Potential Drug Candidates Underway Several Registered Clinical Trials for Battling COVID-19

Fahmida Mina[1], Md. Rahman[1], Sabuj Das[1], Sumon Karmakar[1], and Mutasim Billah[1]

[1]University of Rajshahi

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Abstract

The emergence of new type of viral pneumonia cases in China, on December 31, 2019; identified as the cause of human coronavirus, labeled as "COVID-19," took a heavy toll of death and reported cases of infected people all over the world, with the potential to spread widely and rapidly, achieved worldwide prominence but arose without the procurement guidance. There is an immediate need for active intervention and fast drug discovery against the 2019-nCoV outbreak. Herein, the study provides numerous candidates of drugs (either alone or integrated with another drugs) which could prove to be effective against 2019-nCoV, are under different stages of clinical trials. This review will offer rapid identification of a number of repurposable drugs and potential drug combinations targeting 2019-nCoV and preferentially allow the international research community to evaluate the findings, to validate the efficacy of the proposed drugs in prospective trials and to lead potential clinical practices.

Introduction

A new type of viral pneumonia cases occurred in Wuhan, Hubei Province in China, on December 31, 2019; named "COVID-19" on January 12, 2020 by the World Health Organization (WHO) [1]. Approximately, 292,893 people died as a result of the COVID-19 outbreak, 4,342,685 cases had been confirmed in 212 countries and territories till May 13, 2020. The fatality rate of COVID-19 remains under assessment [2]. However, infections of human coronavirus had resulted in lethal endemics, which include endemic SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) [3]. CoV infection begins with the interaction of the receptor binding domain located in the spike protein (S protein) and target receptor on the host cell surface, such as, Angiotensin Converting Enzyme 2 (ACE2) for SARS-CoV and Dipeptidyl Peptidase-4 (DPP4) for MERS-CoV [4]. Compared to SARS-CoV, the novel coronavirus (2019-nCoV) uses ACE2 as its host-entry receptor. Binding between the receptor-binding domain in S protein and the cellular receptor, mediates membrane fusion and starts the COVID-19 life cycle [5]. S protein on the viral membrane plays a critical role in virus entry and is the key antigenic factor responsible for inducing the immune response of the host [6]. For 2019-nCoV, in addition to knowing the COVID-19 Spike protein (S protein) sequences (GenBank: MN908947.3), there are no studies on how immunogenic this specific protein can go beyond surrogate comparisons to SARS and MERS, which restrict the possible capacity to generate a vaccine quickly [7]. Since it is a respiratory syndrome that has never been seen before and with the potential to spread extensively and rapidly, it gained the attention of the world but without the manual of treatment and management [8]. Several national and international research groups are working on vaccine production and drug repurposing to prevent and treat the 2019-nCoV, but successful vaccines and drugs are still not available. Active prevention and drug discoveries approaches for the 2019-nCoV outbreak are urgently needed [9, 10]. This review will offer an accumulate information to the scientific research community about numerous potential candidates of repurposable drugs that can provide a synergistic effect in potentially treating 2019-nCoV/SARS-CoV-2.

Drug candidates and their progression against 2019-nCoV

As 2019-nCoV has labelled ongoing pandemic, causing a heavy toll of death due to its rapid transmission, the discovery of drugs against 2019-nCoV is therefore a very urgent priority. However, there are no successful drugs currently targeted for 2019-nCoV / SARS-CoV-2. Drug repurposing, representing from existing drugs as an active drug development approach, could cut the time and reduce the cost compared to de novo drug discovery. Following is the accumulated information of potential candidates of drugs screened against 2019-nCoV/SARS-CoV-2.

Remdesivir

Remdesivir (GS-5734) is an adenine derivative phosphoramidate prodrug with a chemical structure similar to that of tenofovir alafenamide, an approved inhibitor of HIV reverse transcriptase. Remdesivir has broad-effects in cell cultures and animal models against RNA viruses, such as - MERS and SARS, and has been checked for Ebola in a clinical trial. A recent research confirmed that Remdesivir inhibited 2019-nCoV, when tested in concentrations of EC50 = 0.77 µM in Vero E6 cells [10] One US patient with 2019-nCoV was reported to get recovered after receiving intravenous remdesivir in January 6, as trials in patients with 2019-nCoV (NCT04252664 and NCT04257656) were initiated in early February to evaluate intravenous Remdesivir (200 mg on day 1 and 100 mg once daily for 9 days), with estimated completion dates in April 2020 [11]. Notably, Remdesivir (EC50 = 0.77 µM; CC50 > 100 µM; SI > 129.87) at low-micromolar concentration, effectively blocked virus infection and showed high SI [12]. Preliminary data suggested that Remdesivir also effectively blocked virus infection in a human cell line (Huh-7 cells of human liver cancer), which is immune to 2019-nCoV and currently, it is in the Phase III of clinical trial established by China.

Favipiravir

Favipiravir (T-705), a guanine analogue, effectively inhibits the RNA-dependent RNA polymerase of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus and enterovirus, adding a recent study, reported its activity against 2019-nCoV [10]. Patients with 2019-nCoV are being recruited in randomized trials to evaluate the efficacy of favipiravir plus interferon-α (ChiCTR2000029600) and favipiravir plus baloxavir-marboxil (an approved influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544) [13]. Although, EC50 value of Favipiravir in Vero E6 cells was as high as 67 µM. It wasreported to reduce viral infection of 2019-nCoV in (EC50 = 61.88 µM, CC50 > 400 µM, SI > 6.46) concentrations [14] suggesting further *in vivo* studies to be screened against 2019-nCoV to test the efficacy of this antiviral nucleoside.

Ribavirin

Ribavirin is a guanine derivative approved for treating Human coronavirus (HCV) and respiratory syncytial virus (RSV), evaluated in patients with SARS and MERS, but it has side effects, such as anaemia might prove severe at high doses, [12] reported to be rapidly and extensively absorbed following oral administration, and whether it could offer sufficient potency against 2019-nCoV is uncertain [15]. Ribavirin, in high concentrations such as (Half- Effective Concentration (EC50) = 109.50 µM, Half- Concentration (CC50) > 400 µM, Selectivity Index (SI) > 3.65) was needed to minimize viral infection [10] and, according to preliminary results, may prove to be resistance to COVID-19.

Pyrazofurin

Pyrazofurin (Pyrazomycin) is a natural product present in Streptomyces candidus, a Ribavirin derived nucleoside analog. It has antibiotic, antiviral, and anti-cancer properties but due to extreme side effects, it was not effective in human clinical trials. Nevertheless, it continues to be the focus of ongoing research as a possible 2019-nCoV drug, or as a blueprint for improved synthetic derivatives [16-22].

Chloroquine

Chloroquine, a commonly used anti-malarial and autoimmune disease medication, has recently been identified as a potential wide-spectrum antiviral drug [23-24]. Chloroquine is known to block infection with the virus by growing the endosomal pH needed for virus / cell fusion, as well as interfering with the glycosylation of SARS-CoV cell receptors [25]. In addition to its antiviral activity, chloroquine has an immune-modulating

activity which can synergistically increase its in vivo antiviral impact. Following the discovery in China of in vitro chloroquine activity against SARS-CoV-2, 50% and 90% effective concentrations of Vero E6 cells (EC50=1,13 μM and EC90=6,90 μM) were discovered during culture tests [12]. Chloroquine, an authorized immune modulator, shows inhibitory activity against 2019-nCoV (EC50 = 1.13μM in Vero E6 cells) [26] and is tested in an open-label trial (ChiCTR2000029609) [27].

Hydroxychloroquine

Hydroxychloroquine (HCQ) sulfate, a derivative of Chloroquine (CQ), was first synthesized in 1946 by inserting a hydroxyl group into CQ and was shown to be much less (~40%) toxic than CQ in animals[13]. More significantly, HCQ is now commonly available for the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. Since CQ and HCQ share similar chemical structures and mechanisms to serve as a weak base and immune-modulator, the idea that HCQ may be a potent candidate for treating SARS-CoV-2 infection is simple to conjure up [28]. As of 23 February 2020, seven registries of clinical trials have been listed in the Chinese Clinical Trial Registry (http:/www.chictr.org.cn) to use HCQ for COVID-19 diagnosis. The experimental evidence still lacks whether HCQ is as effective as CQ in the treatment of SARS-CoV-2 infection [29]. Hydroxychloroquine on viruses is generally the same as chloroquine because the action mechanism of these two molecules is similar, so researchers are more inclined to administer hydroxychloroquine for long periods, which will therefore be the first option in the treatment of SARS-CoV-2. Hydroxychloroquine performed pharmacology based pharmacokinetics (PBPK) modelling to evaluate its activity in the lung. *In vitro* analyses in Vero cells demonstrated that the potency of hydroxychloroquine (EC50 of 0.72 μM) was greater than that of Chloroquine against 2019-nCoV.

Angiotensin Converting Enzyme 1 (ACE1)

Angiotensin Conversion Enzyme 1 inhibitors (ACE-1 inhibitors), such as enalapril and ramipril, and angiotensin receptor antagonists (colloquially known as angiotensin blockers or ARBs), such as candesartan and valsartan, could be of use in the prevention and treatment of the symptoms of coronavirus SARS-CoV-2(also known as 2019-nCoV), the cause of the infection known as COVID 19 [30]. At the moment (as of 21 March 2020) three related trials are listed on the ICTRP website of the WHO, the International Clinical Trials Registry Portal, as being planned or under way in China. The first, entitled "Clinical characteristics difference between patients with and without ACE1 treatment with 2019-nCoV infection in China" was published on 12 February and is stated to be recruiting; it is also listed on clinicaltrials.gov. The other two are not recruiting: "Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for COVID-19 patients" (registered on 21 February but identifiedas withdrawn on clinicaltrials.gov) and "Clinical research on the effects of ACEIs / ARBs on novel coronavirus pneumonia (CoVID-19) infection" (registered on 2 March) [31].

Angiotensin Converting Enzyme 2 (ACE2)

ACE2 is one of the key receptors for SARS-CoV invasion of the human body [32]. Researchers found that SARS-CoV-infected or recombinant wild-type SARS-spike protein-treated mice displayed significantly reduced ACE2 expression in the lung. It has also been shown that the latest outbreak of coronavirus pneumonia (2019-nCoV, SARS-CoV-2) is invading human alveolar epithelial cells and is therefore, could be screened against 2019-nCoV, suggesting further studies [33]. Since ACE2 is abundantly present in human epithelia of the lung and small intestine, may influence the type of therapeutics against 2019-nCoV.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Recent analysis of case-control studies indicates that NSAIDs are associated with higher rates of complications following respiratory tractinfections, including complicated pneumonia, pleural effusions, chronic disease, peritonsillary abscess, spread or suppuration of infection to more than one site [34]. NSAIDs have also been associated with delays in prescribing effective antibiotic treatment to patients requiring admission to hospital. The Food and Drug Administration (FDA) has released a statement on the use of non- anti-drugs (NSAIDS) in patients with 2019-nCoV. There are insufficient clinical evidences to link the use of

NSAIDs in worsening COVID-19 symptoms, according to the agency [35].

Ibuprofen

Ibuprofen is a propionic acid-derived non-steroidal anti-inflammatory drug (NSAID), and is known to be the first propionic. The formula of Ibuprofen is 2-(4-isobutylphenyl) propionic acid, originally discovered in 1960, while looking for a safer alternative of aspirin. Ibuprofen was eventually patented in 1961, and this drug was first introduced in the UK in 1969 and in the USA in 1974 against rheumatoid arthritis. It was the first NSAID available over the counter [36]. The ibuprofen is given as a racemic mixture on the available drugs. The R-enantiomer, undergoes comprehensive interconversion to the S-enantiomer in vivo through the action of racemase alpha-methylacyl-CoA, when its administered. It is commonly proposed; in particular, that the S-enantiomer is capable of generating greater pharmacological activity than the R-enantiomer [37], and its ability against 2019-nCoV is unclear and could be screened for further analysis.

Umifenovir

Umifenovir, an indole-based, hydrophobic, dual-acting active antiviral / host-targeting agent, used for influenza and other respiratory infections treatment and prophylaxis. The ability of Umifenovir to exert antiviral effects across several mechanisms has led to extensive work into its use for a number of enveloped and non-enveloped RNA and DNA viruses, including Flavivirus, Zika virus, Foot-and-mouth disease, Lassa virus, Ebola virus, Herpes simplex, Hepatitis B and C virus, Chikungunya virus, Reovirus, Hantaan virus and Coxsackie virus B5 [38]. Umifenovir is currently being investigated in conjunction with currently available and investigational HIV therapies as a potential treatment and prophylactic agent for COVID-19 caused by SARS-CoV2 infections [37].

Nafamostat mesylate

Nafamostat mesylate, a synthetic serine protease inhibitor, that contains antiviral and anti-cancer properties, used to treat acute pancreatitis. It is apowerful MERS- inhibitor that obstructs membrane fusion, was found inhibitive to 2019-nCoV infection when tested in EC50 = 22,50 µM, CC50 > 100 µM, SI> 4,44 concentration rate, suggested for further studies [10]. As per the researchers at the University of Tokyo, Nafamostat will prevent the fusion of the virus envelope with the host cell surface proteins, the first step in infection with SARS-CoV-2 at one-tenth of the concentration provided by Camostat mesylate (Foypan), which was recently described by a German group as a SARS-CoV-2 inhibitor [39].

Nitazoxanide

It is a commercial antiprotozoal agent with an antiviral capacity against a wide range of viruses, including human and animal coronaviruses, reported to be resistance to 2019-nCoV, at low micromolar concentrations, such as - EC50 = 2.12 µM; CC50 > 35.53 µM; SI > 16.76 [10]. Further in vivo evaluation of this medication is suggested against 2019-nCoV infection. Authorized for diarrhea therapy, Neitazoxanide has the potentiality to inhibit 2019-nCoV and thus, needs clinical trials to determine the antiviral efficacy of this drug [12] [15].

Oseltamivir

Oseltamivir is a neuraminidase antiviral agent used to treat and prophylaxis influenza virus A (including pandemic H1N1) and B infection. Oseltamivir exercises its antiviral function by inhibiting the function of the viral neuraminidase enzymelocated on the virus surface, which inhibits host cell budding, viral replication, and infectivity [37]. According to the CDC, data from clinical trials and observational studies have shown that early antiviral therapy can shorten the length of symptoms of fever and illness, and reduce the risk of other health complications (including pneumonia and respiratory failure).Oseltamivir is being screened against 2019-nCoV and is undergoing clinical trial [40]. The authors do not suggest the use of Oseltamivir for COVID-19, as there are no data that suggest *in vitro* activity of oseltamivir against 2019-nCoV.

TMC-310911

TMC-310911 (also known as ASC-09) is a novel investigational protease inhibitor (PI) that has been investigated for use in HIV-1 infections and is structurally similar to the darunavir. TMC-310911 has demonstrated potential activity against a number of HIV-1 strains, including multi-PI-resistant strains,and may be less likely to produce resistance, making it a potentially suitable therapy for patients who are both native to care and experienced with PI. The Hangzhou-based Ascletis Pharma, applied to the Chinese authorities in January to study Ritonavir and TMC-310911 (two HIV protease inhibitor) in clinical trials for treatment of COVID-19. TMC-310911 as a possible therapy for COVID-19 caused by SARS-CoV-2 in conjunction with other HIV therapies and antivirals.TMC-310911 is currently being investigated, in combination with other HIV therapies and antivirals, as a potential treatment for 2019-nCoV [41][42].

Lopinavir and Ritonavir

In patients infected with 2019-nCoV, clinical trials (e.g., ChiCTR2000029539) were initiated to study HIV protease inhibitors such as Lopinavir and Ritonavir. Lopinavir and Ritonavir were initially suspected to inhibit SARS and MERS 3-chymotrypsin-like protease and seemedto be correlated in a non-randomized open-label trial 2, with improved clinical outcomes of SARS patients. Lopinavir/Ritonavir (dosages: 200mg/50mg/capsule,2 capsules each time,2 times/day, by oral administration, treated no more than 10 days) guidelines (version 6) for treatment of COVID-19. It was revealed that Lopinavir and Ritonavir were associated with significant clinical benefit (less adverse clinical outcomes) among SARS-CoV patients [43]. The combination of Lopinavir and Ritonavir is currently a recommended antivirus regimen approved by the National Health Commission of the People's Republic of China in the latest form of Diagnosis and Treatment of Pneumonia Caused by 2019-nCoV (version 5) [44].

ShuFengJieDu Capsule (SFJDC)

SFJDC is a Traditional Chinese Medicine (TCM), composed of a total of eight medicinal herbs and proven to be clinically effective for the treatment of upper respiratory tract infections, vastly used for influenza diagnosis in China. This medication is also indicated in the current version of Diagnosis and Pneumonia Treatment of 2019-nCoV Infection Caused by COVID-19 [44] and could be possibly screened against 2019-nCoV [43]. No PK data on human *in vitro*evaluation is currently available for this drug.

Arbidol

Arbidol is an antiviral drug used in Russia and China to treat influenza infections [45]. Arbidol was reported to have been successful*in vitro* against 2019-nCoV at a concentration range of 10-30 μM, by oral administration [43]. In China, a randomized multicenter controlled clinical trial of Arbidol was initiated in patients with 2019-nCoV (ChiCTR2000029573) [46] and further studies are in process.

Interferon alfa-2a and alfa-2b

Pegylated Interferon alfa-2a and alfa-2b, approved for the treatment of Hepatitis B virus (HBV) and Human Coronavirus (HCV), may be used to induce innate antiviral responses in patients infected with 2019-nCoV, and studies involving interferons, such as an approved anti-HCV combination of pegylated interferon plus Ribavirin, have been initiated (ChiCTR2000029387). Whether a pegylated interferon and a nucleoside compound could work synergistically against 2019-nCoV however is unclear. Their assessment should be closely monitored and dose reduction or discontinuation of therapy may be needed due to several adverse effects associated with subcutaneous interferon therapies [37].

Galidesivir

Galidesivir (BCX4430), an adenosine analog originally developed for human coronavirus (HCV), is currently undergoing early-stage clinical studies examining its protection in healthy subjects and its effectiveness against yellow fever, and has demonstrated antiviral activity in preclinical studies against many RNA viruses, like SARS and MERS2, and possibilities are that facilities with sufficient bio-containment capabilities may screen Galidesivir against 2019-nCoV and ongoing human pharmacokinetics will be available after its clinical trial [13] [15] [37].

Penciclovir

Penciclovir, a synthetic acyclic guanine derivative, containing antiviral activity, functions as a Herpes Simplex Virus (HSV) DNA inhibitor, is one of the drugs tested against 2019-nCoV. High nucleoside analog concentrations of Penciclovir (EC50 = 95.96 μM, CC50 > 400 μM, SI > 4.17) [10] were needed to reduce the viral infection and could further be examined as a COVID-19 drug [14] [15].

Disulfiram

Disulfiram, an approved medication for the treatment of alcohol dependence, has been reported to inhibit MERS and SARS papain-like protease in cell cultures but there is no clinical evidence of it. However, it is debatable, whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like, as well as, papain-like proteases of 2019-nCoV, although, Disulfiram could possibly be screened against 2019-nCoV by facilities that have sufficient capabilities of bio-containment [37][47].9-nCoV / SARS-CoV-2 outbreak.

Griffithsin

Griffithsin, a lectin derived from red algae, binds on the surface of various viral glycoproteins to oligosaccharides including HIV glycoprotein 120 and SARS-CoV spike glycoprotein2. Griffithsin has low cytotoxicity, is likely to interfere with any coronavirus spike protein due to it is highly glycosylated nature, and may impede the role of coronavirus spike protein. GRFT has been shown to inhibit SARS-CoV replication and cytopathicity, as well as other coronaviridae viruses [48] [49]. In particular, in Vero 76 cells, GRFT inhibited various strains of SARS – infection with a low nanomolar EC50 with limited toxicity on control cells. GRFT can bind with glycans to the surface of the glycoprotein (S protein). A total of three GRFT molecules are capable of binding the S with very high affinity in a dose, a lower number compared to HIV which is presumably due to the lower number of highglycans on the S surface. Interestingly, such an association does not restrict the binding of SARS-CoV S glycoprotein to the human angiotensin I conversion enzyme 2 (ACE2) host cell [49]. Griffithsin has been studied as a gel or enema for HIV prevention in phase I trials, but the efficacy and delivery mechanisms of spike inhibitors should be re-evaluated for the 2019-nCoV treatment or prevention.

Cobicistat

Cobicistat (formerly GS-9350) is a recent pharmacokinetic enhancer with no antiviral function, which still inhibits CYP3A, although more specifically than *in vitro* Ritonavir [51]. Cobicistat is indicated in conjunction with other antiretroviral agents to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in the care of HIV-1 infection. Growing systemic antiretroviral exposure (ARVs) without increasing dose allows for improved patient outcomes and a reduced profile of side effects. In Phase I trials, cobicistat was shown to be a comparable therapeutic enhancer to ritonavir in combination with atazanavir, integrase inhibitor elvitegravir, or midazolam (a CYP3A test substrate) [52]. An atazanavir / cobicistat dependent regimen provided efficacy and protection comparable to an atazanavir / ritonavir regimen in phase II studies [50]. However, a randomized trial at the Shanghai Public Health Clinical Center (SPHCC) evaluating Cobicistat for COVID-19 has shown that it has not been successful and can be reassessed.

Darunavir

The Chinese authorities have indicated that Darunavir against 2019-nCoV may be successful. *In vitro* cell studies have shown that Darunavir can effectively inhibit replication of the new strain, at a concentration of 300 micromolar, according to preliminary research Darunavir, in conjunction with cobicistat, will be used in patients with COVID-19 pneumonia in trial number NCT04252274 [50]. Such a mixture is currently approved by the United States Food and Drug Administration (FDA) in AIDS treatment. Darunavir is another HIV protease inhibitor and cobicistat, like ritonavir, is a booster to enhance the pharmacokinetics and pharmacodynamics of darunavir by inhibiting cytochrome P450 (CYP3A) [53] [54]. Due to in vitro evidence that supports its ability to fight this infection, Darunavir is being studied as a potential cure for SARS-CoV-2, the coronavirus responsible for COVID-19[52]. Clinical trials are under progress and are

scheduled to end in August 2020.Although, HIV-1 protease inhibitor is currently being evaluated in a clinical trial (NCT04252274), but no *in vitro* or human data exist to support its use against 2019-nCoV.

Exploring Current Clinical Trials for Covid-19

As of 2005, the International Committee of Medical Journal Editors (ICMJE) has proposed that all clinical trials be reported in publicly accessible domains before they can be accepted for publication [56]. The implementation of this provision and other efforts to improve transparency in clinical trials has led to such a increasing number of trials being registered in online registries, such as ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform (ICTRP). Logging trials on registries has significantly promoted knowledge sharing in many areas, including research, technique, community of patients, and outcome measures. In addition, if the findings are not released, it means that the trial information remains freely available for analyzation. Under the current global COVID-19 pandemic, we performed an electronic registry review (ClinicalTrials.gov, WHO ICTRP, EU Clinical Trials Register, and Cochrane Central Register of Controlled Trials) to collate all reported therapeutic and preventive procedures under clinical investigation. We hope this will explain recent developments in the investigation and direct possible future strategies. Table -1 & 2 demonstrates interventional therapies and preventive approaches for COVID-19 under clinical review.

Several registered clinical trials are currently being conducted globally to evaluate the efficacy of the drugs against COVID-19 (Table-1 & Table 2)

Table 1: Ongoing Clinical Trials of Potential Drugs for the Treatment of COVID-19 (Antivirals)

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
Clinical trial ID No. (Registry)	Intervention to prevent infection	Participant size	Randomized	Status	Country (Pharma.)
2020-000936-23 (EU-CTR)	**Arm A**: lopinavir/ritonavir **Arm B**: interferon beta 1a **Arm C**: remdesivir	3000	Yes	Recruiting	France
NCT04302766 (ClinicalTrials.gov)	**Arm A**: remdesivir Arm B: standard treatment	Unspecified	Unspecified	Available	USA
NCT04292899 (ClinicalTrials.gov)	**Arm A**: remdesivir Arm B: standard treatment	400	Yes	Recruiting	USA & Asia
NCT04292730 (ClinicalTrials.gov	**Arm A**: remdesivir Arm B: standard treatment	600	Yes	Recruiting	USA & Asia
NCT04280705 (ClinicalTrials.gov)	**Arm A**: remdesivir	394	Yes	Recruiting	USA & South Koria
2020-000841-15 (EU-CTR)	**Arm A**: remdesivir **Arm B**: standard treatment	400	Yes	Recruiting	Worldwide

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Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
2020-000842-32 (EU-CTR)	**Arm A**: remdesivir **Arm B**: standard treatment	600	Yes	Recruiting	Worldwide
NCT04252664 (ClinicalTrials.gov)	**Arm A**: remdesivir	308	Yes	Recruiting	China
NCT04257656 (ClinicalTrials.gov)	**Arm A**: remdesivir	453	Yes	Recruiting	China
NCT04315948 (ClinicalTrials.gov)	**Arm A**: remdesivir **Arm B**: standard treatment	3100	Yes	Recruiting	France
ChiCTR2000029600 (ICTPR)	**Arm A**: favipiravir and interferon alpha Atomisation	90	No	Recruiting	China
ChiCTR2000029544 (ICTPR)	**Arm A**: favipiravir	30	Yes	Not recruiting	China
ChiCTR2000029548 (ICTPR)	**Arm A**: favipiravir	30	Yes	Not recruiting	China
NCT04273763 (ClinicalTrials.gov)	**Arm A**: favipiravir and bromhexine (mucolytic), umifenovir, interferon a2b	60	Yes	Recruiting	China (WanBangDe Pharm. Group)
ChiCTR2000030113 (ICTPR)	**Arm A**: favipiravir	20	Yes	Recruiting	China
ChiCTR2000030254 (ICTPR)	**Arm A**: favipiravir	240	Yes	Recruiting	China
ChiCTR2000030987 (ICTPR)	**Arm A**: favipiravir and chloroquine **Arm B**: favipiravir	150	Yes	Recruiting	China
NCT04310228 (ClinicalTrials.gov)	**Arm A**: favipiravir and tocilizumab **Arm B**: favipiravir	150	Yes	Recruiting	China
JPRN-jRCTs041190120 (ICTPR)	**Arm A**: immediate favipiravir (Day 1–10) **Arm B**: delayed favipiravir (Day 6–15)	86	Yes	Recruiting	Japan

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
ChiCTR2000029996 (ICTPR)	**Arm A**: low-dose favipiravir **Arm B**: medium-dose favipiravir **Arm C**: high-dose favipiravir	60	Yes	Recruiting	China
NCT04303299 (ClinicalTrials.gov)	Arm A: lopinavir/ritonavir and favipiravir	80	Yes	Not recruiting	Thailand
ChiCTR2000030922 (ICTPR)	**Arm A**: ribavirin and interferon alpha 2a **Arm B**: umifenovir and ribavirin	30	Yes	Recruiting	China
NCT04276688 (ClinicalTrials.gov)	**Arm A**: ribavirin + lopinavir/ritonavir + interferon beta 1b	70	Yes	Recruiting	Hong Kong
ChiCTR2000029387 (ICTPR)	**Arm A**: ribavirin and interferon alpha-1b **Arm B**: ribavirin, lopinavir/ritonavir, and interferon alpha-1b	108	Unspecified	Recruiting	China
ChiCTR2000029609 (ICTPR)	**Arm A (mild–moderate):** chloroquine **Arm B (mild–moderate):** lopinavir/ritonavir + chloroquine **Arm C (severe):** chloroquine	205	No	Recruiting	China
NCT04303299 (ClinicalTrials.gov)	**Arm A**: oseltamivir and chloroquine	80	Yes	Not recruiting	Thailand

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
IRCT20100228003449N27 (ICTPR)	**Arm A**: hydroxychloroquine, lopinavir/ritonavir, and interferon beta 1b **Arm B**: hydroxychloroquine and lopinavir/ritonavir	30	Yes	Recruiting	Iran
IRCT20100228003449N28 (ICTPR)	**Arm A**: hydroxychloroquine, lopinavir/ritonavir, and interferon beta 1a **Arm B**: hydroxychloroquine and lopinavir/ritonavir	30	Yes	Recruiting	Iran
IRCT20100228003449N29 (ICTPR	**Arm A**: hydroxychloroquine, lopinavir/ritonavir, and sofosbuvir/ledipasvir **Arm B**: hydroxychloroquine and lopinavir/ritonavir	50	Yes	Recruiting	Iran
JPRN-jRCTs031190227 (ICTPR)	**Arm A**: lopinavir/ritonavir and hydroxychloroquine	50	Unspecified	Not recruiting	Japan
NCT04315948 (ClinicalTrials.gov)	**Arm A**: remdesivir **Arm B**: lopinavir/ritonavir **Arm C**: lopinavir/ritonavir and interferon beta 1a **Arm D**: hydroxychloroquine **Arm E**: standard treatment	3100	Yes	Recruiting	France

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
NCT04273763 (ClinicalTrials.gov)	**Arm A**: bromhexine (mucolytic), umifenovir, interferon a2b, and favipiravir **Arm B**: umifenovir and interferon a2b	60	Yes	Recruiting	China
ChiCTR2000030254 (ICTPR)	**Arm A**: favipiravir **Arm B**: umifenovir	240	Yes	Recruiting	China
ChiCTR2000030922 (ICTPR)	**Arm A**: interferon alpha 2a and ribavirin **Arm B**: umifenovir and ribavirin	30	Yes	Recruiting	China
NCT04252885 (ClinicalTrials.gov)	**Arm A**: lopinavir/ritonavir + basic treatment (unspecified) **Arm B**: umifenovir + basic treatment (unspecified)	125	Yes	Recruiting	China
ChiCTR2000029573 (ICTPR)	**Arm A**: umifenovir **Arm B**: Novaferon and umifenovir **Arm C**: lopinavir/ritonavir **Arm D**: umifenovir **Arm E**: novaferon and lopinavir/ritonavir **Arm F**: novaferon and umifenovir	480	Yes	Not recruiting	China
ChiCTR2000029621 (ICTPR)	**Arm A**: umifenovir **Arm B**: standard treatment	380	Yes	Recruiting	China
NCT04254874 (ClinicalTrials.gov)	**Arm A**: umifenovir **Arm B**: umifenovir and pegylated interferon alpha 2b	100	Yes	Recruiting	China

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
NCT04255017 (ClinicalTrials.gov)	**Arm A:** umifenovir **Arm B:** oseltamivir **Arm C:** lopinavir/ritonavir	400	Yes	Recruiting	China
ChiCTR2000029993 (ICTPR)	**Arm A:** umifenovir and Liushen capsule **Arm B:** standard treatment	40	Yes	Recruiting	China
ChiCTR2000029592 (ICTPR)	**Arm A:** umifenovir **Arm B:** without umifenovir	100	Unspecified	Not recruiting	China
NCT04261270 (ClinicalTrials.gov)	**Arm A:** ASC09 and oseltamivir **Arm B:** ritonavir and oseltamivir **Arm C:** oseltamivir	60	Yes	Recruiting	China
NCT04303299 (ClinicalTrials.gov)	**Arm A:** oseltamivir and chloroquine **Arm B:** lopinavir/ritonavir and favipiravir **Arm C:** lopinavir/ritonavir and oseltamivir **Arm D:** lopinavir/ritonavir and oseltamivir	80	Yes	Not recruiting	Thailand
ChiCTR2000029609 (ICTPR)	**Arm A(mild–moderate):** lopinavir/ritonavir **Arm B(mild–moderate):** lopinavir/ritonavir + chloroquine **Arm C (severe):** lopinavir/ritonavir	205	Yes	Recruiting	China

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
ChiCTR2000029600 (ICTPR)	**Arm A**: interferon alpha atomisation **Arm B**: lopinavir/ritonavir and interferon alpha atomisation	90	No	Recruiting	China
NCT04261907 (ClinicalTrials.gov)	**Arm A**: ASC09/ritonavir **Arm B**: lopinavir/ritonavir	160	Yes	Recruiting	China (Ascletis Pharm)
ChiCTR2000029548 (ICTPR)	**Arm A**: baloxavirmarboxil **Arm B**: favipiravir **Arm C**: lopinavir/ritonavir	30	Yes	Not recruiting	China
ChiCTR2000029541 (ICTPR)	**Arm A**: darunavir/cobicistat and thymosin **Arm B**: lopinavir/ritonavir and thymosin **Arm C**: thymosin	100	Yes	Not recruiting	China
NCT04291729 (ClinicalTrials.gov)	**Arm A**: darunavir/ritonavir and atomised interferon **Arm B**: peginterferon a2 **Arm C**: interferon alpha (Novaferon) **Arm D**: lopinavir/ritonavir **Arm E**: atomised interferon + Chinese medicine (unspecified)	50	Yes	Recruiting	China (Ascletis Pharm)
ChiCTR2000030535 (ICTPR)	**Arm A**: ebastine and interferon alpha inhalation and lopinavir **Arm B**: interferon alpha inhalation and lopinavir	100	Yes	Recruiting	China

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
2020-001113-21 (EU-CTR)	**Arm A**: lopinavir/ritonavir **Arm B**: dexamethasone **Arm C**: interferon beta 1a **Arm D**: placebo	2000	Yes	Recruiting	UK
ChiCTR2000029468 (ICTPR)	**Arm A**: lopinavir/ritonavir and emtricitabine/tenofovir **Arm B**: lopinavir/ritonavir	120	Unspecified	Not recruiting	China
ChiCTR2000030166 (ICTPR)	**Arm A**: lopinavir/ritonavir and interferon alpha 2b and Qing-Wen Bai-Du-Yin granules **Arm B**: lopinavir/ritonavir and interferon alpha 2b	20	Yes	Not recruiting	China
ChiCTR2000030218 (ICTPR)	**Arm A**: lopinavir/ritonavir and Xiyanping injection **Arm B**: ritonavir	80	Unspecified	Recruiting	China
ChiCTR2000029539 (ICTPR)	**Arm A**: lopinavir/ritonavir **Arm B**: standard treatment	328	Yes	Recruiting	China
ChiCTR2000029496 (ICTPR)	**Arm A**: Novaferonatomisation inhalation **Arm B**: lopinavir/ritonavir **Arm C**: Novaferon and lopinavir/ritonavir	90	Yes	Recruiting	China
NCT04252274 (ClinicalTrials.gov)	**Arm A**: darunavir and cobicistat **Arm B**: standard treatment	30	Yes	Recruiting	China

Antiviral	Antiviral	Antiviral	Antiviral	Antiviral	Antiviral
NCT04304053 (ClinicalTrials.gov)	**Arm A**: darunavir/cobicistat **Arm B**: isolation	3040	Yes	Recruiting	Spain

Treatment Strategies: Antiviral Treatments

As described briefly earlier, a number of studies have focused on repurposing existingantiviraltherapies, particularly those showing prior effectiveness against SARS-CoV and MERS-CoV. The most popular exploratory antiviral is the combination of lopinavir / ritonavir which appears in 34 investigational studies (Table 1: antivirals). Both drugs act as protease inhibitors, and are commonly used in HIV-1 management [57]. However, due to the rapid catabolism by the cytochrome P450 enzyme system (specifically 3A4 isoenzyme) [57], lopinavir has inadequate oral bioavailability for substantial therapeutic operation. Ritonavir is thus administered concomitantly to suppress this, greatly improving lopinavir's half-life. In 2004, the efficacy of lopinavir / ritonavir against SARS-CoV was investigated and found to be effective compared with a historical control[58].Nevertheless, efficacy was not seen in a randomized open-label study (lopinavir / ritonavir versus standard care) in 199 COVID-19 patients (Clinical Trial Number: ChiCTR2000029308, recruitment target reported as 160 registry participants; Table 1). There was no majorgain in the overall mortality or viral load [59]. Remdesivir is a novel antiviral analog nucleotide, originally developed to treat the Ebola and Marburg viruses [10, 60]. Nonetheless, it does have efficacy against a number of pathogenic viruses, including both in vitro and in vivo models of SARS-CoV and MERS-CoV[10, 61]. Subsequent diagnosis of the first COVID-19 case and subsequent recovery in the U.S.[11], this molecule was of great interest. A number of globally reported trials are currently underway to examine theefficacy of COVID-19 (Table 1: Antivirals). Many other antiviral medications, especially those with action against various influenza subtypes and other RNA viruses are being studied. Which are favipiravir (T-705, Avigan), umifenovir (Arbidol), triazavirin (TZV), and marboxil (Xofluza) baloxavir. Most trials concentrate on medications widely used to treat RNA viruses, such as HCV and HIV. Which include danoprevir / ritonavir, azvudine, ledipasvir / sofosbuvir, sofosbuvir / daclatasvir, darunavir / cobicistat and emtricitabine / tenofovir (Table 1: antivirals). Additionally, 26 studies examine the efficacy of antiviral interferon-based drugs, and interestingly often look at various routes of administration (e.g., nasal).

Table 2: Ongoing Clinical Trials of Potential Drugs for the Treatment of COVID-19

(Antimalarials)

Antimalarial	Antimalarial	Antimalarial	Antimalarial	Antimalarial	Antimalarial
Clinical trial ID No. (Registry)	**Intervention to prevent infection**	**Participant size**	**Randomized**	**Status**	**Country (Pharma.)**
ChiCTR2000030031 (ICTPR)	**Arm A**: chloroquine	120	Yes	Recruiting	China
ChiCTR2000029988 (ICTPR)	**Arm A**: chloroquine **Arm B**: standard treatment	80	Unspecified	Recruiting	China

Antimalarial	Antimalarial	Antimalarial	Antimalarial	Antimalarial	Antimalarial
ChiCTR2000029939 (ICTPR)	**Arm A**: chloroquine **Arm B**: standard treatment	100	Yes	Recruiting	China
ChiCTR2000029975 (ICTPR)	**Arm A**: chloroquine	10	No	Not recruiting	China
ChiCTR2000029837 (ICTPR)	**Arm A**: chloroquine	120	Yes	Not recruiting	China
ChiCTR2000029935 (ICTPR)	**Arm A**: chloroquine	100	No	Recruiting	China
ChiCTR2000029542 (ICTPR	**Arm A**: chloroquine **Arm B**: standard treatment	20	Unspecified	Recruiting	China
ChiCTR2000030718 (ICTPR)	**Arm A**: chloroquine **Arm B**: standard treatment	80	Yes	Recruiting	China
ChiCTR2000029898 (ICTPR)	**Arm A**: hydroxychloroquine **Arm B**: chloroquine	100	Yes	Recruiting	China
NCT04261517 (ClinicalTrials.gov)	**Arm A**: hydroxychloroquine **Arm B**: standard of care	30	Yes	Recruiting	China
ChiCTR2000030054 (ICTPR	**Arm A**: hydroxychloroquine **Arm B**: standard treatment	100	Yes	Not recruiting	China
ChiCTR2000029868 (ICTPR)	**Arm A**: hydroxychloroquine **Arm B**: standard treatment	200	Yes	Recruiting	China
ChiCTR2000029740 (ICTPR	**Arm A**: hydroxychloroquine **Arm B**: standard treatment	78	Yes	Recruiting	China
ChiCTR2000029899 (ICTPR)	**Arm A**: hydroxychloroquine **Arm B**: chloroquine	100	Yes	Recruiting	China

Antimalarial	Antimalarial	Antimalarial	Antimalarial	Antimalarial	Antimalarial
NCT04316377 (ClinicalTrials.gov)	**Arm A**: hydroxychloroquine **Arm B**: standard treatment	202	Yes	Not recruiting	Norway
NCT04315896 (ClinicalTrials.gov)	**Arm A**: hydroxychloroquine **Arm B**: placebo	500	Yes	Not recruiting	Mexico
ChiCTR2000029559 (ICTPR)	**Arm A**: hydroxychloroquine **Arm B**: hydroxychloroquine	300	Unspecified	Recruiting	China
ChiCTR2000029803 (ICTPR)	**Arm A**: hydroxychloroquine (low dose) **Arm B**: hydroxychloroquine (high dose)	320	Yes	Not recruiting	China
ChiCTR2000030082 (ICTPR)	**Arm A**: dihydroartemisinin/ piperaquine tablets combined with antiviral treatment (presumed alpha-interferon + umifenovir) **Arm B**: alpha-interferon + umifenovir	40	Yes	Suspended	China
ChiCTR2000029803 (ICTPR)	**Arm A**: umifenovir (low dose) **Arm B**: umifenovir (high dose)	320	Yes	Not recruiting	China

Treatment Strategies: Antimalarial Treatments

Twenty trials are currently studying the use of chloroquine and hydroxychloroquine anti-malarial drugs (Table 2: Antimalarials). Chloroquine has been found to have important inhibitory effects on the input and in vitro replication of viral cells [10]. An early study of clinical experience with chloroquine care in 100 COVID-19 patients reported both beneficial clinical and virological outcomes [62]. More recently, a non-randomized open-label study investigating the impact of hydroxychloroquine (EU Clinical Trial Numbervii: 2020-000890-25; recruitment target specified as 25 registry participants) published on a cohort of 36 patients [63]. Six days after inclusion in the hydroxychloroquine community compared with control it showed a substantial reduction in nasopharyngeal swab viral positivity. However, 16 patients were assigned as controls in a departure from their registry-described protocol, and six patients received concomitant azithromycin treatment to avoid bacterial superinfection. Patients receiving azithromycin were chosen based on clinical judgment. After 6 days, the subgroup receiving azithromycin all had negative viral swabs, compared to 57% (8/14) of hydroxychloroquine alone and 12.5% (2/16) of control [63]. This research is constrained by its lack of blinding

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and randomization, and low sample size. There is a great deal of interest in chloroquine or hydroxychloroquine for COVID-19 diagnosis, with another 34 studies reported (Table 2: Antimalarials); however, only four reports using a rigorous double-blind randomized controlled study to examine effectiveness.

Conclusion

It is a pivotal time in overcoming the current outbreak of the 2019-nCoV. The decoction of the specified drugs listed should be assessed for their efficacy and safety and stability, and should also be evaluated for the treatment and recovery of patients suffering from the 2019-nCoV in carefully planned clinical trials, either used alone or integrated with other drugs. Many of the potential drugs under different phases of clinical trials (eg: Remdesivir, Lopinavir, Ritonavir, Darunavir, Cobicistat etc. are in phase III, Oseltamivir is in phase IVof clinical trials, and many others are in preclinical stage of trials) can be successful in battling COVID-19 [10][37][43][47]. The vital ethical concern in the COVID-19 setting for the administration of repurposable drugs are experimental and, thus, require ethical or off-label approval of trials [55].We will keep cautiously optimistic before releasing successful clinical trial results as the lessons from a recent public panic buying spree, which revealed results of a preliminary study and induced irrational purchases overnight, should also be taken into account. In this study, our approach will reduce the translational gap between preclinical research results and clinical outcomes, which is a major problem in the rapid production of successful drugs, discovered for the emerging 2019-nCoV / SARS-CoV-2 outbreak.

Declaration of competing interest

The authors declare no conflicts of interest.

Author contributions

Authors	Conceptualization	Data Curation	Resources	Original draft writing	Citation	Editing a
F.B.Mina	Yes	Yes	Yes	Yes	Yes	Yes
M.S.Rahman	Yes	Yes	Yes	No	No	Yes
S.Das	Yes	Yes	Yes	No	Yes	No
S.Karmakar	Yes	No	No	No	No	Yes
M.Billah	Yes	Yes	No	No	Yes	Yes

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