesser than the control group. On day 13, lopinavir-ritonavir treatment was stopped because of adverse gastrointestinal, renal and immunosuppressive events. Ineffectiveness of drugs may be attributed to a heterogeneous patient population,[131] lower concentration achieved in serum compared with levels needed to inhibit replication of virus.[3] Little is known about the tissue concentration of drug achievable at tissues where SARS-CoV-2 is replicating.[77]

5.3 | Chloroquine/Hydroxychloroquine

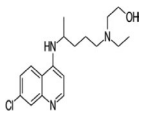
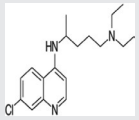
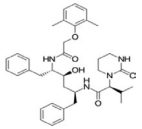
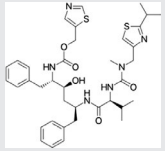
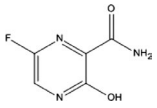
Chloroquine emerged 70 years ago as a substitute for natural quinine and is currently the drug of choice against malaria in most countries.[7,132,133] Hydroxychloroquine is derived by hydroxylation of the side chain of chloroquine. Chloroquine has been found effective in autoimmune diseases,[134] inflammatory processes, human immunodeficiency virus (HIV)[7] bacterial, fungal and viral infections.[135] A clinical trial conducted in Chinese patients found that chloroquine has a profound effect on clinical outcome and decreasing viral load in COVID-19 patients.[136] Recently, chloroquine repurposing was evaluated in 100 patients in China. A clinical study reported encouraging results, including an early decline in viral fevers, resolution of lung pathology (computed tomography images), and earlier clinical recovery compared to the control group in COVID-19 treatment.[136] Studies have reported that chloroquine causes glycosylation of the glycoprotein (gp120) envelope of the human immunodeficiency virus and renders viral particles non-infectious.[10,11] Furthermore, chloroquine has been found to inhibit Quinone Reductase 2,[11] involved in the biosynthesis of sialic acid,[137] an important component of ligand recognition,[7] and it causes alkalization of endosomes—hence inhibiting ph-dependent endosome-mediated viral entry.[138] Chloroquine enhances cell-mediated immune response directed against the viral antigen by increasing export of soluble antigen from dendritic cell to human cytotoxic $CD8^+$ T cell.[7,11]

Recently, contradictory results were published in the New England Journal of Medicine.[139] The study was conducted in a Chinese patient with confirmed COVID-19 infection. The patient was treated with hydroxychloroquine, standard treatment and with standard therapy. After two weeks, the patients received hydroxychloroquine showed deterioration in respiratory symptoms and showed need of respiratory escalation support, while no improvement was reported in clinical presentation, viral load and haematological profile.

5.4 | Remdesivir

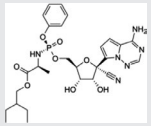
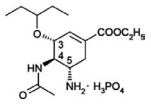
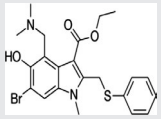
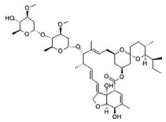
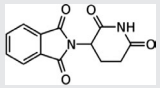
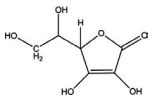
Remdesivir, a broad-spectrum antiviral pro-drug that undergoes metabolism to C-adenosine nucleoside triphosphate

TABLE 2 Repurposed Drugs being tested against human coronavirus

Therapeutic agent	Sponsor	Structure	Original use	Role	Conclusion/phase	Reference/ registration
Hydroxy- chloroquine	Shanghai Public Health Clinical Center		Antimalarial activity	Increase pH within intracellular vacuoles and alter processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes, and post-translation modification of proteins in the Golgi apparatus.	The early use of hydroxychloroquine caused improvement in clinical condition of COVID-19 Patients	112
Chloroquine	University of Oxford		Antimalarial activity	Increase pH within intracellular vacuoles and alter processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes, and post-translation modification of proteins in the Golgi apparatus.	No clinical benefit was reported	113
Lopinavir	Guangzhou 8th People's Hospital		Human Immuno-deficiency syndrome	Protease inhibitor	Completed with results on https://ichgcp.net/clinical-trials-registry/NCT04252885	114,115
Ritonavir	Tongji Hospital		The antiviral activity used to treat influenza	Protease inhibitor	Treatment was associated with pneumonia resolution in COVID-19.	116,117
Favipiravir (Favilavir)	Rajavithi Hospital		The antiviral activity used to treat influenza	It is a pro-drug and is converted to the ribofuranosyl triphosphate derivative by host enzymes and selectively and inhibits the influenza viral RNA-dependent RNA polymerase by structurally resembling the endogenous guanine	Recruiting Last Update Posted: 10 March 2021	118,119

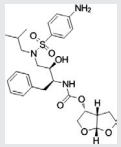
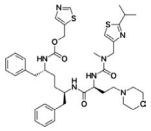
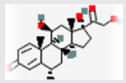
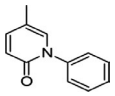
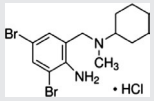
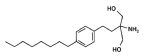
(Continues)

TABLE 2 (Continued)

Therapeutic agent	Sponsor	Structure	Original use	Role	Conclusion/phase	Reference/ registration
Remdesivir	Capital Medical University		Ebola	It is a nucleotide analogue, specifically an adenosine analogue, which inserts into viral RNA chains, causing their premature termination	Terminated (the COVID-19 epidemic has been controlled well in China; no eligible patients can be enrolled at present) Last Update Posted: 15 April 2020	116
Oseltamivir (Tamiflu)	Tongji Hospital		used to treat and prevent influenza A and influenza B	Inhibits neuraminidase enzyme expressed on viral surface	Oseltamivir was found ineffective in treatment of COVID-19	117
Arbidol (Umifenovir)	Jieming QU, Ruijin Hospital		Pneumonia caused by coronavirus	Inhibition of virus-mediated fusion with a target membrane and a resulting block of virus entry into target cells	Not yet recruiting Last Posted: 7 February 2020	117,120
Ivermectin	N/A		a broad-spectrum anti-parasitic agent with anti-viral activities against the broad range of viruses	Inhibitor of the interaction between the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and the importin (IMP) α/β1 heterodimer responsible for IN Nuclear import	Drug in combination with azithromycin and hydroxychloroquine was effective in mild/moderate COVID-19	121
Thalidomide	First Affiliated Hospital of Wenzhou Medical University		Cancers including multiple myeloma, graft-versus-host disease and several skin conditions, including complications of leprosy	Works by several mechanisms, including stimulating T cells and decreasing TNF-α production	Not yet recruiting Last Update Posted: 21 February 2020	122
Vitamin C	ZhiYong Peng		Antimicrobial activity, Prevents scurvy	Works by some mechanisms	Terminated as the number of qualifying COVID-19 patients decreased with the control of the epidemic in China	123

(Continues)

TABLE 2 (Continued)

Therapeutic agent	Sponsor	Structure	Original use	Role	Conclusion/phase	Reference/ registration
Darunavir (Prezista)	Traditional Chinese Medicines		Antiretroviral Activity against Human Immunodeficiency Virus	Protease inhibitor	Not yet recruiting Last update: 31 March 2021	124,125
Cobicistat	Shanghai Public Health Clinical Center		Antiretroviral activity against Human Immunodeficiency Virus proteins	inhibition of human CYP3A	Drug was found ineffective against COVID-19	124,125
Methylpredn-Isolone	Second Affiliated Hospital of Wenzhou Medical University		Arthritis, blood disorders, severe allergic reactions, certain cancers, eye conditions, skin/ kidney/intestinal/lung diseases and immune system disorders	Binds to and activates specific nuclear receptors, resulting in altered gene expression and inhibition of proinflammatory cytokine production	Drug in combination with other drugs was found effective in mild/moderate COVID-19	126
Pirfenidone	Huilan Zhang		Idiopathic pulmonary fibrosis	Reduces fibroblast proliferation, inhibits transforming growth factor-beta (TGF-β) stimulated collagen production and reduces the production of fibrogenic mediators such as TGF-β	Recruiting Last Update Posted: 25 February 2021	126
Bromhexine hydrochloride	Second Affiliated Hospital of Wenzhou Medical University		Respiratory disorders associated with viscid or excessive mucus	Decreases mucus viscosity by increasing lysosomal activity	Beneficial effects of drug were reported	127
Fingolimod	1° Affiliated Hospital of Wenzhou Medical University		Multiple sclerosis	Fingolimod-P binds to S1P receptors and acts as a functional antagonist. It binds and stimulates the receptor, which results in internalization and degradation of the receptor. The functional outcome is a down-regulation of the receptor	Results not available	128

analogue and causes premature termination of RNA transcription, has shown potent activity against COVID-19 in an in vitro study.[4] Earlier studies reported inhibitory action of remdesivir on viral replication of related virus of the beta-coronavirus group at doses well tolerated.[140] Reduced mortality was observed in Ebola virus-infected patients treated with remdesivir (33%) (n = 499) compared to patients (75%) (n = 1900) treated with standard therapy.[141] Currently, Remdesivir is being evaluated in a phase-I, controlled trial (randomized, double-blind, placebo-controlled) with a loading dosage of 200 mg and 100 mg maintenance dosage daily and has not presented any toxic effects.[142] Successful results have been reported in patients showing mild to moderate COVID-19.[143]

6 | COMBINATIONAL THERAPEUTIC INTERVENTIONS

Currently, a clinical trial has found increased efficacy of a combinational therapeutic regimen using widely available drugs, for which large-scale manufacture is possible and those drugs that can be prescribed immediately.[144]

Combinational therapy of non-specific antiviral drugs (lopinavir, ritonavir and favipiravir) used earlier in influenza and HIV are currently under investigation for phase IV clinical trials against COVID-19.[145] Clinical improvement in early viral clearance and improvement in clinical signs has been reported by combinational therapy of antiviral drugs (lopinavir-ritonavir, ribavirin) and interferon-α against Middle East respiratory syndrome coronavirus (MERS-CoV).[146]

Umifenovir (membrane fusion inhibitor) used with remdesivir (RdRp inhibitor) was found to be effective against Ebola virus,[147] SARS-CoV and MERS-CoV. The same combinational therapy is presently under investigation against SARS-CoV-2.[148] Gautret et al[149] conducted a clinical trial (open-label, non-randomized) using hydroxychloroquine and azithromycin for treatment of COVID-19. The results of their study proposed that hydroxychloroquine used in combination with azithromycin causes a significant reduction in viral load and amelioration of symptoms in COVID-19 patients. Their study recommended the possibility of the adoption of this combinational therapeutic protocol to fight the merging viral epidemic in real time. Based on these results, Chinese experts recommended 500 mg chloroquine two times for ten days in patients affected with COVID-19 pneumonia.[150]

7 | CHINESE MEDICINE

COVID-19 patients are primarily presenting with respiratory symptoms,[134] gastrointestinal symptoms[151] and myalgia/arthralgia.[152] A Chinese medicine system is based mainly on symptomatic treatment,[153] and Chinese medicine (CM) has classified the COVID-19 as *dampness* type of sickness.[56,99,154] As per the Chinese system of medicine, the pathogenesis of infectious diseases has a relation with the weather.[155] The pathogenesis of COVID-19 was proposed due to endogenous *stagnated heat* due to warm temperatures in November and an abrupt decrease in temperature during the latter part of November, which resulted in *exogenous cold-dampness*.[156] A phylogenetic analysis and timeline match of the outbreak[157] support these propositions. Accordingly, as per Chinese medicine, treatment of COVID-19 should focus on eliminating *dampness* and releasing *endogenous stagnated heat,* which will result in *removing lungs,* henceforth *expelling pathogenic factors*.[158,159] An In silico study has proposed a plausible Chinese medicine mechanism, and the authors suggested that Chinese medicinal preparations (kaempferol and baicalin in da-yuan decoction) bind to ACE–II receptors and can inhibit cellular infection by COVID-19.[160]

Similarly, a molecular docking study of 24 Chinese medicine preparations recommended a cocktail of seven herbal medicines that can bind with the S-protein of ACE2.[161] Chinese medicinal preparations regulate key immunogenic pathways and pro-inflammatory signalling pathways, which could help alleviate pneumonia in COVID-19 patients.[162-164] Chinese patients have reported potential benefits of Chinese medicine in terms of pyrexia, radiological changes, hospital stay and viral load reduction.[93,109] These findings support the use of Chinese medicine with proper standardization and caution as an adjuvant for the management of COVID-19.

8 | CORTICOSTEROIDS AND IMMUNOMODULATORY AGENTS

Studies investigating the viral pathogenesis of pneumonia have attributed cytokine storm as a possible pathogenesis pathway involved in viral pneumonia and have found a beneficial role of corticosteroids in H1N1 pneumonia, SARS-CoV, (MERS)-CoV and other types of pneumonia.[153,163,164,165] This is further supported by in vitro studies in A549 lung epithelial cells where dexamethasone was found to block cytokine-induced apoptosis.[3] So, beneficial effects of corticosteroids have been attributed to suppression of unwanted immunopathological response—hence cytokine storm in viral pneumonia,[3,166] However, contradictory findings were reported with the use of corticosteroids in COVID-19 patients as these drugs modulate inflammation and immune activation that delays viral clearance.[167] Furthermore, the use of corticosteroids in COVID-19 has reported of adverse effects, which include osteoporosis, diabetes and psychosis with its use.[167] A meta-analysis has reported increased mortality, secondary

bacterial infection and fungal infection in influenza patients receiving corticosteroids.[168] Despite these limitations, there are few clinical trials underway in different parts of the world to use corticosteroids against COVID-19. Because of insufficient clinical evidence, WHO does not support the clinical use of corticosteroids in COVID-19 patients.[169] In spite of this, encouraging results have been reported in Spain using corticosteroids against SARS-CoV-2. Clinical investigators reported significant reduction in all-cause mortality without any complications. In addition, almost 10 randomized, controlled trials have reported significant reduction in mortality, need of high-pressure ventilation and hospital stay in patients treated with corticosteroids.[170] In patients with severe manifestation of COVID-19, hyperinflammatory response has been reported which results in pulmonary thrombosis henceforth acute lung injury and extravasations of cellular debris, which eventually causes multiple organ failure.[171] So, a plethora of studies have proposed a beneficial role of corticosteroid in COVID-19 to mitigation of hyper-inflammation and acute respiratory distress syndrome.[170,172,173,174] There is ample evidence to support elevation of cytokine profile in COVID-19, which is an indication of secondary haemophagocytic lymphohistiocytosis, which is effectively responsive to use of corticosteroids.[175] In addition, corticosteroids cause down-regulation of inflammatory pathways, which is a prerequisite to restore tissue homeostasis and cause resolution of pulmonary and extra-pulmonary organ damage.[176] Hence, the beneficial role of corticosteroids may be attributed to pathophysiological reasoning.

The rationale of using immunomodulatory agents in COVID-19 is to spare host tissue from unwanted inflammatory response induced by cytokine storm. Early studies in China found that IL-6 (Interleukin-6) is a key proinflammatory cytokine, which plays a role in multiple organ failure in COVID-19 patients.[83] Subsequently, a clinical trial was designed in 21 patients treated with Tocilizumab (400 mg), a monoclonal antibody IL-6 receptor antagonist.[21] Results were encouraging as 91% of patients showed clinical recovery and enhanced blood oxygen levels, amelioration of pulmonary tissue damage and reduced hospitalization time.[21] This trail's limitations were fewer patients recruited, absence of placebo comparator and a heterogeneous patient group.[48] Pirfenidone, an inhibitor of IL-1β and IL-4, and Sarilumab, another IL-6 receptor antagonist, are being evaluated for beneficial effects against COVID-19 patients.[177,178] Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth, has revealed successful pulmonary oedema resolution in COVID-19 patients. Fingolimod, a sphingosine-1-phosphate receptor regulator, has been successfully used against multiple sclerosis; a clinical trial [128,179] using Fingolimod and ventilator support has reported resolution of inflammation and histopathological change in pulmonary tissue of COVID-19 patients.

9 | IMMUNOGLOBULIN

Immunoglobulins have found applicability in a diverse set of diseases ranging from acute idiopathic thrombocytopenic purpura to chronic inflammatory demyelinating polyneuropathy.[180] The main advantage of using immunoglobulins in those diseases which are refractory to conventional therapeutic options is that immunoglobulins recognize a broad set of glycoproteins and protein shell in enveloped and un-enveloped virus, respectively.[181,182] There is no commercial preparation of immunoglobulin to offer protection against COVID-19, so the only option left is convalescent plasma obtained from recovered patients. There are reports of successful use of plasma therapy in SARS-CoV-1 and MERS patients.[183] Currently, immunoglobulins are being clinically evaluated in uncontrolled case series comprising 5 patients and other series of 3 patients in China.[184] Reports suggest immunoglobulin efficacy with 7-10 days of infection when the primary immune response is insufficiently developed.[185] Subsequently, the FDA has issued a guideline to study the use of immunoglobulins obtained from patients recovered from COVID-19. Some authors have questioned the use of immunoglobulin in SARS-CoV-2 owing to its high rate mutation to change surface glycoprotein to evade the immune system.[182]

10 | TELEMEDICINE

Telemedicine involves the use of information technology for providing expert advice from a distance.[186] Face-to-face contact plays an essential role in patient and doctor relationship.[187] However, overcrowded patient wards create more infection and contamination in an environment that renders the health of medical staff and patients at higher risk.[128] To avoid transmission of infection to the healthy population, telemedicine offers an alternative for providing health care without physical contact between patient and physician with the added advantage of low cost and extensive coverage.[188] Presently, western countries [189] are focusing and investing in telemedicine to contain the spread of COVID-19 infection.[190] The Brazilian government has launched the "Coronavírus SUS" app to track and identify COVID-19-infected patients on similar lines; the United Kingdom has developed a mobile application that enables patients to self-report their health conditions.[191] Furthermore, the American Psychological Society, 2020 and WHO, 2020 has proposed the use of telemedicine in alleviating the adverse psychological effects associated with loneliness, lockdown and quarantine.

11 | OTHER INTERVENTIONS

Due to the non-availability of evidence-based pharmaceutical preparation against COVID-19, the disease is currently

managed by symptomatic care in combination with full intensive care support. This section will discuss adjunctive therapies under clinical investigation. Vitamin C, evaluated in COVID-19 patients because of its antioxidant activity, immune-modulator action and anti-inflammatory action,[123] has reported improvement in clinical conditions and sepsis, and reduced mortality.[192] Thalidomide causes increased degradation of mRNA of tumour necrosis factor-α (TNFα), which explains its anti-inflammatory action.[193] In addition to this, thalidomide causes release of interleukins and activation of natural killer cells. Therefore, being evaluated as supportive therapy in addition to conventional therapy.[194] An important issue related to thalidomide use the development of Amelia in new born babies from mothers who are underwent with thalidomide treatment during pregnancy.[194] Recombinant human interferon α2β is reported to have an inhibitory effect on MERS-CoV and SARS-CoV[195] and has been proposed for evaluation against COVID-19. Synergistic action of pegylated interferon alfa-2a and alfa-2b in combination with ribavirin is under investigation[196] with a rationale to activate an innate immune response against SARS-CoV-2. Researchers have cautioned against using interferons due to side effects associated with their use and recommended close monitoring of patients undergoing interferon therapy.[197] Griffithsin, a gel obtained from red algae, contains lectins that specially bind with surface glycoprotein (gp-120) of HIV and spike (S) proteins of SARS-CoV-1, and it inhibits penetration of the virus into the cell.[198] Given its encouraging results in SARS-CoV-1 and HIV, chemical constituents should be evaluated in SARS-CoV-2.

12 | DISCUSSION

Coronaviruses have a propensity to spread in a broad host range, and they periodically jump into new host species and emerge as an epidemic for immunologically naïve humans; the current outbreak of COVID-19 is the 3rd outbreak in the 21st century after SARS-CoV and MERS-CoV. Therefore, broad-spectrum antiviral therapy is an unmet medical demand at present to control the epidemic of CoVs infection. In silico and in vitro are rapid time-saving and cost-saving strategies that can guide research in a situation like COVID-19 with a higher likelihood of finding desired results with the added advantage of screening drugs for toxic action. The development of novel drugs/vaccines against COVID-19 will take months to years. However, scientist needs to focus on repurposing of drugs with special emphasis on drugs used against other human coronaviruses SARAS-CoV and MERS. Utmost caution should be taken as the published reports are mostly from countries affected early in the pandemic; therefore, results from these studies should be cautiously extrapolated.

During a pandemic like the COVID-19, there is a need to emphasise time-tested approaches for drug evaluation in randomized, controlled clinical trials. Drugs yet to be marketed should be evaluated by well-controlled randomized trials with substantial evidence of safety and efficacy. It is unclear whether combinational therapy provides an added synergistic advantage over monotherapy in terms of a favourable risk/benefit ratio because of the lack of monotherapy primary data. Since COVID-19 has an immense number of treatment interventions, we did not cover all available therapeutic approaches. Moreover, the findings of the studies are complex and modify as new evidence arises. Besides, only English articles/publications were reviewed, so some important international data could be lacking.

13 | CONCLUSION

Although there are conserved druggable SARS-CoV-2 targets, including S protein, RdRp, helicase, PLpro and 3-CL protease, unfortunately, no drug or vaccine is currently available against the coronavirus. The pandemics have raised serious concerns and have put pressure on researchers throughout the world for evaluating and approving drugs against COVID-19. There is limited evidence of the effectiveness and adequacy of studies of drugs currently used in the treatment of COVID-19. The FDA has currently approved drugs against COVID-19 on little evidence, lesser clinical trials/drugs and suboptimal design of the clinical trial, which may not give the actual picture of the efficacy of these drugs. Recently, USA issued an Emergency Use Authorization (EUA) to use hydroxychloroquine, and there is no conclusive evidence of its efficacy. Although currently undergoing clinical trials based on repurposing of drugs have not yielded enough encouraging results, there are some takeaways from these trials. The speed, efficacy and priority with which the studies were designed to provide early answers can be extrapolated for other drugs and other epidemic situations.

Furthermore, these studies give convincing evidence regarding potential adverse effects of active pharmaceutical preparations used in a clinical trials. With the ongoing effort, we hope that COVID-19 will subside in the coming months. Still, there is an urgent need to develop a universal vaccine or broad-spectrum antiviral against human coronavirus.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Naveed Nazir Shah, Showkat Ul Nabi, Showkeen Muzamil Bashir and Muzafar Ahmad Rather contributed significantly to the conception and design of the study. Sofi Imtiyaz Ali, Qudratullah Kalwar, Wajid Mohammad Sheikh and Alveena Ganai assisted in writing the manuscript and revised the manuscript decisively for imperative intellectual content. All authors read and approved the final manuscript.

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REFERENCES

1. Ahmed SF, Quadeer AA, McKay MR. Preliminary identification of potential vaccine targetsfor the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. *Viruses*. 2020;12(3):254. https://doi.org/10.3390/v12030254
2. Centers for Disease Control and Prevention (CDC). Confirmed 2019-nCoV Cases Globally Global Map. https://www.cdc.gov/coronavirus/2019-ncov/locations-confirmed-cases.html. Accessed February 8, 2020.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2019;2020:497-506.
4. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2019;2020:1061-1069.
5. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Eng J Med*. 2019;2020:727-733.
6. World Health Organization (WHO). Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-%282005%29-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-%282019-ncov%29. Accessed February 5, 2020.
7. Christian D, Jean-Mar R, Philippe C, Didier R. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Author links open overlay panel. *Int J Antimicrob Agents*. 2020;55(5):105938.
8. Hui DS, Azhar EI, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis*. 2019;2020:264-266.
9. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microb Infect*. 2020;221-236.
10. Savarino A, Gennero L, Sperber K, Boelaert JR. The anti-HIV-1 activity of chloroquine. *J Clin Virol* 2001;20(3):131-135.
11. Kwiek JJ, Haystead TA, Rudolph J. Kinetic mechanism of quinone oxidoreductase 2 and its inhibition by the antimalarial quinolines. *Biochemistry*. 2004;43(15):4538-4547.
12. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med*. 2019;2020:929-936.
13. Chen N, Zhou M, Dong X. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2019;2020:507-513.
14. Drexler JF, Gloza-Rausch F, Glende J, et al. Genomic characterization of severe acute respiratory syndrome-related coronavirus in European bats and classification of coronaviruses based on partial RNA-dependent RNA polymerase gene sequences. *J Virol*. 2010;84:11336-11349.
15. Cavanagh D, Mawditt K, Welchman DB, Britton P, Gough RE. Coronaviruses from pheasants (*Phasianus colchicus*) are genetically closely related to coronaviruses of domestic fowl (infectious bronchitis virus) and turkeys. *Avian Pathol*. 2002;31(1):81-93.
16. Parry J. WHO investigates China's fall in SARS cases. *BMJ*. 2003;326(7402):1285.
17. Sharmin R, Islam AB. A highly conserved WDYPKCDRA epitope in the RNA directed RNA polymerase of human coronaviruses can be used as epitope-based universal vaccine design. *BMC Bioinform*. 2014;15(1):161.
18. Lizbeth RS, Jazmín GM, José CB, Marlet MA. Immunoinformatics study to search epitopes of spike glycoprotein from SARS-CoV-2 as potential vaccine. *J Biomolecule Struc Dynam*. 2020;23:1-5.
19. Wever BA, Van der Hoek L. Recently discovered human coronaviruses. *Clin Lab Med*. 2009;29(4):715-724.
20. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Eng J Med*. 2012;367(19):1814-1820.
21. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci*. 2020;457-460.
22. Angeletti S, Benvenuto D, Bianchi M, Giovanetti M, Pascarella S, Ciccozzi M. COVID-2019: the role of the nsp2 and nsp3 in its pathogenesis. *J Med Virol*. 2020;92(6):584-588.
23. Williams AE, Chambers RC. The mercurial nature of neutrophils: still an enigma in ARDS? *Am J Physiol-Lung Cell Mol Physiol*. 2014;306(3):L217-L230.
24. Cameron MJ, Bermejo-Martin JF, Danesh A, Muller MP, Kelvin DJ. Human immunopathogenesis of severe acute respiratory syndrome (SARS). *Virus Res*. 2008;133(1):13-19.
25. Crosby AW. *America's Forgotten Pandemic: The Influenza of 1918*. Cambridge: Cambridge University Press, 2003: 100.
26. Byerly CR. *Fever of War: the Influenza Epidemic in the US Army During World War I*. New York, NY: NYU Press, 2005: 5.
27. Humphries MO. *The Last Plague: Spanish Influenza and the Politics of Public Health in Canada*. Toronto: University of Toronto Press, 2013.
28. Phillips H. The recent wave of 'Spanish'flu historiography. *Soc History Med*. 2014;27(4):789-808.
29. Olson DR, Simonsen L, Edelson PJ, Morse SS. Epidemiological evidence of an early wave of the 1918 influenza pandemic in New York City. *Proc Nat Acad Sci*. 1918;2005:11059-11063.
30. Barry JM. Pandemics: avoiding the mistakes of 1918. *Nature*. 2009;459:324-325.

31. Flahault A, Zylberman P. Influenza pandemics: past, present and future challenges. *Public Health Rev*. 2010;32(1):319-340.
32. Gaydos JC, Top FH Jr, Hodder RA, Russell PK. Swine Influenza A Outbreak, Fort Dix, New Jersey, 1976. *Emerg Infect Dis*. 2006;12(1):23-28.
33. Krause JC, Tsibane T, Tumpey TM, et al. Human Monoclonal Antibodies to Pandemic 1957 H2N2 and Pandemic 1968 H3N2 Influenza Viruses. *J Virol*. 2012;86(11):6334-6340.
34. World Health Organization (WHO). Prevention of hospital-acquired infections: a practical guide. 2002. https://www.who.int/csr/resources/publications/drugresist/en/whocdscsreph200212.pdf?ua=1. Accessed June 4, 2019.
35. Sencer DJ, Millar JD. Reflections on the 1976 Swine Flu Vaccination Program. *Emerg Infect Dis*. 2006;12(1):23-28.
36. Neustadt RE, Fineberg HV. *The Epidemic that Never Was*. New York, NY: Vintage Books; 1983:293. http://hdl.handle.net/10822/796245. Accessed March 18, 2020.
37. Markus HS, Brainin M. COVID-19 and stroke—A global World Stroke Organization perspective. *Int J Stroke*. 2020;15(4):361.
38. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. *Advan Vir Res*. 2011;85-164.
39. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol*. 2019;17(3):1-92.
40. Perlman S, Zhao J. Human coronavirus EMC is not the same as severe acute respiratory syndrome coronavirus. *MBio*. 2013;4(1):e00002-13. https://doi.org/10.1128/mBio.00002-13
41. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol*. 2016;24(6):490-502.
42. Hon KL, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet.* 2003;361(9370):1701-1703.
43. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. 2016;14(8):523-534.
44. Liljander A, Meyer B, Jores J, et al. MERS-CoV Antibodies in Humans, Africa, 2013–2014. *Emerg Infect Dis*. 2016;22(6):1086-1089.
45. Zumla AN, Alagaili M, Cotton EI. Azhar, Infectious diseases epidemic threats and mass gatherings: refocusing global attention on the continuing spread of the Middle East Respiratory syndrome coronavirus (MERS-CoV). *BMC Med*. 2016;14(1):1-4.
46. https://clinicaltrials.gov/ct2/show/record/NCT04333550?cond=-COVID-19&draw=2&rank=1. Accessed May 4, 2020.
47. Ma C, Sacco MD, Hurst B, et al. Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. *Cell Res*. 2020;30:678-692. https://doi.org/10.1038/s41422-020-0356-z
48. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2019;2020:1824-1836.
49. Fehr AR, Perlman S. *Coronaviruses: an overview of their replication and pathogenesis*. New York, NY: In Coronaviruses Humana Press, 2015;1-23.
50. Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. *Science*. 2003;300(5626):1763-1767.
51. Zhang L, Shen FM, Chen F, Lin Z. Origin and evolution of the 2019 novel coronavirus. *Clin Infect Dis*. 2020;71(15):882-883.
52. Dyall J, Coleman CM, Hart BJ, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrob Agents Chemother*. 2014;58(8):4885-4893.
53. Wrapp DN, Wang KS, Corbett JA, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020;367(6483):1260-1263.
54. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature*. 503(7477):535-538.
55. Wu Y, Liu Y, Yang P, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica*. 2020;10(5):766-788.
56. Boopathirajan P, Muthu K, Vijayakumar K. In-Silico Drug Discovery for Covid19 by Targeting Spike Glycoprotein of SARS COV - 2 (Wuhan Corona Virus 2019 Outbreak) Against the Docking Analysis with Structure Predicted Human 'ACE2-FC Region of IGG1' Fusion Protein As a Protein Based Drug. 2020;8.
57. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2019;2020:565-574.
58. Zhao JK, Li C, Wohlford-Lenane SS, Agnihothram C, Fett JZ. Rapid generation of a mouse model for Middle East respiratory syndrome. *Proc Nat Acad Sci U S A*. 2014;4970-4975.
59. Peter R, Ivan G, Catherine T, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395:31-32.
60. Kumar S, Maurya V-K, Prasad A-K, Bhatt M-L, Saxena S-K. Structural, glycosylation and antigenic variation between 2019 novel coronavirus (2019-nCoV) and SARS coronavirus (SARS-CoV). *Virusdisease*. 2019;2020:1-9.
61. Agrawal AS, Garron T, Tao X, Peng BH, Wakamiya M, Chan TS. Generation of a transgenic mouse model of Middle East respiratory syndrome coronavirus infection and disease. *J Virol*. 2015;89:3659-3670.
62. Chen Y, Lu S, Jia H, et al. A novel neutralizing monoclonal antibody targeting the N-terminal domain of the MERS-CoV spike protein. *Emerg Microb Infect*. 2017;6:1-7.
63. Duan J, Yan X, Guo X, et al. A human SARS-CoV neutralizing antibody against epitope on S2 protein. *Biochem Biophys Res Comm*. 2005;333:186-193.
64. Lei J, Mesters J-R, Drosten C, Anemüller S. Ma Q, Hilgenfeld R Crystal structure of the papain-like protease of MERS coronavirus reveals unusual, potentially druggable active-site features. *Antiviral Res*. 2014;109:72-82.
65. Sharma ADE. Eucalyptol (1, 8 cineole) from eucalyptus essential Oil a potential inhibitor of COVID 19 corona virus infection by molecular docking studies; 2020.
66. Elfiky AA, Ribavirin R, Sofosbuvir G. Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sci*. 2020;11:7592.
67. Wai-Yan C, Shu-Guang L, Paul KS, et al. Synthetic Peptide Studies on the Severe Acute Respiratory Syndrome (SARS) Coronavirus Spike Glycoprotein: Perspective for SARS Vaccine Development. *Clin Chem*. 2004;50:1036-1042.
68. Sharmin R, Islam AB. A highly conserved WDYPKCDRA epitope in the RNA directed RNA polymerase of human coronaviruses can be used as epitope-based universal vaccine design. *BMC Bioinformat*. 2014;15,161.

69. Peters HL. *The Design, Synthesis, and Biological Evaluation of a Series of Acyclic Fleximer Nucleoside Antivirals*. Baltimore, MA: University of Maryland, 2015.
70. Alba G, John S, Yun Z, Scheuermann RH, Sette BPA. A Sequence Homology and Bioinformatic Approach Can Predict Candidate Targets for Immune Responses to SARS-CoV-2. *Cell Host Microbe*. 2020;27(4):671-680.
71. Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *J Virol*. 2019;93:e01815-18.
72. Hoffmann M, Kleine-Weber H, Krüger N, Muelle MA, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *BioRxiv*. 2020. https://doi.org/10.1101/2020.01.31.929042
73. Glover TD. Neighboring in the time of coronavirus? Paying civil attention while walking the neighborhood. *Leisure Sci*. 2020;24:1-7.
74. Kleine-Weber H, Schroeder S, Krüger N, et al. Polymorphisms in dipeptidyl peptidase 4 reduce host cell entry of Middle East respiratory syndrome coronavirus. *Emerg Microb Infect*. 2020;9:155-168.
75. Liu C, Zhou Q, Li Y, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. *ACS Cent Sci.* 2020;6:315-331.
76. Wagstaff KM, Sivakumaran H, Heaton S-M, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J.* 2012;443:851-856.
77. Mastrangelo E, Pezzullo M, De B, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *J Antimicrob. Chemother.* 2012;67:1884-1894.
78. Kosyna FK, Nagel M, Kluxen L, Kraushaar K, Depping R. The importin α/β-specific inhibitor Ivermectin affects HIF-dependent hypoxia response pathways. *Biological Chem.* 2015;396:1357-1367.
79. Zhou C, Pourmal S, Pavletich N-P. Dna2 nuclease-helicase structure, mechanism and regulation by Rpa. *Elife*. 2015;4:e09832.
80. Caly L, Druce J-D, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir Res*. 2020;178:104787.
81. Al-Tawfiq JA, Memish ZA. Diagnosis of SARS-CoV-2 infection based on CT scan vs RT-PCR: reflecting on experience from MERS-CoV. *J Hospital Infect*. 2020;105:154-155.
82. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature Commun*. 2020;11:1-4.
83. Savarino A, Boelaert J-R, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. *Lancet Infect Dis*. 2003;3:722-727.
84. Paton N-I, Lee L, Xu Y, et al. Chloroquine for influenza prevention: a randomized, double-blind, placebo controlled trial. *Lancet Infect Dis*. 2011;11:677-683.
85. Yan Y, Zou Z, Sun Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. *Cell Res*. 2013;23:300-302.
86. Delogu I, Pastorino B, Baronti C, Nougairède A, Bonnet E, de Lamballerie X. In vitro antiviral activity of arbidol against Chikungunya virus and characteristics of a selected resistant mutant. *Antivir Res*. 2011;90:99-107.
87. Delvecchio R, Higa L-M, Pezzuto P, et al. Chloroquine, an endocytosis blocking agent, inhibits Zika virus infection in different cell models. *Viruses*. 2016;8:322.
88. Ferraris O, Moroso M, Perne TO, et al. Evaluation of Crimean-Congo hemorrhagic fever virus in vitro inhibition by chloroquine and chlorpromazine, two FDA approved molecules. *Antivir Res*. 2015;118:75-81.
89. Koyama AH, Uchida T. Inhibition of multiplication of herpes simplex virus type 1 by ammonium chloride and chloroquine. *Virology*. 1984;138:332-335.
90. Kono M, Tatsumi K, Imai A-M, Saito K, Kuriyama T, Shirasawa H. Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: involvement of p38 MAPK and ERK. *Antiviral Res*. 2008;77:150-152.
91. Vincent M-J, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:1.
92. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020;55(4):105932.
93. Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55(3):105924.
94. Liu P, Jiang JZ, Wan XF, et al. Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)? *PLoS Pathog*. 2020;16:e1008421.
95. Yao X, Ye F, Zhang M, et al. 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*. 2020;71(15):732-739.
96. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. *Diabet Metabol Syndr Clin. Res. Rev*. 2020;14(3):241-246.
97. Yao X, Ye F, Zhang M, et al. 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*. 2020;71(15):732-739.
98. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020;55(4):105932.
99. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323:1843-1844.
100. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antivir Res*. 2020;178:104786.
101. Li X, Song Y, Wong G, Cui J. Bat origin of a new human coronavirus: there and back again. *Sci China Life Sci*. 2020;63:461-462.
102. Van der Watt P-J, Chi A, Stelma T, et al. Targeting the nuclear import receptor Kpnβ1 as an anticancer therapeutic. *Mol Can Therap*. 2016;15:560-573.
103. Yang S-N, Atkinson S-C, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antivir Res*. 2020;177:104760.

104. Caly L, Druce J-D, Catton M-G, Jans D, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir Res*. 2020;178:104787.
105. Jans D-A, Martin A-J, Wagstaff K-M. Inhibitors of nuclear transport. *Curr Opin Cell Biol*. 2019;58:50-60.
106. Lv C, Liu W, Wang B, et al. Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. *Antivir Res*. 2018;159:55-62.
107. Vuong W, Khan MB, Fischer C, et al. Feline coronavirus drug inhibits the main protease of SARS-CoV-2 and blocks virus replication. *Nat Commun*. 2020;11(1):4282.
108. Sacco MD, Ma C, Lagarias P, et al. Structure and inhibition of the SARS-CoV-2 main protease reveals strategy for developing dual inhibitors against Mpro and cathepsin L. *Sci Adv*. 2020;6:eabe0751.
109. Harcourt BH, Jukneliene D, Kanjanahaluethai A, et al. Identification of severe acute respiratory syndrome coronavirus replicase products and characterization of papain-like protease activity. *J Virol*. 2004;78:13600-13612.
110. Shin D, Mukherjee R, Grewe D, et al. Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. *Nature*. 2020;587:657-662.
111. Rut W, Lv Z, Zmudzinski M, et al. Activity profiling and crystal structures of inhibitor-bound SARS-CoV-2 papain-like protease: A framework for anti–COVID-19 drug design. *Sci Advanc*. 2020;6(42):eabd4596.
112. ClinicalTrials.gov [Internet]. *Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)*, Identifier NCT04261517. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04261517. Accessed March 12, 2020.
113. *Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV)*, Identifier NCT04303507. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04303507?term=NCT04303507&draw=2&rank=1. Accessed March 12, 2020.
114. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Eng J Med*. 2020;382(19):1787-1799.
115. ClinicalTrials.gov [Internet]. *The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection (ELACOI)*, Identifier NCT04252885. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/study/NCT04252885. Accessed March 12, 2020.
116. Cao Y-C, Deng Q-X, Dai S-X. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. *Trav Med Infect Dis*. 2020;35:101647.
117. ClinicalTrials.gov [Internet]. *A Prospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia*, Identifier NCT04255017. Bethesda, MD: National Library of Medicine (US); 2020. https://www.clinicaltrials.gov/ct2/show/NCT04255017. Accessed March 12, 2020.
118. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering*. 2020;6(10):1192-1198.
119. ClinicalTrials.gov [Internet]. *Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquin for Treatment of COVID-19: A Randomized Control Trial (THDMS-COVID19)*, Identifier NCT04303299. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04303299. Accessed March 12, 2020.
120. Habib MAG. General overview of coronavirus disease 2019 (COVID-19): A summary of evidence. *Asian J Immunol*. 2019;2020:24-33.
121. Buonfrate DI, Salas-Coronas J, Muñoz J, et al. Multiple-dose versus single-dose ivermectin for Strongyloides stercoralis infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomized controlled superiority trial. *Lancet Infect Dis*. 2019;19:1181-1190.
122. ClinicalTrials.gov [Internet]. *The Efficacy and Safety of Thalidomide Combined with Low-Dose Hormones in the Treatment of Severe Covid-19*, Identifier NCT04273581. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04273581?term=NCT04273581&draw=2&rank=1. Accessed March 12, 2020.
123. ClinicalTrials.gov [Internet]. *Vitamina C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia*, Identifier NCT04264533. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04264533?term=NCT04264533&draw=2&rank=1. Accessed March 12, 2020.
124. ClinicalTrials.gov [Internet]. *Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV (DACO-nCoV)*, Identifier NCT04252274. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04252274. Accessed March 12, 2020.
125. Belhadi D, Peiffer-Smadja N, Lescure FX, Yazdanpanah Y, Mentré F, Laouénan C. A brief review of antiviral drugs evaluated in registered clinical trials for COVID-19. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.18.20038190
126. Arabi YM, Mandourah Y, Al-Hameed F, et al. Saudi critical care trial group. corticosteroid therapy for critically Ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197:757-767.
127. ClinicalTrials.gov Identifier: NCT04273763. 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 February 18, 2020.
128. ClinicalTrials.gov Identifier: NCT04280588. Efficacy of Fingolimod in the Treatment of New Coronavirus Pneumonia (COVID-19). https://clinicaltrials.gov/ct2/show/NCT04280588. Accessed February 21, 2020.
129. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nature Med*. 2020;26:450-452.
130. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect*. 2020;9:382-385.
131. Xia S, Liu M, Wang C, et al. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. *Cell Res*. 2020;30:343-355.
132. Mina F, Rahman M, Das S, Karmakar S, Billah M. Potential Drug Candidates Underway Several Registered Clinical Trials for Battling COVID-19.
133. White N, Watson JA, Hoglund RM, Chan XHS, Cheah PY, Tarning J. COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. *PLOS Med.* 2020;17(9):e1003252.

134. Wellems TE, Plowe CV. Chloroquine-resistant malaria. *J Infect Dis*. 2001;184:770-776.
135. Li P, Zheng Y, Chen X. Drugs for autoimmune inflammatory diseases: from small molecule compounds to anti-TNF biologics. *Front Mincrobiol*. 2017;8:460.
136. Raoult D. Host factors in the severity of Q fever. *Ann New York Acad Sci*. 1990;590:33-38.
137. Gao L, Jiang D, Wen X-S, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. *Resp Res*. 2020;21:1-7.
138. Olofsson S, Bergström T. Glycoconjugate glycans as viral receptors. *Ann Med*. 2005;37:154-172.
139. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotech*. 2020;38:379-381.
140. Sharfstein JM, Becker SJ, Mello M-M. Diagnostic testing for the novel coronavirus. *JAMA*. 2020;323:1437-1438.
141. Ko WC, Rolain JM, Lee NY, et al. Remdesivir for SARS-CoV-2 pneumonia. *Int J Antimicrob Agents*. 2020;5(4):105933.
142. Dyer O. Two Ebola treatments halve deaths in trial in DRC outbreak. *BMJ* 2019;366:15140.
143. Drożdżal S, Rosik J, Lechowicz K, et al. FDA approved drugs with pharmacotherapeutic potential for SARS-CoV-2 (COVID-19) therapy. *Drug Resist Updates*. 2020;53:100719.
144. Verma HK, Merchant N, Verma MK, et al. Current Updates on the European and WHO Registered Clinical Trials of Coronavirus Disease 2019 (COVID-19). *Biomed J*. 2020;43(5):424-433.
145. MERS-CoV Infection Treated With A Combination of Lopinavir /Ritonavir and InterferonBeta-1b. https://clinicaltrials.gov/ct2/show/NCT02845843. Accessed May 20, 2020.
146. Kim UJ, Won E-J, Kee SJ, Jung SI, Jang HC. Case report Combination therapy with lopinavir/ritonavir, ribavirin and interferon-α for Middle East respiratory syndrome. *Antivir Ther*. 2016;21:455-459.
147. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med*. 2019;381(24):2293-2303.
148. Gordon CJ, Tchesnokov EP, Woolner E, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biolog Chem*. 2020;295:6785-6797.
149. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56(1):105949.
150. Zhonghua J, He H, Xi H, Zhi Z. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. 2020;43:E019.
151. Pongpirul W-A, Pongpirul K, Ratnarathon A-C, Prasithsirikul W. Journey of a Thai taxi driver and novel coronavirus. *New Eng J Med*. 2020;382:1067-1068.
152. Yu M, Ismail M-M, Qureshi M-A, Dearth R-N, Barnes H-J, Saif Y-M. Viral agents associated with poult enteritis and mortality syndrome: the role of a small round virus and a turkey coronavirus. *Avian Dis*. 2000;1:297-304.
153. Holshue M-L, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med*. 2020;382(10):929-936.
154. Del R, Malani PN. COVID-19—new insights on a rapidly changing epidemic. *JAMA*. 2020;323:1339-1340.
155. Shereen M-A, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *J Adv Res*. 2020;24:91-98.
156. Time and Date AS. *Past Weather in Wuhan, Hubei, China*. Stavanger, 2020.
157. GISAID Initiative. Genomic epidemiology of BetaCoV 2019–2020.
158. Wang SX, Wang Y, Lu YB, et al. Diagnosis and treatment of novel coronavirus pneumonia based on the theory of traditional Chinese medicine. *J Integr Med*. 2020;18(4):275-283. https://doi.org/10.1016/j.joim.2020.04.001
159. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res*. 2020;7(1):1-23.
160. Zong Y, Ding ML, Jia KK, Ma ST, Ju WZ. Exploring the active compounds of Da-Yuan-Yin in treatment of novel coronavirus (2019-nCoV) pneumonia based on network pharmacology and molecular docking method. *Chin Trad Herb Drugs*. 2020;4(51):836–844.
161. Niu M, Wang R, Wang Z, et al. Rapid establishment of traditional Chinese medicine prevention and treatment for the novel coronavirus pneumonia based on clinical experience and molecular docking. *Chin J Chin Mater Med*. 2020;45(6):1-8.
162. Li C-Y, Zhang X-Y, Liu S, Shang H. Current evidence and research prospects of Xuebijing injection in treating novel coronavirus-infected pneumonia (COVID-19). *World Sci Technol Modern Tradit Chin Med Mater Med*. 2020;19:2-19.
163. Luo H, Tang QL, Shang YX, et al. Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. *Chin J Integr Med*. 2020;26(4):243-250.
164. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Inter Med*. 2015;163:519-528.
165. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *MedRxiv*. 2020. https://doi.org/10.1101/2020.02.06.20020974
166. Russell B, Moss C, Rigg A, Van MH. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedicalscience* 2020;30:1023.
167. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*. 2019;23:99.
168. WHO. https://www.who.int/docs/default-source/coronaviruse/mental-health-considerations.pdf?sfvrsn=6d3578af_8. Accessed March 15, 2020.
169. Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol*. 2020;2(6):e358-e367.
170. Villar J, Confalonieri M, Pastores SM, et al. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. *Crit Care Explor*. 2020;2(4):e0111.
171. Polak SB, Van Gool IC, Cohen D, et al. A systematic review of pathological findings in COVID-19: a pathophysiological

timeline and possible mechanisms of disease progression. *Mod Pathol*. 2020;33(11):2128-2138.

172. Alijotas-Reig J, Esteve-Valverde E, Belizna C, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: a comprehensive review. *Autoimmun Rev*. 2020;19(7):102569.
173. Jiang S, Liu T, Hu Y, et al. Efficacy and safety of glucocorticoids in the treatment of severe community-acquired pneumonia: a meta-analysis. *Medicine (Baltimore)*. 2019;98(26):e16239.
174. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276.
175. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-550.
176. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med*. 2017;45:2078-2088.
177. ClinicalTrials.gov [Internet]. *A Study To Evaluate The Efficacy And Safety Of Pirfenidone With Novel Coronavirus Infection*, Identifier NCT04282902. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04282902?term=NCT04282902&draw=2&rank=1. https://clinicaltrials.gov/ct2/show/NCT04282902?term=NCT04282902&draw=2&rank=1altrials.Gov. Accessed March 12, 2020.
178. Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID19. https://clinicaltrials.gov/ct2/results?cond=NCT04315298. Accessed March 19, 2020.
179. Cherin P. Treatment of inclusion body myositis. *Curr Opin Rheumatol*. 1999;11(6):456-461.
180. Varadarajan S, Balaji TM, Sarode SC, et al. EMMPRIN/BASIGIN as a biological modulator of oral cancer and COVID-19 interaction: novel propositions. *Med Hypoth*. 2020;143:110089.
181. ClinicalTrials.gov [Internet]. *The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia*, Identifier NCT04261426. Bethesda, MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04261426. Accessed March 12, 2020.
182. Kim SS, Kaplowitz S, Johnston MV. The effects of physician empathy on patient satisfaction and compliance. *Eval Health Prof*. 2004;27:237-251.
183. Arabi Y, Balkhy H, Hajeer AH, et al. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *Spring Plus*. 2015;4:1-8.
184. Strehle EM, Shabde N. One hundred years of telemedicine: does this new technology have a place in paediatrics? *Arch Dis Childhood*. 2006;91:956-959.
185. Duffy S, Lee T-H. In-person health care as option B. *N Engl J Med*. 2018;378:104-106.
186. Gainer RS, Vergnaud G, Hugh-Jones ME. A Review of Arguments for the Existence of Latent Infections of Bacillus anthracis, and Research Needed to Understand their Role in the Outbreaks of Anthrax. *Microorga*. 2020;8:800.
187. Leite H, Hodgkinson IR, Gruber T. New development: 'Healing at a distance'—telemedicine and COVID-19. *Pub Money Manage*. 2020;10:1-3.
188. Fisk M, Livingstone SW. Pit, Telehealth in the Context of COVID-19: Changing Perspectives in Australia, the United Kingdom, and the United States. *J Med Int Res*. 2020; 22:e19264.
189. Gavidia M. https://www.ajmc.com/focus-of-the-week/telehealth-during-covid19-how-hospitals-healthcare-providers-are-optimizing-virtual-care. Accessed March 14, 2020.
190. COVID Symptom Study. Zoe Global Limited Health & Fitness. https://play.google.com/store/apps/details?id=com.joinzoe.covid_zoe&hl=en_IN. Accessed March 13, 2020.
191. Rosa SG, Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. *Rev Panam Salud Publica*. 2020;20:44.
192. Newfield C. New medical indications for thalidomide and its derivatives. *Sci J Lander College of Arts and Sci*. 2018;12(1):3.
193. ClinicalTrials.gov [Internet]. *The Efficacy and Safety of Thalidomide Combined With Low-dose Hormones in the Treatment of Severe New Coronavirus (COVID-19) Pneumonia: a Prospective, Multicenter, Randomized, Double-blind, Placebo, Parallel Controlled Clinical Study*. https://clinicaltrials.gov/ct2/show/NCT04273581. Accessed February 18, 2020.
194. ClinicalTrials.gov [Internet]. *Efficacy and Safety of IFN-α2β in the Treatment Of Novel Coronavirus Patients*, Identifier NCT04293887. Bethesda,MD: National Library of Medicine (US); 2020. https://clinicaltrials.gov/ct2/show/NCT04293887?term=NCT04293887&draw=2&rank=1. https://clinicaltrials.gov/ct2/show/NCT04293887?term=NCT04293887&draw=2&rank=1. Accessed February 25, 2020.
195. ClinicalTrials.gov [Internet]. *Randomized, Open, Blank Control Study on the Efficacy and Safety of Recombinant Human Interferon α1β in the Treatment of Patients With New Type of Coronavirus Infection in Wuhan*. https://clinicaltrials.gov/ct2/show/NCT04293887. Accessed March 3, 2020.
196. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov*. 2020;19(3):149-150.
197. Zumla O, Dar R, Kock M, et al. Taking forward a 'One Health' approach for turning the tide against the Middle East respiratory syndrome coronavirus and other zoonotic pathogens with epidemic potential. *Int J Infect Dis*. 2016;47:5-9.
198. O'Keefe BR, Giomarelli B, Barnard DL, et al. Broad-spectrum in vitro activity and in vivo efficacy of the antiviral protein griffithsin against emerging viruses of the family Coronaviridae. *J Virol*. 2010;84(5):2511-2521.

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