Investigating Side Effects of Existing Drugs Used in Covid-19 Treatment

Sleiman Alhajj and Salih Gencer
School of Medicine
Istanbul Medipol University
Istanbul, Turkey

***Abstract*—Following the rapid spread and evolution of the novel Corona virus starting in December 2019, the lack of a vaccine or a medication that proved to be effective for Covid-19 was addressed as a major concern by the World Health Organization (WHO), the Center for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA) [1]. Accordingly, physicians from countries like China and Korea rushed to provide some potential treatment for Covid-19 from their experience in treating patients of the novel Coronavirus - they used antiviral medications like lopinavir, ritonavir, chloroquine, hydroxychloroquine, ribavirin, interferon, remdesivir, sofosbuvir, nitazoxanide, favipiravir, ivermectin, etc. [1]–[3]. These drugs showed improvement in conditions of Covid-19 patients when used individually, or sometimes using a combination of multiple of them. This does not mean that any combinations of these drugs could be beneficial. Some combinations can be lethal and may lead to increasing health risks or mortality. The drugs are being used in vitro (i.e., on cells in a laboratory for experiments) and vivo (i.e., on humans or animals as clinical trials). In vitro analysis, the chemical structure of the drug and the disease are analyzed to generate a hypothesis on the performance of the drug, then the hypothesis is tested in vivo to measure the actual performance of the drug on a living creature. Although these drugs showed promising results with proper dosage, overdose and incorrect combination with other drugs sometimes proved to be lethal. The effectiveness and side-effects of some of these drugs as reported by recent researchers and trials are described in this paper. We address some related research questions concerning the side effects of the covered drugs and their interaction with other drugs based on some well tested results extracted from approved websites of drug-drug interactions. The findings are interesting and confirmed favipiravir as the most effective and safe compared to the others, and this coincides with and supports the announcement by Turkish Ministry of Health where favipiravir has been used in treating COVID-19 patients since the early days.**

***Index Terms*—COVID-19, Drug-Drug interaction, side effects, infectious disease.**

I. Introduction

Inhabitants are subject to be exposed to and infected by various viruses leading to mild or severe diseases which may result in hospitalization and may ultimately end up with mortality or long-term disability. Thanks to pharmacological companies who since early days invested huge in developing drugs that have demonstrated effectiveness in the treatment of most of the diseases encountered so far, though not all drugs have been equally effective. However, no effective drug has been announced for the cure of many serious and life-threatening disease like COVID-19, HIV, cancer, etc. Some of these diseases are transmittal and infectious like HIV [4], [7] and COVID-19, while others are not like Cancer [5].

Regardless of whether a disease is transmittal or not, it is essential to have or (if does not exist) to develop effective drugs to save lives of people infected and to avoid or stop the wide spread of a disease into an epidemic or a pandemic [6]. However, developing a new drug is tedious, time and effort consuming challenge through all of its stages from lab development to actual approval and usage on a mass. Consequently, it is encouraged and highly welcomed to try to adapt or reposition some existing drugs [8] which have been proven effectiveness in the treatment of existing known diseases to treat emerging diseases which may share some symptoms or genetic mutations with already known and almost completely understood diseases.

Drug repositioning is a research area which has attracted considerable attention in the past decades [8]. It has been demonstrated effective for a number of emerging diseases. COVID-19 is one such disease which since it was detected in China in late December 2019 has attracted the attention of governments, healthcare professionals, and normal people at all levels. It may be considered as the most serious source of fear and death globally since the end of the second world war. It has been spreading widely and swiftly without clear anticipation of its causes or ways for effective treatment [3].

Avoiding the COVID-19 associated virus or stopping its spread is beyond discussion at this stage though some countries like Turkey have achieved great noteworthy success by tracing infected cases and all potential contacts [3]. Local and global governments have implemented some measures [9] to at least slow down the spread of the virus. These include locking down shopping malls, places of worship, restaurants, coffee shops, travel ban, shutting down university campuses and schools at all levels, etc. Though these measures have shown some effectiveness when they were applied seriously and the population helped officials in implementing them, still there has always been a need for an effective drug to treat infected persons who may range from mild to severe. Most of the latter cases have been admitted to an intensive care unit to be watched closely with ventilation. Indeed, the ventilation equipment has been announced as a major scarce resource desperately needed for a large number of COVID-19 patients. We have witnessed some countries prioritizing patients to put on ventilation machines leaving hopeless cases to face their

fate; this has been mostly a tragedy for elderly and seniors who passed away. Actually, the sudden emergence of COVID-19 and its fast widespread had revealed the weaknesses in the healthcare systems of many countries, including well developed Western countries where exhibition centers, sport arenas, etc. were turned into temporal hospitals to accommodate more severe cases.

Luckily, it did not take researchers and practitioners long to analyze the genetic properties of COVID-19, linking it to other existing similar diseases [2] like seasonal flu, pneumonia, malaria, SARS, MARS, etc. Indeed, COVID-19 had several predecessor viruses which may share several common symptoms and hence their treatment plans might enlighten the discovery of drugs and vaccines from COVID-19. These include, the Spanish epidemic, influenza pandemics and most recently SARS, MARS, N1H1 pandemics, among many other. This has stimulated another stream of research to investigate the opportunity to go for drug repositioning [9] by adapting some of the drugs which have been proven effective for diseases which share some symptoms with COVID-19. Some of these drugs have been addressed in this research.

This study will namely consider Ribavirin, Chloroquine, Ritonavir, Azathioprine, Favipiravi, and Hydroxychloroquine. Their side effects will be addressed along with their effectiveness in treating COVID-19 patients from a wide spectrum of cases ranging from mild to severe. This may be needed to look into because the effectiveness of a drug may diminish with severity of the cases or vice versa. This task will be accomplished by incorporating drug interactions extracted from University of Liverpool site: https://www.covid19-druginteractions.org/checker. For this study, the drug-drug-interactions will be used to identify the nature of a relationship between two drugs. In particular, the investigation will try to address as much as possible of the following research questions related to each of the COVID-19 drugs mentioned above:

- Which other drugs could be effectively used in combination with the given drug?
- What are the most commonly witnessed side effects in connection with the usage of the specific drug?
- What is the relationship between the level of side effects and the risk level of the specific drug?

The findings are interesting and revealed some valuable information in support of healthcare officials who have been desperately defending the effectiveness of some existing drugs for treating COVID-19 patients.

II. Materials and Methods

International organizations like WHO, CDC and FDA have been seeking a treatment for COVID-19 which continues to be the most threatening encountered virus. As domain experts in drug and vaccine development have almost agreed that a new drug or vaccine is not expected to be developed in the near future. Some anticipated at least a year to pass until a vaccine could be used. This motivated healthcare professionals and researchers to investigate whether some existing drugs could be adopted for the treatment of COVID-19 patients.

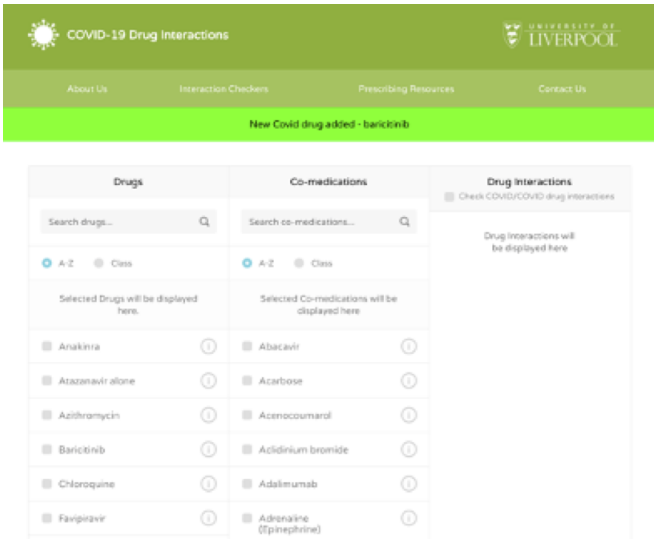


Fig. 1: Figure 1: A screen shot of the COVID-19 Drug Interactions Website developed by the University of Liverpool.

The literature has reported a large number of existing drugs which have been used by various countries and healthcare communities to treat COVID-19 patients. The list includes antiviral medications like lopinavir, ritonavir, chloroquine, hydroxychloroquine, ribavirin, interferon, remdesivir, sofosbuvir, nitazoxanide, favipiravir, ivermectin, etc. [1]–[3].

From the list, this study will concentrate on drugs which have been reported effective to either confirm their effectiveness or to highlight the risks associated with them. Inspiring from the daily announcement of the Turkish Minister of Health who always emphasizes the usage of an algorithm in their daily process, we have decided to develop our own algorithm for this task. Al algorithm is a sequence of steps once completed will lead to an outcome to be evaluated and reveal some knowledge.

The Algorithm: The process employed in this study consists of the following steps:

1) Decide on the drugs to be investigated in correlation with COVID-19 treatment
2) Use trusted and publicly available websites to retrieve the targeted data related to the specified drugs. This includes Drug-drug interactions and the side effects item Summarize the retrieved data for informative analysis. item Compare the outcome related to each of the investigated drugs.

The two main sites used by the algorithm are:

1) COVID-19 Drug Interactions Website developed by the University of Liverpool and shown in Figure 1, where a user can select the drugs he/she is interested in to get the consequences of their interaction, if any.
2) Drugs.com Website depicted in Figure 2. This site allows a user to retrieve a variety of information about drugs he/she is interested in.

III. Findings

Five COVID-19 related drugs, namely, Favipiravir, Chloroquine, Hydroxychloroquine, Lopinavir/ritonavir and Ribavirin

TABLE I: Table I: 50 from the 512 drugs which have interaction with the five drugs: Favipiravir, Chloroquine, Hydroxychloroquine, Lopinavir/ritonavir and Ribavirin that are used in treating COVID-19 patients. Drug combinations may have been assessed either by studying them or within the product label, or an interaction may have been predicted based on the metabolic profiles of the drugs, where 1 means no clinically significant interaction expected, 2 means potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration, 3 means potential interaction likely to be of weak intensity; additional action/monitoring or dosage adjustment is unlikely to be required; and 4 means the two drugs should not be co-administered

	Favipiravir	Chloroquine	Hydroxychloroquine	Lopinavir/ritonavir	Ribavirin
Metamizole	1	4	4	2	4
Atazanavir/cobicistat	1	2	2	4	2
Atazanavir + ritonavir	1	2	2	2	2
Atazanavir alone	1	2	2	2	2
Clozapine	1	2	2	2	2
Chloroquine	1		4	2	2
Baricitinib	3	2	2	1	2
Adalimumab	1	2	2	1	2
Anakinra	1	2	2	1	2
Azathioprine	1	2	2	1	2
Sarilumab	1	2	2	1	2
Tocilizumab	1	2	2	1	2
Belatacept	1	1	1	1	2
Linezolid	1	1	1	1	2
Lopinavir/ritonavir	1	2	2		1
Amiodarone	1	4	4	4	1
Bepridil	1	4	4	4	1
Carbamazepine	1	4	4	4	1
Cisapride	1	4	4	4	1
Disopyramide	1	4	4	4	1
Dofetilide	1	4	4	4	1
Domperidone	1	4	4	4	1
Erythromycin	1	4	4	4	1
Flecainide	1	4	4	4	1
Haloperidol	1	4	4	4	1
Ivabradine	1	4	4	4	1
Phenobarbital (Phenobarbitone)	1	4	4	4	1
Phenytoin	1	4	4	4	1
Pimozide	1	4	4	4	1
Primidone	1	4	4	4	1
Quinidine	1	4	4	4	1
Rifampicin	1	4	4	4	1
Rifapentine	1	4	4	4	1
St John's Wort	1	4	4	4	1
Ziprasidone	1	4	4	4	1
Aliskiren	3	3	3	4	1
Elvitegravir/Cobicistat/ Emtricitabine	2	3	3	4	1
Apixaban	1	3	3	4	1
Darunavir + ritonavir	1	3	3	4	1
Darunavir/cobicistat	1	3	3	4	1
Darunavir/Cobicistat/ Emtricitabine/	1	3	3	4	1
Elvitegravir/Cobicistat/ Emtricitabine	1	3	3	4	1
Rivaroxaban	1	3	3	4	1
Quetiapine	3	2	2	4	1
Clopidogrel	1	2	2	4	1
Ranolazine	1	2	2	4	1
Sirolimus	1	2	2	4	1
Budesonide	1	1	1	4	1
Dextropropoxyphene	1	1	1	4	1
Elbasvir/Grazoprevir	1	1	1	4	1

have been selected from the COVID-19 interactions website to find their influence on existing 512 drugs. The full list

Considering the four categories of interactions between drugs as mentioned in the caption of Table I, Figure 3 shows in relation to the five studied drugs a summary of the distribution of the retrieved 512 drugs into each of the four categories. The bar chart and the associated table clearly show how favipiravir and ribavirin are better than the others for not having negative effect with high risk. The bar chart shows how each two of the five drugs interact. Here, favipiravir looks the best among the five. This may better support the positive declaration by Turkish health Authorities regarding favipiravir. Here, it is worth sharing in Table II the interactions of the top 50 drugs from the University of Liverpool with the considered five COVID-19 related drugs. The ranking has been produced based on the interaction scores of favipiravir which is different from the others in the sense that it does not have any score of value 4, and only two of the top drugs on the list have a score of value 4 linked to other drugs. This may be a good indicator regarding the effectiveness of favipiravir.

Concerning the side effects of the considered COVID-19 drugs, they may be summarized as follows from the drugs.com website shown in Figure 2. First, it is important to mention that the website did not return any side effects for Favipiravir. No other site has been tried because Favipiravir has been reported to have positive impact on COVID-19 patients in Turkey; its

TABLE II: Table II: A list of the top drugs interacting with Favipiravir, which has been reported by healthcare professionals as one of the most successful drug in treating COVID-19 patients, these are the top 50 from the 512 drugs which have interaction with the five drugs: Favipiravir, Chloroquine, Hydroxychloroquine, Lopinavir/ritonavir and Ribavirin that are used in treating COVID-19 patients. Drug combinations may have been assessed either by a study or within the product label, or an interaction may have been predicted based on the metabolic profiles of the drugs, where 1 means no clinically significant interaction expected, 2 means potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration, 3 means potential interaction likely to be of weak intensity; additional action/monitoring or dosage adjustment is unlikely to be required; and 4 means the two drugs should not be co-administered

	Favipiravir	Chloroquine	Hydroxychloroquine	Lopinavir/ritonavir	Ribavirin
Alcuronium	3	1	1	1	1
Aliskiren	3	3	3	4	1
Amitriptyline	3	2	2	2	1
Baricitinib	3	2	2	1	2
Chlorpromazine	3	2	2	2	1
Clomipramine	3	4	4	2	1
Desogestrel (COC)	3	1	1	3	1
Desogestrel (POP)	3	1	1	3	1
Drospirenone (COC)	3	1	1	3	1
Drospirenone (HRT)	3	1	1	3	1
Dydrogesterone (HRT)	3	1	1	3	1
Estradiol	3	1	1	3	1
Ethinylestradiol	3	1	1	3	1
Etonogestrel (implant)	3	1	1	3	1
Etonogestrel (vaginal ring)	3	1	1	3	1
Felodipine	3	2	2	2	1
Gestodene (COC)	3	1	1	3	1
Levonorgestrel (COC)	3	1	1	3	1
Levonorgestrel (Emergency Contraception)	3	1	1	3	1
Levonorgestrel (HRT)	3	1	1	3	1
Levonorgestrel (implant)	3	1	1	3	1
Levonorgestrel (POP)	3	1	1	3	1
Maprotiline	3	2	2	2	1
Medroxyprogesterone (oral)	3	1	1	3	1
Norelgestromin (patch)	3	1	1	3	1
Norethisterone [Norethindrone] (COC)	3	1	1	3	1
Norethisterone [Norethindrone] (HRT)	3	1	1	3	1
Norethisterone [Norethindrone] (IM depot in	3	1	1	1	1
Norethisterone [Norethindrone] (POP)	3	1	1	3	1
Norgestimate (COC)	3	1	1	3	1
Norgestrel (COC)	3	1	1	3	1
Norgestrel (HRT)	3	1	1	3	1
Nortriptyline	3	2	2	2	1
Pethidine (Meperidine)	3	1	1	3	1
Quetiapine	3	2	2	4	1
Thioridazine	3	4	4	2	1
Ulipristal	3	1	1	3	1
Aminophylline	2	1	1	2	1
Cimetidine	2	2	2	1	1
Doravirine/ Lamivudine/ Tenofovir-DF	2	1	1	2	1
Elvitegravir/Cobicistat/ Emtricitabine/ Tenofo	2	3	3	4	1
Emtricitabine/ Tenofovir-DF	2	1	1	2	1
Paracetamol (Acetaminophen)	2	1	1	1	1
Pioglitazone	2	2	2	3	1
Pyrazinamide	2	1	1	1	1
Repaglinide	2	2	2	2	1
Rosiglitazone	2	2	2	3	1
Tenofovir-DF	2	1	1	2	1
Theophylline	2	1	1	2	1
Treprostinil	2	1	1	1	1
Zaleplon	2	1	1	3	1

side effects may not be considered to have high risk.

Commonly reported side effects of ribavirin include hemolytic anemia, decreased hemoglobin, insomnia, dyspnea, lack of concentration, emotional lability, and irritability. Other side effects include nervousness. Lopinavir/ritonavir may lead to changes in food taste, fat redistribution in the body, diarrhea, insulin resistance, high blood sugar levels, high cholesterol or triglyceride levels, liver problems, nausea, vomiting, rash, and jaundice. Hydroxychloroquine is linked to headache, dizziness, diarrhea, stomach cramps, vomiting blurred vision or other vision changes, heart disease, severe hypoglycemia, sore throat, among others. Chloroquine may have the following side effects: loss of appetite, mild dizziness, mild diarrhea, clumsiness, mild headache, nausea or stomach cramps, unusual behavior or mood changes, severe diarrhea vision problems or blurred vision, etc. Some more details have been added to the discussion section.

IV. Discussion

This section covers more details related to four of the COVID-19 drugs considered in this study. Again, favipiravir has been left out because it is a clear winner from all the information reported above in this study.

Ribavirin:: Given its effectiveness and availability, ribavirin is one of the antiviral drugs that have been suggested by the physicians with different dosages and sometimes with

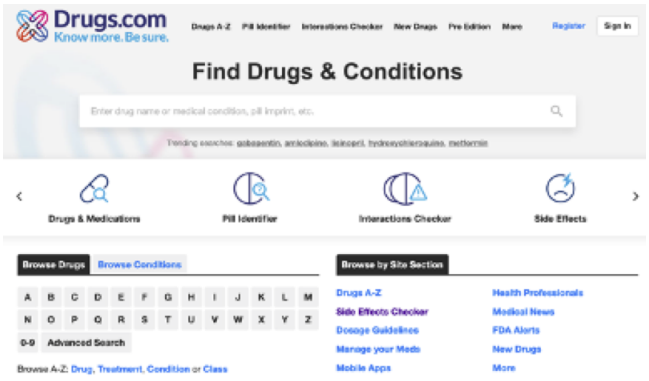


Fig. 2: A screen shot of the Drugs.com Website where it is possible to retrieve a lot of information about drugs, including their side-effects.

other medications for Covid-19 treatment [10]. The effect of Ribavirin in the analysis of RdRp protein encoding sequences (i.e., protein for RNA-based viruses) of coronavirus shows that Ribavirin can tightly bind with the RdRp of Covid-19 that can reduce the spread of the viral infection [21]. Different dosages from 500mg to 2g for 8 to 10 days showed efficacy in Covid-19 treatment. The attractions of Ribavirin may be listed as follows [1], [10], [11]:

- It is very effective on RNA or DNA viruses that cause multiple organ infections.
- It is useful on acute respiratory syndrome, or pneumonia, and it reduces the chance of the infection causing organ failures.
- A combination of Ribavirin and Corticosteroids shows initial improvement of fever and pneumonia.
- It is also effective for viral hemorrhagic fever caused by damage in the complete vascular system (i.e., a severe multisystem syndrome effecting multiple organs simultaneously).
- A combination of Ribavirin and Lopinavir or Ritonavir is more effective than the combination of Ribavirin and Corticosteroids in case of prolonging the infections of various organs.
- The usage of Ribavirin showed 2.16 times more effectiveness in curing the viral infections for Middle East Respiratory Syndrome (MERS-CoV).
- Viral replication maybe blocked, and this increased the survival rate of MERS-CoV patients by reducing the amount of intensive care unit admissions compared to patients on other medications.
- A combination of Lopinavir/Ritonavir, Ribavirin, and IFN-α2a showed very impressive results for a case study on MERS-CoV patients.

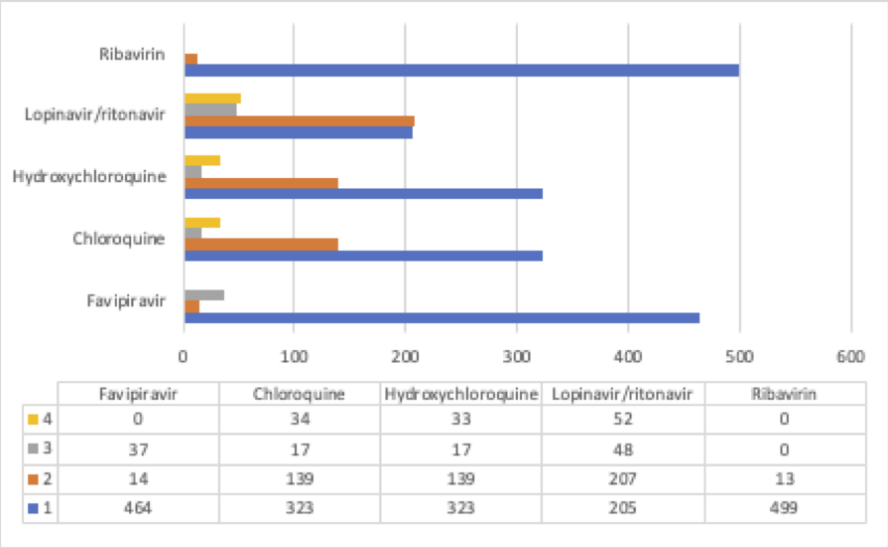
Some of its side effects may be listed as follows:

- Hemolysis (i.e., destruction of red blood cells) is one of the adverse effects which increases bilirubin or decreases haptoglobin in blood by 1.5 times.
- It causes 2 g/dL decrease in hemoglobin level leading to Anemia.
- Acute liver toxicity by increased transaminases leading to liver damage is one severe side-effect. Ribavirin increases aspartate aminotransferase or alanine aminotransferase by 1.5 folds.
- It affects children with abnormalities in rental functions (i.e., creatinine clearance and serum creatinine below or above a specific range).
- Children can suffer from fever, fatigue, headache and neutropenia (i.e., low concentration in a type of white blood cell).
- Decreased level of hemoglobin in blood can cause severe heart damage in children.
- Recurrent fevers, severe respiratory conditions, radiographic lesions, watery diarrhea are some adverse effects of a combination of Ribavirin and Corticosteroids.

Chloroquine:: Chloroquine is one of the mostly suggested drugs for Covid-19 treatment; it is characterized by low cost [12]. It has been used for malaria and other autoimmune diseases for the last 70 years. It is an antimalarial drug that reduces infections caused by viruses and has been effective in Severe acute respiratory syndrome (SARS), chikungunya, autoimmune and chronic diseases [13], [14]. Results of clinical trials on different numbers of Covid-19 patients divided into intervention (i.e., Chloroquine treatment) and comparison (i.e., other treatments) groups showed promising outcome in case of body temperature, respiratory system, co-infections, nucleic acid conversion rate, recovery time, mortality rate etc. [15]. A dosage of 500mg for 10 days showed improvements in Covid-19 patients. As Chloroquine has toxicity property, it can be either used for a short period with high dosage or a long period with low dosage [16]. The basic highlights of Chloroquine can be listed as follows [13], [15]–[18]:

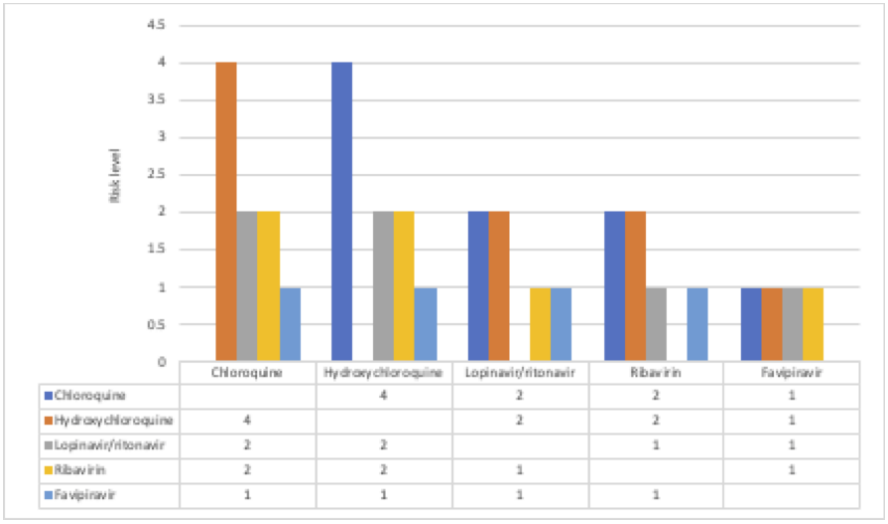
- It can interfere and reduce the virus entry to cells, virus life cycle, virus replication to different body parts, translations of virus proteins to reduce the effect of a virus on human body.
- It increases cell fusions by changing the level of endosomal pH that reduces viral infections.
- The communication between cells and plasma membrane by cellular receptors or membrane recycling due to Covid-19 is reduced by Chloroquine interference which decreases the spread of the virus in the whole body.
- A standard dose of Chloroquine can reduce the virus replication process which in turn reduces the entry of Covid-19 to cells, and hence decreases the damage in tissues and lungs.
- As Chloroquine can reach the tissues of every organ of the body (specially the lungs), it can enhance the viral infections drastically.
- It can reduce the fever caused by Covid-19 rapidly.
- It can improve lung conditions and pneumonia.
- Recovery time for Covid-19 patients treated with Chloroquine is considerably less that other treatments.
- It improves the immune system by activating the necessary cells, proteins and creating anti-inflammatory responses of cells.

Some ‘side-effects’ of Chloroquine may be listed as follows [14]–[16], [18]–[20]:



	Favipiravir	Chloroquine	Hydroxychloroquine	Lopinavir/ritonavir	Ribavirin
4	0	34	33	52	0
3	37	17	17	48	0
2	14	139	139	207	13
1	464	323	323	205	499

Fig. 3: Figure 3. A bar graph showing how the COVID-19 website show in Figure 1 identified correlations between drugs from neutral (1) to very risky (4) – refer to the caption of Table I.



	Chloroquine	Hydroxychloroquine	Lopinavir/ritonavir	Ribavirin	Favipiravir
Chloroquine		4	2	2	1
Hydroxychloroquine	4		2	2	1
Lopinavir/ritonavir	2	2		1	1
Ribavirin	2	2	1		1
Favipiravir	1	1	1	1	

Fig. 4: Figure 4. A bar chart showing risk level of the interaction between each pair of the five COVID-19 drugs considered in this study.

- It can lead to cardiovascular disorders, bradycardia (i.e., low heart rate), prolonged QT interval (i.e., measurements of electrical properties of heart) with incorrect dosage [14]–[16], [18].
- Blood disorders like anemia, electrolyte imbalance, thrombocytopenia (i.e., low amount of blood platelet), leukopenia (i.e., low amount of white blood cells), hypotension (i.e., low blood pressure) are possible side-effects of Chloroquine.
- It can cause damage to liver functions.
- Renal dysfunction is another adverse effect of Chloroquine.
- Long term Chloroquine treatment can cause rheumatoid arthritis by creating painful swellings in small joints.
- Vision loss and irreversible retinal damage can be caused by long term overdose of Chloroquine as it reacts to the retinal pigment melanin, inner and outer layers of retina, chronic exposure of light absorption and photo reception.
- Visual impairments like diplopia or double vision can be caused by combination of Chloroquine with other drugs.
- A combination of chloroquine with antidepressants may lead to psychological impairments.
- Its overdose affects the central nervous system. Overdosage can lead to gastrointestinal and neurological issues, arrhythmia and blood disorders within only few hours of overdose. Overdose of Chloroquine can also lead to death of the patients with mild or severe respiratory failure.
- It can cause obesity in patient.
- Its poisoning in children is a potential risk of overdose that can lead to death in extreme cases of toxicity.

Lopinavir–Ritonavir:: Ritonavir is a drug mostly used for HIV related diseases, but it is also used for SARS and MERS [11]. It interrupts the structures of the core proteins of the virus, while helps to produce non-infectious virus components to reduce the virus infections. It increases the immunity

of the body and decreases the virus cells in blood. The non-structural protein of Covid-19 called 3C-like proteases are responsible for virus replication and Ritonavir attacks that protein to reduce the virus replication and to produce more immature, non-infectious virus cells [22]. 400/100 mg Lopinavir–Ritonavir for 14 days is suggested; that can work similar to a standard care system [23]. The basic attractions of Ritonavir can be listed as follows: [23]–[26]

- It can help patients at early stage of Covid-19 with less severe symptoms to control the severity of the disease.
- It can reduce viral loads in blood, and treats the infections caused by Covid-19.
- Mortality rate can be decreased with Lopinavir–Ritonavir treatment within a shorter period of intensive care unit treatment.
- It potentially reduces recovery time for Covid-19 patients.
- It helps decreasing the body temperature rapidly by recovering from fever.
- It can reduce the abnormalities in blood components like white blood cells, lymphocytes, C-reactive proteins, platelets, hemoglobin, granulocytes etc.
- It reduces the recovery time for Covid-19 patients by almost 3 days.
- It reduces the effect of pneumonia
- A combination of Ribavirin and Lopinavir–Ritonavir can reduce the risk of respiratory distress leading to death for patients with Covid-19.
- A combination of three drugs Interferon beta-1b, Lopinavir–Ritonavir, and Ribavirin can be more effective in case of recovery time and virus replication.

Some 'side-effects' of Ritonavir may be listed as follows [11], [16], [18], [26], [27]

- It increases bilirubin levels in patients.
- It causes liver damage for patients with severe liver diseases or hepatic insufficiency.
- It has an adverse effect on children suffering from jaundice as Ritonavir can increase the bilirubin level and effect the jaundice.
- A higher degree cardiac block, sinus bradycardia (i.e., lower heart rate) or prolonged QT interval (i.e., measurements of electrical properties of heart) are possible with Ritonavir overdose.
- It may cause hypokalemia (i.e., low potassium level in blood).
- Patients can suffer from rash, nausea, vomiting and diarrhea
- It can lead to gastrointestinal damages.

Hydroxychloroquine:: Hydroxychloroquine is an available antimalarial drug. It is a derivative of Chloroquine with less toxic side-effects, hence can be used for longer period for treatments [28]. The N-diethyl group of Chloroquine is replaced by a side chain of N-hydroxyethyl making it more soluble into body [29]. Hydroxychloroquine also increases the pH level to reduce virus replication and infection, but also increases the immune system protein (i.e., toll-like receptors) and decreases the proteins that communicate for virus transmission. A 400mg daily dose of Hydroxychloroquine for 5 to 6 days is normally suggested for Covid-19 [1], [30]. The basic characteristics of Hydroxychloroquine can be listed as follows [28]–[30]-

- It can decrease the body temperature/fever and cough in less time.
- Pneumonia, lung damages and other respiratory issues improve significantly by Hydroxychloroquine treatment.
- Quick recovery from viral infections can be achieved by Hydroxychloroquine.
- Visual impairments due to Hydroxychloroquine are less severe than Chloroquine.
- It prevents receptor binding and fusion of membranes to reduce the entry of Covid-19 virus.
- Covid-19 spread can be prevented, and the viral replications can be reduced by Hydroxychloroquine at early stages of coronavirus.
- It is less likely to create infectious complications like immunosuppressant drugs.
- It can be used on pregnant patients with autoimmune diseases; it is a potential drug for pregnant women with Covid-19 [31].
- Congenital heart blocks (i.e., heart blocks due to a structural birth defect of heart) can be prevented with Hydroxychloroquine.

Some 'side-effects' of Hydroxychloroquine are as follows:

- It may cause abnormalities in liver functions.
- Rash, diarrhea, nausea, vomiting, headache are some common side-effects of Hydroxychloroquine.
- Vision impairment like retinopathy (i.e., damage in retina) or blurring are possible side-effects of long-term Hydroxychloroquine overdose.
- It sometimes shows prolonged QT interval (i.e., measurements of electrical properties of heart) and cardiac arrests in patients.
- Severe renal damages are potential adverse effects of Hydroxychloroquine.
- It can increase the risk of arrhythmia in Covid-19 patients.

V. Conclusion

As concluding remark, it is obvious that some of the existing drugs could be repositioned or repurposed to be adapted to treat COVID-19 patients. Though favipiravir has shown the best results in some countries like Turkey, other drugs like ribavirin and Hydroxychloroquine have already been reported successful by other countries. This requires some deep investigation to determine whether there are particular reasons associated with the healthcare system in the specific country, the body characteristics and genetics of people living in each country which make a specific drug more useful for them than for those who live in other countries.

References

[1] Smith T. and Prosser T., "COVID-19 Drug Therapy–Potential Options". In: Clinical Drug Information, Clinical Solutions, Elsevier (March 2020).

[2] Lai C.C., Tzu-Ping Shih T.P., Ko W.C., Tang H.J. and Hsueh P.R., "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease- 2019 (COVID-19): the epidemic and the challenges". In: International journal of antimicrobial agents, Elsevier (February 2020), p. 105924.

[3] Yavuz S., and Unal S. “Antiviral treatment of COVID-19”. In: Turkish Journal of Medical Sciences 50.SI-1 (April 2020), pp. 611–619.

[4] Orrell, C., Hagins, D. P., Belonosova, E., Porteiro, N., Walmsley, S., Falcó, V., Man, C. Y., Aylott, A., Buchanan, A. M., Wynne, B., Vavro, C., Aboud, M., Smith, K. Y., Cahn, P. E., Cassetti, L. I., Porteiro Barreira, N., Angel, J. B., de Pokomandy, A., Harris, M., … Van Dam, C. N. (). Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. The Lancet HIV, 4(12), e536–e546. 2017, https://doi.org/10.1016/S2352-3018(17)30095-4

[5] Gunn, G. B., Debnam, J. M., Fuller, C. D., Morrison, W. H., Frank, S. J., Beadle, B. M., Sturgis, E. M., Glisson, B. S., Phan, J., Rosenthal, D. I., & Garden, A. S. The impact of radiographic retropharyngeal adenopathy in oropharyngeal cancer. Cancer, 119(17), 3162–3169, 2013. https://doi.org/10.1002/cncr.28195

[6] Price E., MacPhie E., Kay L., Lanyon P., Griffiths B., Holroyd C., Abhishek A., et al. “Identifying rheumatic disease patients at high risk and requiring shielding during the COVID-19 pandemic”. In: Clinical Medicine (May 2020).

[7] Wood, R. Atazanavir: Its role in HIV treatment. Expert Review of Anti-Infective Therapy, 6(6), 785–796.2008. https://doi.org/10.1586/14787210.6.6.785

[8] Sun, W., Sanderson, P. E., & Zheng, W., Drug combination therapy increases successful drug repositioning. Drug Discovery Today, 21(7), 1189–1195. 2016. https://doi.org/10.1016/j.drudis.2016.05.015

[9] Fong M.W. , H. Gao, J. Y. Wong, J. Xiao, E. Y.C. Shiu, et al., Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Social Distancing Measures, Emerging Infectious Diseases, Vol. 26, No. 5, May 2020

[10] Khalili J.S., Zhu H., Mak N.S.A., Yan Y., and Zhu Y.. “Novel coronavirus treatment with ribavirin: Groundwork for an evaluation concerning COVID- 19”. Journal of medical virology (March 2020), pp. 1–7.

[11] Wang Y., and Zhu L.Q., “Pharmaceutical care recommendations for antiviral treatments in children with coronavirus disease 2019”. In: World Journal of Pediatrics, Springer (March 2020), pp. 1–4.

[12] Gao J., Tian Z., and Yang X., “Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies”. In: Bioscience trends (2020).

[13] Wang M., Cao R., Zhang L., Yang X., Liu J., Xu M., Shi Z., Hu Z., Zhong W. and Xiao G.. “Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro”. In: Cell research, Nature 30.3 (March 2020), pp. 269–271.

[14] Touret F. and de Lamballerie X., “Of chloroquine and COVID-19”. In: Antiviral research, Elsevier (March 2020), p. 104762.

[15] Cortegiani A., Ingoglia G., Ippolito M., Giarratano A. and Einav S.. “A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19”. In: Journal of critical care, Elsevier (March 2020).

[16] Devaux C.A., Rolain J.M., Colson P., and Raoult D. “New in- sights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?” In: International journal of antimicrobial agents, Elsevier (March 2020), p. 105938.

[22] Nutho B., Mahalapbutr P., Hengphasatporn K., Pattaranggoon N.C., Simanon N., Shigeta Y., Hannongbua S., and Rungrotmongkol T.. “Why are lopinavir and ritonavir effective against the newly emerged Coronavirus 2019? Atomistic insights into the inhibitory mechanisms”. In: Biochemistry 59.18 (April 2020), pp. 1769–1779.

[17] Hu T.Y., Frieman M., and Wolfram J., “Insights from nanomedicine into chloroquine efficacy against COVID-19”. In: Nature Nanotechnology, Nature 15.4 (April 2020), pp. 247–249

[18] Smit C., Peeters M.Y.M., van den Anker J.N., and Knibbe C.A.J. “Chloroquine for SARS-CoV-2: implications of its unique pharmacokinetic and safety properties”. In: Clinical Pharmacokinetics, Springer (April 2020).

[19] Ruamviboonsuk P., Timothy YY Lai, Chang A., Lai C.C., Mieler W.F., and Lam D.S.C. “Chloroquine and Hydroxychloroquine Retinal Toxicity Consideration in the Treatment of COVID-19”. In: Asia-Pacific Journal of Ophthalmol- ogy (Philadelphia, Pa.) (March 2020).

[20] Moore N.. “Chloroquine for COVID-19 infection”. In: Nature Switzerland, Springer (April 2020), pp. 1–2.

[21] Elfiky A. “Anti-HCV, nucleotide inhibitors, repurposing against COVID-19”. In:Life sciences, Elsevier (February 2020), p. 117477.

[23] Cao B., Wang Y., Wen D., Liu W., Wang J., Fan G., Ruan L., et al. “A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19”. In: New England Journal of Medicine (March 2020).

[24] Klement-Frutos E., Burrel S., Peytavin G., Marot S., Leˆ M.P., Godefroy N., Vincent Calvez V., et al. “Early administration of ritonavir-boosted lopinavir could prevent severe COVID-19”. In: Journal of Infection, Elsevier (May 2020).

[25] Lim J., Jeon S., Shin H.Y., Kim M.J., Seong Y.M., Lee W.J., Choe K.W., Kang Y.M., Lee B. and Park S.J.. “Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 pneu- monia monitored by quantitative RT-PCR”. In: Journal of Korean Medical Science 35.6 (January 2020).

[26] Hung I.F.N., Lung K.C., Eugene Tso Y.K., Liu R., Chung T.W.H., Chu M.Y., Ng Y.Y., et al. “Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial”. In: The Lancet 395.10238 (May 2020).

[27] Deng L., Li C., Zeng Q., Liu X., Li X., Zhang H., Zhongsi Hong, and Jinyu Xia. “Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study”. In: Journal of Infection, Elsevier (March 2020).

[28] Sarma P., Hardeep Kaur, Harish Kumar, Dhruv Mahendru, Pramod Avti, Anusuya Bhattacharyya, Manisha Prajapat et al. “Virological and clinical cure in COVID-19 pa- tients treated with hydroxychloroquine: a systematic review and meta-analysis”. In: Jour- nal of medical virology (April 2020).

[29] Sahraei Z., Shabani M., Shervin Shokouhi, and Ali Saffaei. “Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine”. In: Int J Antimicrob Agents 105945.10.1016 (March 2020).

[30] Geleris J., Sun Y., Platt J., Zucker J., Baldwin M., Hripcsak G., Labella A., et al. “Observational study of hydroxychloroquine in hospitalized patients with Covid-19”. In: New England Journal of Medicine (May 2020).

[31] Zhou D., Dai S.M., and Tong Q.. “COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression”. In: Journal of Antimicrobial Chemotherapy (March 2020).

[32] Ye X. T., Y. L. Luo, S. C. Xia, Q. F. Sun, J. G. Ding, Y. Zhou, W. Chen et al. “Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019”. In: Eur Rev Med Pharmacol Sci 24.6 (March 2020), pp. 3390–3396.