Literature Review of Prospective Drugs for COVID-19

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Brac University
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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
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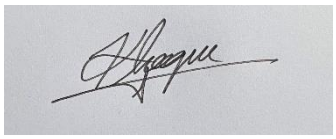

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Approval

The thesis titled “Literature Review of Prospective Drugs for COVID-19” submitted by Md Ikramul Hoque (16346029) of Summer, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor Of Pharmacy on 1st February.

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Ethics Statement

This study comprises no animal or human trial.

Abstract

A new public health disaster arises with the spreading of novel coronavirus in early December 2019, originated in Wuhan City, Hubei Province, China. The novel coronavirus which is identified as Coronavirus Disease 2019 (COVID-19) was accountable for causing pneumonia like disease to patients after that novel coronavirus is identified as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). It is assumed that bat is the primary source of coronavirus because its homology matches 80% to SARS-CoV which is responsible for acute respiratory distress syndrome (ADRS). Because of this virus World Health Organization (WHO) officially announced a pandemic throughout the world on March 11, 2020. SARS-CoV-2 is highly transmittable from human to human, more than 99,804,787 confirmed cases and 2,139,791 thousand confirmed deaths and 71,797,201 recovered cases globally to date (25/01/2021) according to WHO. SARS-CoV-2 virus firstly affects respiratory system and other organ systems too as time passes. Symptoms starting from fever, dry cough, tiredness and to serious symptoms includes difficulty breathing or shortness of breath, chest pain, loss of speech or movement and multiple organ dysfunction which leads to death. As a result, an immediate treatment option in needed for this current situation. Although, several potent antiviral drugs, vaccines are under urgent investigation but no candidate found so far for SARS-CoV-2 virus. In this literature review we summarized all the latest research progress of the causative agent, pathogenesis, epidemiology, immune response, clinical characteristics, diagnosis, treatment, management of diseases, control, prevention strategies of COVID-19.

Keywords: coronavirus diseases 2019; Novel coronavirus; SARS-CoV-2; WHO; vaccines; pathogenesis;

Dedication

Dedicated to my parents and to all the victims who have died due to COVID-19.

Acknowledgement

First of all, I am grateful to my Almighty Allah for the good health and wellbeing during the project which were vital to complete the project work on time.

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Also, I take this opportunity to express my gratitude to all the faculty members and lab officer for their help and support.

Last but not the least, I would like to express my greatest regards to my parents for their cooperation, continuous support, unconditional love throughout my life.

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List of Acronyms

COVID-19	Coronavirus Diseases-2019
WHO	World Health Organization
FDA	Food and Drug Administration
HFNC	High Flow Nasal Cannula
ACE2	Angiotensin Converting Enzyme 2
IMP	Importin
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
RdRp	RNA dependent RNA polymerase
SOC	Standard of Care
HFNC	High Flow Nasal Cannula
IFN-α	Interferon-α
HIV-1	Human Immunodeficiency Virus-1

Chapter 1

Introduction

The small local fish and wild animal market located in Wuhan, Hubei Province, China where the beginning of this COVID-19 pandemic has started and number of patients had been identified suffering from pneumonia from a unknown viral infection in December 2019 (Mohamed et al., 2020; Singhal, 2020). But it did not take time to identify that novel coronavirus was responsible. The coronavirus is named as 2019-new coronavirus disease (2019-nCoV) and later known as COVID-19 by the World Health Organization (WHO) and Coronavirus Study Group (CSG) (Sohrabi et al., 2020). SARS-CoV-2 is highly transmittable from human to human, more than 99,804,787 confirmed cases and 2,139,791 thousand confirmed deaths and 71,797,201 recovered cases globally to date (25/01/2021) according to WHO. If we consider this novel coronavirus history then coronavirus belongs to family ***Coronaviridae*** and order ***Nidovirales*** which is a single strand, positive sense RNA genome and it is 60-140 nm in diameter and 26-32 kbs in length. In addition, the four genera of Coronaviridae family are α-CoV (Alpha-coronavirus), β-CoV (Beta-coronavirus), δ-CoV (Delta-coronavirus) and γ-CoV (Gamma-coronavirus). Based on the representation of coronavirus under electron microscope are named because they are covered with pointed structure like crown as a result of presence of spike glycoproteins on envelope(Adnan et al., 2020; Mohamed et al., 2020). It was thought that coronavirus was only pathogenic to animals until the outbreak of SARS-CoV-2, a new novel strain was developed as a result of constant development of transcription error which accelerated recombination rates, high mutation rate and RNA dependent RNA polymerase (RdRP) jumps of this virus as a result virus is able to do human to human transmission (Madabhavi et al., 2020). The novel coronavirus typically affects the respiratory system and binds with host cell's angiotensin-converting enzyme 2 (ACE2)

receptors which is usually present on epithelial cells of alveoli, trachea, and bronchi of the respiratory tract causing minimal symptoms to severe hypoxia with ADRS. Initial symptoms started from which includes fever, dry cough, tiredness and to serious symptoms includes difficulty breathing or shortness of breath, chest pain, loss of speech or movement and multiple organ dysfunction which eventually leads to death (Mohamed et al., 2020; Yuki et al., 2020). In the starting of 21st century the world had faced two events of global epidemic where a virus name coronavirus, genera of β-CoV caused mild respiratory disease. Previously it was believed that coronavirus only transmits from animal to animal until the world has faced a SARS epidemic caused by SARS-CoV, 2002 in Guangdong Province of China. In 2002-2003 epidemic, it was found that bats were the primary reservoirs of SARS-CoV and it was transmitted to human via an intermediary host called palm civet cats. During that period, total of 8422 confirmed cases and 916 confirmed deaths with mortality rate of 11%. After a decade later in 2012, another highly pathogenic coronavirus known as Middle East respiratory syndrome coronavirus (MERS-CoV) out broke, bats were also the primary reservoirs and transmitted to human via an intermediary host called dromedary camels, originated in Saudi Arabia. During that period, 2494 confirmed cases and 858 confirmed deaths with mortality rate of 34% (Singhal, 2020). Several antiviral agents were proposed for the treatment including Chloroquine diphosphate, Mafloquine, Tamoxifane citrate, Anisomycin, Thiothixene, Dasatinib which were specific for both SARS-CoV and MERS-COV (Dyall et al., 2014).

1.1 Methods

A search method was conducted on the ClinicalTrials.gov for the ongoing or completed trials on the antiviral drugs which has possible therapeutic effects or antiviral action on coronavirus. The search method is based on the keyword including Remsedivir, Favipiravir, Lopinavir/Ritonavir, Chloroquine and Hydroxychloroquine, Ivermectin, Umifenovir, Convalescent plasma and COVID-19. The collected data from the ClinicalTrials.gov is tabulated and the outcome measures are discussed and the updates of the trials are also searched on National Center for Biotechnology Information (NCBI) databases and the finding of the trials are collected and discussed and a literature review is written based on the collected data.

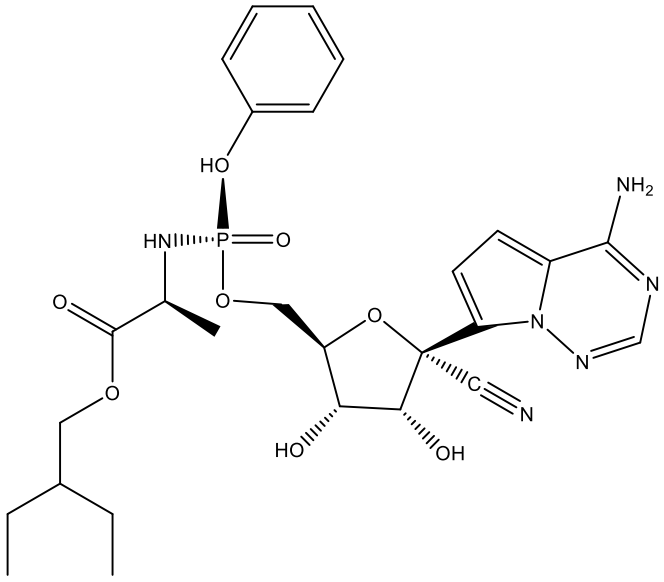
Chapter 2

Antiviral Agents

2.1 Remdesivir

In 2017, a new broad spectrum antiviral drug was developed for the purpose of Ebola virus infections. Gilead Sciences were the company who first synthesized remdesivir which is a prodrug of c-nucleoside (Wu et al., 2020). Remdesivir is a potential antiviral drug against COVID-19 and it has shown more activity than other antiviral drugs used in the treatment of COVID-19 infected patients and is proven to be most promising and helpful antiviral therapeutic. The drug is metabolized to its active form then inhibits the viral replication and it is much effective especially at the beginning of life cycle into host cells when virus starts to multiplies in the upper respiratory part of the body. Remdesivir probable mechanism of action is the inhibition of the essential protein complex RNA-dependent RNA polymerase (RdRp) for the viral replication (Jean et al., 2020). A phase 3 clinical trial was conducted on February 5 where the safety and therapeutic effects of remdesivir was evaluated. The experimental patients

received remdesivir intravenous infusion loading dose 200mg and maintenance dose 100mg for 9 day of course. In addition, remdesivir was given to the first coronavirus infected patient found in the USA on the 7th day hospitalization in January, 2020 clinical improvements was seen in that patient. So current recommendation of remdesivir including the 10 day course which includes 200mg loading dose on first day and 100mg maintenance dose for following 9 days. In conclusion, patients taking remdesivir have shown improvements of their condition but it will be too early to suggest remdesivir as a specific antiviral drug of COVID-19. Despite having therapeutic effects some adverse effects including nausea, vomiting and rectal hemorrhage are associated with remdesivir.



Remdesivir

Figure 1 Structure of Remdesivir

2.1.1 Mechanism of Action

Remdesivir a broad spectrum antiviral drug invented by Gilead Science Inc. which is a nucleotide analogue. The RNA-dependent RNA polymerase (RdRp) protein complex is inhibited when the triphosphate form of remdesivir is used as substrate. The coronavirus uses this protein complex to replicate their RNA based genome by a mechanism called delayed chain termination. The active form of remdesivir gets into host and competes with ATP which is a natural nucleotide and gets attached to the viral RNA strand which inhibits the RNA synthesis of viral genome. After adding few new nucleotide bases RNA synthesis stopped.

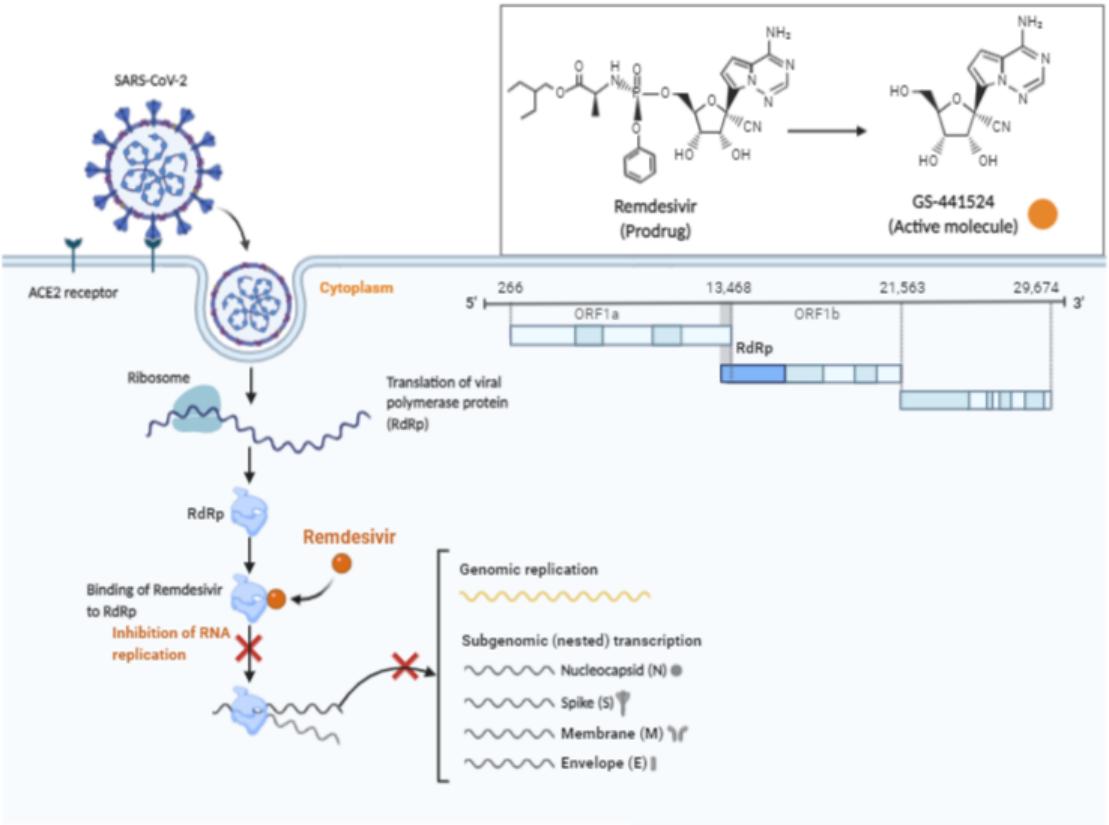


Figure 2 Molecular Mechanism of action of Remdesivir against SARS-CoV-2(Saha et al., 2020)

2.1.2 Clinical Trials on Remdesivir

A number of clinical study was conducted by Gilead Science on the antiviral drug remdesivir a potential antiviral drug which has therapeutic effects on novel coronavirus. The primary purpose of the study was to determine the efficacy, antiviral activity, safety profile and pharmacokinetics of remdesivir for treating the infection caused by SARS-CoV-2. These are randomized, blinded, placebo-controlled, single- and multiple-dose study in healthy volunteers to determine the safety of remdesivir administered by inhalation. The inclusion criteria of the participants are at least 12 years of age male and females. In addition, no healthy volunteers are eligible because participants with confirm SARS-CoV-2 are need. Likewise, in a study registered as (NCT04501952) remdesivir was administered as an intravenous infusion and placebo was also administered as an intravenous infusion. The initial dose of remdesivir (IV) was 200mg on day 1 and maintenance IV dose of 100mg on day 2 and 3.In another study of the Gilead Sciences registered as (NCT04539262) where in experimental part A remdesivir dose was 31mg and given as intravenous infusion along with placebo for 5 days. In experimental part B remdesivir was given through inhalation of 62mg of dose for 3 days followed by placebo for 5 days. Similarly, National Institute of Allergy and Infectious Diseases (NIAID) conducted an adaptive, randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of remdesivir in hospitalized adults with confirmed COVID-19. The interventions including investigational drug remdesivir along with Interferon beta-1a, placebo and standard care to the hospitalized patients. In a study registered as (NCT04492475) the participants received 200mg of remdesivir as an initial dose and 100mg maintenance dose for up to 10 days. Along with that 44 mcg of interferon beta-1a and subcutaneously 0.5 mL placebo injection is administered to the participants. A total of 4 doses are given to the participants. In another study registered as (NCT04501978) where participants received remdesivir with standard of care (SOC) or placebo with standard of care (SOC)

2.1.3 Outcome measures

The primary outcome measures of the study includes the number of participants experiencing any adverse effects and laboratory abnormalities within 30 days follow up. The concentration of plasma and other metabolites are also measured. In addition, the time of recovery, number of participants hospitalized and death within 14 days of randomization, time required for baseline to severe condition of COVID-19 patients are also measured in this study. However, the secondary outcome measures includes the changes from baseline in WBC, creatinine, Glucose, hemoglobin, platelets etc. of COVID-19 participants. The other measures are all-cause mortality, pulmonary ordinal outcome, incidence of clinical organ failure, time to resolution of COVID-19 related symptoms, time to discharge from the hospital are also measured.

Table 1 Clinical trials registered at ClinicalTrials.gov to determine the safety and efficacy of Remdesivir for the treatment of COVID-19 patients.

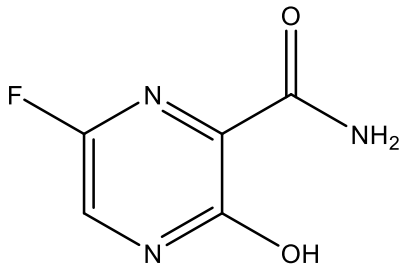
Study Identifier	Status	Interventions	Sponsor	Phase	Study Design			
					Study Type	Masking; Primary Purpose	Intervention Model	Enrolled Patients
NCT04431453	Recruiting	Remdesivir	Gilead Sciences	2 3	Interventional (Clinical Trial)	None (Open Label)	Single Group Assignment,	52
NCT04292899	Completed	Remdesivir; Standard of Care	Gilead Sciences	3	Interventional (Clinical Trial)	None (Open Label)	Randomized, Parallel Assignment,	408
NCT04539262	Recruiting	Remdesivir (RDV); Placebo	Gilead Sciences	1 2	Interventional (Clinical Trial)	Double (Participant, Investigator)	Randomized; Parallel Assignment	282
NCT04501952	Not yet recruiting	RDV; Placebo to Match RDV	Gilead Sciences	3	Interventional (Clinical Trial)	Double (Participant, Investigator)	Randomized, Parallel Assignment	1230
NCT04492475	Recruiting	Interferon beta-1a; Placebo; Remdesivir	National Institute of Allergy and Infectious Diseases (NIAID)	3	Interventional (Clinical Trial)	Double (Participant, Investigator)	Randomized; Parallel Assignment	1038

NCT04280705	Completed	Remdesivir; Placebo	National Institute of Allergy and Infectious Diseases (NIAID)	3	Interventional (Clinical Trial)	Double (Participant, Investigator)	Randomized; Parallel Assignment	1062
NCT04501978	Recruiting	Placebo Remdesivir	National Institute of Allergy and Infectious Diseases (NIAID)	3	Interventional (Clinical Trial)	Triple (Participant, Care Provider, Investigator)	Randomized; Parallel Assignment;	10000

2.2 Favipiravir (Avigan)

Favipiravir is a RNA-dependent RNA polymerase inhibitors branded as Avigan and in 2014 first developed by Chemical Company Limited called Fujifilm Toyama Tokyo of Japan for the treatment of influenza virus and recommended for SARS-CoV-2 as it is a RNA virus. In February, 2020 a preliminary clinical trial was conducted on favipiravir in China on 80 patients and which indicated better results. The active form of favipiravir act as a substrate when it enters into the cell by endocytosis process. The protein complex present in the virus called RNA-dependent RNA polymerase recognize the active phosphoribosylated form of favipiravir and cause interruption to viral RNA replication process. In the viral RNA replication process when the nucleotide base attached a dysregulation occurs when cytosine (C) is replaced by thymine (T) and guanine (G) is replace by adenine (A) as a result of favipiravir. Due to this interruption destructive mutagenesis occurs in RNA viruses including SARS-CoV, SARS-CoV-2 (Wu et al., 2020). A loading dose of 1600 mg is given on the first day of treatment for 2 times and a maintenance dose of 600mg is given to the patients for 2 times on following days for 5 day. On the 6^{th} day another 600mg dose is given to the patient to complete the course. Unfortunately, favipiravir has not shown much effective with patients with severe condition and did not show much promising results. Despite of its disadvantages, the primary outcome

of clinical studies have shown that favipiravir shows a promising antiviral activity in treatment of patients with confirm COVID-19 in China (Cai et al., 2020). So it better to give favipiravir before the viral load peaks in the body.



Favipiravir

Figure 3 Structure of Favipiravir

2.2.1 Mechanism of Action

The mechanism of action of Avigan is ultimately preventing the viral replication process. The protein complex RNA-dependent RNA polymerase is inhibited by the active form of favipiravir when it is recognized as a substrate and incorporated into the viral replication process. It acts as a purine analogue in the viral replication process and the nucleotide base guanine and adenine is replaced by this purine analogue. As a result the elongation step of viral replication is terminated by Favipiravir molecule (Seneviratne et al., 2020).

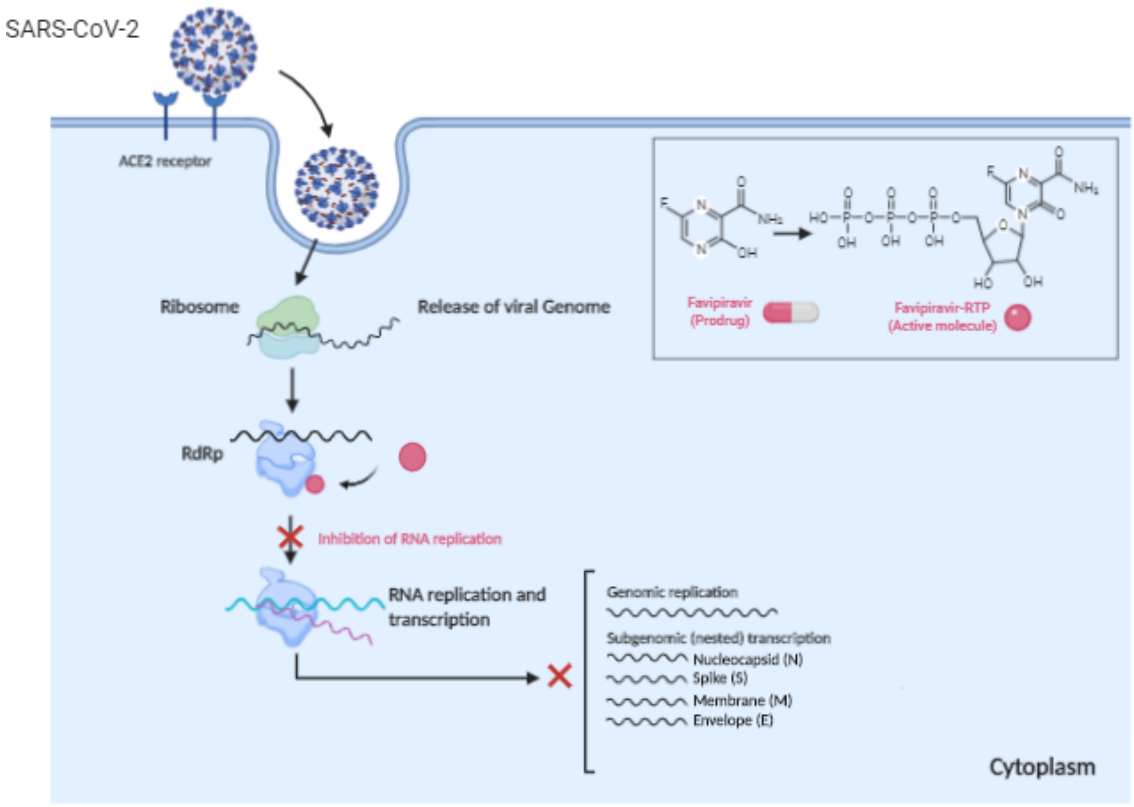


Figure 4 Mechanism of action of Favipiravir which selectively inhibits RdRp thus inhibiting viral replication process of Coronavirus (Agrawal et al., 2020; Seneviratne et al., 2020)

2.2.2 Clinical Trials on Favipiravir (Avigan)

The clinical study organized by Indonesia University a phase 3 study which is an open-label trial to determining the effectiveness of favipiravir along with Oseltamivir used as an adjacent therapy. On April 16, 2020, registered as (NCT04558463) on clinicaltrial.gov where participants were divided into two groups. The favipiravir group received 1600mg of favipiravir two times a day on day one as a loading dose and maintenance dose 600mg two time a day for 7 days along with the standard care. On July 23, 2020, another study sponsored by King Abdullah International Medical Research Center which was a multicenter, randomized double-blinded, parallel-group study. The primary purpose of the study was to identify the efficacy of favipiravir in compared to placebo in confirmed COVID-19 patients. The

participants were divided into two groups and favipiravir group received loading dose of 1800mg two times a day on day 1 and maintenance dose of 800mg two times a day for 7 days. In addition, total of 9 tablets of placebo was given orally twice a day on day 1 and 4 tablets was given two times a day for 7 days. Moreover, Ain Shams University also conducted a clinical trial registered as (NCT04349241) which is a randomized, open label study to evaluate the efficacy of favipiravir in compared to standard care in hospitalized patients with confirmed COVID-19. In this study the favipiravir was given as a loading dose of 3200mg twice a day on day 1 and maintenance dose 1200mg on the following day up to 10 days.

2.2.3 Outcome measures of Favipiravir

The primary outcome measures of the study of favipiravir includes measures of viral clearance by two negative RT-PCR results of COVID-19 and clinical improvements within 14 days from randomization. Also the changes in the lungs infiltrate in chest x-ray after 14 days of followed up which will show improvement or no changes or deterioration of the radiological results. However, the secondary outcome measures of the study was to measures the adverse event, hospital stay period time, case fatality rate, radiological improvements, Time from randomization to clinical recovery, Rate of requirement of hospitalization, ICU admission or Mechanical ventilation.

Table 2 Registered Favipiravir trails at ClinicalTrials.gov for SARS-CoV-2.

Study Identifier	Recruiting Status	Sponsor	Interventions	Phase	Study Design			
					Study Type	Masking	Intervention Model	Estimated Enrollment
NCT04558463	Recruiting	Indonesia University	Favipiravir; Oseltamivir 75mg	3	Interventional (Clinical Trial)	None (Open Label)	Randomized; Parallel Assignment;	100
NCT04349241	Completed	Ain Shams University	Favipiravir; Standard of care therapy	3	Interventional (Clinical Trial)	None (Open Label)	Randomized; Parallel Assignment;	100
NCT04529499	Recruiting	Dr. Reddy's Laboratories Limited	AVIGAN; Placebo Comparator	3	Interventional (Clinical Trial)	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Randomized; Parallel Assignment;	780
NCT04359615	Not yet recruiting	Shahid Beheshti University of Medical Sciences	Favipiravir; Hydroxychloroquine	4	Interventional (Clinical Trial)	Triple (Participant, Care Provider, Investigator)	Randomized; Parallel Assignment;	40
NCT04542694	Completed	Promomed, LLC	Favipiravir; Standard of care	3	Interventional (Clinical Trial)	None (Open Label)	Randomized; Parallel Assignment;	200

2.3 Interferons

The interferon-α (IFN-α) is recommended due to its broad spectrum antiviral activity approved for the treatment of viral hepatitis. The therapeutic dose of interferons is 5 million units and it is given through vapor inhalation 2 times a day. It is also formulated and administrated in combination with ribavirin at a dose of 500mg 2-3 times a day and lopinavir/ritonavir at a dose of (400mg/100mg) for 10 consecutive days. Due to the susceptibility of SARS-CoV-2 to IFN-α, it reduces the infection rate significantly. It is also recommended for prophylaxis of infections caused by COVID-19 (Ahsan et al., 2020). The other interferon, interferon-β (IFN-β) is known for improving lungs condition and increase the ability to fight against viral infections and treatment of chronic obstructive pulmonary disorder (COPD). It was found that the production of INF-β is suppressed by SARS-CoV-2 infection which results in protection from immune system.

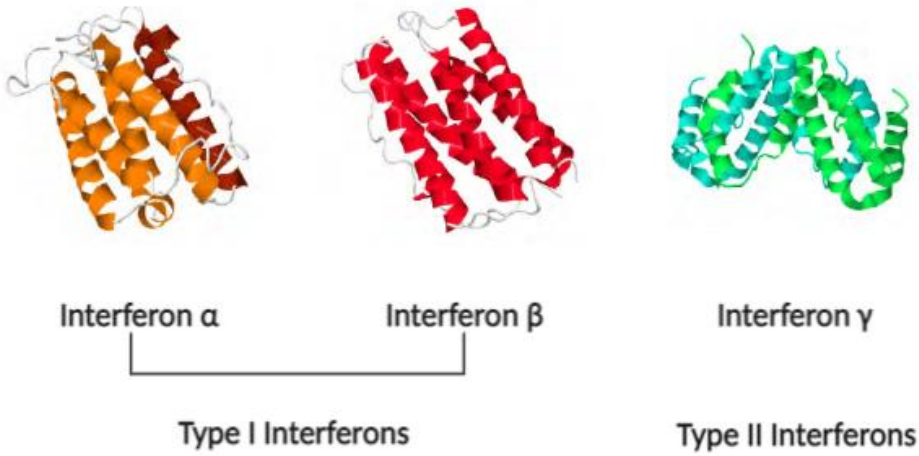


Figure 5 Molecular structure of Interferon proteins which has probable activity against SARS-CoV-2(N. & D., 2012)

2.4 Lopinavir/Ritonavir

Lopinavir is an antiretroviral drug which is another effective protease inhibitor and has a specific antiviral activity for Human Immunodeficiency Virus-1 (HIV-1). In order to lopinavir metabolism into the body, lopinavir is formulated and administrated along with the ritonavir. This combination of Lopinavir/Ritonavir was first came to the market by Abbott as a brand name of Kaletra in 2002 (Wu et al., 2020). The oral bioavailability of lopinavir in body is less when it is used alone and the biotransformation is extensive. So in order to enhance its exposure it is co-formulated with ritonavir. As lopinavir is a peptidomimetic molecule, the HIV-1 protease enzyme mainly targets the peptide linkage process which is essential for viral replication and lopinavir mimics the peptide linkage thus inhibiting the replication process. In addition, ritonavir is also an inhibitor of the protease enzyme and boost up the expression of lopinavir as well as improves antiviral activity. (Wu et al., 2020). Therefore, a clinical trial is conducted in China on patients with severe illness from COVID-19 on 199 patients. Out of 199 patients, 99 patients were given combination of Lopinavir/Ritonavir (400mg/100mg), whereas, 100 patients were given standard care only. No significant improvement in those participants received Lopinavir/Ritonavir combination (Owa & Owa, 2020). Along with that, nausea, diarrhea, asthenia are the common side effects from Lopinavir/Ritonavir combination.

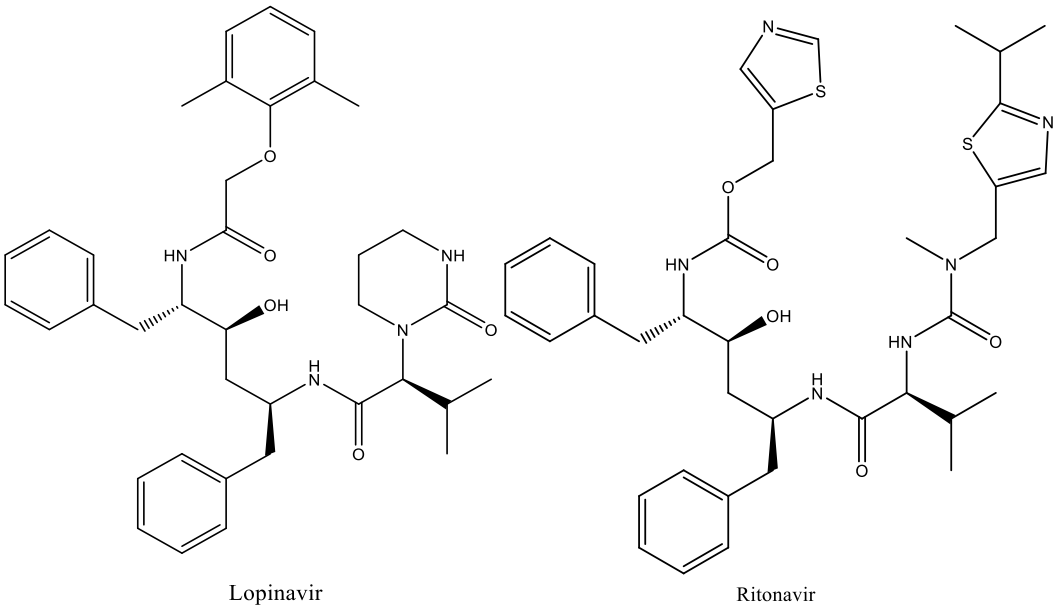


Figure 6 Structure of Lopinavir/Ritonavir

2.4.1 Mechanism of Action

The protease enzyme is an essential for the viral replication once it's inside the host cell. In addition, this enzyme helps the virus to replicate and produce infectious particles which ultimately infect the host. Kaletra is a combination of Lopinavir/Ritonavir which is a protease inhibitor. The mechanism of action of kaletra for the prevention of coronavirus replication inside the host cell is by binding with the viral proteases and as a result the proteolytic cleavage of the protein is inhibited and ultimately the infectious viral particles are not released and unable to infect the host. The same mechanism is predicted for the coronavirus as they also replicate using the same protease enzyme to infect the host. Moreover, Lopinavir/Ritonavir is under clinical trial for the purpose to use for coronavirus.

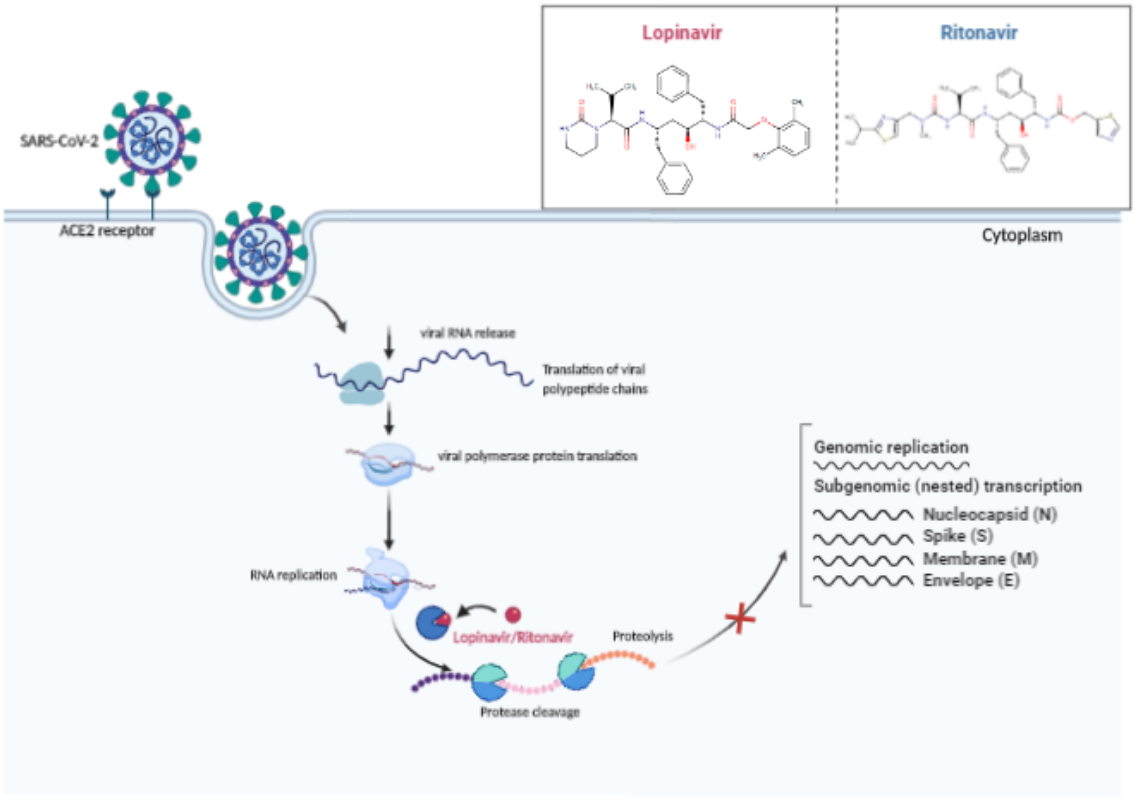


Figure 7 Mechanism of action by inhibiting viral replication process through inhibiting protease enzyme

2.4.2 Clinical Trials on Lopinavir/Ritonavir

Lopinavir/Ritonavir is a potential antiviral drug for COVID-19. On June 1, Vanderbilt University Medical Center conducted a clinical trial registered as (NCT04372628) on clinical trials.gov which is a placebo-controlled, blinded, multicenter, randomized clinical trial to evaluate the efficacy of lopinavir/ritonavir vs placebo for COVID-19 patients. The lopinavir/ritonavir group received an initial dose of 400 mg/100 mg orally twice a day from day 1 to 14. In addition, the trial participant of placebo group received unmatched placebo for two times a day for 14 days. In addition to this, Sunnybrook Health Sciences Centre also organized a study on March 18 which was an adaptive, randomized, open-label, controlled clinical trial. In this study participants were divided based on the medication receiving plus standard care. The participants of control group only received standard supportive care. On the

other hand the part b experimental participant received 400 mg/100 mg of lopinavir/ritonavir for 14 days along with the standard supportive care. The other experimental part c participant's receiver hydroxychloroquine 800mf dose for day 1 and 400 mg of dose for 10 day of course along with supportive care. Likewise, remdesivir was also given as an intravenous infusion of 200mg of dose for day 1 and 100mg of dose for 9 day course along with supportive care.

2.4.3 Outcome Measures

The primary outcome measures of the interventions was measures the efficacy of the interventions determined by all-cause mortality within a time frame of 29 days. In addition, the difference between National Institute of Allergy and Infectious Diseases severity ordinal score is measured in these study. A 21 days of exposure to SARS-CoV-2 who were basically asymptomatic was also measured. However. The secondary outcome measures was number of patients hospitalized from day 1 to 29, time to symptoms resolution, oxygen free days, fever free days, participants clinical status, duration of mechanical ventilation, Severity of participants from COVID-19 on a ordinal scale point 7 was measured.

Table 3 Registered clinical trials of Lopinavir/Ritonavir on ClinicalTrials.gov to determine the efficacy and safety of COVID-19

Study Identifier	Status	Sponsor	Interventions	Phase	Study Design			
					Study Type	Masking	Intervention Model	Estimated Enrollment
NCT04372628	Recruiting	Vanderbilt University Medical Center	Lopinavir/Ritonavir 400 mg/100 mg; Placebo	2	Interventional (Clinical Trial);	Triple (Participant, Care Provider, Investigator)	Randomized; Sequential Assignment;	600
NCT04330690	Recruiting	Sunnybrook Health Sciences Centre	Lopinavir/ritonavir; Hydroxychloroquine; remdesivir	2	Interventional (Clinical Trial);	None (Open Label)	Randomized; Parallel Assignment;	2900
NCT04328012	Recruiting	Bassett Healthcare	lopinavir/ritonavir; Losartan; Placebos	2 3	Interventional (Clinical Trial);	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Randomized; Parallel Assignment; randomized, double blind, placebo controlled clinical trial;	4000
NCT04364022	Recruiting	Calmy Alexandra	Lopinavir/ritonavir	3	Interventional (Clinical Trial);	None (Open Label).	Randomized; Parallel Assignment;	300

2.5 Chloroquine and Hydroxychloroquine

The chemical structure of both chloroquine and hydroxychloroquine are similar. A hydroxyl group is present on hydroxychloroquine as a result it becomes less toxic as well as maintaining the antiviral activity. Lysosome is a membrane bound organelle and these drugs effectively incorporate into the lysosome and the pH level is greatly altered and the activity of protease enzyme is affected and which ultimately results degradation of proteins of the virus (Hashem et al., 2020). In addition, chloroquine acts on the inhibition of the entry of coronavirus and by interfering with glycosylation process where the spike proteins of the virus is attached with the ACE2 receptor of the host cell. Therefore, if the treatment begins at the early stage of infections

of COVID-19 then it will greatly reduce the ACE2 expression (Wu et al., 2020). On the other hand hydroxychloroquine is also responsible for controlling the cytokine storm occurs in COVID-19 patients. As a result due to its potentiality the use of chloroquine and hydroxychloroquine has been recommended for the treatment of COVID-19 by the FDA. Despite of its advantages there is a chance of cardiac risks for using chloroquine and contraindicated for pregnant or breastfeeding receiving Hydroxychloroquine (Lucas et al., 2020).

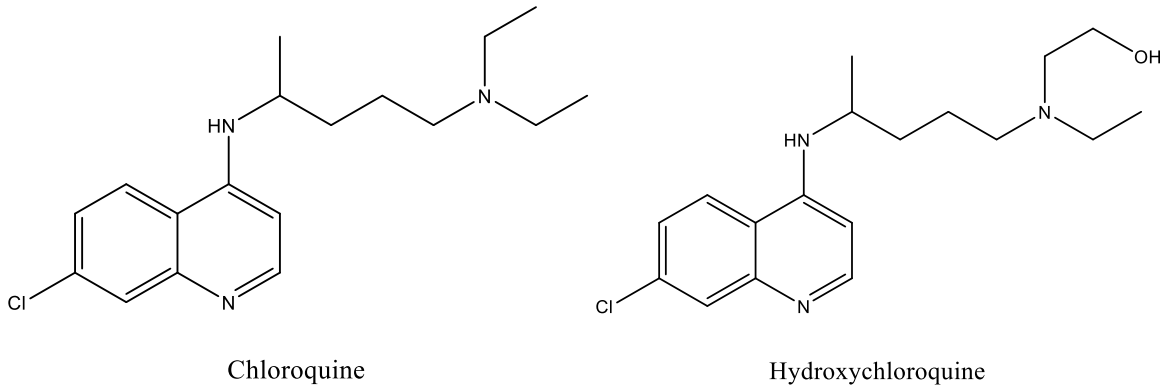


Figure 8 Structure of Chloroquine and Hydroxychloroquine

2.5.1 Mechanism of Action

The mechanism of action of chloroquine and hydroxychloroquine happens both in vivo and in vitro of the target cell. The in vitro antiviral activity of chloroquine and hydroxychloroquine is by inhibiting the entry of the virus into the target cell. It is known that the mechanism of entry of any virus into a target cell is done through sialic acid which is responsible for the incorporation of virus entry. Chloroquine and hydroxychloroquine effectively inhibit the quinone reductase 2 an enzyme essential for the synthesis of sialic acid thus inhibiting the biosynthesis of sialic acid. As a result, the attachment is restricted into the target cell. Another mechanism of action is that in the glycosylation reaction where the glycoprotein of coronavirus is attached with the host cell membrane and chloroquine and hydroxychloroquine inhibits the

glycosylation process thus inhibiting the virus cell entry. Additionally, the post translational protein modification and viral assembly is also believe to inhibit. Moreover, the in vivo mechanism of action of chloroquine and hydroxychloroquine is done by preventing vacuole formation and budding process (Hashem et al., 2020).

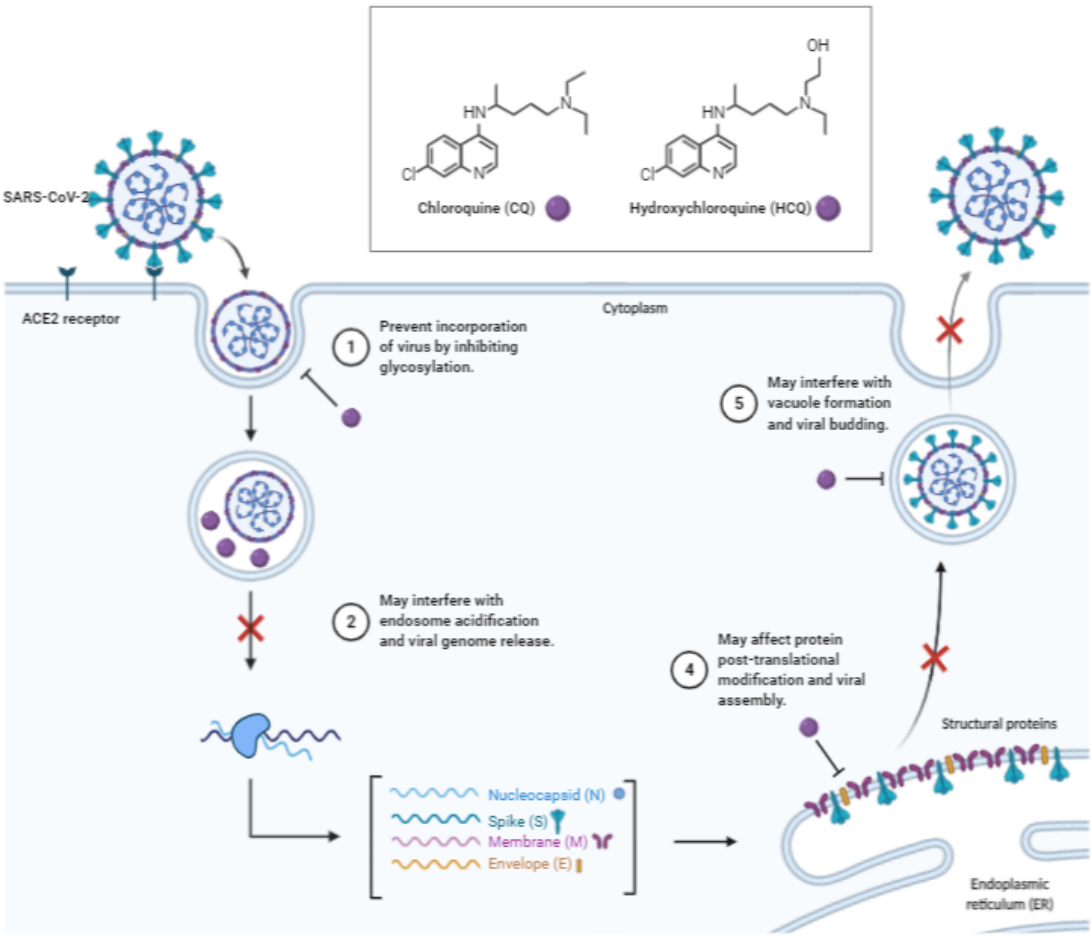


Figure 9 Probable Mechanism of action of Chloroquine and Hydroxychloroquine during the life cycle of Coronavirus (Hashem et al., 2020)

2.5.2 Clinical trials on Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are two drugs with similar structure and believed to have potential antiviral activity against COVID-19. University of Oxford organized a clinical trial on April 29 which registration number is (NCT04303507) on the clinicaltrials.gov. The study

is still recruiting participant and an estimated enrollment of participants are 40000. Healthcare workers, staffs worked into the COVID-19 facilities are selected from different sites and are randomized into 1:1 randomization into chloroquine or placebo or hydroxychloroquine or placebo group. This trial is a double-blind, randomized, placebo-controlled trial which has the primary purpose of preventing the spreading of coronavirus into the healthcare personnel. The participants of Asia will receive chloroquine at an initial dose of 10mg/kg which is equivalent to 155mg for an average 60 kg person. The maintenance dose is similar to 155mg for 3 months. Likewise, 250mg of chloroquine phosphate salt or 200mg of hydroxychloroquine sulphate will be given to the participants. Another clinical trials was conducted by Tanta University in Egypt which is a randomized, open label trial to evaluate the efficacy of antiviral activity of chloroquine and hydroxychloroquine. The usual intervention of the study was chloroquine or hydroxychloroquine along with standard of care for COVID-19 patients.

2.5.3 Outcome Measures

The primary outcome measures of the studied drug will be compared between the participants receiving chloroquine or hydroxychloroquine or placebo within a time frame of 90 days. In addition to that another primary outcome was to number of participants to the cure or death within 1 month of course. Moreover, evaluation of the clinical status of the participants within the 15 days of randomization by the ordinal scale of 6 points. The secondary outcome measures was to measure the symptoms severity of COVID-19 and severity of the symptomatic acute respiratory illnesses. In addition to that evaluation of the clinical status, duration of mechanical ventilation, ventilation free days and all-cause mortality within a 7 to 29 days of randomization. Moreover, other outcome measures includes gastrointestinal disturbance, laboratory abnormalities and adverse events within 29 days of randomization.

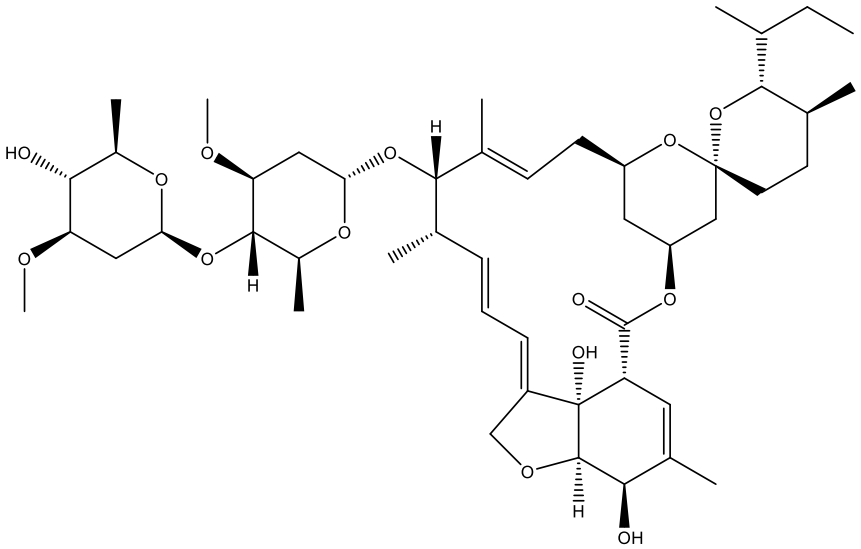
Table 4 Clinical trials registered at ClinicalTrials.gov of Chloroquine and Hydroxychloroquine for determining safety and efficacy

Study Identifier	Recruitment Status	Sponsor	Interventions	Phase	Study Design			
					Study Type	Masking	Intervention Model	Estimated Enrollment
NCT04353336	Recruiting	Tanta University	Chloroquine or Hydroxychloroquine	2 3	Interventional (Clinical Trial);	None (Open Label)	Randomized; Parallel Assignment;	200
NCT04303507	Recruiting	University of Oxford	Chloroquine or Hydroxychloroquine; Placebo	Not Applicable	Interventional (Clinical Trial);	Double (Participant, Investigator)	Randomized; Parallel Assignment;	40000
NCT04420247	Recruiting	Centro de Estudos e Pesquisa em Emergencias Medicas e Terapia Intensiva	Chloroquine; Hydroxychloroquine; standard care	3	Interventional (Clinical Trial);	Single (Outcomes Assessor)	Randomized; Parallel Assignment;	100
NCT04321278	Completed	Hospital Israelita Albert Einstein	Hydroxychloroquine + azithromycin Hydroxychloroquine	3	Interventional (Clinical Trial);	None (Open Label)	Randomized; Parallel Assignment;	440

2.6 Ivermectin

Ivermectin is a strong antiviral drug which is effective against many viral infections like human immunodeficiency virus, influenza virus, Zika virus, chikungunya virus and several ribonucleic acid (RNA) viruses. In addition it also has a promising result against coronavirus. It is a broad spectrum antiviral drug with minimal adverse effects. In 1970 two scientist name William C. Campbell and Satoshi Omura first discovered ivermectin. Not far ahead in 1980 it was first approved for animal use to determine its therapeutic efficacy and safety profile. For their excellent discovery both scientists received Nobel Prize in Medicine in 2015 (Heidary & Gharebaghi, 2020). The antiviral activity of ivermectin against COVID-19 is promising and

considered as a second choice of drug due to its high lipid solubility. The way ivermectin works is by inhibiting the viral replication of coronavirus. In culture studies it was seen that the viral load was reduced up to 5000- fold.



Ivermectin

Figure 10 Structure of Ivermectin

2.6.1 Mechanism of Action

The transportation of protein molecules from cell cytoplasm to cell nucleus is done by the help of importin (IMP) a special kind of karyopherin. In addition, the importin-α is responsible for interaction with the nucleus pore whereas importin-β1 is responsible for protein binding to the nucleus site of action. Most probably ivermectin plays a potential role in inhibition the transportation of these protein molecule through the cytoplasm of the host cells. As the RNA viruses are dependent of the importin α and β1 and ivermectin works on it and increase its antiviral activity (Choudhary & Sharma, 2020; Rizzo, 2020).

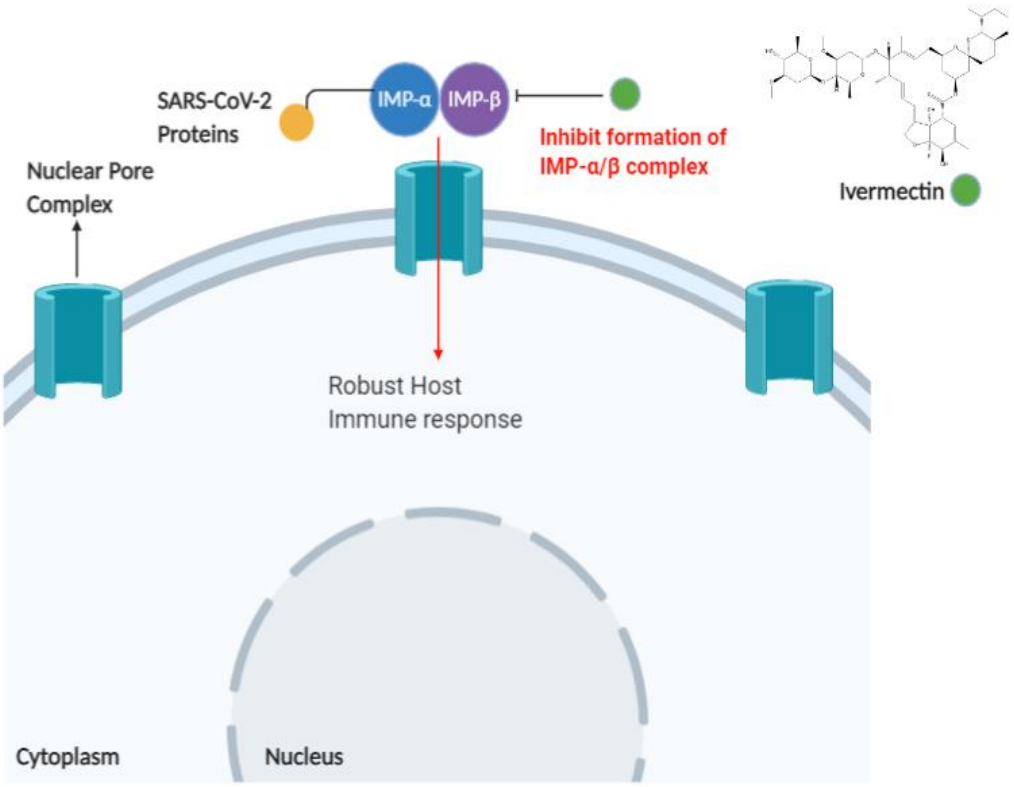


Figure 11 Mechanism of action of Ivermectin against Coronavirus by inhibiting formation of complex (Rizzo, 2020)

2.6.2 Clinical Trials on Ivermectin

The clinical trial sponsored by Dhaka Medical College which was first posted on August 24 where ivermectin is combined with another antiviral drug doxycycline for the treatment purpose of COVID-19. The objective of the trial registered as (NCT04523831) was to measure the outcome between trial group and placebo group and also determining the duration of controlling the viral load of the participants. This was a randomized, double blinded, placebo controlled study where participants were randomized into 1:1 to combined ivermectin and doxycycline and standard care group or placebo or standard care group. The dose of ivermectin and doxycycline was 6mg for 5 days and 100mg for 5 days as well along with the standard care. Similarly another case was also registered in clinicaltrial.gov as (NCT04434144)

sponsored by Upazila Health & Family Planning Officer's (UHFPO) Office, Chakoria, and Cox's Bazar where it first started on May 2 to find the efficacy of these drugs. This was an observational clinical study where enrolled participants were divided into group A and group B. The group A participant's received 200µgm/kg of ivermectin and 100mg of doxycycline for 10 days. On the other hand group B participants received hydroxychloroquine loading dose of 400mg at day 1 and maintenance dose 200mg of for 10 days and azithromycin 500mg daily for 5 days.

2.6.3 Outcome Measures

The primary outcome measures of the discussed trails is the reduction of SARS-CoV-2 viral load within 1 to 5 days treatment with ivermectin. Patients with improved clinical symptoms in consistent temperature of the body, improved respiratory symptoms and SpO2 level increased above 93%. The number of the participant treatment success is based on the outcome of every RT-PCR test which indicates the negative results. Because the negative result indicates the success of the trial. Moreover, the adverse effects of the participants will also be evaluated from the beginning of treatment. Additionally, the secondary outcome measures of the studies includes the evaluation of the clinical symptoms of enrolled patients and evaluation of the adverse effects for the measurement of safety and efficacy of ivermectin. The number of patient with worse clinical condition is also measured among the COVID-19 patients.

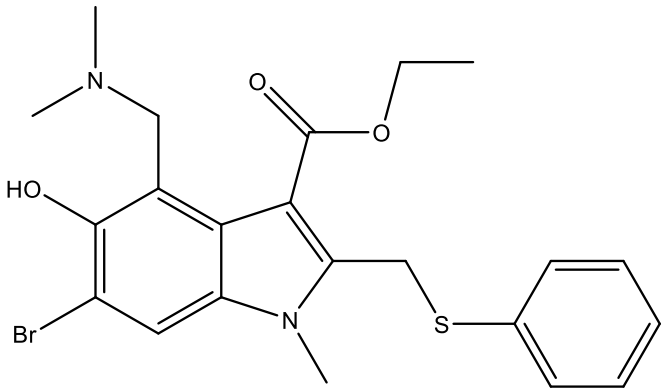
Table 5 Registered clinical trials at ClinicalTriails.gov to determining the safety and efficacy of Ivermectin

Study Identifier	Recruitment Status	Sponsor	Interventions	Phase	Study Design			
					Study Type	Masking	Intervention Model	Estimated Enrollment
NCT04381884	Recruiting	Laboratorio Elea Phoenix S.A.	IVERMECTIN (IVER P®) 600 µg / kg; Standard care.	2	Interventional (Clinical Trial);	None (Open Label)	Randomized; Parallel Assignment;	45
NCT04523831	Completed	Dhaka Medical College	Ivermectin and Doxycycline	3	Interventional (Clinical Trial);	Double (Participant, Investigator)	Randomized; Parallel Assignment;	400
NCT04529525	Recruiting	Instituto de Cardiología de Corrientes	Ivermectin and Placebo	2 3	Interventional (Clinical Trial);	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Randomized; Parallel Assignment;	500
NCT04343092	Completed	University of Baghdad	Ivermectin (IVM)	1	Interventional (Clinical Trial);	Double (Participant, Investigator)	Randomized; Parallel Assignment;	100

2.7 Umifenovir (Arbidol)

Umifenovir (arbidol) is a broad spectrum antiviral drug and it works by inhibiting the viral entry to the cell of interest and also inhibits the fusion of virus cell membrane. Branded as arbidol, Pharmstandard first successfully invented umifenovir and it was used for influenza virus infection. Firstly, in 1988 Russia used umifenovir for treating prophylaxis and influenza A and B and followed by China in 2006. The antiviral activity is promising against RNA and DNA viruses including Zika virus, Ebola virus, Hepatitis B and C and found also effective against SARS infections. Umifenovir is a derivative of indole carboxylic acids and is now on

under investigation for the treatment of SARS-CoV-2 infections due to its ability to reduce viral concentration at first and for its minimal side effects (Wu et al., 2020).



Umifenovir

Figure 12 Structure of Umifenovir

2.7.1 Mechanism of Action

A new class of antiviral drugs consider as direct acting antiviral (DAA) drugs are able to act on the different stages of life cycle of viruses an also consider as a host targeting agent (HTA) because of their ability to directly act on the cell receptors and enzymes and inhibits the infection caused by the virus. In addition, umifenovir is that type of DAA and HTA drug which is assumed to have similar mechanism of action for coronavirus and in under investigation for COVID-19. The dual mechanism of umifenovir has made it a broad spectrum antiviral agent and due to its interaction with the viral glycoproteins it can interfere with the attachments with the host cell membrane. Moreover, umifenovir can selectively interact with the viral lipid and proteins and as a result it can interfere with the later stages of the life cycle of the virus (Blaising et al., 2014).

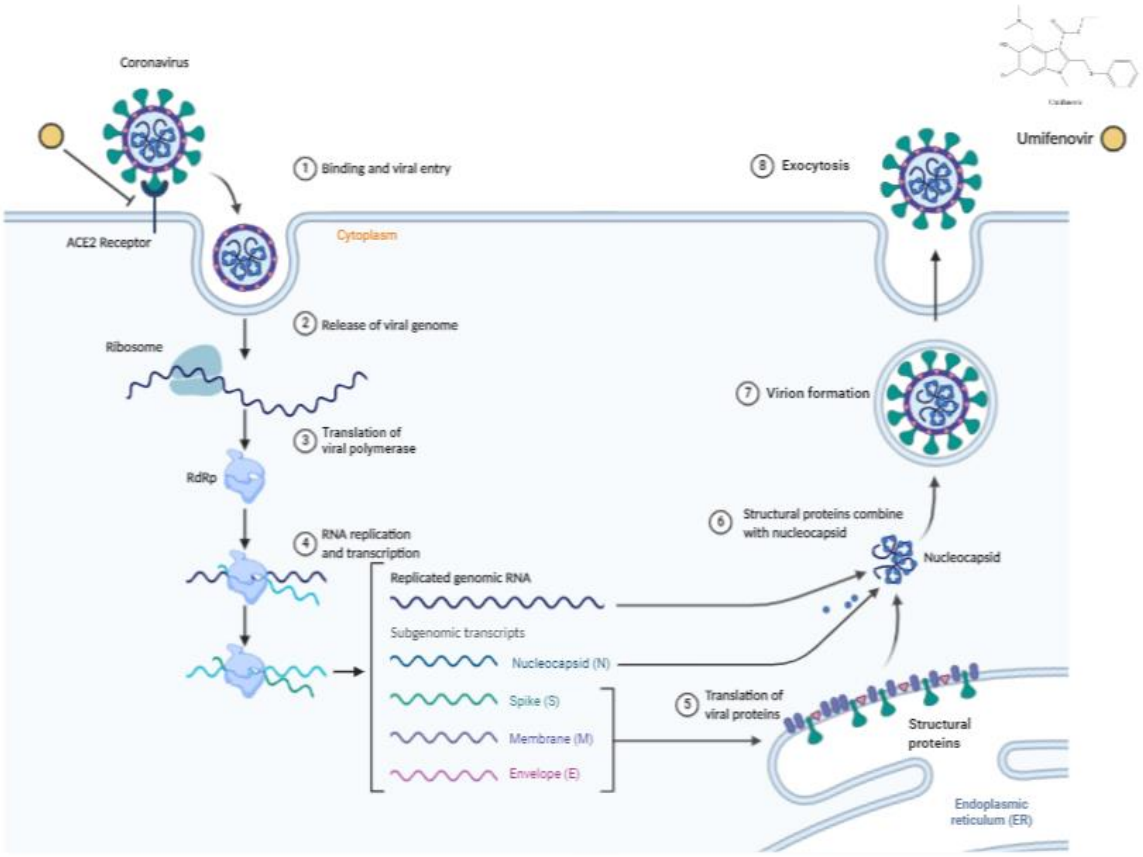


Figure 13 Probable Mechanism of action of Umifenovir by inhibiting receptor binding of Coronavirus(Blaising et al., 2014)

2.7.2 Clinical Trial on Umifenovir (Arbidol)

Arbidol is a strong antiviral drug which has believed to have antiviral property against novel coronavirus. For this purpose on February 7 a clinical trial was registered on clinicaltrial.gov as (NCT04260594) and the purpose of the study was to evaluate the safety and efficacy of arbidol for the COVID-19 patients. This study was sponsored by Jieming QU where the participants received 2 tablets of arbidol for 3 times a day for a course of 14 to 20 days. Along with that basic standard treatment were given to the participants. Another randomized, double-blind, placebo-controlled, clinical trial was conducted on April 15 sponsored by Shahid Beheshti University of Medical Sciences of Iran. The attended participants have a positive test

of coronavirus and the efficacy and safety profile f umifenovir was evaluated as an adjacent therapy along with other therapeutics.

2.7.3 Outcome Measures

The primary outcome measures of the clinical trial is measure of time to clinical improvements from a time period of randomization to up to 14 days. The decrease in two points from seven-category ordinal scale is recommended by the World Health Organization. In addition to that reduction in the virus negative conversion rate in 7 days of the randomization is also measured. The secondary outcome measure is the mortality if the patient dies then outcome achieved. Improvement of SpO2, virus negative conversion rate, antipyretic rate decreased to ≤37.5 ℃ for at least 48h. In addition, relief of symptoms like fever, cough and incidence of severe adverse reaction is measured.

Table 6 Clinical trials registered at ClinicalTrials.gov of Umifenovir to determine safety and efficacy of COVID-19 patients

Study Identifier	Recruiting Status	Sponsor	Interventions	Phase	Study Design			
					Study Type	Masking	Intervention Model	Estimated Enrollment
NCT04260594	Not yet recruiting	Jieming QU	Arbidol; basic treatment	4	Interventional (Clinical Trial);	None (Open Label)	Randomized; Parallel Assignment;	380
NCT04350684	Enrolling by invitation	Shahid Beheshti University of Medical Sciences	Umifenovir; Interferon-β 1a; Lopinavir / Ritonavir; Single Dose of Hydroxychloroquine; Standards of Care	4	Interventional (Clinical Trial);	Triple (Participant, Care Provider, Investigator)	Randomized; Parallel Assignment	40

Chapter 3

Convalescent plasma

Another treatment strategies of COVID-19 is the plasma of patients who recovered from COVID-19 in order for treatment purpose and improve the condition of severely ill COVID-19 patients. The convalescent plasma contains the antibodies which is developed by body in response to viral infection and then transfuse to infected patient in order to reduce clinical severity (Chen et al., 2020). It was also used for previous SARS-CoV, MERS-CoV pandemics and it significantly improves the condition of some patient. The mechanism of action of convalescent plasma is by attachment of transfused antibodies to infection causing pathogen which initiates phagocytosis. cytotoxicity of cell and neutralization of the pathogen (Wu et al., 2020). Therefore, it will be worthwhile to test the efficacy of convalescent plasma to treat COVID-19 infected patients. A clinical trial was conducted on January 23, 2020, where plasma of 40 recovered COVID-19 were collected and 10 of the patients with severe infections were given convalescent plasma transfusion of 200mL. In addition, along with that standard care and antiviral drugs were given also. Among 10 patients, 5 patients showed rapid improvement on clinical symptoms, better oxyhemoglobin saturation, increased lymphocytes count (Ahsan et al., 2020). The concerns about convalescent plasma is the difficulty in scaling up for widespread use and there is a great chance of transmission of other diseases from the plasma. In addition, the concentration of plasma is generally lesser which may not be significant for the treatment.

Chapter 4

Relavent findings of COVID-19 Drugs

4.1 Remdesivir

The clinical trial registered as (NCT04292899) where patients were randomly assigned in a 1:1 ratio and all patients received intravenous 100 mg of remdesivir on day 1 and 200 mg for subsequent days. In 408 patients, 397 were eligible patients began treatment (200 patients for 5 days and 197 for 10 days). The patients were assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group. The findings were clinical improvement occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. The most common adverse events were seen including nausea in 9% of patients, worsening respiratory failure in 8%, elevated alanine aminotransferase level in 7%, and constipation in 7% patients among 397 patients (Goldman et al., 2020). In another trial registered as (NCT04539262) where the findings were shorter recovery time, better clinical status, decreased mortality and increased survival among patients received remdesivir compared with the control groups (Pimentel et al., 2020). Additionally, in the clinical trial (NCT04280705) a total of 1062 patients underwent randomization among 541 assigned to remdesivir for 10 days and 521 to placebo for 15 days. Remdesivir 200 mg loading dose on day 1 and maintenance dose 100 mg daily for 10 days were given and clinical improvements were observed in remdesivir group compared to placebo group (Beigel et al., 2020)

4.2 Favipiravir (Avigan)

The clinical trial registered as (NCT04349241) in ClinicalTrials.gov where efficacy and safety profile is measured in COVID-19 patients. In the clinical trial the results were significant shorter viral clearance time and chest X-ray imaging were improved at a higher rate in the

Favipiravir group compared to standard group (91.43% and 62%, respectively). The study also shows confirmed Favipiravir's efficacy with a 7-day clinical recovery with a rate of 71.43% and reduction of fever and cough. This study also demonstrated that Favipiravir 2 has faster viral clearance than Lopinavir/Ritonavir and Umifenovir (Anum S. Minhas, M.D.). In another clinical trial registered as (NCT04542694, NCT04359615) in ClinicalTrials.gov where the relevant results were clinical status improvement of two points on a seven-category ordinal scale. In addition rate of viral elimination was significantly improved within a time frame of 10 days.

4.3 Lopinavir/Ritonavir

The trial registered as NCT04364022 determine whether Lopinavir/Ritonavir is effective as post exposure chemoprophylaxis against clinical COVID-19. Furthermore, this trial will also determine whether Lopinavir/Ritonavir reduces the severity of clinical COVID-19 and whether these prophylaxes are safe and acceptable for post exposure prophylaxis of SARS-CoV-2 and COVID-19 (Smit et al., 2020).

4.4 Chloroquine/Hydroxychloroquine

The clinical trial registered as (NCT04353336) where the patients receiving Hydroxychloroquine had an average 9 days to show clinical improvement and 11 days to hospital discharge, on the other hand the control group had an average of 10 days to clinical improvement and 11 days to hospital discharge. There was no significant difference between the two groups in the clinical outcome after 28 days of observation. In 52 cases (53.6%) complete recovery was obtained in Hydroxychloroquine group whereas in the control group, 33 patients (34.0%) recovered completely. However, the overall mortality was not significant who received Hydroxychloroquine (Abd-Elsalam et al., 2020).

4.5 Ivermectin

In the clinical trial registered as (NCT04523831) in ClinicalTrials.gov where Ivermectin plus Doxycycline and standard of care is used for the treatment of COVID-19 patients. This trial was sponsored by Dhaka Medical College which was a phase 3 clinical trial. The results were Number of patients have clinical improvement as their Body temperature remains normal for at least 3 days, Respiratory symptoms are significantly improved, Lung imaging shows obvious improvement in lesions, SpO2, >93% without assisted oxygen inhalation within time frame of 7 days. Although there were some adverse effects like Erosive esophagitis seen in patients taking Ivermectin plus Doxycycline about 1.09% which is 2 patient out of 183 patient in Ivermectin plus Doxycycline group.

4.6 Umifenovir (Arbidol)

Umifenovir (arbidol) is a broad spectrum antiviral drug and it works by inhibiting the viral entry to the cell of interest and also inhibits the fusion of virus cell membrane. Branded as arbidol, Pharmstandard first successfully invented umifenovir and it was used for influenza virus infection. Although there is no published clinical trial result to publicly so the significance of umifenovir against COVID-19 is uncertain.

Chapter 5

Conclusion

To conclude, the current COVID-19 pandemic is spreading and more than 200 Countries and territories around the world got affected and a total of 99,804,787 confirmed cases and a total of 2,139,791 confirmed deaths to date 25/01/2020. It was believed that the outbreak of COVID-19 has originated from Hunan seafood market located at Wuhan, China where wild animals including bats, snakes, dogs, raccoon, and palm civets are being sold. However, the zoonotic

source of COVD-19 is not confirmed, however the sequence-based analysis shows that bats are primary source of this novel coronavirus. This epidemic outbreak has challenged the social, emotional, psychological, economic, and medical and public health infrastructure of the whole world. Scientist have identified the characteristics of SARS-CoV-2 and it is equally pathogenic like SARS-CoV and MERS-CoV. Firstly, SARS-CoV-2 binds to ACE2 receptor with high affinity to infect the host and people will pre medical conditions are susceptible to this SARS-CoV-2. It is now a top priority for scientist to develop an efficient therapeutic strategies to cope with the novel coronavirus. Various broad-spectrum antivirals or combination of antivirals like Remsedivir, Lopinavir, Ritonavir, Oseltamivir, Azithromycin, Chloroquine and Hydroxychloroquine has shown significantly blocked the SARS-CoV-2 infection in COVID-19 patients. Apart from developing drugs, a rapid diagnostic method of SARS-CoV-2 is required for suspected person in order to prevent transmission of novel coronavirus. Altogether, SARS-CoV-2 is indeed a global pandemic and it is still getting worse day by day. So it is our responsibility to prevent the transmission of SARS-CoV-2 at any cost by maintaining and following guideline of World Health Organization (WHO). In conclusion, to prevent future outbreaks of zoonotic origin it is necessary to monitor of wildlife for high-risk pathogens and improve surveillance in wildlife trade and animal markets and put more focus on researches to develop new drugs.

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