*Sys Rev Pharm 2021;12(1):786-804*
A multifaceted review journal in the field of pharmacy

# Pharmacological Insight into Possible Treatment Agents for the Lethal Covid-19 Pandemic in Kurdistan Region- Iraq

**Diyar Salahuddin Ali** [a,*] (ID), **Hazha Omar Othman** [b] (ID)

[a,b] Chemistry Department, College of Science, Salahaddin University, 44002, Erbil, Iraq
* Corresponding Author
E.mail: diyar.ali@su.edu.krd, Mobile no. +9647504471393

**ABSTRACT**

The magnitude of the risks in the face of the COVID-19 disease is increasing every day, and foreshadowing a catastrophe facing humanity. It is clear, the levels of health services in different countries around the world are very different, therefore there will be many health risks in countries that are suffering in terms of health services. The objective of this study was to compare different therapy for patients with severe coronaviruses diseases (COVID-19). Nowadays, different medicines have been used to reduce the severity of symptoms of this disease such as Ribavirin, Chloroquine, Arbidol, Lopinavir/Ritonavir, Favipiravir, Remdesivir, Azithromycin, and Sputnik V. These medications are used in every region of the world to make some progress in finding a solution to (COVID-19), including Kurdistan region which is in the north of Iraq. As is the case in most third world countries, the health service is not at the required level, and despite that, we were able to make a comprehensive list of medicines used in many countries of the world and here in Kurdistan, Iraq. In addition to this narrative and comparison of the best medication used to treat this pandemic, we also surveyed the opinions of over 100 people on the medicines discussed in this study throughout their treatment. The medicinal properties of medications used for COVID-19 and the results of their use on humans were studied in this review to promote appropriate medications for the treatment of coronavirus.

**Keywords:** COVID-19, coronavirus, SARS-CoV-2, Medicine, Ribavirin, Chloroquine, Arbidol, Lopinavir/Ritonavir, Favipiravir, Remdesivir, Azithromycin and Sputnik V

**Correspondence**:
Diyar Salahuddin Ali
Chemistry Department, College of Science, Salahaddin University, 44002, Erbil, Iraq
E.mail: diyar.ali@su.edu.krd

## INTRODUCTION

A case appeared in the Chinese city of Wuhan in late 2019 that caused a concern until this day, which is the disease of corona. A new pandemic coronavirus disease such as human coronaviruses, SARS pneumonia and coronavirus has been identified, called COVID-19, COVID-19 has lots of pharmacological medicines. Due to the urgent need for effective medicine, we had to return to the previously used drugs in treating such kind of diseases(Ouassou, Kharchoufa et al. 2020). Around the world, a prevailing belief made people tend to drugs that has been used to treat common diseases such as SARS and the common flu. Because SARS-CoV-2 was the cause of this pandemic (Zhang, Chen et al. 2013), an enormous number of infections, their rapidly widespread and similarity of symptoms were the reasons for choosing this methodology. Coronaviruses are RNA viruses that are considered to be one of the viruses that cause multiple illnesses and vary in severity. It may be a common cold and may be in the form of strong pneumonia(Li, Zai et al. 2020). This type of virus appeared in the thirties in birds and caused many diseases in different systems in the human body, just seven coronaviruses are known to cause infection in people. Three of them caused severe infections in humans and deadly pneumonia (MSD Manual Professional Versio 2020, July).

**SARS-CoV-2**: is an enveloped single-stranded positive-sense RNA virus (Ma, Su et al. 2020). In Wuhan, China, at the end of 2019, this virus was identified as the cause of coronavirus disease 2019.

**MERS-CoV:** The first infection of this virus was detected in 2012 (Zhang, Chen et al. 2013) it got this name because it was first discovered in Saudi Arabia in the Middle East, also known camel flu.

**SARS-CoV**: This virus was detected in 2003 and considered a main source of SARS, which appeared in 2002 in China (Li, Zai et al. 2020). The effect of this virus on humans is in the form of successive steps, as it starts with normal flu, progresses to respiratory failure, reaches pneumonia, and may sometimes reach death.

In late 2019, a group of people with a disease similar to coronavirus-related symptoms appeared in China(Ezhilan, Suresh et al. 2021), at first they were treated as normal patients, but the World Health Organization classified that case as a new type of virus and it was called 2019-nCoV. Later, the virus was renamed to SARS-CoV-2 and considered as the main cause of coronavirus diseases (COVID-19). Initially, this virus was connected to animals in China, and this is evidence that the virus has been transmitted from animals to humans, the virus spreads by different ways between humans, it may be the result of contact with infected secretions or by touching a surface contaminated with respiratory droplets. COVID-19 is transmitted from people who suffer from the disease to healthy people. According to the National Health Commission, 2020 data, it appears to us clearly that this virus is more widespread than SARS (MSD Manual Professional Versio 2020, July).

In the first few days of the pandemic many researchers begun their experiments with various drugs, they also studied how these medicines are different in the quality and effectiveness for fighting the virus (Jeevaratnam 2020), within a short period many researches have been conducted on drugs, and we here in this review conduct a survey of the most important drugs and make a comparison between them, in addition to a questionnaire, about the drugs that used and their effects, by involving more than 100 people here in Kurdistan, Iraq.

## LITERATURE

Finding of the investigation of the literature, in the official websites, and worldwide famous publishing centers and

databases to identify the best medicine used for coronavirus treatment. Those papers with a description with medicines for coronavirus treatments were selected including articles comments, treatment strategy, results, and review. The vast majority of studies included in the review found that similarity between the drugs which were used for disease treatment around the world including Kurdistan region- Iraq. Our review will be updated with the increase of more studies on these medicines which are used for coronavirus treatment.

**Purpose of the work**

In addition to make a review about the best medicine used for coronavirus treatment, also in this study we evaluated the antiviral effect of these medicines in patients with the coronavirus (COVID-19) disease. Our study includes more than 100 patients with laboratory-confirmed (COVID-19) disease in the Kurdistan region which includes (Erbil- Sulaminya- Duhok and Garmiyan) governorate.

**Medicine against COVID-19**

At the moment, coronavirus is mainly treated with drugs that could fight viruses, according to previous laboratory experiences. All information about these medicines are listed below.

**Ribavirin**

Ribavirin was discovered in 1972 and is used to treat HCV-contamination patients, the mechanism by which the atom adds to an antiviral reaction in these patients remains largly tricky. Ribavirin's antiviral action is a mix of different mechanisms (Paeshuyse, Dallmeier et al. 2011). It is a widespread antiviral that may be in the form of phosphorylated in red blood cells to produce ribavirin monophosphate, diphosphate, and triphosphate, the first type is a strong inhibitor of inosine monophosphate dehydrogenase and thus it inhibits the viral DNA, leading to the inability of the virus to coexist within the host body (Pan, Dong et al. 2020). The action of this antivirus can be explained more in Fig. (1) (Te, Randall et al. 2007).

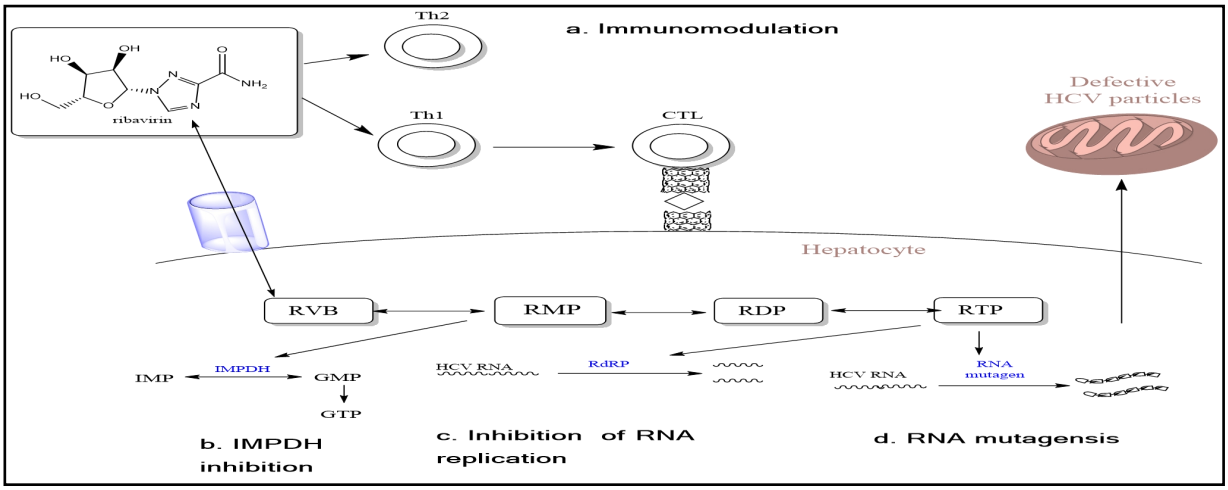


**Figure 1: Active site for ribavirin against HCV virus**

Ribavirin is simply an antiviral that restrains viral RNA-subordinate RNA polymerase (Fig. 2.). Its capabilities are few if compared with another antivirus, it was used through the 2003 SARS-CoV and 2012 MERS-CoV outbreaks (Khalili, Zhu et al. 2020). According to the available data that examined the ribavirin effects on coronavirus. These results have unfortunately yielded unclear benefits (Infectious Diseases Society of America Guideli 2020, September 15 ). The scientists proposed that ribavirin was less effective if compared with therapeutic agents (Wang, Zhang et al. 2020).

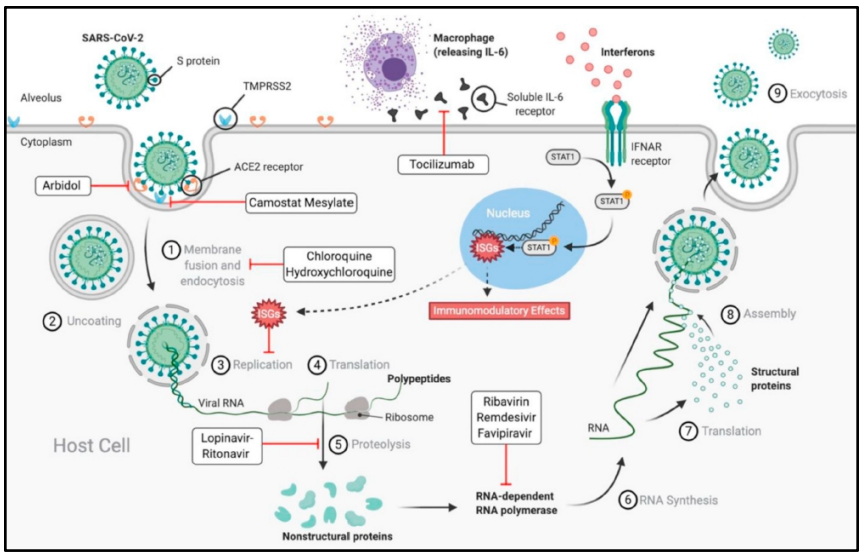

**Figure 2:** Ribavirin against coronavirus mechanism

Hung and his co-workers exposed 127 patients in six different hospitals in Hong Kong to this treatment at a dose of 400 mg per 12 hours for 14 days in addition to taking control samples. During the time between Feb 10 and March 20, 2020. The results showed that early treatment with ribavirin is appropriate for the treatment of coronavirus because the virus (COVID-19) reaches peak activity shortly after the appearance of the symptoms, and this is exactly the opposite of the case of SARS and MERS. No side effects were observed for the patients (Hung, Lung et al. 2020).

Another group of researchers in China have tried this treatment on more than 115 patients suffering from the coronavirus disease, and the results showed that ribavirin might be useful for treating coronavirus infection because of its ability to inhibit the RNA of the virus (Tong, Su et al. 2020). This study has conclusively proved the importance of this virus in reducing the symptoms of this disease, but it proved that using this drug may reduce the mortality rate of this disease. Table (1) showed that there are no significant differences in laboratory parameters in some blood tests

**Table 1:** Parameters therapy for COVID-19.

| Parameter | Control group | Ribavirin group |
|---|---|---|
| **Hemoglobin g/L** | 115.8 ±19.8 | 116 ±16.7 |
| **Hemoglobin change g/L** | -10.4 ±12.6 | -5.3 ±13.5 |
| **Platelet count (x $10^9$/L)** | 243.3 ±103.8 | 263.4 ±128.2 |
| **Serum creatinine µmol/L** | 69.7 ±26.8 | 63.3 ±21.4 |

Another therapy mechanism was applied to moderate COVID-19 patients admitted to the Ghaem Shahr Razi Hospital in Mazandaran Province, Iran (Pourghasemi, Pouyan et al. 2020). Patients were assigned antiviral mixture including ribavirin. This study showed that using ribavirin in a combination of antivirals resulted in a slight clinical improvement, especially in the moderate COVID-19 patients, and the results of this study showed that it reduces the number of patients in ICU. In general, the differences between disease and control cases were not significant as mentioned in Table (2).

**Table 2:** Clinical comparison between two groups.

| Parameter | Mix antiviral (Ribavirin included) n(24) | Control n(24) |
|---|---|---|
| **Duration of hospitalization (days)** | 6(5-7) | 6(5.5-7.5) |
| **Recovery** | 24(100) | 21(88) |
| **Death** | 0(0) | 3(13) |
| **Time to recovery (days)** | 6(5-7) | 6(6-8) |
| **ICU admission** | 0(0) | 4(17) |

Six different specialists in infectious diseases exposed a group of COVID-19 patients in Taleghani hospital, Iran, to doses of ribavirin and compared it with a combination of antivirals, and the results are showed in Table (3) (Nabian, Vosoughi et al. 2020).

**Table 3:** Comparison between ribavirin and mix antivirals.

| Parameter | Mix antiviral (Ribavirin not included) n(45) | Ribavirin n(35) |
|---|---|---|
| **Duration of hospitalization (days)** | 6(5-7) | 9(6-11) |
| **Recovery** | 33(94) | 18(67) |
| **Death** | 2(5.7) | 9(33) |
| **Time to recovery (days)** | 6(5-8) | 11(9-!) |
| **ICU admission** | 6(17) | 13(48) |

Ribavirin has been definitively proven to prevent the SARS-CoV from multiplying in five types of human and animal cells at an acceptable healthy concentration (Morgenstern, Michaelis et al. 2005). Adverse reactions noted during ribavirin treatment, due to some patients suffering from hemolytic anemia, hypocalcemia, and hypomagnesemia (Knowles, Phillips et al. 2003).
Through the questionnaire that we did in the governorates in northern Iraq, in the Kurdistan region, out of 100 patients with COVID-19, it was found that the percentage of the usage of this drug in treatment was zero as shown in Fig. (3).

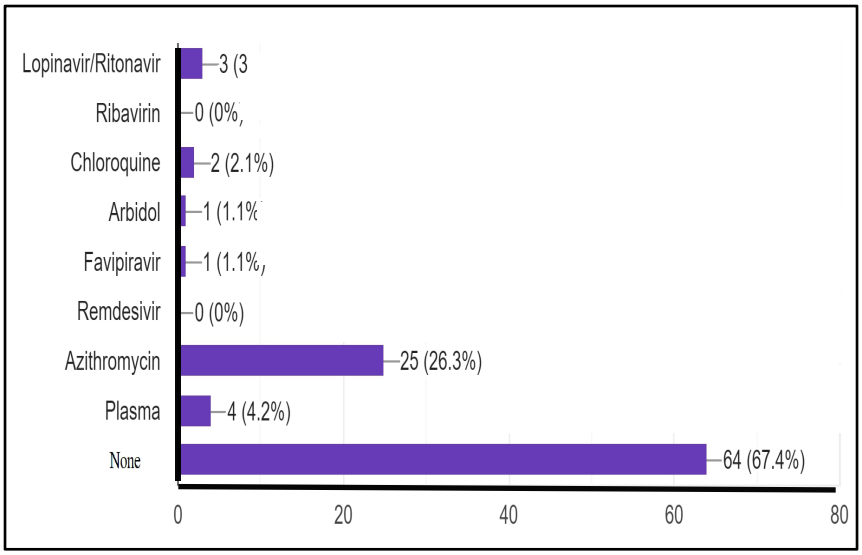


**Figure 3:** Using antiviral for COVVID-19 treatment.

**Lopinavir/ritonavir**

A combination of the drugs ritonavir and lopinavir is called Kaletra, it is used to treat AIDS (HIV), and also it is used for cancer treatment. This combination of drugs tries to block the virus' ability to repeat itself. The existence of ritonavir is to block the breakdown of lopinavir. Kaletra is a type of protease inhibitor and called lopinavir/ritonavir{National Cancer Institute, 2020`, August 25 #26}. Lopinavir/ritonavir reduces the level of SARS-CoV and MERS-CoV (Chu 2004). As it is used for treating SARS-CoV, it was expected that it would also be useful in treating coronavirus(Huang, Wang et al. 2020). Usually, this combination is used with a high limit of lopinavir and low amount of ritonavir to enhance the immune deficiency syndrome(Binois, Hachad et al. 2020). Until now, no clinical evidence exists on lopinavir/ritonavir that it helps patients with coronavirus (Zhu, Lu et al. 2020). Fig. (4) shows the chemical structure of Kaletra.

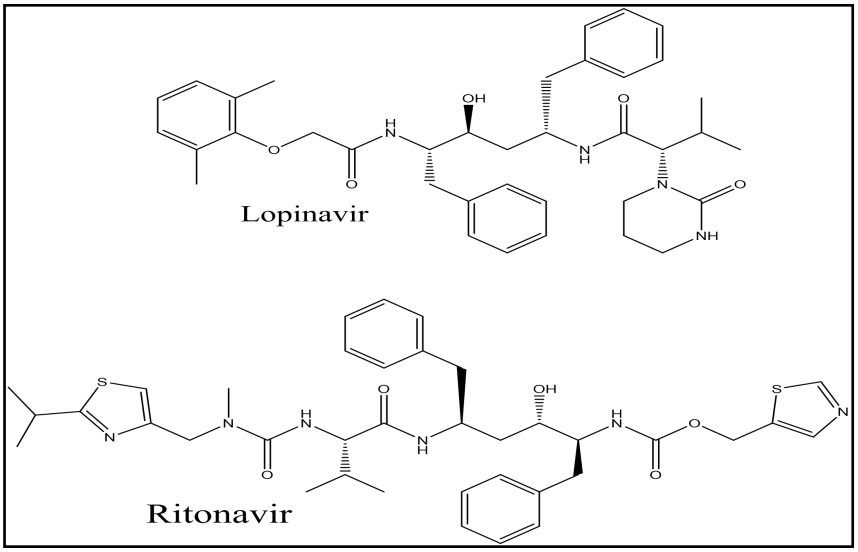


**Figure 4:** Chemical structure of lopinavir/ritonavir

361 patients with coronavirus, their average age (14-62) were exposed to this drug, the results showed that COVID-19 patients under treatment with lopinavir/ritonavir are exposed to a high prevalence of potential interactions, behaving as associated risk factors age (> 65), admission to the ICU, previous respiratory, psychiatric disease. Dyslipidemia and the number of drugs prescribed. The knowledge of the profile of potential interactions in COVID-19 patients undergoing treatment with lopinavir/ritonavir can improve the safety and effectiveness of the treatments (Brandariz-Nunez, Correas-Sanahuja et al. 2020).

Lopinavir/ritonavir was used in the past in the treatment of SARS-CoV, and it is considered the main treatment for AIDS, however, it causes some cardiac problems such as QTc interval prolongation on the electrocardiogram and its arrhythmogenic consequences (Gerard, Romani et al. 2020). French pharmacovigilance network has assessed the effect of lopinavir/ritonavir on cardiac adverse drug reactions associated with lopinavir/ritonavir in

COVID-19 patients. They found out that there is still no specific treatment for coronavirus.

The use of antivirals takes a long time to be allowed for clinical use, but the coronavirus pandemic and its effects have forced many health and scientific centers in the world to administer these antivirals on patients so that they can know their effects and their healing ability. Between Feb to March 2020, 127 COVID-19 patients were examined with lopinavir/ritonavir and the results showed that similar effects to placebo on reducing viral load when treatment was started in the middle of 13 days after the beginning of side effects (Hung, Lung et al. 2020).

Fifty coronavirus patients in Third People's Hospital of Changzhou and the Second People's Hospital of Wuhu were exposed to the lopinavir/ritonavir antiviral, all data from these patients were collected from Jan to Feb 2020. Table (4) shows the laboratory findings of patients with coronavirus (Binois, Hachad et al. 2020).

**Table 4:** Lab test of patients with COVID-19.

| Variable | Lopinavir/ritonavir (n=34) |
|---|---|
| **Age, years** | 40,5(34.8-52.3) |
| **Duration of fever, days** | 2.5(0-5) |
| **WBC, E+09/L** | 5.2(3.9-6.4) |
| **ALT, U/L** | 20.9(12.2-24.1) |
| **Duration of positive RNA test, days** | 11.5(8.8-17) |

Despite the combination lopinavir/ritonavir recommended by the NHC (National Health Commission), but it is still limited.

Acute kidney injuries (AKI) are also related to the use lopinavir/ritonavir as a treatment for coronavirus. Yannick and his coworkers describe a small case series of acute kidney injuries associated with using Kaletra for coronavirus treatment. 62.5% of the candidate for this work are men, all of them are admitted to COVID-19. They noticed that all required intensive care with a median sepsis-related organ (Binois, Hachad et al. 2020).

199 patients with coronavirus diseases demonstrated that there was no critical decrease in death rate with lopinavir/ritonavir in the United Kingdom. Otherwise they concluded that there was a little decrease in less intensive care unit stay (Owa and Owa 2020).

Lopinavir/ritonavir is a readily obtainable and relatively cheap drug. It is on the WHO list of vital treatments. Same as the rest of the world, the use of this drug has been studied here in the Kurdistan region of Iraq, random samples were taken from cases with this disease, and the percentage was small, where it reached 3-3.2% as shown in Fig. (2).

**Chloroquine**

Chloroquine is an anti-malarial and anti-inflammatory drug(Pan, Dong et al. 2020), which is used for malaria treatment and other parasite infections, cheapness according to WHO lists (Cortegiani, Ingoglia et al. 2020). the chloroquine activity for the treatment of SARS-CoV-2 (COVID-19) pneumonia remains unclear. Fig. (5) shows the chemical structure of chloroquine.

According to the phosphate and hydroxychloroquine ability to damage the terminal glycosylation of angiotensin, they suggested it to be a potent inhibitor for coronavirus infection (Pan, Dong et al. 2020).

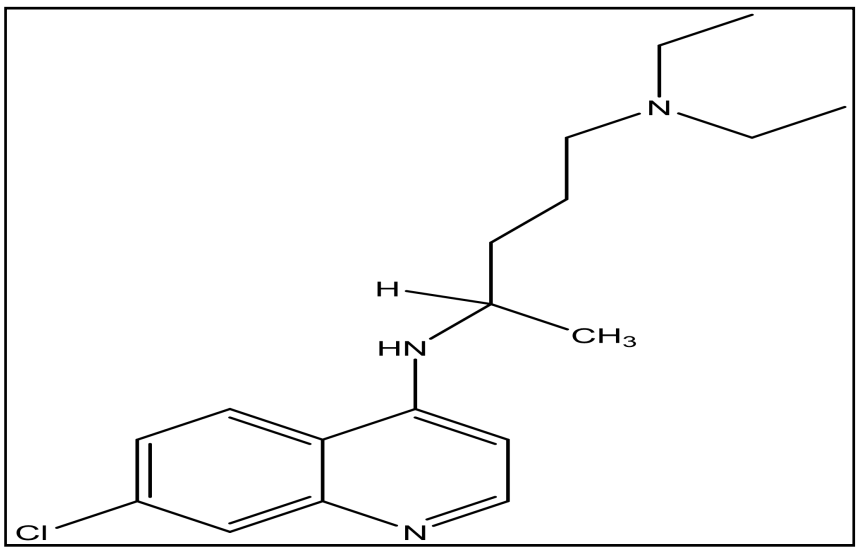


**Figure 5:** Chemical structure of chloroquine

Despite its many uses as a medicine for malaria, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary Sjogren syndrome and antiphospholipid syndrome (APS) (Smolen, Landewe et al. 2014, Vivino, Carsons et al. 2016, Fanouriakis, Kostopoulou et al. 2019, Tektonidou, Andreoli et al. 2019, Colson, Rolain et al. 2020). It has been nominated to be an effective drug against coronavirus (Bagheri Novir and Aram 2020).

When SARS appeared in 2003, many medicines were chosen to treat the repercussions of this virus, including chloroquine, and indeed its efficacy was proven. This

information has been overlooked due to the end of the SARS disease (Yu, Qiu et al. 2014).

Statistically, it appeared that the use of this medicine was the highest among all the other medicines used in the treatment of malaria, and the reason is due to the large number of civilians traveling to the countries where this disease abounds (White, Pukrittayakamee et al. 2014).

hydroxychloroquine has been used for decades to treat autoimmune diseases (Lee, Silverman et al. 2011).

One of the most important advantages of using this drug in treating coronavirus is it is rapidly absorbed by body cells and tissues; it is mainly broken down and metabolized in the liver and ability to accumulate in cells can cause blurred vision and impaired eyesight (Microbone Notes 2020) as explained in Fig. (6).

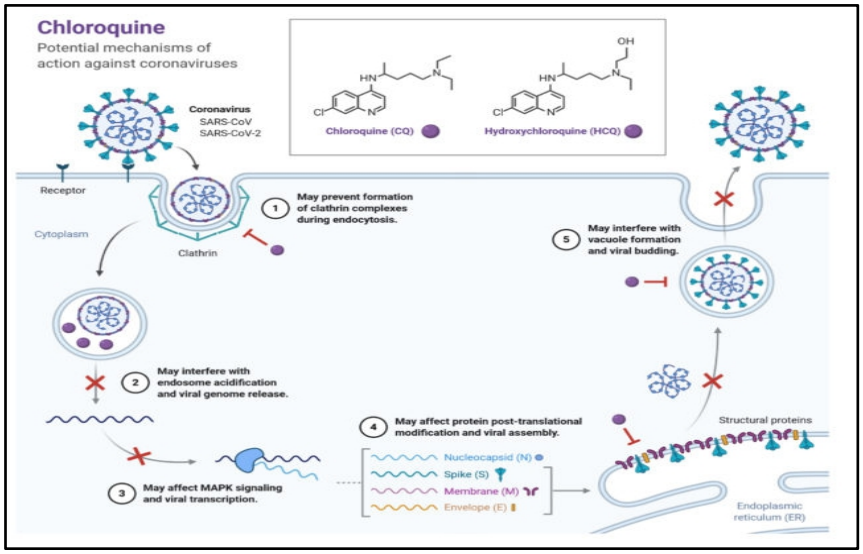


**Figure 6:** Suggest mechanism for the drug against coronavirus.

Chloroquine [7-chloro-4-[4-(diethylamino)-1-methylbutyl]amino] quinoline is an antimalarial medicine that was improved in Germany in 1934 (Wang, Cao et al. 2020). As a result of the hydroxylated of one of the ethyl groups in the alkyl side chain of chloroquine, hydroxychloroquine, an equivale to chloroquine, was progressed in 1946. Generally, hydroxychloroquine has less intense toxicities and less drug-drug interactions than chloroquine(Tropical Health Network 2020, June 20). Fig. (7) shows the metabolism of chloroquine and hydroxychloroquine. The effectiveness of chloroquine in inhibiting the SARS virus makes this drug one of the first treating for SARS as well as chikungunya fever (Microbone Notes 2020). Chloroquine and hydroxychloroquine have been studied in clinical trials for the treatment of COVID-19.

PubMed and EMBASE databases were checked to find articles about using chloroquine and hydroxychloroquine as a treatment for coronavirus (Cortegiani, Ingoglia et al. 2020). They noticed that this vaccine has been effective in limiting the repetition of coronavirus in more than 23 clinical trials in China. The use of chloroquine may be supported by the expert view, the clinical use of this drug in patients with coronavirus.

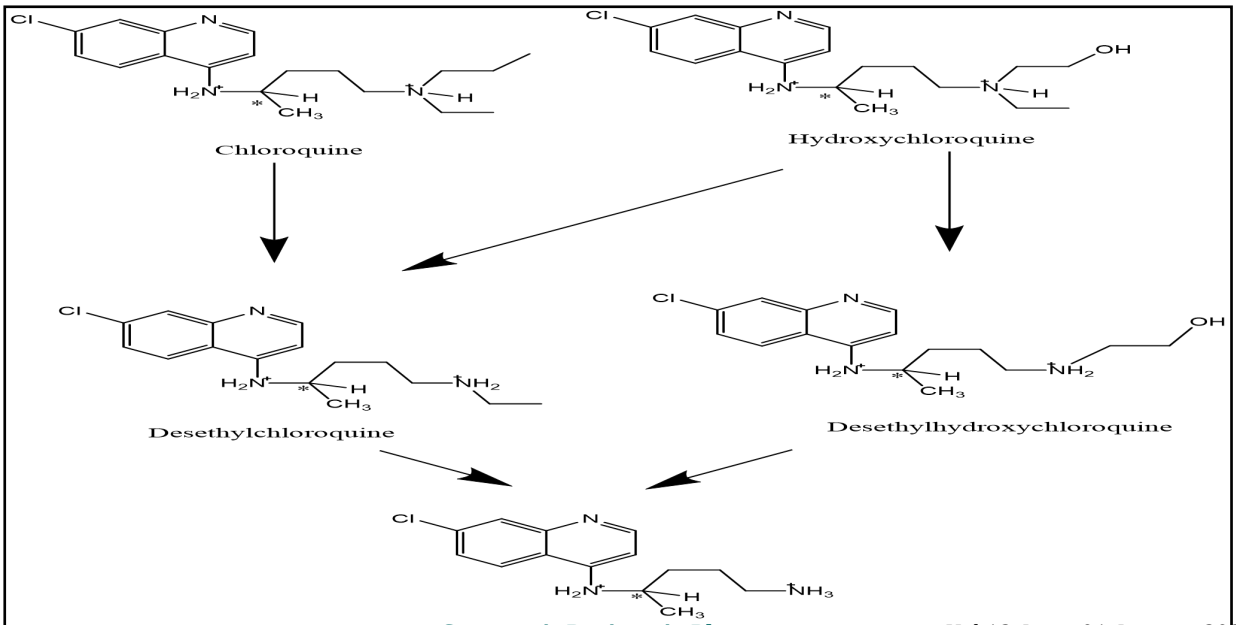

**Figure 7:** Metabolism of chloroquine and hydroxychloroquine

One of the reasons for using chloroquine in coronavirus treatment is that it reduces the amount of time patients stay in the hospital and also improves the progression of the associated COVID-19 pandemic (Karalis, Ismailos et al. 2020), pulmonary oedemic with respiratory insufficiency and circulatory collapse can be observed by using chloroquine overdosing, therefore, the use of chloroquine must be controlled. For example, using this drug in parallel with other drugs which are used for coronavirus treatment like azithromycin may cause some real health problems such as increasing the risk of QT prolongation and cardiomyopathy (Svanstrom, Pasternak et al. 2013). Table (5) shows chloroquine dosage regimens currently in use.

**Table 5:** Chloroquine dosage used.

| Dosing | Indication | Ref. |
|---|---|---|
| **Adult 500 mg x 2 (10 days)** | Coronavirus | (Wong, Yang et al. 2020) |
| **Adult 500 mg x 2 (7 days) less than 50 kg** | Coronavirus | (Wong, Yang et al.2020) |
| **500 mg daily for 2-10 days. It is also suggest the potential of a loding dose of 1 g** | Coronavirus | (Zhou, Dai et al.2020) |
| **Two tablets chloroquine phosphate twice daily** | Critical coronavirus | (Cortegiani, 2020) |
| **Adults: 1000 mg once a day taken for 2 days. This is followed by 500 mg once a day for at least 2 to 3 weeks.** | Treatment of liver infection | (MAYO Clinic, 2020) |

The effect of this drug in patients with chronic diseases such as diabetes has been svaluated and the results show that only two small human studies have been conducted in coronavirus with both of these drugs and have shown significant improvement in some parameters in patients with COVID-19 (Singh, Singh et al. 2020).

Chloroquine and its derivative hydroxychloroquine have been used in the treatment of COVID-19. Starting from February 2020, results from more than 100 patients in China with COVID-19 showed that chloroquine phosphate had good efficacy (Gao, Tian et al. 2020). The French doctors have used hydroxychloroquine on more than 20 patients with coronavirus and the results show that they have actually improved (Gautret, Lagier et al. 2020). Finally, the reason for choosing chloroquine and hydroxychloroquine as a coronavirus treatment is that they are weak bases and with and the pH of the body increases with their prsence, and this causes the virus replicationto be inhibited (Devaux, Rolain et al. 2020).

The following key data were extracted from a questionnaire for this study, as referred to in Fig. (2), this drug has also been used here in the Kurdistan region as we see it. All the participants showed a clear understanding of the questionnaire. We made the following following observations based on the results, 2% of the patients are exposed to chloroquine and have improved.

**Arbidol**

This drug is an indol derivative and has been licensed for use in Russia and China for years in the field of treating influenza (Blaising, Polyak et al. 2014), Arbidol react with aromatic amino acids and effects on the virus replications, either by direct targeting proteins or virus-associated host factors (Vankadari 2020). The chemical formula for arbidol is (ethyl-6-bromo-4-[ (dimethylamino) methyl]-5-hydroxy-1-methyl-2] (phenylthio) methyl]-indole-3-carboxylate hydrochloride monohydrate, is a small indole derivative, it is also called umifenovir (Blaising, Polyak et al. 2014). Fig. (8) shows the chemical structure of arbidol.

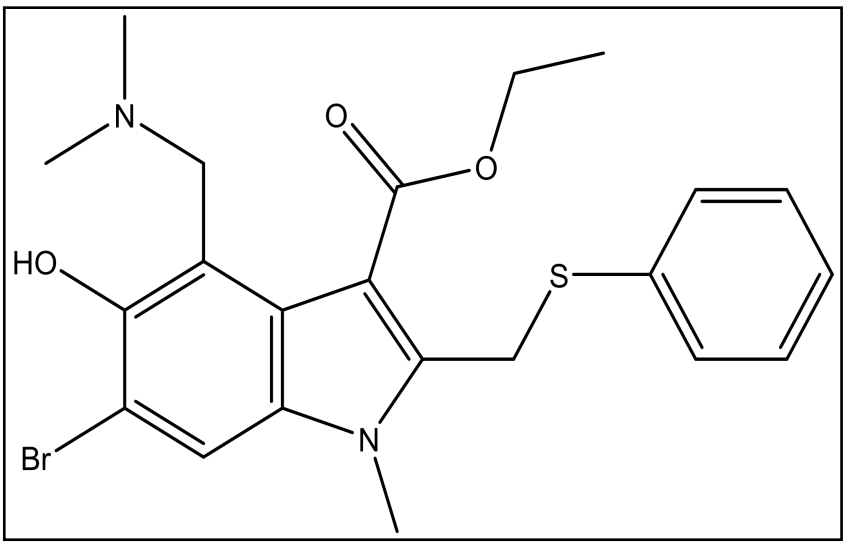

**Figure 8:** Chemical structure of arbidol

Six currently available (including arbidol) anti-influenza drugs used to treat patients with coronavirus were tested (Wang, Cao et al. 2020). Arbidol shows good efficiently for inhibiting the in vitro. The maximal effective concentration of 50% for arbidol was approximately 4.11 (3.55–4.73). A review of this drug has suggested that respiratory coronavirus syndrome can be transmitted from person to another. A pathogen that causes coronavirus disease is very efficient (Zhang, Wang et al. 2020), A total of 66 members in 27 families and 124 health care workers exposure to patients with coronavirus, arbidol shows that was a protective factor against the development of COVID-19.

Another study includes 164 subjects, 82 cases in the infected group and 82 controls in the uninfected group, with a median age of 37 years, including 63 males and 101 females, all of them were exposed to arbidol. This study found that taking arbidol by oral was associated with reduced coronavirus infection rates among health workers, Table (6) lists the parameters used in this study (Yang, Ke et al. 2020).

**Table 6:** p- value for using arbidol.

| Factor | All subject n=164 | Infected group | Uninfected group | p-value |
|---|---|---|---|---|
| **Age (year)** | 37(31-46) | 37(31-46) | 37(32-43) | 0.958 |
| **High risk** | 60(37%) | 30(37%) | 30(37%) | 1.000 |
| **Arbidol (yes)** | 67(41%) | 19(23%) | 48(59%) | <0.001 |
| **Arbidol (no)** | 98(59%) | 63(77%) | 34(41%) | <0.001 |

Arbidol is a broad-spectrum antiviral compound that blocks the content, cohesion and fusion of viral lipid capsules and host cell membranes and blocks the replication of the virus (Khamitov, Loginova et al. 2008). Previous studies have shown that arbidol can inhibit RNA viruses such as SARS and MERS (Guan 2018).

Based on the review, we make the following observations, arbidol show efficiently inhibition of coronavirus infection. Practically, it appears to block virus entry by impeding viral attachment, and maximal concentration is more important for predicting efficacy.

The evaluation included a comparison between results from our questionniare for cases in the Kurdistan region which included in this study and the published work. Fig. (2) show that just 1% of patients with coronavirus here took arbidol as a treatment. **Favipiravir**

Several research groups have been working on the design of selecting and choosing the best medicine for coronavirus patients around the world, Favipiravir is one of the medicines understudies for this pandemic. This has been a topic of interest in the fight against the novel coronavirus that burdens human health (Pan, Dong et al. 2020).

Favipiravir (structure mentioned in Fig. (9), is authorized for influenza virus treatment in Japan and has been shown to have antiviral efficacy against several highly pathogenic RNA viruses including Ebola, Lassa, Hantavirus, Nipah and others in multiple animal models (Hawman, Haddock et al. 2020).

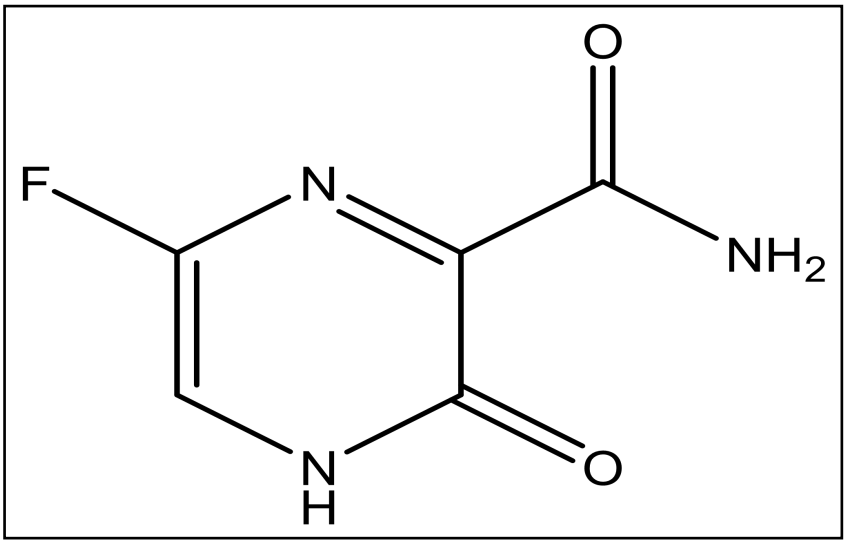


**Figure 9:** Chemical structure of favipiavir

Favipiravir is the first approved drug with a potential cur ative effect on coronavirus that will play an important role in the prevention and control of corona virus infections (Yuji Kumagai 2015). Favipiravir is currently being tested as an antiviral treatment candidate in clinical studies (Wang, Cao et al. 2020). Antiviral favipiravir was first used against coronavirus in Wuhan at the beginning of the pandemic and in the world.

This drug has been approved in Italy for emergency use and is currently in use in Japan, Russia,

Ukraine, Uzbek, Moldova and Kazakhstan. In countries of the Middle East such as Saudi Arabia and the UAE, Egypt (Agrawal, Raju et al. 2020), as well. It is being used in Iraq and the Kurdistan region recently.

The first time this drug got approval for usage as a treatment for coronavirus patients was Jun 2020, in India for mild and moderate cases (CISION PR Newswire 2020, June 20). The main advantage of favipiravir is that it can be given orally and can be used in patients who are symptomatic but not sufficiently ill to be hospitalized. Since most coronavirus patients have mild to moderate illness and can be treated at home, this drug could potentially be used in many patients (Clinical Trials 2020, May 26).

After an initial overview of this drug, twenty-nine studies were identified as potential sources of evidence of the clinical safety of favipiravir, according to the specific search across EMBASE and MEDLINE databases. The researchers also proved that evidence exists to support the safety and tolerability of favipiravir for short-term use. However, more evidence is needed to evaluate the long-term effects of treatment, caution is warranted in the widespread use of favipiravir against the COVID-19 pandemic (Pilkington, Pepperrell et al. 2020).

Another study showed that using favipiravir had better and faster viral effect clearance and better change in chest imagery than individuals treated with other antivirals (Cai, Yang et al. 2020).

Another reason for adopting this drug as a good antiviral against coronavirus was being a novel RNA-dependent RNA polymerase inhibitor that is effective in the treatment of influenza and Ebola virus (Oestereich, Ludtke et al. 2014).

To confirm the safety of the usage of this drug in treating coronavirus, it has been used in 18 laboratories subject to the World Health Organization (WHO), the results obtained from this study proved that favipiravir could lead to positive therapeutic outcomes for influenza. The unavailability of results of > 85% of favipiravir completed clinical trials in registries or published papers prevented data pooling and meta-analysis to provide conclusive evidence to support the recommendation for use of favipiravir in COVID-19 or to be aware of its safety and efficacy profile (Khambholja and Asudani 2020).

The results of using favipiravir in Kurdistan region is summarized in Fig. (2), The analysis of the data was performed with the help of questionnaire by google form t was filled out from coronavirus patients in the Kurdistan region - Iraq. We also note that the rate of use of this drug here is close to using arbidol which is about 1 %.

**Azithromycin**

The antibacterial macrolide azithromycin has a special an d interesting profile in this search for drug therapy for CO VID-19. Preliminary information proves that the coronavirus directly affects the lungs and leads to inflammation and damage to the surrounding tissues, and the level of damage may be between moderate to severe (Ye, Wang et al. 2020). The use of medicines that increase the body's immunity was one of the first options in the field of coronavirus treatment, so the antibacterial macrolide azithromycin structure mentioned in Fig. (10).

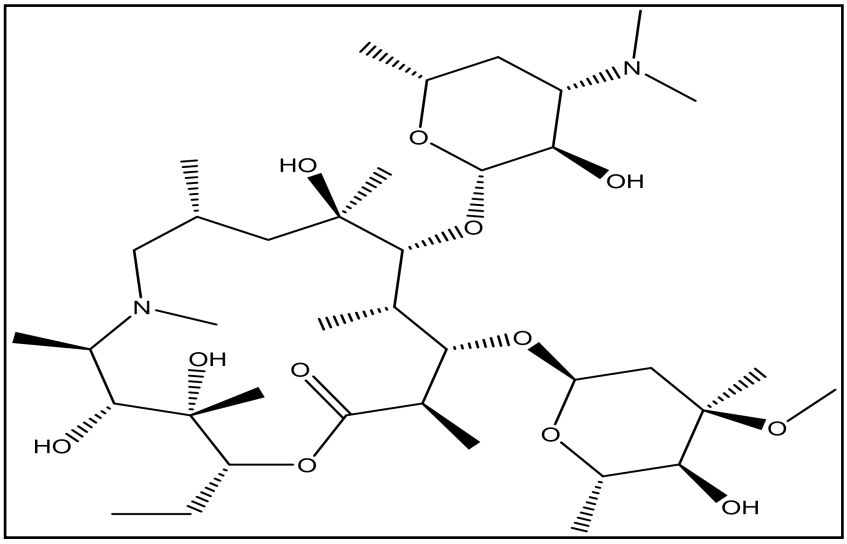


**Figure 10:** Chemical structure of azithromycin

Azithromycin is characterized by its ability to treat inflammatory conditions that may lead to lung diseases (Kawamura, Ichikado et al. 2014). There are many antivirals, but azithromycin has proven to be strongly useful against viruses in the laboratory and in vivo more than chloroquine and hydroxychloroquine, furthermore, it has resisted viruses such as syncytial virus, Zika, Ebola, H1N1 virus, influenzae and rhinovirus (Retallack, Di Lullo et al. 2016, Wu, Tseng et al. 2018, Du, Zuo et al. 2020).

Research has shown that when azithromycin is given to a patient with hydroxychloroquine, it effects on the coronavirus (Andreani, Le Bideau et al. 2020). Besides, azithromycin provides an antiviral effect, as it reduces the entry of viruses into cells (Yao, Ye et al. 2020).

A group of researchers in Iran conducted experiments on the effect of this drug on patients with coronavirus and noticed that those who received treatment had less time in hospital and a respiratory rate at discharge (Sekhavati, Jafari et al. 2020).

Majority of studies that have been conducted on this drug have shown that its use gives better results if it is used with hydroxychloroquine (Dubernet, Larsen et al. 2020, Fiolet, Guihur et al. 2020, Million, Lagier et al. 2020).

Several quarrels are supporting the potential efficacy of azithromycin in coronavirus infection, including its antiviral and immunomodulatory effects. We trust that azithromycin should be clinically tested as monotherapy in coronavirus patients.

Here in the Kurdistan region – Iraq, as mentioned in Fig. (2), this drug has the grteatest importance of use, and according to our questionnaire, more than 25 % of the number of coronavirus patients in hospitals in Kurdistan have been administrated this drug.

**Remdesivir**

Remdesivir (also named GS-5734) is a broad spectrum antiviral drug that has appeared to inhibit SARS-CoV-2, in vitro and in vivo (Singh, Singh et al. 2020). Fig. (11) shows the chemical structure of this drug which is an adenosine analog with a wide range of antiviral activity against several viruses such as respiratory syncytial virus, Nipah virus, Ebola virus, Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV) which causes the coronavirus 1 (Lo, Jordan et al. 2017, Timothy P. Sheahan 2017, January 28, Vankadari 2020). The drug's main job is delivering monophosphate nucleoside analogue GS-441524 into the cells, inside the cells, the monophosphate nucleoside is rapidly converted into triphosphate form GS-443902 pharmacologically active substances (Agrawal, Raju et al. 2020), as mentioned in Fig. (12).

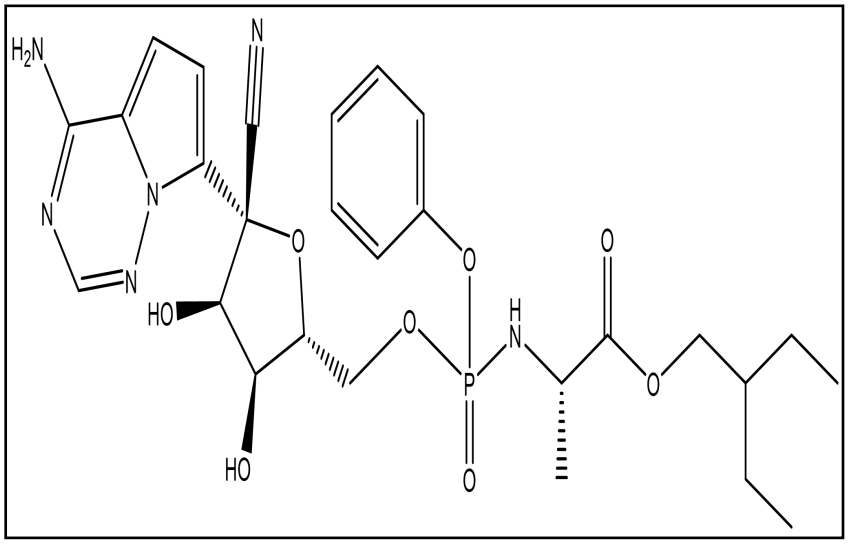


**Figure 11:** Chemical structure of remdesivir

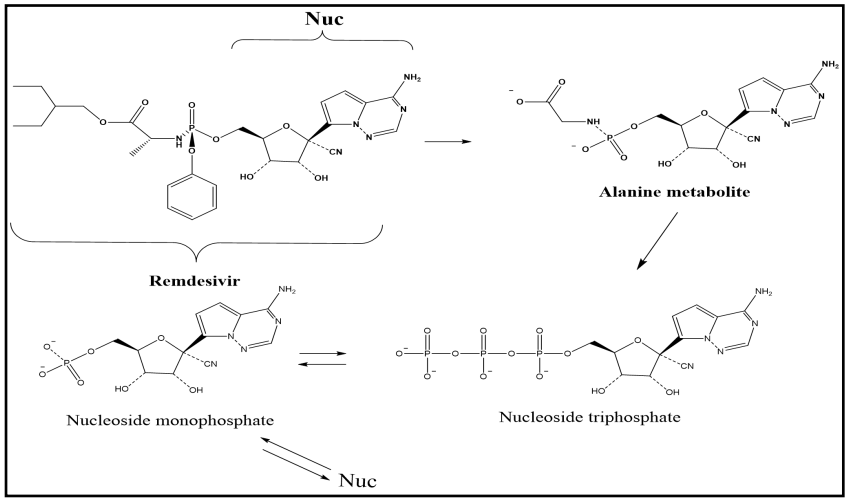


**Figure 12:** Metabolic conversion of remdesivir

The benfit of this medicationfor the treatment of coronavirus has been taken into account for certain reasons, including the drug is considered an antiviral and is widely used in the world. Initial laboratory experiments have shown that it has activity against the virus, just as its results were decisive in the body of infected organisms CoV (Sun 2020).

Some studies have proven the inconclusive effectiveness of this drug against coronavirus, as it was noticed that out of a total of 53 patients with coronavirus, 36 of them recovered (68%) (Grein, Ohmagari et al. 2020). A summary of clinical characteristic of the patients are given in Table (7).

**Table 7**: Clinical Characteristic of the patients.

| Characteristic | Need Ventilation (n = 34) | No need for Oxygen support (n = 19) | Total (n = 53) |
|---|---|---|---|
| **Median Range (year)** | 67(56-72) | 53(41-68) | 64(48-71) |
| **Region no. (%)** | | | |
| **United State** | 14(41) | 8(42) | 22(42) |
| **Japan** | 8(24) | 1(5) | 9(17) |
| **Europe or Canada** | 12(35) | 10(53) | 22(42) |
| **Invasive ventilation no. (%)** | 34(100) | -- | 34(64) |
| **Noninvasive oxygen support no. (%)** | -- | 19(100) | 19(36) |
| **Median duration of symptoms before remdesivir therapy (days)** | 11(8-15) | 13(10-14) | 12(9-15) |

No new safety signals detected during in this compassionate-use during short-term treatment with remdesivir, as shown in the table above.

Another study showed that in the United States, the first confirmed case of COVID-19 prompted the use of intravenous remdesivir for compassionate use, leading to marked improvements in the clinical status of the patient within 24 hours (Musa, Pendi et al. 2020). Both in vitro and lack of clinical evidence that enforce remdesivir use for the treatment of coronavirus. Remdesivir side effects remain similar and insufficiently mentioned due to the need for more studies with high improvements in the administration of remdesivir (Musa, Pendi et al. 2020). The efficacy of remdesivir as a standard of care therapy for coronavirus patients remains to be established.

Remdesivir is one of the few antiviral drugs, due to its effeicieny in treating SARS-CoV and MERS-CoV (Unidad de Virología 2020, March 23). Most studies have shown that remdesivir inhibits the proliferation of the animal beta virus, which causes viral hepatitis, because it interferes with RpRd despite the presence of the exoribonuclease enzyme. This viral enzyme is responsible for cleaving the antiviral and determining the decrease in sensitivity or resistance to it (Smith, Blanc et al. 2013). Most studies show remdesivir to be highly effective in controlling coronavirus infection iun vitro. Because this compound has been used and shown to be effective against different diseases in human patients with a safety track record (Wang, Cao et al. 2020).

After examining most of the research and scientific articles on remdesivir and its efficacy on the coronavirus infection, we found that patients taking this medicine have a cure rate of more than 31%, This indicates that this drug can have a great significance in treating this disease, even in a small percentage.

The results of our questionnaire lead to the conclusion that no apparent advantage exists in using this drug here in the Kurdistan region- Iraq, as mentioned in Fig. (2).

**Sputnik V**

There are many vaccines for COVID-19 that are currently being developed around the world. Vector, inactivated nuclear-acid (DNA, mRNA), and recombinant protein-based vaccines include the most important types of vaccines (Spuntik V 2020). First, it is essential to know what dose vector mean, the vector is like when some vehicles induce genetic material into a cell from another virus. So, the adenovirus gene which causes the infection is removed while inserting a gene with a protein code from another virus spike. The extra element that is inserted is safe for the body, it provokes the immune system to react and produce antibiotics that protect the human body. Vector is the main principle on which the Russian vaccine was based, this vaccine was registered by the Russian Ministry of Health on Aug 11 and officially became the first registered coronavirus treatment on the market. Gamaleya Research Institute of Epidemiology and Microbiology in Moscow developed this vaccine, named Sputnik V is based on a human adenovirus carrier inserted with the SARS-CoV-2 gene sequence (Petersen, Wejse et al. 2020). Sputnik V is based on an adenoviral vector that normally causes acute respiratory viral infection. Fig. (13) shows the suggested mechanism for Sputnik V.

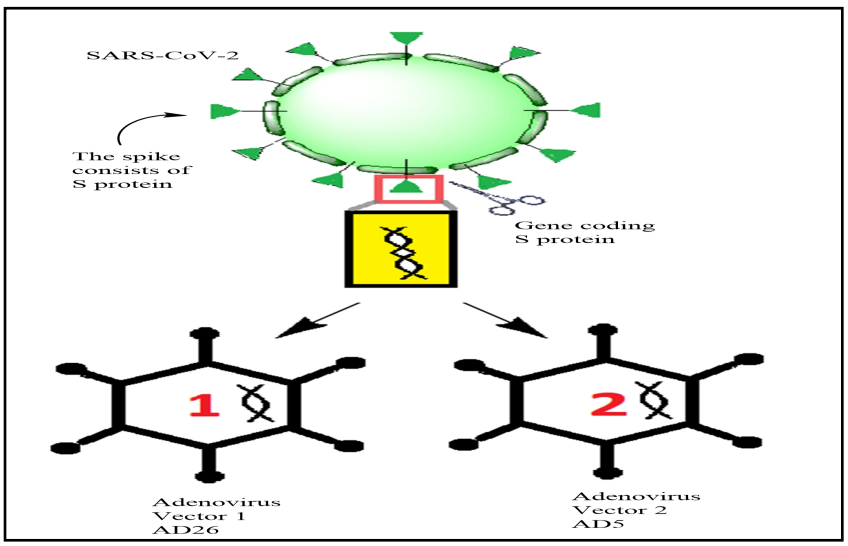


**Figure 13:** Suggested mechanism for sputnik V

**Plasma**

Plasma therapy is used to treat patients with infectious di seases by extracting plasma, serum or immunoglobulin from cured patients, it has been widely used in outbreaks of infectious diseases in recent years, such as the Spanish influenza, SARS and MERS (Arabi, Balkhy et al. 2015). Since Spanish flu era, which shook the world with its serious consequences on humanity, until this time, while we are confronted with the coronavirus epidemic, plasma has played an important role in reducing the fatality rates of cases (Rojas, Rodriguez et al. 2020). Also, the use of plasma in other coronaviruses such as SARS-CoV and MERS-CoV reduces the hospital stays in critical patients (Kong 2003, Wong and Yuen 2008). There are protective antibiotics in plasma such as immunoglobulin G (IgG) and immunoglobulin M (IgM), which contribute in the prevention of the diseases and rapid improvement in the patients, but do not affect the ability of the virus to reproduce (Bloch, Shoham et al. 2020). Fig. (14) shows the antiviral effect of IgG and IgM.

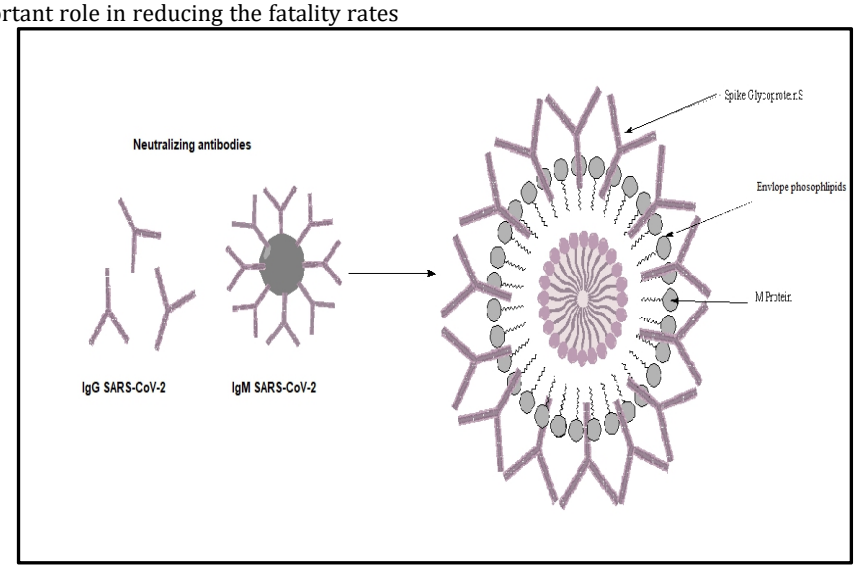


**Figure 14:** Antivirial effect of IgG and IgM

Once proven effective, plasma therapy is an attractive therapeutic option for the infection of the acute respiratory syndrome. In addition to the biological plausibility of this therapy, obtaining and administration is relatively inexpensive, and is likely to be acceptable to patients and treatment teams. We believe this protocol of study may pay off if it is studied in more detail. We also note that the percentage of its use here in the Kurdistan region – Iraq has exceeded expectations, as shows in Fig. (2).

## DISCUSSION

This group of drugs and treatments were chosen due to their popularity throughout many SARS-CoV-2 treatments in research papers. There are currently 165 drugs trying to treat this worldwide pandemic. Based on the research and our review about the best vaccines currently in the world to treat or even alleviate the symptoms of this pandemic, we reached some general conclusions, including any vaccine that is worked on must be clear with all its pros and cons and every vaccine reached must be under the supervision of the regulatory authorities and the World Health organization. The surveillance must be present in all countries of the world that use new vaccines for coronavirus so that all its side effects are recorded.

The impact of the coronavirus epidemic on the world seemed to show its effects clearly, and the world knows at every moment the magnitude of the disaster that awaits humanity if things worsen and they are unable to reveal the appropriate treatment for this pandemic. The development of vaccines for the treatment of coronavirus infection has become a demand in the world, and for this reason, scientists from all parts of the world have tried many marketed drugs, especially antivirals, and some of them have shown good effects, whether in vitro or preliminary clinical trials that have emerged. However, there is still insufficient evidence to support those drugs' effectiveness and safety against coronavirus. Chemical drugs are not like natural medicines that give a slow action, chemical drugs have a fast effect on the host body and the necessary strength to resist viruses as antiviral more than others. Given that the coronavirus disaster has become a pandemic with official recognition from the World Health Organization, therefore, the world now needs quick and effective solutions. There were some strengths and limitations associated with using these drugs, according to our scientific review that we have done, it is clear to us that the majority of the global research published in well-known and internationally recognized sites focused on Ribavirin, Chloroquine, Arbidol, Lopinavir/Ritonavir, Favipiravir, Remdesivir, Azithromycin, plasma and Sputnik V.

Clearly from the aforementioned researches that these drugs deal with the virus with different mechanisms, as arbidol prevents the virus from merging with the cell, as it directly affects the viral envelope, that will not allow the virus to adhere to the target's cell membrane. While ribavirin, favipiravir and remdesivir work on inhibiting of the virus RNA which in turn prevent it from reproducing. Azithromycin helps the body to enhance the immunity to viruses, plasma plays an important role, it was used in moderate to severe cases as a possible immunotherapy treatment option depend on the transfusion of plasma

from people who has recovered from the virus to infected people. Lopinavir/ritonavir is made up of two protease inhibitors, which prevent the Gag-Pol polyprotein cleavage and result in the production of non- infectious virions. Chloroquine may affect the replication and pathogenic DNA transcript, The last drug sputnik V depends on the extraction of part of the genetic material in the virus, which contains sufficient information on the structure of the protein in the virus that is responsible for connecting to the cell in the host body, and then loading it onto a specific vector to ensure permanent immunity.

There were a number of strengths and limitations associated with this study, as Fig. (2) showed that the percentage of using many drugs for coronavirus treatment is different, so according to that we concluded that there are big differences in the rates of using drugs for COVID-19 infection in Kurdistan Region-Iraq, due to the lack of conclusive results in the ability of these antivirals to fight COVID-19. Because of the high rates of recovery from this disease without taking any antiviral medicines, we noticed that a high percentage of patients in the Kurdistan- Region – Iraq had recovered without taking medicine, while those who used the proposed drugs had varied cure rates according to the different drugs. The use of these different drugs was very close to the ratios that appeared in different studies around the world.

The lack of response of patients to our questionnaire and awareness necessary are notable important limitations of this study. Despite this limitation, the findings of this study are important because our study proved that there is a kind of scientific communication between Kurdistan Region-Iraq and the latest scientific developments which are the focus of the work of universities and health institutions around the world in facing the COVID-19 pandemic. Our review of many medicines for COVID-19 infections which had around 100 participants took place in four governorates in north of IRAQ (Kurdistan Region).

Using different medicines for COVID-19 treatment may cause some side effects; it may be unpleasant, because these medicines are not usually intended for this infection, some of them are used for HIV infections and some other work as antimalaria, but since the closure of 2019, the world has encountered pandemic conditions attributable to coronavirus infection, so according to this pandemic the world needs urgent treatment. This, in principle, can give rise to a conclusion that there is no effective treatment for COVID-19 till now. Some of them are used for reducing the staying time in the hospital and reducing the rate of mortality.

The results of our review for the drugs used here in Kurdistan Region-Iraq are summarized in Table (8).

| Parameter | Results |
|---|---|
| **Stay in Hospital** | 2 % (102) |
| **Positive test for COVID-19** | 61.8% (102) |
| **Stay in Home** | 98 % (102) |
| **Kurdistan Region Citizen** | 96 5 (102) |
| **Taking medicine** | 38 % (102) |

**Table 8:** Results for our questionnaire in Kurdistan region.

Fig. (15) schematically shows the process of staying in the hospital for our samples, these results suggest that staying in a hospital in Kurdistan Region-Iraq is very rare due to the trust issues with the health system, differences in our results might be attributed to the lack of health awareness among people here.

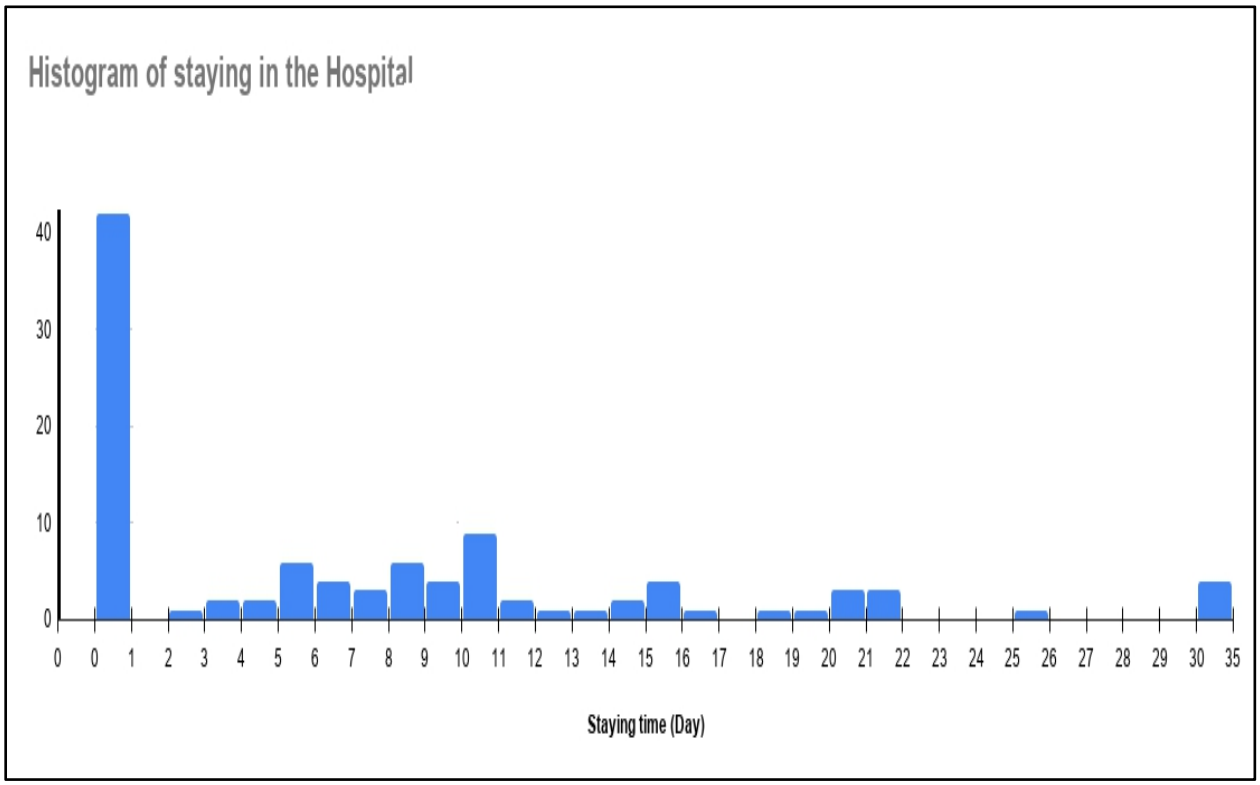


**Figure 15:** Staying in the hospital (days)

Fig. (16) clearly shows the difference of samples taken from the different Iraqi governorate in Kurdistan region in Northern Iraq.

This might be explained by that the Kurdistan Region-Iraq is no different from other countries of the world in terms of its confrontation with this pandemic, as we see that the number of infected people continues to increase. The results for the most medicines are used in Kurdistan Region-Iraq are shown in Fig. (2), as it's known azithromycin used to treat infections like bronchitis, pneumonia and mycobacterium avium complex infections, so they just suggest using it, which is why we see a high percentage of patients that have used it and recovered and this is agreed upon with therapeutic effects of azithromycin against COVID-19.

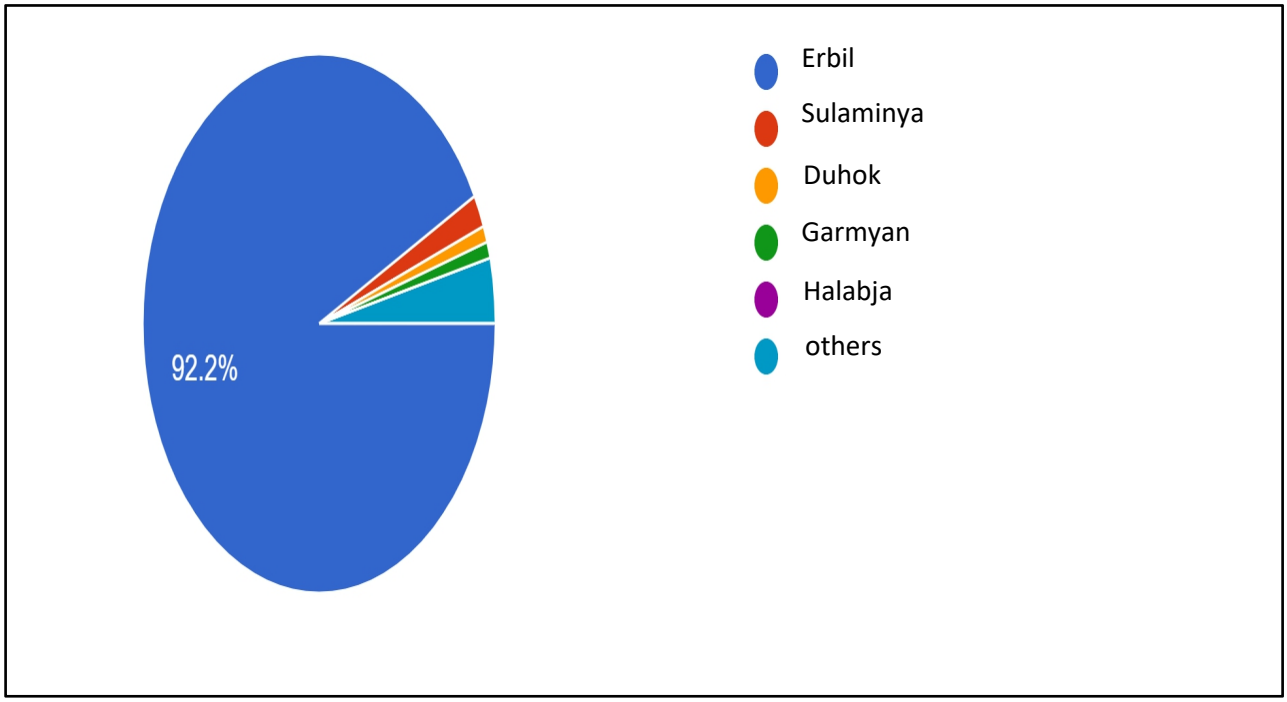

**Figure 16:** Sample distibution in Kurdistan region-Iraq

The causes of the high percentage of infected people who have been cured from coronavirus without any drugs are difficult to demonstrate, but we think these results are also agreed upon with studies, that confirm that a high percentage of patients are cured without any medicine.

## CONCLUSION

In order to deal with this pandemic, our article review performs the following steps: using these medicines should be done only when they're needed, clearly the side effect of the medicine may be worse than the disease itself. It is obvious that in the Kurdistan Region - Iraq it was noticed that the lack of use of the medicine has given a good rate of recovery, and the use of plasma has also had good results in its use here. Till now all proof of these medicines is limited because of the clinical data and lack of human trials, in Kurdistan Region- Iraq using plasma and azithromycin might be the best solution, according to our belief that such therapy may be useful in the present environment of the outbreak of the COVID-19 pandemic.

## ACKNOWLEDGEMENT

We would like to thank our colleagues for their encouragement and support for us to complete this study at College of Science, Chemistry Department at Salahaddin university- Erbil, Iraq. We are extremely grateful for all their help, willingness, and support.

## REFERENCES

1. Agrawal, U., R. Raju and Z. F. Udwadia (2020). "Favipiravir: A new and emerging antiviral option in COVID-19." Med J Armed Forces India.
2. Andreani, J., M. Le Bideau, I. Duflot, P. Jardot, C. Rolland, M. Boxberger, N. Wurtz, J. M. Rolain, P. Colson, B. La Scola and D. Raoult (2020). "In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect." Microb Pathog **145**: 104228.
3. Arabi, Y., H. Balkhy, A. H. Hajeer, A. Bouchama, F. G. Hayden, A. Al-Omari, F. M. Al-Hameed, Y. Taha, N. Shindo, J. Whitehead, L. Merson, S. AlJohani, K. Al-Khairy, G. Carson, T. C. Luke, L. Hensley, A. Al-Dawood, S. Al-Qahtani, K. Modjarrad, M. Sadat, G. Rohde, C. Leport and R. Fowler (2015). "Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol." Springerplus **4**: 709.
4. Bagheri Novir, S. and M. R. Aram (2020). "Quantum mechanical simulation of Chloroquine drug interaction with C60 fullerene for treatment of COVID-19." Chem Phys Lett **757**: 137869.
5. Binois, Y., H. Hachad, J. E. Salem, J. Charpentier, B. Lebrun-Vignes, F. Pene, A. Cariou, J. D. Chiche, J. P. Mira and L. S. Nguyen (2020). "Acute kidney injury associated with lopinavir/ritonavir combined therapy in patients with Covid-19." Kidney Int Rep.
6. Blaising, J., S. J. Polyak and E. I. Pecheur (2014). "Arbidol as a broad-spectrum antiviral: an update." Antiviral Res **107**: 84-94.
7. Bloch, E. M., S. Shoham, A. Casadevall, B. S. Sachais, B. Shaz, J. L. Winters, C. van Buskirk, B. J. Grossman, M. Joyner, J. P. Henderson, A. Pekosz, B. Lau, A. Wesolowski, L. Katz, H. Shan, P. G. Auwaerter, D. Thomas, D. J. Sullivan, N. Paneth, E. Gehrie, S. Spitalnik, E. A. Hod, L. Pollack, W. T. Nicholson, L. A. Pirofski, J. A. Bailey and A. A. Tobian (2020). "Deployment of convalescent plasma for the prevention and treatment of COVID-19." J Clin Invest **130**(6): 2757-2765.
8. Brandariz-Nunez, D., M. Correas-Sanahuja, E. Guarc, R. Picon, B. Garcia and R. Gil (2020). "Potential drug-drug interactions in COVID 19 patients in treatment with lopinavir/ritonavir." Med Clin (Barc).
9. Cai, Q., M. Yang, D. Liu, J. Chen, D. Shu, J. Xia, X. Liao, Y. Gu, Q. Cai, Y. Yang, C. Shen, X. Li, L. Peng, D. Huang, J. Zhang, S. Zhang, F. Wang, J. Liu, L. Chen, S. Chen, Z. Wang, Z. Zhang, R. Cao, W. Zhong, Y. Liu and L. Liu (2020). "Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study." Engineering (Beijing).
10. Chu, C. M. (2004). "Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings." Thorax **59**(3): 252-256.
11. CISION PR Newswire. (2020, June 20). "Glenmark becomes the first pharmaceutical company in India to receive regulatory approval for oral antiviral favipiravir, for the treatment of mild to moderate COVID-19." from https://www.prnewswire.com/in/news-releases/glenmark-becomes-the-first-pharmaceutical-company-in-india-to-receive-regulatory-approval-for-oral-antiviral-favipiravir-for-the-treatment-of-mild-to-moderate-covid-19-855346546.html.
12. Clinical Trials. (2020, May 26). "Glenmark starts Phase III Favipiravir combination study for Covid-19." from https://www.clinicaltrialsarena.com/news/glenmark-favipiravir-combo-trial/.
13. Colson, P., J. M. Rolain and D. Raoult (2020). "Chloroquine for the 2019 novel coronavirus SARS-CoV-2." Int J Antimicrob Agents **55**(3): 105923.
14. Cortegiani, A., G. Ingoglia, M. Ippolito, A. Giarratano and S. Einav (2020). "A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19." J Crit Care **57**: 279-283.
15. Devaux, C. A., J. M. Rolain, P. Colson and D. Raoult (2020). "New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?" Int J Antimicrob Agents **55**(5): 105938.
16. Du, X., X. Zuo, F. Meng, F. Wu, X. Zhao, C. Li, G. Cheng and F. X.-F. Qin (2020). "Combinatorial screening of a panel of FDA-approved drugs identifies several candidates with anti-Ebola activities." Biochemical and Biophysical Research Communications **522**(4): 862-868.
17. Dubernet, A., K. Larsen, L. Masse, J. Allyn, E. Foch, L. Bruneau, A. Maillot, M. Lagrange-Xelot, V. Thomas, M. C. Jaffar-Bandjee, L. Gauzere, L. Raffray, K. Borsu, S. Dibernardo, S. Renaud, M. Andre, D. Moreau, J. Jabot, N. Coolen-Allou and N. Allou (2020). "A comprehensive strategy for the early treatment of COVID-19 with azithromycin/hydroxychloroquine and/or corticosteroids: Results of a retrospective observational study in the French overseas

department of Reunion Island." J Glob Antimicrob Resist **23**: 1-3.
18. Ezhilan, M., I. Suresh and N. Nesakumar (2021). "SARS-CoV, MERS-CoV and SARS-CoV-2: A Diagnostic Challenge." Measurement **168**: 108335.
19. Fanouriakis, A., M. Kostopoulou, A. Alunno, M. Aringer, I. Bajema, J. N. Boletis, R. Cervera, A. Doria, C. Gordon, M. Govoni, F. Houssiau, D. Jayne, M. Kouloumas, A. Kuhn, J. L. Larsen, K. Lerstrøm, G. Moroni, M. Mosca, M. Schneider, J. S. Smolen, E. Svenungsson, V. Tesar, A. Tincani, A. Troldborg, R. van Vollenhoven, J. Wenzel, G. Bertsias and D. T. Boumpas (2019). "2019 update of the EULAR recommendations for the management of systemic lupus erythematosus." Annals of the Rheumatic Diseases **78**(6): 736.
20. Fiolet, T., A. Guihur, M. E. Rebeaud, M. Mulot, N. Peiffer-Smadja and Y. Mahamat-Saleh (2020). "Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis." Clin Microbiol Infect.
21. Gao, J., Z. Tian and X. Yang (2020). "Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies." Biosci Trends **14**(1): 72-73.
22. Gautret, P., J. C. Lagier, P. Parola, V. T. Hoang, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V. E. Vieira, H. Tissot Dupont, S. Honore, P. Colson, E. Chabriere, B. La Scola, J. M. Rolain, P. Brouqui and D. Raoult (2020). "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial." Int J Antimicrob Agents **56**(1): 105949.
23. Gerard, A., S. Romani, A. Fresse, D. Viard, N. Parassol, A. Granvuillemin, L. Chouchana, F. Rocher, M. D. Drici and C. French Network of Pharmacovigilance (2020). ""Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers." Therapie **75**(4): 371-379.
24. Grein, J., N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M. L. Green, F. X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S. H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A. O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S. K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R. P. Myers, D. M. Brainard, R. Childs and T. Flanigan (2020). "Compassionate Use of Remdesivir for Patients with Severe Covid-19." N Engl J Med **382**(24): 2327-2336.
25. Guan, W. D., Du, Q.L., Jiang, H.M., Zhao, J.C., Yang, Z.F., (2018). "Comparison of inhibitory effects of arbidol and Lianhuaqingwen Capsules on Middle East respiratory syndrome coronavirus in vitro and in vivo." Guangdong Med. J. (广东医学) **39**(23): 3454–3458.
26. Hawman, D. W., E. Haddock, K. Meade-White, G. Nardone, F. Feldmann, P. W. Hanley, J. Lovaglio, D. Scott, T. Komeno, N. Nakajima, Y. Furuta, B. B. Gowen and H. Feldmann (2020). "Efficacy of favipiravir (T-705) against Crimean-Congo hemorrhagic fever virus infection in cynomolgus macaques." Antiviral Res **181**: 104858.
27. Huang, C., Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang and B. Cao (2020). "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." The Lancet **395**(10223): 497-506.
28. Hung, I. F.-N., K.-C. Lung, E. Y.-K. Tso, R. Liu, T. W.-H. Chung, M.-Y. Chu, Y.-Y. Ng, J. Lo, J. Chan, A. R. Tam, H.-P. Shum, V. Chan, A. K.-L. Wu, K.-M. Sin, W.-S. Leung, W.-L. Law, D. C. Lung, S. Sin, P. Yeung, C. C.-Y. Yip, R. R. Zhang, A. Y.-F. Fung, E. Y.-W. Yan, K.-H. Leung, J. D. Ip, A. W.-H. Chu, W.-M. Chan, A. C.-K. Ng, R. Lee, K. Fung, A. Yeung, T.-C. Wu, J. W.-M. Chan, W.-W. Yan, W.-M. Chan, J. F.-W. Chan, A. K.-W. Lie, O. T.-Y. Tsang, V. C.-C. Cheng, T.-L. Que, C.-S. Lau, K.-H. Chan, K. K.-W. To and K.-Y. Yuen (2020). "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." The Lancet **395**(10238): 1695-1704.
29. Infectious Diseases Society of America Guideli. (2020, September 15 ). "Infectious diseases society of america guidelines on the treatment and management of patients with COVID-19." from https://www.idsociety.org/covid19guidelines%EF%BB%BF.
30. Jeevaratnam, K. (2020). "Chloroquine and hydroxychloroquine for COVID-19: implications for cardiac safety." Eur Heart J Cardiovasc Pharmacother **6**(4): 256-257.
31. Karalis, V., G. Ismailos and E. Karatza (2020). "Chloroquine dosage regimens in patients with COVID-19: Safety risks and optimization using simulations." Saf Sci **129**: 104842.
32. Kawamura, K., K. Ichikado, M. Suga and M. Yoshioka (2014). "Efficacy of Azithromycin for Treatment of Acute Exacerbation of Chronic Fibrosing Interstitial Pneumonia: A Prospective, Open-Label Study with Historical Controls." Respiration **87**(6): 478-484.
33. Khalili, J. S., H. Zhu, N. S. A. Mak, Y. Yan and Y. Zhu (2020). "Novel coronavirus treatment with ribavirin: Groundwork for an evaluation concerning COVID-19." Journal of Medical Virology **92**(7): 740-746.
34. Khambholja, K. and D. Asudani (2020). "Potential repurposing of Favipiravir in COVID-19 outbreak based on current evidence." Travel Med Infect Dis **35**: 101710.
35. Khamitov, R. A., S. Loginova, V. N. Shchukina, S. V. Borisevich, V. A. Maksimov and A. M. Shuster (2008). "[Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures]." Vopr Virusol **53**(4): 9-13.

36. Knowles, S. R., E. J. Phillips, L. Dresser and L. Matukas (2003). "Common Adverse Events Associated with the Use of Ribavirin for Severe Acute Respiratory Syndrome in Canada." Clinical Infectious Diseases **37**(8): 1139-1142.
37. Kong, L. (2003). Transfusion and Apheresis Science **29**(1): 101.
38. Lee, S. J., E. Silverman and J. M. Bargman (2011). "The role of antimalarial agents in the treatment of SLE and lupus nephritis." Nat Rev Nephrol **7**(12): 718-729.
39. Li, X., J. Zai, Q. Zhao, Q. Nie, Y. Li, B. T. Foley and A. Chaillon (2020). "Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2." Journal of Medical Virology **92**(6): 602-611.
40. Lo, M. K., R. Jordan, A. Arvey, J. Sudhamsu, P. Shrivastava-Ranjan, A. L. Hotard, M. Flint, L. K. McMullan, D. Siegel, M. O. Clarke, R. L. Mackman, H. C. Hui, M. Perron, A. S. Ray, T. Cihlar, S. T. Nichol and C. F. Spiropoulou (2017). "GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses." Sci Rep **7**: 43395.
41. Ma, C., S. Su, J. Wang, L. Wei, L. Du and S. Jiang (2020). "From SARS-CoV to SARS-CoV-2: safety and broad-spectrum are important for coronavirus vaccine development." Microbes and Infection **22**(6-7): 245-253.
42. Microbone Notes. (2020). "Chloroquine (chloroquine phosphate)." from https://microbenotes.com/chloroquine/.
43. Million, M., J. C. Lagier, P. Gautret, P. Colson, P. E. Fournier, S. Amrane, M. Hocquart, M. Mailhe, V. Esteves-Vieira, B. Doudier, C. Aubry, F. Correard, A. Giraud-Gatineau, Y. Roussel, C. Berenger, N. Cassir, P. Seng, C. Zandotti, C. Dhiver, I. Ravaux, C. Tomei, C. Eldin, H. Tissot-Dupont, S. Honore, A. Stein, A. Jacquier, J. C. Deharo, E. Chabriere, A. Levasseur, F. Fenollar, J. M. Rolain, Y. Obadia, P. Brouqui, M. Drancourt, B. La Scola, P. Parola and D. Raoult (2020). "Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France." Travel Med Infect Dis **35**: 101738.
44. Morgenstern, B., M. Michaelis, P. C. Baer, H. W. Doerr and J. Cinatl (2005). "Ribavirin and interferon-β synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines." Biochemical and Biophysical Research Communications **326**(4): 905-908.
45. MSD Manual Professional Versio (2020, July). "Coronaviruses and acute respiratory syndromes (COVID-19, MERS, and SARS)." from https://www.msdmanuals.com/professional/infectious-diseases/respiratory-viruses/coronaviruses-and-acute-respiratory-syndromes-covid-19-mers-and-sars.
46. Musa, A., K. Pendi, A. Hashemi, E. Warbasse, S. Kouyoumjian, J. Yousif, E. Blodget, S. Stevens, B. Aly and D. A. Baron (2020). "Remdesivir for the Treatment of COVID-19: A Systematic Review of the Literature." West J Emerg Med **21**(4): 737-741.
47. Nabian, M. H., F. Vosoughi, F. Najafi, S. S. Khabiri, M. Nafisi, J. Veisi, V. Rastgou, S. Ghamari, A. Aakhashi, N. Bahrami, M. Naderi, S. Maleki and M. S. Yekaninejad (2020). "Epidemiological pattern of pediatric trauma in COVID-19 outbreak: Data from a tertiary trauma center in Iran." Injury.
48. Oestereich, L., A. Ludtke, S. Wurr, T. Rieger, C. Munoz-Fontela and S. Gunther (2014). "Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model." Antiviral Res **105**: 17-21.
49. Ouassou, H., L. Kharchoufa, M. Bouhrim, N. E. Daoudi, H. Imtara, N. Bencheikh, E. L. A and M. Bnouham (2020). "The Pathogenesis of Coronavirus Disease 2019 (COVID-19): Evaluation and Prevention." J Immunol Res **2020**: 1357983.
50. Owa, A. B. and O. T. Owa (2020). "Lopinavir/ritonavir use in Covid-19 infection: is it completely non-beneficial?" J Microbiol Immunol Infect.
51. Paeshuyse, J., K. Dallmeier and J. Neyts (2011). "Ribavirin for the treatment of chronic hepatitis C virus infection: a review of the proposed mechanisms of action." Current Opinion in Virology **1**(6): 590-598.
52. Pan, X., L. Dong, L. Yang, D. Chen and C. Peng (2020). "Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China." Virus Research **286**: 198057.
53. Petersen, E., C. Wejse and A. Zumla (2020). "Advancing COVID-19 vaccines - avoiding different regulatory standards for different vaccines and need for open and transparent data sharing." Int J Infect Dis **98**: 501-502.
54. Pilkington, V., T. Pepperrell and A. Hill (2020). "A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic?" Journal of Virus Eradication **6**(2): 45-51.
55. Pourghasemi, H. R., S. Pouyan, B. Heidari, Z. Farajzadeh, S. R. Fallah Shamsi, S. Babaei, R. Khosravi, M. Etemadi, G. Ghanbarian, A. Farhadi, R. Safaeian, Z. Heidari, M. H. Tarazkar, J. P. Tiefenbacher, A. Azmi and F. Sadeghian (2020). "Spatial modeling, risk mapping, change detection, and outbreak trend analysis of coronavirus (COVID-19) in Iran (days between February 19 and June 14, 2020)." International Journal of Infectious Diseases **98**: 90-108.
56. Retallack, H., E. Di Lullo, C. Arias, K. A. Knopp, M. T. Laurie, C. Sandoval-Espinosa, W. R. Mancia Leon, R. Krencik, E. M. Ullian, J. Spatazza, A. A. Pollen, C. Mandel-Brehm, T. J. Nowakowski, A. R. Kriegstein and J. L. DeRisi (2016). "Zika virus cell tropism in the developing human brain and inhibition by azithromycin." Proc Natl Acad Sci U S A **113**(50): 14408-14413.
57. Rojas, M., Y. Rodriguez, D. M. Monsalve, Y. Acosta-Ampudia, B. Camacho, J. E. Gallo, A. Rojas-Villarraga, C. Ramirez-Santana, J. C. Diaz-Coronado, R. Manrique, R. D. Mantilla, Y. Shoenfeld and J. M. Anaya (2020). "Convalescent plasma in Covid-19: Possible mechanisms of action." Autoimmun Rev **19**(7): 102554.
58. Sekhavati, E., F. Jafari, S. SeyedAlinaghi, S. Jamalimoghadamsiahkali, S. Sadr, M. Tabarestani, M.

Pirhayati, A. Zendehdel, N. Manafi, M. Hajiabdolbaghi, Z. Ahmadinejad, H. E. Kouchak, S. Jafari, H. Khalili, M. Salehi, A. Seifi, F. S. Golestan and F. Ghiasvand (2020). "Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial." Int J Antimicrob Agents **56**(4): 106143.

59. Singh, A. K., A. Singh, A. Shaikh, R. Singh and A. Misra (2020). "Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries." Diabetes Metab Syndr **14**(3): 241-246.
60. Singh, A. K., A. Singh, R. Singh and A. Misra (2020). "Remdesivir in COVID-19: A critical review of pharmacology, pre-clinical and clinical studies." Diabetes Metab Syndr **14**(4): 641-648.
61. Smith, E. C., H. Blanc, M. C. Surdel, M. Vignuzzi and M. R. Denison (2013). "Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics." PLoS Pathog **9**(8): e1003565.
62. Smolen, J. S., R. Landewe, F. C. Breedveld, M. Buch, G. Burmester, M. Dougados, P. Emery, C. Gaujoux-Viala, L. Gossec, J. Nam, S. Ramiro, K. Winthrop, M. de Wit, D. Aletaha, N. Betteridge, J. W. Bijlsma, M. Boers, F. Buttgereit, B. Combe, M. Cutolo, N. Damjanov, J. M. Hazes, M. Kouloumas, T. K. Kvien, X. Mariette, K. Pavelka, P. L. van Riel, A. Rubbert-Roth, M. Scholte-Voshaar, D. L. Scott, T. Sokka-Isler, J. B. Wong and D. van der Heijde (2014). "EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update." Ann Rheum Dis **73**(3): 492-509.
63. Sputnik V (2020). "About Vaccine."
64. Sun, D. (2020). "Remdesivir for Treatment of COVID-19: Combination of Pulmonary and IV Administration May Offer Aditional Benefit." AAPS J **22**(4): 77.
65. Svanstrom, H., B. Pasternak and A. Hviid (2013). "Use of azithromycin and death from cardiovascular causes." N Engl J Med **368**(18): 1704-1712.
66. Te, H. S., G. Randall and D. M. Jensen (2007). "Mechanism of action of ribavirin in the treatment of chronic hepatitis C." Gastroenterology & hepatology **3**(3): 218-225.
67. Tektonidou, M. G., L. Andreoli, M. Limper, Z. Amoura, R. Cervera, N. Costedoat-Chalumeau, M. J. Cuadrado, T. Dorner, R. Ferrer-Oliveras, K. Hambly, M. A. Khamashta, J. King, F. Marchiori, P. L. Meroni, M. Mosca, V. Pengo, L. Raio, G. Ruiz-Irastorza, Y. Shoenfeld, L. Stojanovich, E. Svenungsson, D. Wahl, A. Tincani and M. M. Ward (2019). "EULAR recommendations for the management of antiphospholipid syndrome in adults." Ann Rheum Dis **78**(10): 1296-1304.
68. Timothy P. Sheahan, A. C. S., Rachel L. Graham,Vineet D. Menachery, Lisa E. Gralinski, (2017, January 28). "Research ArticleEMERGING INFECTIONS
69. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses." Science Translational Medicine **9**(396): 1-10.
70. Tong, S., Y. Su, Y. Yu, C. Wu, J. Chen, S. Wang and J. Jiang (2020). "Ribavirin therapy for severe COVID-19: a retrospective cohort study." International Journal of Antimicrobial Agents **56**(3): 106114.
71. Tropical Health Network. (2020, June 20). "COVID-19 prevention and treatment: a critical analysis of chloroquine and hydroxychloroquine clinical pharmacology." from https://www.tropmedres.ac/news/covid-19-prevention-and-treatment-a-critical-analysis-of-chloroquine-and-hydroxychloroquine-clinical-pharmacology.
72. Unidad de Virología, S. d. M., Hospital Universitario Son Espases, Palma de Mallorca (2020, March 23). "Remdesivir, la esperanza antiviral frente al SARS-CoV-2." Rev Esp Quimioter **33**(3): 176-179.
73. Vankadari, N. (2020). "Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein." Int J Antimicrob Agents **56**(2): 105998.
74. Vivino, F. B., S. E. Carsons, G. Foulks, T. E. Daniels, A. Parke, M. T. Brennan, S. L. Forstot, R. H. Scofield and K. M. Hammitt (2016). "New Treatment Guidelines for Sjogren's Disease." Rheum Dis Clin North Am **42**(3): 531-551.
75. Wang, M., R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong and G. Xiao (2020). "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro." Cell Research **30**(3): 269-271.
76. Wang, M., R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong and G. Xiao (2020). "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro." Cell Res **30**(3): 269-271.
77. Wang, X., R. Cao, H. Zhang, J. Liu, M. Xu, H. Hu, Y. Li, L. Zhao, W. Li, X. Sun, X. Yang, Z. Shi, F. Deng, Z. Hu, W. Zhong and M. Wang (2020). "The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro." Cell Discov **6**: 28.
78. Wang, Y., D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Y. Hu, G. Luo, K. Wang, Y. Lu, H. Li, S. Wang, S. Ruan, C. Yang, C. Mei, Y. Wang, D. Ding, F. Wu, X. Tang, X. Ye, Y. Ye, B. Liu, J. Yang, W. Yin, A. Wang, G. Fan, F. Zhou, Z. Liu, X. Gu, J. Xu, L. Shang, Y. Zhang, L. Cao, T. Guo, Y. Wan, H. Qin, Y. Jiang, T. Jaki, F. G. Hayden, P. W. Horby, B. Cao and C. Wang (2020). "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial." The Lancet **395**(10236): 1569-1578.
79. White, N. J., S. Pukrittayakamee, T. T. Hien, M. A. Faiz, O. A. Mokuolu and A. M. Dondorp (2014). "Malaria." The Lancet **383**(9918): 723-735.
80. Wong, S. S. and K. Y. Yuen (2008). "The management of coronavirus infections with particular reference to SARS." J Antimicrob Chemother **62**(3): 437-441.
81. Wu, Y. H., C. K. Tseng, C. K. Lin, C. K. Wei, J. C. Lee and K. C. Young (2018). "ICR suckling mouse model of Zika virus infection for disease modeling and drug validation." PLoS Negl Trop Dis **12**(10): e0006848.
82. Yang, C., C. Ke, D. Yue, W. Li, Z. Hu, W. Liu, S. Hu, S. Wang and J. Liu (2020). "Effectiveness of Arbidol for COVID-19 Prevention in Health Professionals." Front Public Health **8**: 249.

83. Yao, X., F. Ye, M. Zhang, C. Cui, B. Huang, P. Niu, X. Liu, L. Zhao, E. Dong, C. Song, S. Zhan, R. Lu, H. Li, W. Tan and D. Liu (2020). "In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)." Clin Infect Dis **71**(15): 732-739.
84. Ye, Q., B. Wang and J. Mao (2020). "The pathogenesis and treatment of the `Cytokine Storm' in COVID-19." J Infect **80**(6): 607-613.
85. Yu, I. T., H. Qiu, L. A. Tse and T. W. Wong (2014). "Severe acute respiratory syndrome beyond Amoy Gardens: completing the incomplete legacy." Clin Infect Dis **58**(5): 683-686.
86. Yuji Kumagai, Y. M., Tomoko Hasunuma, Masako Aso, Wakako Yuji, Tsutomu Sakurai, Masahiko Noto, Tetsuya Oe, and Akiko Kaneko (2015). "Lack of effect of favipiravir, a novel antiviral agent, on QT interval in healthy Japanese adults." Int. Journal of Clinical Pharmacology and Therapeutics **53**: 866-874.
87. Zhang, H., Q. Chen, W. Zhou, S. Gao, H. Lin, S. Ye, Y. Xu and J. Cai (2013). "Chinese medicine injection shuanghuanglian for treatment of acute upper respiratory tract infection: a systematic review of randomized controlled trials." Evid Based Complement Alternat Med **2013**: 987326.
88. Zhang, J. N., W. J. Wang, B. Peng, W. Peng, Y. S. Zhang, Y. L. Wang, Y. Wan, J. Chang, L. Mao, X. P. Miao, Y. N. Li, Y. F. Zhou and B. Hu (2020). "Potential of Arbidol for Post-exposure Prophylaxis of COVID-19 Transmission: A Preliminary Report of a Retrospective Cohort Study." Curr Med Sci **40**(3): 480-485.
89. Zhu, Z., Z. Lu, T. Xu, C. Chen, G. Yang, T. Zha, J. Lu and Y. Xue (2020). "Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19." J Infect **81**(1): e21-e23.