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Repurposable Drug Candidates are Potential Therapeutic Target against Global SARS-CoV-2 Crisis

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ABSTRACT

This review provides a pharmacological approach to combat Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) based on two comprehensive denominations which could be specifically intended for viral replication process by either inhibiting essential genomic viral enzymes or preventing viral entry to human cells. These denominations focused on immune therapies either to improve innate antiviral immune responses or to reduce impairment triggered by underactive inflammatory reactions. A variety of drug candidates are available which can inhibit SARS-CoV-2 infection and replication, comprising serine protease inhibitors: Transmembrane Orotease/Serine Subfamily member 2 (TMPRSS2), camostat mesylate, nafamostat mesylate, and angiotensin-converting enzyme inhibitors. This review is also concerned with identifying drugs and ongoing clinical trials with their mechanisms of action against SARS-CoV-2. Chloroquine and hydroxychloroquine, monoclonal antibody, off-label antiviral drugs, nucleotide analog remdesivir and broad-spectrum antiviral drugs also could be used as inhibitors of SARS-CoV-2. Moreover, non-steroidal anti-inflammatory drugs (NSAIDs), dexamethasone, and antiviral phytochemicals that are currently reachable, can prevent SARS-CoV-2 pandemic morbidity and mortality.

Keywords: COVID-19; Antiviral drugs; NSAIDs; ACE2; Clinical trials

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INTRODUCTION

A viral pneumonia outbreak was reported in Wuhan, Hubei Province, China on 30 December 2019; initially referred to as the novel Coronavirus 2019 (nCoV-2019), officially ratified COVID-19 by the World Health Organization (WHO) on February 12, 2020[1]. However, recently it has been demonstrated that infections of human coronavirus had resulted in lethal endemics, which include endemic SARS-CoV and Middle East Respiratory Syndrome Corona Virus (MERS-CoV). Coronavirus infection commences with the interaction of the binding receptor domain found in the spike protein (S protein) and target receptor on the host cell surface, including SARS-CoV, Angiotensin Converting Enzyme 2 (ACE2) and Middle East Respiratory Syndrome–related Coronavirus (MERS-CoV) dipeptidyl peptidase-4 (DPP4)[2]. SARS-CoV and SARS-CoV-2 S proteins exhibit structural homology and retained ectodomains, therefore earlier strategies used to prevent SARS-CoV through binding to its ACE2 host cell receptor may be applicable, whereas SARS-CoV-2 is also used ACE2 for cell entry[3]. The SARS-CoV-2 used ACE2 as in its host cell entry receptor compared with SARS-CoV. Adhesion between both the S-protein receptor-binding domain and cellular receptor mediates membrane fusion and initiates the SARS-CoV-2 life cycle. S proteins on the viral cell membrane may take a crucial part in virus entry and serve as the main antigenic factor responsible for enhancing the immune response of the host. For the SARS-CoV-2, in addition to recognizing the SARS-CoV-2 spike protein (S protein) sequences (Accession No. MN908947.3), no studies on how immunogenic were conducted this

specific protein can go beyond substitute comparisons to SARS-CoV and MERS-CoV which impede the potential capacity to generate a vaccine immediately[4]. Numerous national and international research groups are currently focused on the development of Western medicines, natural products, and traditional Chinese medicines[5] and repurposing of vaccines to prevent and treat the pandemic COVID-19, but successful vaccines and drugs are still not available. Active prevention and drug discoveries approach for the SARS-CoV-2 is urgently needed[6]. The conventional method of drug development involves more than 15 years, including target recognition, aim validation, score selection, lead optimization and preclinical and clinical trials. Therefore, within the expected time frame, development of a new drug to overcome the current crisis of SARS-CoV-2 is nearly impossible. The most realistic solution then, is the repurposing, reprofiling, redirecting or rediscovering as alternative solutions for prescribed drugs. This study will provide the medical research community with cumulative knowledge on several possible candidates for repurposable drugs that can have a synergistic impact in potentially treating COVID-19 outbreaks.

RESULTS AND DISCUSSION

Cell entrance potent inhibitors of SARS-CoV-2

Serine protease inhibitor TMPRSS2: The cleavage and induction of SARS-CoV spike protein(S) are necessary for the fusion of membrane and entry into host cell is negotiated by the action of TMPRSS2, airway and serine protease of alveolar cell[7]. SARS-CoV-2 also requires TMPRSS2 for the SARS-CoV-2 S protein priming and S protein-driven cell entry subsequently demonstrated by Pöhlmann and his colleagues[3]. TMPRSS2 is a serine protease which is required by SARS-CoV-2 for the priming of S protein and the ACE2, the receptor molecule of SARS-CoV which is needed for the host entry. TMPRSS2 inhibitor approved blocked entry for clinical use and may constitute a therapeutic option. A clinically verified and commercial serine protease inhibitor using camostat mesilate, which partially blocks infection in HeLa cell expressing ACE2 and TMPRSS2, SARS-CoV and HCoV-NL63 showed that TMPRSS2 inhibition in the human lung Calu-3 cells with camostat mesilate dramatically reduced the infection from SARS-CoV-2[3].

Camostat Mesilate (Foipan TM): A synthetic serine protease inhibitor labeled as Camostat [N, N-dimethyl-carbamoylmethyl 4-(4-guanidinobenzoyloxy)-] (FOY-305), alternatively known as camostat mesylate (NI-03), methanesulfate and camostat mesilate (FoipanTM), (CAS number: 59721-28-7), which was produced decades earlier to control dystrophic epidermolysis, exocrine pancreatic enzyme inhibition, oral squamous cell carcinoma and chronic pancreatitis[8]. As a drug repurposing candidate, camostat mesylate recently received attention regarding its status as an effective agent that was administered orally, reliably and well tolerated in humans and can significantly inhibited cellular entry. There are currently at least six clinical studies ongoing to treat with. However, while there was imperceptible evidence that camostat and relavant compounds inhibit SARS-CoV-2 mediated TMPRSS2 cell entry; there was no significant biochemical evidence in the literature. Ono Pharmaceuticals produced Camostat[9]. A clinical investigation of camostat mesilate was applied against non-alcoholic, intermediate pancreatic dyspepsia infection, which exhibited just minor, but no significant adverse effects[8].

Angiotensin Converting Enzyme 1 (ACE1): ACE1 antagonists, including ramipril, enalapril and angiotensin receptor antagonists like, valsartan and candesartan may be effective in preventing and treating coronavirus symptoms SARS-CoV-2. There was a true balance between maintaining or suspending ACE1/ARB therapy in COVID-19 patients[10], taking into account the entirety of evidence. In a new retrospective study of the patients who were hospitalized due to COVID-19 suffering, all causes of mortality for ACE1/ARB therapy patients was lower compared to those who did not use ACE1/ARBs[10]. On 21 March 2020, three existing trials were identified as being planned or under way in China on the WHO's ICTRP website, the International Clinical Trials Registry Portal. The first, entitled "Clinical characteristics difference between patients with and without ACE1 treatment with SARS-COV-2 caused infection in China" was published on 12 February 2020 and was confirmed to be recruiting; it was also mentioned on clinicaltrials.gov. The other two were not recruiting: "Clinical research on the effects of ACE1s/ARBs on COVID-19 infection and the other two were not recruiting: "Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a medication for COVID-19 patients[11].

Angiotensin-converting enzyme 2 (ACE2): SARS-CoV and corresponding coronaviruses directly interact with the ACE2 that is a key receptor for the incursion of the human body by SARS-CoV. It was demonstrated that the mice treated with both recombinant and wild-type spike protein from SARS-CoV have shown a significant reduction in ACE2 expression in lung. The new epidemic of SARS-CoV-2 has also been observed to infect the epithelial cells of human alveoli and may also be tested against SARS-COV-2, suggesting further studies[12]. Since ACE2 is present predominantly in the epithelia of human small intestine and human lung, may influence the type of therapeutics against SARS-COV-2 caused infections. Finally, a recent study has found a degree in hrsACE2 clinics which prevents SARS-CoV-2 by attaching simian Vero-E6 cells and protects human capillary organoids and kidney organoids from being influenced by SARS-CoV-2 extracted in the nasopharyngeal sample from a patient with confirmed COVID-19 disease[13], which suggests hrsACE2 will block the host.

Nafamostat Mesilate (BuipelTM): A serine protease synthetic inhibitor which is clinically tested and recommended for treating acute pancreatitis with disseminated intravascular coagulation and Nafamostat mesilate (BuipelTM) (6-amidino-2-naphthyl-4-guanidine benzoate-dimethane-sulfonate) in extracorporeal form (FUT-175)[14]. Recent research confirms this serine protease inhibitor, Camostat mesylate (NI -03) which is active against TMPRSS2 and used for the treatment of pancreatitis in Japan, prevents human lung cell infection with SARS -CoV-2[3]. Again experiments on simian Vero E6 cells infected with SARS-CoV-2 in cell culture nafamostat mesilate has been shown to be 22.50 μM inhibitive in EC_{50} in ipposition to SARS-CoV-2 infection[15].

Hydrochloride/Cepharanthine selamectin:

Hydrochloride/cepharanthine selamectin is the triple combination of cepharanthine, selamectin and mefloquine hydrochloriden[16].GX P2V can also be seen to require ACE2 as the viral receptor entry cell[17]. For the ability to inhibit cytopathic effects of GX P2V on Vero E6 cells, two libraries of 2,406 medically approved drugs have been examined and only the combination of cepharanthin, selamectin and mefloquine hydrochloride was identified as a potential medicine alliance to treat SARS-CoV-2 caused infections[17].

Chloroquine phosphate and hydroxychloroquine the potential inhibitor: For decades, chloroquine phosphate (ResochinTM) and its derivative hydroxychloroquine have been used be used for the prophylaxis and treatment of malaria, chronic Q-fever and numerous autoimmune disease

and prospective broad-spectrum antiviral drugs have been approved recently. Chloroquine phosphate prohibits terminal phosphorylation of ACE2, and hydroxychloroquine elevates the pH in virus cell entry endosomes[18], both of which constitute important antiviral pathways for chloroquine phosphate and hydroxychloroquine. The hydroxychloroquine gets converted into chloroquine *in vivo*. Chloroquine phosphate has been previously reported to significantly prevent infection with SARS-CoV and disperse *in vitro*[19]. These drugs are susceptible of preventing infection with COVID-19 at minimum micromolar concentrations, suggesting its potential use in COVID-19 patients[19].

Numerous Chinese multicenter clinical trials (ChiCTR2000029899, ChiCTR2000029898, ChiCTR20000 29939, ChiCTR2000029935, ChiCTR2000029868, ChiCTR 200002 9837, ChiCTR20 00029762, ChiCTR2000029761, ChiCTR2000029826, ChiCTR2000029803, ChiCTR2000029760, ChiCTR2000029740, ChiCTR2000029559, ChiCTR20000 29609 and ChiCTR2000029542) have been conducted to highlight the effectiveness and safety of hydroxychloroquine and chloroquine phosphate in COVID-19 treatment could obtain promising outcomes on this issue[18]. So, chloroquine phosphate and hydroxychloroquine can be effective for the treatment CoV pneumonia without significant side effects. The need for cautious selection and control of patients has been demonstrated through the use of either chloroquine phosphate or hydroxychloroquine for the treatment or prevention of SARS-CoV-2[20]. Notwithstanding, the continued use of either chloroquine or hydroxychloroquine in treating SARS-CoV-2 caused infection, this would be predominantly confirmed by *in vitro* results, as the human clinical studies are extremely poor. Therefore, clinical studies on patients with COVID-19 treatment or prevention should be conceived taking into consideration the potential adverse effects induced by the use of certain drugs[20]. A recent clinical review on the use of oral chloroquine for COVID-19 affected patients has been published by Zhou et al.[21]. This study recorded a high incidence of adverse reactions by oral chloroquine phosphate tablets, indicating that a clinical study of chloroquine phosphate for treatment with COVID-19 should be used. It should be noted that Swedish chloroquine clinical trials have stopped due to toxicity, and use of this drug has stopped entirely in Sweden. An early study in China indicated that the use of chloroquine was associated with reduced disease progression and reduced symptom duration[22]. As an antiviral prophylaxis candidate against the existing pandemic COVID-19 Chloroquine phosphate and hydroxychloroquine have been recommended for their demonstrated mode of action. However, the evidence to support this statement is also negligible and these agents should not be used as prophylactic agents of SARS-CoV-2, except clinical trials[22]. So far, inadequate data are available to know whether hydroxychloroquine or chloroquine has a role in either COVID-19 therapy or prophylaxis. For these reasons, patients should be referred to a clinical trial whenever possible, is highly recommended. Ongoing studies of hydroxychloroquine vigorously recruit hopes of further delineating its function in COVID-19 therapy and prophylaxis[23].

Monoclonal antibody which inhibits interleukin (IL)-6

Tocilizumab: Tocilizumab first humanized recombinant monoclonal antibody used for the prevention of autoimmune and inflammatory disorders. It is an immunoglobulin belonging to class G1 (IgG1 class), interacting with the interleukin 6 dissolved receptor (sIL-6R). This is an antagonist of the IL-6 receptor. Tissue fibrosis, lipid metabolism and T-cells activation are induced by a pro-inflammatory cytokine known as IL-6. Tocilizumab was approved by FDA for the treatment of extreme rheumatoid arthritis, chronic idiopathic juvenile arthritis[24]. Tocilizumab is provided to the COVID-19 patient at a dosage of 400 mg. The major side effects caused by tocilizumab are hypertension, gastrointestinal perforations, headaches and skin reactions. A 400mg dose provided to 21 COVID-19 patients demonstrates an improvement in 91% of patients' respiratory function and a successful discharge with only one dose[25]. A multicenter research on COVID-19 was performed on 330 patients of Nepal for the analysis of tocilizumab tolerability and effectiveness in severe COVID-19 patients[26]. A diagnostic study design exploring the use of tocilizumab in the treatment of COVID-19 patients suspected of having pulmonary hyper inflammation has been initiated in Nepal[27]. Tocilizumab was applied intravenously to twenty patients 400 mg once together with the required anti-virus treatment. The fever of the patient returned to normal within some days. Oxygenation was improved by 75% of patients and 90.5% of patients showed a decrease within the opacity lung lesions on CT scans. In addition, peripheral lymphocytes count normalized in 52.6% of patients. These data indicate that tocilizumab in critical patients might prove to be life-saving[28].

SARS-CoV-2 membrane fusion inhibitors, replication, and assembly

Lopinavir/ritonavir: Lopinavir (ABT-378), a highly effective blocker of human immunodeficiency virus (HIV) protease was produced in 1998 to overcome resistance against HIV to ritonavir[29]. Since ritonavir strongly inhibits the metabolic activity of lopinavir, lopinavir and ritonavir have been conquered by >50 times in the plasma of rats, pigs and monkeys *in vitro* by 8 h through combined oral ingestion of lopinavir and ritonavir[29].

An initial study in 2003 demonstrated that lopinavir ingestion at 4μg/ml prevented the cytopathical impact of a plaque removal assay with SARS-CoV contaminated kidney-4-cells of fetal rhesus[30]. From this study, the conclusion was drawn that the improvement in the clinic results of mild/moderate COVID-19, LPV/r appeared to have a little impact in case of arbidol or LPV/r mono therapy and LPV/r may result in more unfavorable events[31].

A randomly assigned open-label, controlled clinical study comprising 199 hospitalized adult patients affected with SARS-CoV-2 infection in Wuhan, China; the oral ingestion of 400mg lopinavir twice per day and ritonavir at 100mg for 14 days showed some misleading results comparative to the control category[32]. At the end of the study, 40.7% of patients in the lopinavir / ritonavir community were already identified with the RNA from SARS-CoV-2 on day 28th. Another study observed that duration from disease invasion to antiviral is a hazard factor for serious illness and patients had antiviral treatment initiation[33]. So, it is necessary to investigate whether prior LPV / r therapy in COVID-19 will have therapeutic efficacy or not.

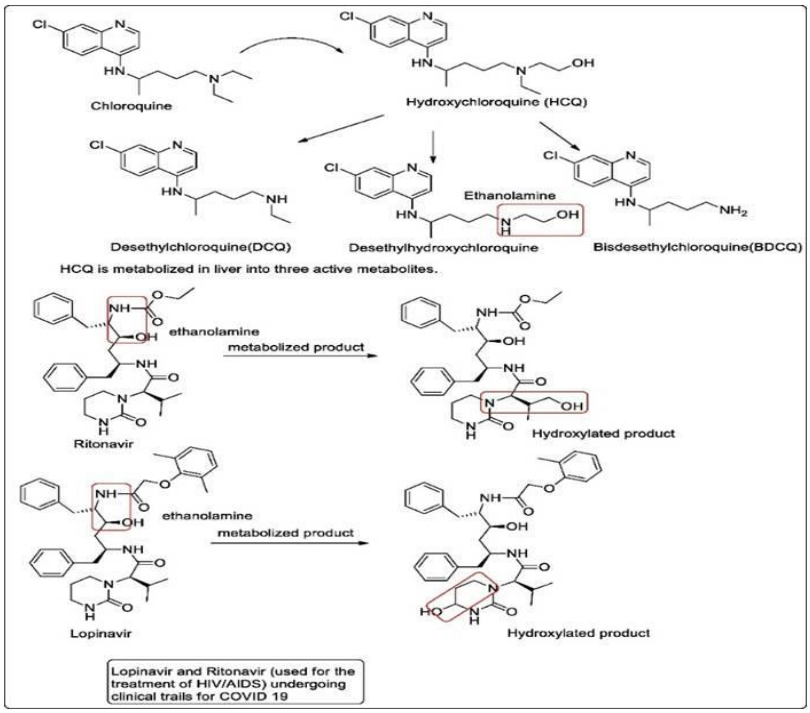

Figure 1: Showing the compounds from the metabolism of hydroxychloroquine and drugs Lopinavir/Ritonavir which are effective against SARS-CoV-2[34].

Remdesivir: Remdesivir (GS number-5734) is a new, small molecular antiviral analog of adenine containing nucleotide drug shown to be useful in Ebola virus of rhesus monkeys. Once a day, 10mg/kg remdesivir was given intravenously for 12 days and the replication of Ebola virus was inhibited deeply and 100% of animals infected with Ebola virus from fatal disease were preserved[35]. Remdesivir was ingested in its activated state GS-441524, which prevents the operation of RNA-polymerase of virus and induces elusion of the exoribonuclease proofreading of virus. Remdesivir functions in the earlier period of infection onset and reduces dose-dependent concentrations of viral RNA compared to *in vitro* viral load impairment[36]. However, a new clinical study was conducted with remdesivir involving the compassionate uptake in 53 patients affected with COVID-19 consuming oxygen assistance or mechanical ventilation because of 94% or less saturation of oxygen showed that remdesivir treatment was done intravenously at 200mg on 1st day, after that 100mg per day for 9 days led to clinical progress in 36 out of 53 patients[19]. It was noted that the first patient in the United States with COVID-19 was successfully treated for pneumonia progressions with remdesivir on day seventh of the hospitalization in January 2020[37]. Moreover, phase 3 human trials were performed to assess the effectiveness of SARS-CoV-2 infection in patients since March 2020. The experimental and clinical findings in China (NCT04252664, NCT04257656), the United States, Korea, Singapore (NCT04280705), Hong Kong, Singapore, Taiwan (NCT04292730, NCT04292899), the USA (NCT04302766), and France (NCT04314817, NCT04315948) have shown that clinical studies have recently been started on remdesivire for COVID-19 patients.

Umifenovir: Umifenovir (Arbidol), a small molecule which is the derivative of indole, produced in the JSC Pharmstandard, Russia. Umifenovir is currently being studied as a possible therapy and prophylactic factor for COVID-19[38]. Umifenovir prevents the entry of virus in host cells by inhibiting the fusion of membrane of the viral envelope and the membrane of the host cells' cytoplasm by inhibiting clathrin-mediated endocytosis, ultimately preventing virus infection. In a clinical study, in Wuhan, China (in January 2020), where 36 COVID-19 patients were given 400 mg of umifenovir thrice per day for 9 days and 31 patients with COVID-19 who remained untreated served as control category[38]. The therapy with umifenovir had a potential to lower viral RT-PCR load and reduce mortality (0% vs. 16%) compared to the control category[39]. The identification of SARS-COV-2 through RT-PCR after 14 days of treatment where 94% of umifenovir-treated patients were negative compared to 53% in the control category and 69% of umifenovir-treated patients progressed on chest CT scans compared to 29% in the control category[39].

Finally, therapies involving umifenovir or darunavir in combination with umifenovir were recommended as possible strategies for combating SARS-CoV-2 outbreak with numerous recorded cases of patients recovering from the disease in China.

Favipiravir: Favipiravir (Avigan), (T705), is an edible derivative of pyrazinecarboxamide, and a guanine analog, its name obtained from chemical structure of 6-fluoro-3-hydroxy-2-pyrazinecarboxamide, produced by Toyama Chemical in Japan which specifically and powerfully prevents RNA-dependent RNA polymerase (RdRP) from RNA viruses and promotes the transversion mutations of RNA which are lethal, thus creating an unviable virus phenotype[40]. Favipiravir prevents the replication process of a broad RNA virus category, such as influenza-A virus, flavivirus, alphavirus, filovirus, bunyavirus and coronavirus. Some other virus belongs to above category of West Nile, yellow fever, foot and mouth virus, Ebola and Lassa virus[40].

Favipiravir-RTP inhibits RdRp of influenza virus with 0.022µg / ml IC_{50} which would not invade the DNA polymerases of human of up to 100µg /ml (α, β, ć subunits). In addition to the inhibition of influenza virus, favipiravir inhibits arenavirus, bunyavirus, flavivirus and filovirus that induce hemorrhagic viral fever[41]. A retrospective study of patients affected with particular disease (EVD) caused by Ebola virus showed that the patients taking favipiravir with extra care revealed a higher total surviving rate, greater average survival time and higher proportion of patients with

a >100 times viral load depletion compared to the patients undergoing complementary therapies approved by WHO[42].

A clinical trial (ChiCTR2000029600) was performed in Shenzhen to determine the security and effectiveness of favipiravir to treat 80 COVID-19 patients[42]. Furthermore, an efficient regulation of favipiravir on COVID-19 was indicated by a multicentre randomized clinical trial (ChiCTR200030254)[43]. Therefore, favipiravir is thought to be one of the possible COVID-19 drug candidates, although *in vitro* and pre-clinical animal trials have not yet been proven. Throughout the *in vitro* study of vero E6 cells with 61. 88μMol EC_{50}, SARS-CoV-2 was inhibited by favipiravir[44].

In China, COVID-19 patients recovered with drugs, such as favipiravir, remdesivir, a mixture of lopinavir and ritonavir, chloroquine, azithromycin and pyrimidine, using a mixture of pre-existing anti-viral medicines (for Ebola, SARS and AIDS). It was stated that favipiravir and chloroquin, azithromycin and pyrimidine were most powerful mixture, combined with normal treatment[19]. In another research, COVID-19 patients, receiving favipiravir had higher rates of clinical success compared with a control group[34]. Limited clinical experience to support the application of favipiravir in treating COVID-19 has been published[45]. This finding helps further research with RCTs to enhance the effectiveness of favipiravir therapy in COVID-19.

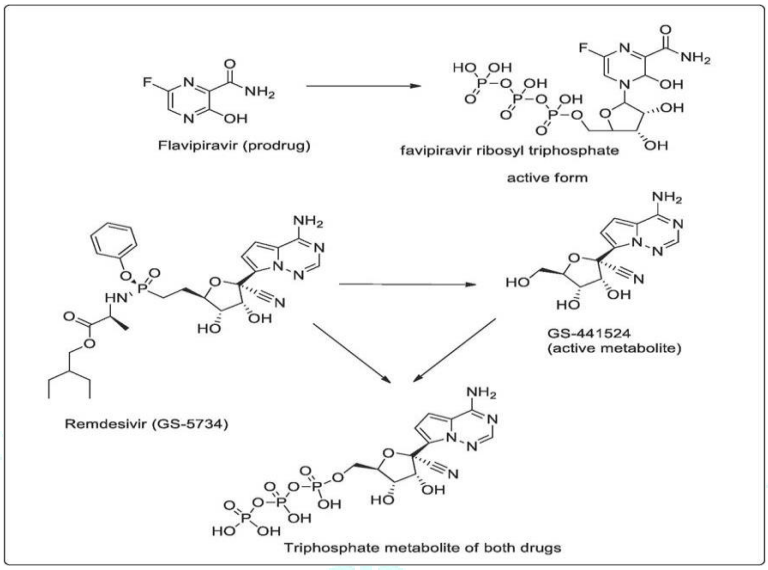

Figure 2: Showing active metabolized products of Favipiravir and Remdesivir[34].

Itraconazole: Itraconazole (ITZ) is an antifungal broad-spectrum triazole with an antiviral activity recently indicated. Shim et al.[46] reported ITZ's therapeutic and preventive action against the infection caused by human rhinovirus (HRV), in a murine model. ITZ enhanced inflammatory changes in the histological acute lung, especially infiltration of neutrophils, pulmonary edema and hemorrhage. This immunomodulatory role of ITZ could be advantageous against SARS-CoV-2 created cytokine storm, being significantly higher in patients requiring transfer to ICU[47]. Interestingly, itraconazole may be a promising inhibitor of Nsp12 which is a non-structural protein and RNA-dependent RNA polymerase (RdRp) can also be inhibited by itraconazole; RdRp plays a key role in coronavirus replication and transcription. In the SARS-CoV and MERS-CoV inhibitors research, Nsp12-RdRp has been utilized as an incredibly successful drug objective. Targeted Nsp12-RdRp inhibition was suggested to be safe with no major toxicity and adverse effects on host cells[48]. Itraconazole, alone or in conjunction with neutrophil depletion, achieved improvement of the response within inflammation and the sequelae of pulmonary fibrosis by the expression of gene through down-regulation process, associated with both the process of inflammation and fibrosis in a research model for pulmonary paracoccidioidomycosis. This could point to the significance of ITZ in reducing the risk of fibrotic lung disease if used in SARS-CoV-2 treatment[49]. Notably, the combination of azithromycin, with itraconazole, could lead to synergistic interactions with better therapeutic outcome[50]. Therefore, itraconazole could be recommended in a new COVID-19 protocol, and it should be encourage to enrollment for clinical trials of this fairly inexpensive, accessible, well-tolerated drug to investigate its potential for COVID-19 treatment.

SARS-CoV-2 protease inhibitors (3Clpro)

Mpro protein can also be defined as 3Clpro protein, is crucial for SARS-CoV-2 proteolytic maturation. Mpro cleaves the polyproteins of virus, producing 12 proteins (Nsp4–Nsp16) which are non-structural in nature and RdRp and helicase were included into them. Mpro inhibition can prevent replication of the virus, and is therefore one of the possiblel anti-coronaviral techniques[51]. The unbounded SARS-Cov-2 3Clpro X-ray structures and their a-ketoamide group have recently been identified as unique 3Clpro inhibitors. On March, 2020, Jeon et al.[52] reported that the replication of SARS-CoV-2 could be prevented by hexachlorophene. As indicated by Liu et al.[53], hexachlorophene has an inhibitory effect on Mpro protease. The crystal configuration of SARS-CoV-2 Mpro in combination with the inhibitor of a Michael acceptor named as N3 which can directly prevent multiple SARS-CoV as well as MERS-CoV at 2.1 Å resolutions, was published on 9 April 2020[54]. N3, an inhibitor of michael acceptor able to inhibit SARS-CoV Mpro and MERS-CoV Mpro, has been observed to create a covalent bond and to become a constant inhibitor for the Mpro within SARS-CoV-2. On 22 April 2020, two leading compounds -11a and 11b have been engineered and synthesized to target the Mpro within SARS-CoV-2[55]. SARS-CoV-2 Mpro X-ray crystal structures in 11a or 11b complex, both of which were assessed at a resolution of 1.5 Å, revealed that two groups containing aldehyde-11a and 11b are covalently bound to Mpro Cys145. Compound entitled as 13b inhibits the purified Mpro of SARS-CoV-2 recombinant by 0.67 ± 0.18μM of IC_{50} and

inhibits the replication process at SARS-CoV-2 in Calu-3 lung cells of human by 4-5μM of EC_{50}[56]. Structural knowledge from these relevant proteins could be critical in furthering our understanding SARS-CoV-2 and in discovering as well as developing specific drugs against SARS-CoV-2.

Ongoing Clinical Trials

There is currently not enough support for efficient implementation of COVID-19 through any approved antiviral drugs or other medications. The International Committee of Medical Journal Editors (ICMJE) proposed the documentation of all clinical trials in publicly accessible fields, as of 2005, before they can be accepted for publishing[57]. Numerous research trials on potential antiviral drugs however are carried out. The therapies can be split into two categories according to their target. Coronavirus is specifically impaired by either inhibiting main viral enzymes that duplicate the genome or by preventing viruses entering human cells. The second is designed to modulate the human immune system either by enhancing the innate response to a virus, or by inhibit the inflammatory processes which cause lung injury. Many of these medicines were initially designed for other pathogens and, for new COVID-19 clinical trials, they were repurposed rapidly.

A variety of clinical trials are currently aimed at repurposing proven antiviral drugs, in particular, with past SARS-CoV and MERS-CoV efficacy. Lopinavir / ritonavir in 34 investigation trials have become the most popular studies in antiviral combination[58]. Both drugs are used in HIV-1 treatment as inhibitors of protease. Due to the quick catabolism of the cytochrome P450, lopinavir is insufficient for substantial therapeutic operations due to its oral bioavailability in the enzyme system (specifically 3A4 isoenzymes). Thus, ritonavir is co-administered to curtail this, significantly improving the lopinavir's half lifespan. In 2004, it was investigated and found to be effective in evaluating the efficacy of lopinavir / ritonavir against SARS-CoV with a historical monitoring[59]. Among 199 COVID-19 patients (Clinical Trial Number: ChiCTR2000029308, registration target identified as 160 registry participants), effectiveness was never shown in the open-label randomized study. The average mortality or viral load was not substantially increased[60]. Remdesivir is a new analog nucleotide antiviral, originally developed for the diagnosis and prevention of Ebola and Marburg viruses[5]. It is nevertheless effective against a number of pathogenic viruses, including SARS-CoV and MERS-CoV in vitro and in vivo models[61]. This enzyme was of considerable concern after a treatment of the first COVID-19 and a further regeneration in the U.S[56]. A number of worldwide trials for the efficacy of COVID-19 are currently under way[59]. Many other antiviral medicines are being tested, especially those that have an effect on different forms of influenza and other RNA viruses, such as, favipiravir (T-705, Avigan), umifenovir (Arbidol), triazavirin (TZV), and marboxil (Xofluza) baloxavir. For certain trials, RNA viruses like HCV and HIV are commonly used in drugs including danoprevir/ ritonavir, azvudine, ledipasvir/ sofosbuvir, sofosbuvir/ daclatasvir, darunavir/ cobicistat, and emtricitabine/ tenofovir[59]. Additionally, 26 studies also investigate the effectiveness and surprisingly also discuss the various ways (i.e. nasal) of prescribing antiviral interferon drugs[59].

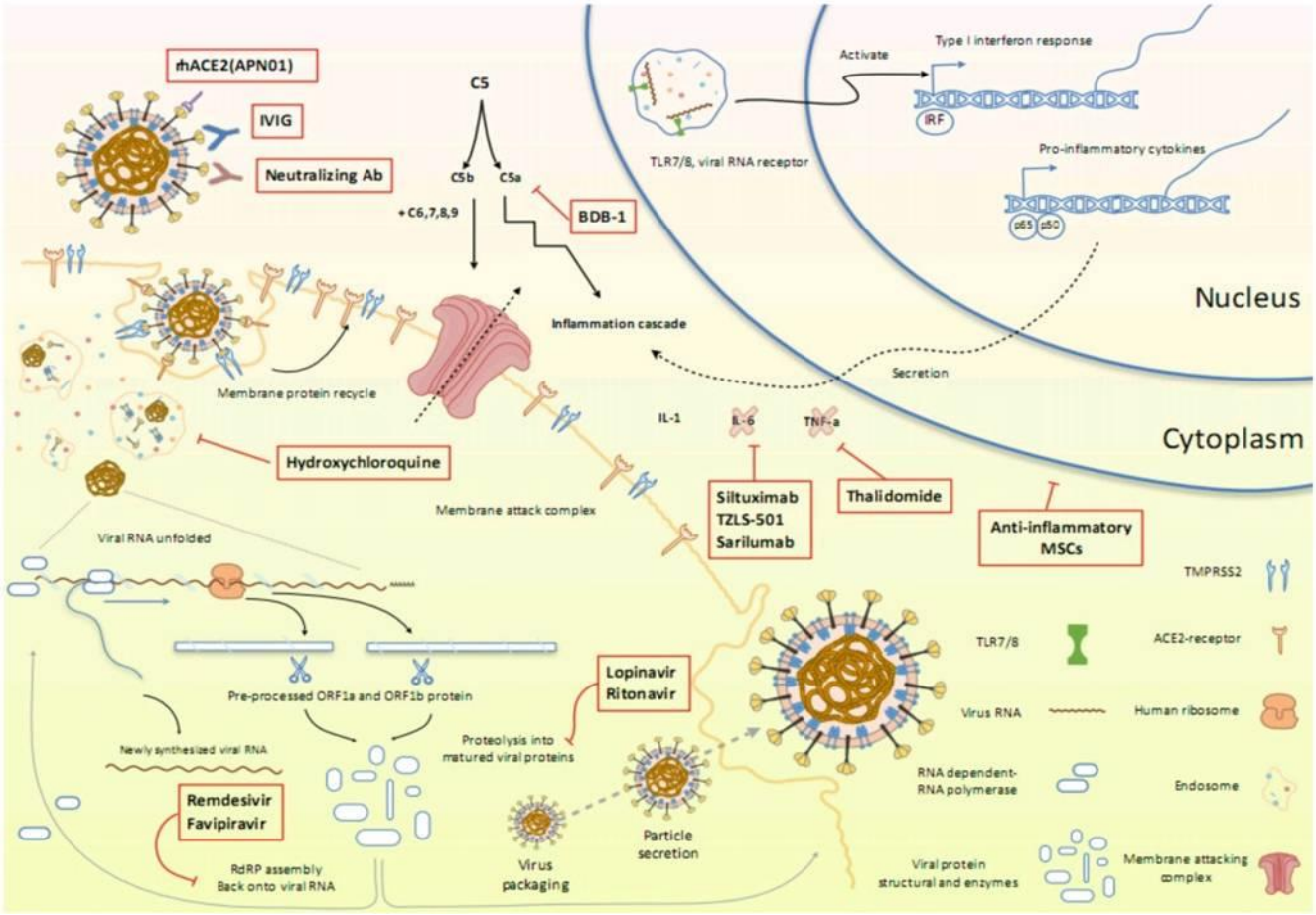

Figure 3: An overview in the perspective of host pathways and mechanisms of virus replication of repurposed therapeutic medicines undergoing clinical trials against the COVID-19[61].

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Latest case-control studies suggest that NSAIDs are related to higher risk of complications following infections of the respiratory tract such as severe pneumonia, pleural effusions, chronic illness, peritonsillary lesion, and spread or infection suppurations to multiple sites[62]. Delays in prescribing for successful diagnosis of antibiotics for patients needing hospital admission were also linked of NSAIDs. A recommendation on the use (NSAIDS) of patients with SARS-CoV-2 was issued by the Food and Drug Administration[63] (FDA). There is no compelling evidence that NSAIDs are incredibly hazardous for COVID-19 patients, but in any patient that could be precarious for chronically ill patients will induce GI leakage, fluid accumulation, and renal dysfunction. NSAIDs block endoperoxide synthesis enzymes, such as cyclooxygenases (COX), which catalyzes arachidonic acid two-stage conversion into thromboxanes, prostaglandins and prostacyclines. Two different types of COX are currently being re-known, COX-1 and COX-2. The development of the prostanoids is the responsibility for COX-2. Such lipid mediators are part of vasodilating mechanisms, enhanced vascular permeability and leucocyte chemotaxis[64].

Fang et al.[64] reported early on COVID-19 stating that inhibitors of ACE or ARBs could be related to worse COVID-19 outcomes and added that ibuprofen could be consistent with upregulation of ACE2 receptors a potential input point of SARS-CoV-2. The French Minister of Health has warned that the use for COVID-19 patients, of non-steroidal anti-inflammatory drugs (NSAIDs) such as, ibuprofen (Advil and Motrin), in order to minimize the opioid risk decreases and suggests the use of acetaminophen[65]. The reason against the use of NSAIDs and acetaminophen is that antipyretic medications are capable of masking COVID-19 associated fiber and thereby hinder the detection and effective treatment of infections. There is apparently no conclusive proof to endorse or reject usage of NSAID in COVID-19 patients.

Dexamethasone: Dexamethasone is used as an anti-inflammatory and immunosuppressive function by the glucocorticoid receptor in the same way as most corticosteroids. The complex of receptor-corticosteroidal molecules moves to the cell nucleus after bound with the ligand, where it dimmers and attaches to glucocorticoidal reaction elements (GREs), acting as a transcriptional suppressor or as a transactivator of several gene sets. Nevertheless, recently it has discovered that dexamethasone can also induce the lipid mediator route of the D-series, which contributes to the development of 17-HDHA as well as D1 and DX protectins[66]. The molecular system is efficient of dexamethasone and contributes to the resolution of inflammation, for example, the proper regulatory termination of pro-inflammatory reactions involving pro-inflammatory mediator catabolism, timely and high-organisational removal of inflammatory cells and the regeneration of the tissue[67]. Dexamethasone was shown in a recovery trial to improve survival levels in extreme COVID-19 patients requiring oxygen or mechanical ventilation with a noteworthy 30% when treated with oral or intravenous doses at 6 mg daily for 10 days[68]. Death decreased by ⅓, in patients on ventilators and by $^1/_5$ in patients requiring oxygen therapy. The benefit was limited to patients with respiratory assistance, although in milder cases, this was not apparent. The extraordinary efficacy of dexamethasone therapy challenges the current viewpoint on the application on corticosteroids in respiratory virus infections. Although corticosteroids can improve ventilator weakness, decrease host response speed, moderate the 'cytokine storm' and minimize immunopatology, viral clearance can also be decreased and contribute to serious illness. So, it is of utmost importance to consider how dexamethasone mediates its effects.

Phytochemicals and natural products effective against SARS-CoV-2

In viral infection or replication, natural products can inhibit different stages, and many of them have widespread antiviral effects that are not completely established. These also serve as immunomodulators to inhibit inflammatory reactions that cause severe morbidity and mortality from SARS-CoV-2. The fact that NLRP3 inflammatory signaling is interfered with was found to involve phytochemicals, particularly those of flavonoids, commonly distributed in food and botanicals[69]. A number of flavonoids that interact with the activation of NLRP3 are modulating the inflammatory response to SARS beta coronaviruses[71]. Such flavonoids have proven effective against various types of viruses across various pathways and are available in a dosage range from 100 to 500mg daily as supplements for nutraceuticals. It has been shown that the dose-dependent association between the S protein of SARS-CoV and ACE2 receptor was inhibited by emodin[70]. Resveratrol (trans-3,5,4′-tryhydroxystilbene) has shown *in vitro* to suppress MERS-CoV infection and improve cell survival as a consequence of virus infection[71]. In addition, resveratrol suppresses the MERS-CoV nucleocapsid protein expressions which are needed for viral replication, as well as MERS-CoV-induced apoptosis of the host cells[72], suggesting that resveratrol is also potential in preventing SARS-CoV-2 infection.

CONCLUSIONS

We are now confronted by a more deadly debilitating virus than the 2003 SARS-CoV pandemic. SARS-CoV-2 infection may cause significant bilateral pneumonia that can lead to multiple organ failure and death due to COVID-19 disease, with 2-5% mortality risk. However, this may be underestimated since the true number of cases in countries recording extreme symptoms alone, is not accurately understood to the population. With no large numbers of vaccines available in near future, it is mandatory that authorized off-label and experimental drugs be detected against SARS-CoV-2 infections and COVID-19 disease. Such medicines will constitute inhibitors of TMPRSS2, ACE2, antimalarial drugs, antiviral medicines that inhibit viral RNA polymerase, proteases, and virus / host cell membrane convergence, as well as antiviral drugs listed herein. We also expected that it may be effective at avoiding disease after potential exposure to viruses and positively checked outcomes and at minimizing the likelihood of secondary virus transmission and COVID-19 disease including HIV and influenza viruses, post-exposure prophylaxis with potential drugs candidates against SARS-CoV-2 infection. Clinically validated drugs like camostat mesilate that inhibits entry of viruses into host cells by inhibiting TMPRSS2 and chloroquine phosphate, suppressing ACE2 or hydroxychloroquine terminal phosphorylation, metabolized *in vivo* to chloroquine, may be relevant for post exposure prophylaxis against SARS-CoV-2 infection. Antiviral candidates include remdesivir, favipiravir, ostelmavir, ganciclovir, triazavirin, penciclovir, umifenovir, baloxavir, marboxil, danoprevir/ ritonavir, lopinavir/ ritonavir, azvudine, sofosbuvir/ ledipasvir, sofosbuvir/ daclatasvir, emtricitabine/ tenofovir, darunavir/ cobicistat, and ribavirin. For the treatment of common and moderate COVID-19 and to minimize the mortality ratio of COVID-19, antiviral drugs: remdesivir, favipiravir and lopinavir/ritonavir, plus β-1a interferon should be

administered. In addition, we have outlined the clinical trials carried out quickly since the onset of the emergency pandemic study. Many of them were focused on repurposing for other uses of previously developed therapeutic agents and such agent demonstrations classified into two broader categories: those that can be directed at the viral replication cycle and those that can be aimed at strengthening immune responses and reducing inflammatory dysregulation, based on immunotherapy procedures. In addition, administration of antiviral candidate medicines immediately after the onset of symptoms will decrease the infectiousness of other individuals by reducing viral shedding in the respiratory secretions of patients infected with SARS-CoV-2, who usually reach their height 5 to 6 days after symptoms and last until 14 days, and prophylactic interaction therapy may reduce the risk of infection. We advised that the ACE inhibitor and ARB in patients, with a SARS-CoV-2 infection, be used with greater caution. For COVID-19 patients as compared to NSAIDs, acetaminophen can be a safer drug for treating fever.

Phytochemical drugs such as flavonoids, emodin and resveratrol, hypothesized therapeutic effectiveness against SARS-CoV-2 infection, owing to their wide protection profile, less pharmacological side-effects and easy processing, also available to large populations for the pre-exposure and post-exposure prophylaxis of SARS-CoV-2 infection. Finally, we firmly believe that in SARS-CoV-2 patients, further clinical trials with these suggested medications are needed to show their effectiveness and reliability.

DECLARATIONS

Author contribution

Rahman MS, Mina FB and Das S: Performed the literature search and prepared the manuscript

Karmakar S, Akhtar S and Acharjee UK: Assisted to prepared the manuscript

Billah M, Khan A and Hasan MF: Critically revised and finalized the manuscript.

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Competing interest

The authors declare no conflict of interest.

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