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REVIEW ARTICLE

Pharmacological repurposed agents for COVID-19

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ABSTRACT:
Coronavirus 2019 (COVID-19) pandemic has created a significant global challenge with respect to the search for specific and effective pharmacological agents with fewer adverse effects for treating this disease. To date, no effective therapy for COVID-19 has been established. Recent virological studies suggest an assortment of potential therapeutics, which could be good candidates for minimizing disease development. One of the most effective potential medications is Remdesivir, which has demonstrated *in-vitro* antiviral activity and is the first COVID-19 drug approved by the United States Food and Drug Administration (FDA). Adjunct medical care is used as an extra treatment method in addition to the essential treatment, for example, glucocorticoids, which cause a decline in the death rate in mechanically ventilated COVID-19 patients. More clinical preliminary studies should be conducted to explore the most effective pharmacological agent for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19. Numerous possible drug-drug interactions (DDIs) that may take place with the COVID-19 repurposed drugs and other medications have been identified. These facts might be beneficial for physicians to screen and identify potential DDIs with adverse consequences, and accordingly styling preventive and management approaches for their avoidance.

KEYWORDS: Antiviral drugs, COVID-19, Drug-drug interactions, Pharmacology, Treatment.

INTRODUCTION:
Coronaviruses (CoVs) are single-stranded ribonucleic acid (ssRNA), that may cause respiratory tract infections in mammals[1]. It became more destructive from November 16, 2002, to May 19, 2004, in Shunde, Guangdong, China. They cause an extreme acute respiratory disorder Covid (SARS-CoV) that surge was accountable for 813 deaths on the world[1,2]. From April 2012 to June 2015, a subsequent flare-up perceived as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) from Saudi Arabia spread to 24 nations and caused 400 deaths on the planet[3]. In December 2019, a few etiologically obscure instances of pneumonia began to spread in Wuhan, China, which drew global attention since cases spread in a fast logarithm. The common factor of initial cases was working or living close to the fish market in Wuhan[4].

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The Chinese Centers for Disease Control and Prevention (CDC) distinguished the novel Covid by utilizing an investigation of a throat swab from an affirmed case on January 7, 2020. Subsequently, this infection was called COVID-19 by World Health Organization (WHO). The WHO states COVID-19 outbreak a pandemic on 11 March, 2020[5,6]. According to the published epidemiology and virology researches, COVID-19 can be transmitted from an infected patient to another by small respiratory droplets from coughing, sneezing, or talking, or by contacting the contaminated surfaces[7]. Presently, the randomized clinical trials (RCTs) have not provided any evidence for a potential therapy protocol for positive cases[8]. This review will elucidate the current therapy programs used in dealing with confirmed COVID-19 patients. The possible DDIs that could occur with the COVID-19 repurposed drugs and other medications will also be summarized.

SARS-CoV-2: virology and drug targets:
The viral primary spike (S) protein of the SARS-CoV-2 ties to angiotensin-converting enzyme 2 (ACE2) receptor in an alveoli cell, the viral melding into respiratory epithelium through binding to ACE2 can be

stimulated by transmembrane protease serine 2 (TMPRSS2) which is an endothelial cell surface enzyme [9,10]. Fig. 1 displays the targets for the potential anti-COVID 19 agents.

Pharmacological repurposed antiviral agents Chloroquine phosphate, and hydroxychloroquine sulfate (CQ/HCQ):

Both drugs have the same potential mode of action[11] against SARS-CoV-2 infection which include: inhibition of the glycosylation of ACE-2 receptor consequently obstructing virus-receptor attachment[12]; the elevation of the pH inside cellular organelles thus blocking endocytosis, virion transport and inducing alteration of newly produced viral RNA; and suppressing the synthesis of viral protein and virion gathering[11]. Additionally, in the host cells, CQ and HCQ induce immunomodulatory effects, which might intensify their anti-COVID-19 properties, by reducing the discharge of cytokines and hindering the lysosomal action and autophagy[13]. These drugs are contraindicated in individuals who are allergic to 4-aminoquinoline, and chloroquine compound, and in those with retinal sicknesses. The most well-known adverse reactions are; anorexia, cardiovascular effects because of QTC prolongation, retinal harmfulness, or hypoglycemia. Nevertheless, HCQ has fewer adverse effects in comparison with CQ. People who are allergic to the HCQ should not use this agent to avoid anaphylaxis reactions. The effective therapeutic dose for COVID-19 is 500 mg orally – twice daily. Both drugs[7,8,9] can interfere with CYP2D6, CYP3A4, CYP3A5, and CYP2C8 substrates which are responsible for their major drug's interaction. A clinical Chinese experiment achieved successful management of more than one hundred COVID-19 patients and reduced the intensity of symptoms[14]. The dosing of HCQ in the case of COVID-19 is 400 mg orally once daily[14].

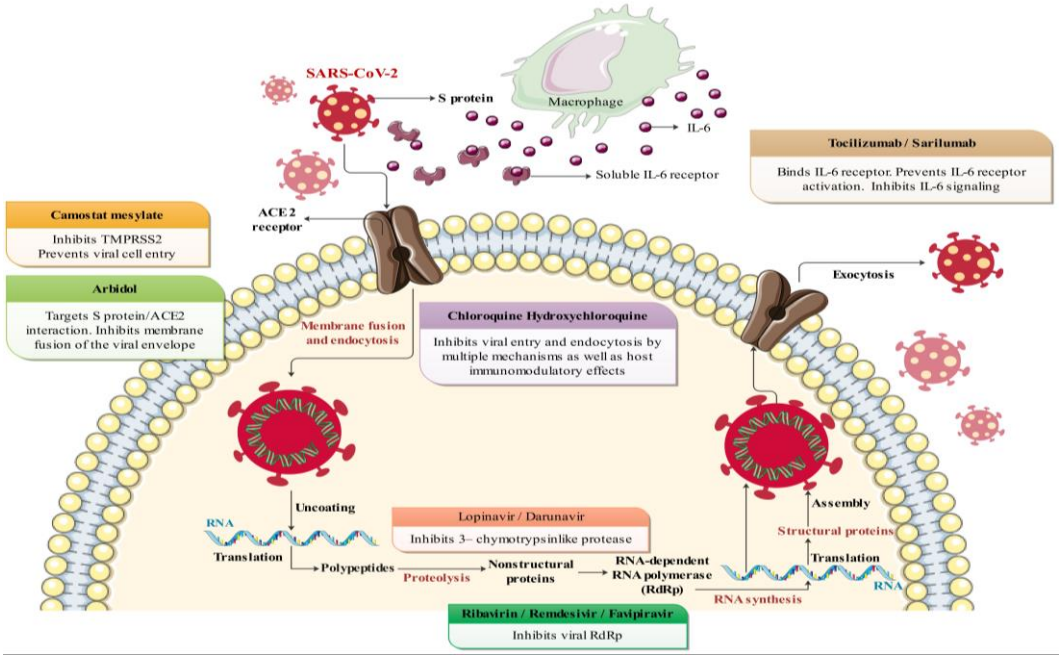

Figure 1-demonstrates the potential antiviral agents and their mechanisms.

Remdesivir: It is a prodrug that acts on the C-adenosine nucleoside triphosphate analog[15]. In the Ebola virus outbreak, this agent showed a good antiviral activity[16] due to its high selectivity, low EC50 which was approximately 0.77 μM, and the EC90 that was 1.76 μM. It reduced the lung hemorrhage and confined viral lung titers in the murine lung infected models with MERS-CoV. A double-blind, randomized, trial demonstrated that remdesivir shortened the hours of recuperation in adults hospitalized with COVID-19 and respiratory tract infection compared with patients on placebo[17]. Based on that, on October 22/2020 U.S. Food and Drug Administration (FDA) approved this agent to be the first COVID-19 drug[18].

Favipiravir: It is a prodrug that is transformed to the active form, favipiravir ribofuranosyl-5′-triphosphate, which is a purine nucleotide. It obstructs the RNA-dependent RNA polymerase and prevents viral replication. It showed good antiviral activity against the Ebola virus[19]. A randomized clinical trial was conducted to compare favipiravir and arbidol against moderate to severe cases of COVID-19, favipiravir caused 71.4% recovery of these cases in comparison to 55.9% recovery caused by arbidol[20].

Lopinavir/ritonavir: This is a protease inhibitor compound, which inhibits the 3 chymotrypsin-like proteases [21]. Although this compound is effective against earlier SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV), there is no adequate clinical evidence for its effectiveness in the cure of COVID-19 patients[22]. Conversely, it has been suggested that giving this compound at the initial stage of infection will inhibit the tremendously powerful multiplication that SARS-CoV-2 appears to have, and thus avoiding the injury that is caused by the infection which generates acute inflammation consequently multisystem organ dysfunction [23]. Therefore, randomized double-blind controlled clinical trials to evaluate this preparation as prophylaxis for COVID 19 patients are urgent.

Ribavirin: It is a guanine analog, acts by blocking the RNA-dependent RNA polymerase, its ability to fight the SARS-CoV required high doses of 1.2 g - 2.4 g every eight hours orally. A recent retrospective study has shown that there was no clinical evidence for the efficiency of inhaled ribavirin in the treatment of nCoV [24,25]. Due to large doses used, hematologic toxicity has occurred in more than 60% of patients[26]. Ribavirin is contraindicated in pregnancy[27]. The recommendation is to combine ribavirin with another antiviral agent to achieve better efficacy with less toxicity[28]. However, further assessment in designed randomized controlled trials is recommended.

Oseltamivir: It is a neuraminidase inhibitor and approved for influenzas' treatment. The role of this agent is to exclude influenza symptoms from COVID symptoms. It was utilized in the prior phases of the pandemic in China [29].

Umifenovir: It prevents the membrane fusion of the viral envelope, and the S protein/ACE2 interaction[30]. As of now, it has been affirmed for COVID management in Russia and China. The remedial dose for flu is 200 mg orally every 8 hours, and it has been researched to assess the adequacy of this dose in COVID treatment[31].

Miscellaneous agents:

Interferon β:

Interferon β has shown significant activity against MERS[32]. The Chinese guidelines listed interferons as an additional optional agent for the combination treatment with ribavirin or lopinavir[33]. A recent clinical trial indicated that this agent was beneficial for severe COVID-19 patients[34]. Another randomized, double-blind, placebo-controlled, study demonstrated that inhaled nebulized interferon beta-1a was associated with significant improvement and recovery from SARS-CoV-2 infection compared with patients who received placebo[35]. Moreover, the combination of this agent with other antiviral agents revealed a marked efficacy against COVID-19[36].

Corticosteroids:

These agents (e.g.; dexamethasone) inhibit the production of pro-inflammatory cytokines, for example, interleukins such as interleukin IL-1, IL-2, IL-6, IL-8, TNF, IFN-gamma, VEGF, and prostaglandins[37,38]. Significantly, five of these are linked to SARS-CoV-2 severity[39]. At the same time, they also activate the anti-inflammatory cytokine synthesis, particularly IL-10 and lipocortin-1[38]. Accordingly, many clinical trials demonstrated the advantage of corticosteroids for the management of solely severe critically ill COVID-19 patients who need oxygen therapy; i.e. corticosteroids reduced the risk of death among these patients[40,41].

Table I summarizes the pharmacokinetic and pharmacodynamic parameters of some repurposed antiviral agents for SARS-CoV-2 infection.

Table I. PK/PD parameters of some repurposed antiviral drugs for SARS-CoV-2 infections

Drug	Pharmacokinetic/pharmacodynamic data
Remdesivir	A substrate for CYP2C8, CYP2D6, and CYP3A4 – note: for interactions with drugs that inhibit these cytochrome P450 isoenzymes, simultaneously is capable of inducing CYP1A2 and CYP2B6 - possible interactions pharmacokinetic, the drug does not prolong QTc
Atazanavir	A substrate for CYP3A4 - high risk of pharmacokinetic interactions with drugs that inhibit the activity of this isoenzyme, it is additionally an inhibitor of CYP3A4 and UGT1A1, prolong the QTc and PR interval in the ECG recording; note: in patients taking drugs that increase the pH in the ŧdigestive tract system (proton pump inhibitors, H2 antagonists) reduced solubility of the drug, which can reduce absorption from the conduit gastrointestinal tract and decrease the clinical efficacy of the drug
Lopinavir/ Ritonavir	lopinavir is metabolized by CYP3A4, both lopinavir and ritonavir are inhibitors of CYP3A4 and P-glycoprotein - high-risk interaction with other drugs used simultaneously is possible during therapy prolongation of PR on the ECG
Ribavirin	It does not prolong QTc, exercises caution when necessary simultaneous use in patients taking daclatasvir and sofosbuvir
Chloroquine, and Hydroxychloroquine	They have a slight inhibitory effect on the activity of CYP2D6 and P-glycoprotein (these pharmacokinetic interactions have no clinical significance), may cause prolongation of QTc, the need to monitor the ECG, especially when they are used in combination therapy with other drugs with a similar profile of undesirable action. Do not use simultaneously with amiodarone, flecainide, digoxin. Use caution when the patient is concomitantly taking bupropion. Don't administer to patients suffering from porphyria
Tocilizumab	Exercise caution when other myelotoxic drugs are used at the same time, no clinically significant pharmacokinetic interactions with other drugs, does not prolong QTc

Drug-drug Interactions:

Ritonavir, lopinavir, and atazanavir may cause numerous interactions of clinical relevance with antimicrobial agents, and with common cardiovascular disease drugs[42], they are collated in Table II, Antiviral medications utilized in Covid diseases can likewise cause harmful interactions with agents utilized in pain relief, psychotropic medications, drugs utilized in the ICU and with a different agent[43], for example, omeprazole, ondansetron or glucocorticosteroids. Table III contains the main medication interactions from the clinical perspective that should be borne at the top of the mind when taking mixed treatment. None of the antiviral drugs used in coronavirus infections can induce clinically significant interactions with norepinephrine, dobutamine, and vasopressin. Low risk of a clinically significant drug interaction may occur with ribavirin[43,44,45].

Table II. Interactions of drugs used in the pharmacotherapy of bacterial and fungal infections, and drugs used in the treatment of cardiovascular disease with antiviral agents used in SARS-CoV-2 infection

Drug/s	Interactions with drugs used in the treatment of coronavirus infection
Rifampicin	CYP3A4 inducer, diminished serum levels of lopinavir, ritonavir, and atazanavir; diminished clinical viability
Clindamycin	rises the serum levels of lopinavir, ritonavir, and atazanavir; augmented risk of side effects
Clarithromycin	increases the serum levels of lopinavir, ritonavir, and atazanavir; increased risk of side effects
Azithromycin	increases the serum levels of atazanavir; increased the risk of side effects
Azole antifungal drugs	all antifungal azoles increase the serum levels of lopinavir, ritonavir, and atazanavir; increased the risk of side effects
Valsartan	increases the serum levels of lopinavir, ritonavir, and atazanavir
Benazepril	increases the serum levels of atazanavir
Dihydropyridine calcium channel blockers	they cause an increase in the serum levels of lopinavir, ritonavir, and atazanavir
Beta-blockers	metoprolol, nebivolol, bisoprolol, and propranolol increase serum levels of lopinavir, and ritonavir; carvedilol increase the serum levels of atazanavir, esmolol, and landiolol does not induce adverse interactions with antiviral drugs
Statins - atorvastatin, and simvastatin	statins - atorvastatin and simvastatin cause an increase in the serum concentration of lopinavir, ritonavir, and atazanavir. Absolutely contraindicated in combination with atorvastatin
Sildenafil	increases the serum levels of lopinavir, ritonavir, and atazanavir
Eplerenone	increases the serum levels of lopinavir, ritonavir, and atazanavir
Torasemide	accelerates the elimination of lopinavir and ritonavir
Sacubitril	increases the serum levels of lopinavir, ritonavir, and atazanavir
Flecainide, amiodarone	increase the serum levels of lopinavir, ritonavir, and atazanavir, with chloroquine they increase the risk of arrhythmias
Digoxin	contraindication when combined with chloroquine
Clopidogrel	may decrease the serum levels of lopinavir, ritonavir, and atazanavir, and thus reducing their clinical efficacy
Rivaroxaban, and apixaban	increase the serum levels of lopinavir, ritonavir, atazanavir, and chloroquine
Dabigatran	may decrease the serum levels of lopinavir and ritonavir and increase the serum level of atazanavir
Ticagrelor	increases the serum levels of lopinavir, ritonavir, and atazanavir; does not affect the serum concentration of chloroquine

Table III. Interactions of drugs used in the treatment of; pain, anesthesia, psychosis and drugs used in ICUs with antiviral agents used in SARS-CoV-2 infection

Drug/s	Interactions with drugs used in the treatment of coronavirus infection
Tramadol	increases the serum levels of lopinavir, ritonavir, and atazanavir
Oxycodone	increases the serum levels of lopinavir, ritonavir, and atazanavir by up to 160% - the combination is not recommended
Morphine	decreases the serum concentration and the effectiveness of lopinavir and ritonavir (clinical trials)
Buprenorphine	increases the serum levels of atazanavir
Fentanyl	increases the serum levels of lopinavir, ritonavir, and atazanavir
Sufentanil	increases the serum levels of lopinavir, ritonavir, and atazanavir
Alfentanil	increases the serum levels of lopinavir, ritonavir, and atazanavir
Rocuronium	increases the serum levels of lopinavir, ritonavir, and atazanavir
Ketamine	increases the serum levels of lopinavir, ritonavir, and atazanavir
Bupiwakaina	increases the serum levels of lopinavir, ritonavir, and atazanavir
Mirtazapine	contraindication when combined with ritonavir, lopinavir, and atazanavir
Duloxetine, and bupropion	contraindication when combined with chloroquine
Zolpidem, and zopiclone	contraindication when combined with ritonavir, lopinavir, and atazanavir
Citaloparm, escitalopram	increase the serum levels of lopinavir, ritonavir, and atazanavir
Quetiapine	increases the serum levels of lopinavir, ritonavir, and atazanavir (simultaneous use is not recommended); no contraindication when combined with chloroquine
Midazolam	increases the serum levels of lopinavir, ritonavir, and atazanavir
Haloperidol	increases the serum levels of lopinavir, ritonavir, and atazanavir; no contraindication when combined with chloroquine
Methylpred-nisolone	increases the serum levels of lopinavir, ritonavir, and atazanavir
Ondansetron	increases the serum levels of lopinavir, ritonavir, and atazanavir
Omeprazole, esomeprazole	increase the serum levels of lopinavir, ritonavir, and atazanavir (simultaneous use is not recommended).

CONCLUSIONS:

The coronavirus pandemic is a global health crisis which is the most prominent challenge we have endured since World War II. No medicines have been confirmed sufficiently efficient to date yet. This review article points out corticosteroids can probably decline the death rate and need for mechanical ventilation in patients with severe COVID-19. Remdesivir perhaps lessens the amount of time that the symptoms need to resolve, but whether it influences further patient-important outcomes such as death remains indeterminate. Hydroxy chloroquine might not lessen mortality or mechanical ventilation, and it seems questionable to have any additional welfares. The properties of most drug interventions are presently extremely unclear, and no absolute proof occurs that further interventions result in significant benefits or harms for any outcomes. This article is also an effort to guide the clinicians to minimize the adverse effects resulting from drug-drug interactions of potential COVID-19 drugs.

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COMPETING INTERESTS:

The author declares that he has no competing interests.

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