

SARS-CoV-2 Disease COVID-19: Infection, Precaution, and Clinical Advances of the Imminent Herbal and Modern Drugs Therapeutics

Abstract 18

A recent outbreak of Coronavirus SARS-CoV-2 disease COVID-19 in China and the spread of this infection are very rapid to other countries in the world. All countries worry about the COVID-19 pandemic disease which has alarmed the medical and the scientific community mainly because of the lethal nature of this virus infection. COVID-19 is a novel virus that is not yet known the drugs and to cure infected patients causing fear in everyone, social problems in the community and people who are infected. In this case, scientists and researchers have to know the epidemiological cases of COVID-19 infection, the characteristics of SARS-CoV-2 transmission and the spread of viruses, the effectiveness of preventive measures, the nature and life cycle of viruses, current literature advances in diagnostic development such as RT-PCR, CT-Scan, Elisa and the development of modern and herbal drugs for the treatment of infected patients which are viewed from the classification of antiviral drugs such as entry inhibitors, replication inhibitors, nucleosides, nucleotides, protease inhibitors, heterocyclic drugs, including biological therapies namely monoclonal antibodies therapy, vaccines development and herbal formulations that have been pre-clinically tested in vitro or in the form of molecular docking and clinical evaluation. Chemical drug molecules with prospective applications in the treatment of COVID-19 have been included in this review.

Keywords: COVID-19, antiviral, infection, herbal, modern drugs, pandemic

Introduction

The spread of infectious diseases in China in December 2019 has emerged with a very high number of deaths and the spread of this infection also involves other countries.¹ Infected people show symptoms of pneumonia which gives symptoms of SARS (Acute Respiratory Syndrome). This infection is caused by a deadly virus in nature and produces the highest number of deaths caused by respiratory infections. The first reported transmission of this infectious disease in China² and has spread to almost all other countries and between continents. The largest numbers of cases of infection were observed in South Korea, Italy, Iran, and several cases in South Africa, USA, and other countries including Indonesia. In recent update from WHO and other live updates observing institute, the infection has tainted in excess of 90,000 people worldwide with in excess of 3,000 deaths in various areas and nations. The China, the significant hit nation, alone recorded in excess of 2,500 deaths by end of February 2020.³

The sudden emergence of the corona virus and its spread is very rapid in all countries where WHO reported that this situation creates a pandemic situation. From the investigation results this virus is found from bats which are commonly consumed by people in China. Early transmission studies report that the relationship between local fish and wild animal markets in China with most initial infections indicates the possibility of virus transmission from animals to humans and then viruses spreading new infections mainly through human to human transmission. This disease which caused by Corona Virus has proven and caused a very high death in the world so that WHO has issued a statement for this virus is a pandemic disease caused by the new corona virus, namely corona virus disease 2019 (COVID-19) or under another name severe acute respiratory syndrome SARS-CoV-2 (**Figure 1**) taken based on the International Virus Taxonomy Committee on 11 February 2020.⁴

In Indonesia, the case of corona virus until now based on data from the Ministry of Health of the Republic of Indonesia until March 22, 2020 reported that 514 people have been infected with this

Covid-19.⁵ Based on these data, the Indonesian government quickly responded and took preventive measures to reduce cases of people infected with COVID-19. Until now there is no drug or vaccine that can be proven to kill or inhibit the Covid-19 corona virus. However, the World Health Organization (WHO) announced that governments and pharmaceutical companies around the world are developing vaccines and drugs to fight the corona virus. More than 20 candidates for the corona virus vaccine are being developed worldwide.⁶ Unfortunately, it seems that the development of the vaccines took at least one year before it was completed and could be distributed throughout the world. Meanwhile, there are several types of corona virus treatment that have entered the stage of clinical testing both modern medicines and herbal medicines.

The emergence of this coronavirus novel suddenly and continues to spread rapidly which has led experts to think of developing methods of rapid diagnosis for COVID-19 infectious diseases. Specifically in Indonesia, doctors have used several existing medicines both using modern and herbal medicines. Researchers have been directly involved from international and national institutions at the university and ministry of health to understand the mechanism of infection, virulence, pharmacology, and possible drug and vaccine interactions as a beginning of development. This review discusses the literature report on progress regarding diagnostic methods and developmental therapies with the possible use of new compounds of modern and herbal medicines as candidates for new antiviral compounds for COVID-19 infectious diseases.

8 The Coronaviruses

Coronavirus (CoV), a genus of the *Corona viridae* family, is a positive-strand RNA virus with the largest viral genome of all RNA viruses (27–32 kb)⁶ causing wide range of diseases mainly related to respiratory system and infection may vary from the common cold to more severe respiratory diseases.⁷ Besides that, coronavirus¹³ are enveloped 80 to 160 nm particles which all coronaviruses virion particles contain 4 or 5 structural proteins, spike (S) protein, membrane protein (M), hemagglutinin-esterase (HE) protein, nucleocapsid (N) protein, and¹⁷ small envelope protein.⁸ In addition, The virion structure of coronaviruses consists of the S glycoprotein forms the large, petal-shaped spikes on the surface of the virion having 180 to 200 kDa molecule that is cotranslationally glycosylated in the endoplasmic reticulum (Figure 2).⁸

¹⁵ There are 2 infectious diseases that occur recently which are caused by Coronavirus namely middle east respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).⁹⁻¹⁰ In the end of 2019 a new coronavirus (nCoV) was discovered is a new strain of coronavirus that has not been found in previous events in humans. For example zoonoses that indicate this virus is found in animals and then transmitted from animals to humans.¹¹ Some of these coronaviruses can cause disease in humans and many other viruses such as dogs and cat viruses are known to only infect animals and recently the corona virus has infected humans and can infect humans spread through human-to-human transmission. This case is thought to occur in a new coronavirus that causes COVID-19 disease.

COVID-19 symptoms and infection transmission

COVID-19 can spread rapidly through transmission of infection from humans to other people both in people who have symptoms or are asymptomatic or carrier. In people infected with this virus easily spread through breathing when the patient coughs or sneezes. Transmission in certain cases is usually found in the closest people where transmission so far can be through the

air.¹² Meanwhile, in cases without symptoms, people who have the SARS-CoV-2 virus are infected by people who shake hands or surface contamination with their hands such as coughing and sneezing. This manual transmission can also spread if the patient has symptoms. In addition, vertical transmission of the virus from mother to child has not been observed according to research conducted by H. Chen et al in a small group of pregnant women. They suggest the absence of COVID-19 interuterine vertical transmission from unborn mothers. The emergence and the spread of this new virus, focused on the increase in human populations as the main factor. This increase shows that population density increases the likelihood of transmission of new infections due to an increase in humans which causes proximity of the population which rarely results in auto-separation or reduction of infection.¹³

In summary, these and other researchers have determined that nCoV-2019 is transmitted from person to person when a person comes into contact with the secretions of an infected person. This means the virus is transmitted via coughing, sneezing, shaking hands, touching infected object then touching eyes, mouth or nose, and handling the waste of an infected person.¹⁴

Symptoms of patients infected with COVID-19

Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to severe acute respiratory syndrome which marked respiratory infections on COVID-19 patients including runny nose, fever, cough, shortness of breath, sore throat, and mild to moderate upper respiratory tract illness. In severe cases, patients can experience pneumonia, acute respiratory syndrome (SARS), kidney failure and even death in many cases. There are many people who do not show symptoms of being infected with COVID-19 but only as carriers of this virus because that person has a good immune system so this virus cannot infect these patients but can infect others whose immune systems are low.¹⁵

In clinical research studies conducted by Guan, et al. showed a pattern of various diseases in which the middle-aged infected patients studied were 47 years indicating an infection in people of all ages.¹⁶ Furthermore, of the total patients studied, 41.9% were women showing no gender differences in the spread of infection on all patients. The report states that the primary composite endpoint occurred in 6% of patients. Whereas in Indonesia, data show similar cases that occur with residents of Wuhan city, there is no gender difference in people infected with COVID-19 which data showed the highest death rates until 20 March 2020 showing 8.4% of patients.^{17,18} Meanwhile, the elderly and young children are most at risk from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal than SARS and MERS. Around 15 to 20% of cases can become severe. The lethal rate is about 1 in 10 according to doctors. The nCoV-2019 virus, just as was SARS and MERS, is an enveloped virus. This means the virus is protected by a glycoprotein shell. This is why these viruses are so difficult to treat.¹⁹

The general symptoms which experienced by some patients are coughing and fever but some patients also do not experience fever symptoms. It means that the patient can infect other patients without symptoms (43.8% at admission and 88.7% during hospitalization) and almost two-thirds of patients experience coughing (67.8%). Blood tests show lymphocytopenia showing the level of lymphocytes is low and abnormal in the majority of patients around 83.2% which are admitted to the hospital. In addition, diarrhea is uncommon in most patients, only about 3.8% of patients experience diarrhea. These symptoms were observed for 2 to 7 days²⁰ in which the incubation

period of infection progressed for 4 days with an interquartile range of 2 to 7 days in all patients.²¹

Preventive measures

All countries including Indonesia need the preventive measures in overcoming the spread of COVID-19 as a pandemic disease which there is no known availability of emergency medicines or vaccines as therapies for COVID-19. Therefore, handling of infected patients has been recommended as one step to control the rampant spread among people and is difficult to force the isolation of infected patients because this causes many social problems. Like many reports in the Indonesian media, the practice of forced confinement of infected people at home is very difficult to be done by health workers and the police. Isolation is very limited because the availability of medical care equipment is incomplete in hospitals where a better and ethical place of control for treating infected people with COVID-19.²² In this direction, appropriate research studies must be carried out to understand the best approach in infection prevention including assessing whether Indonesia is able to slow the spread of COVID-19 to infected people.²³

In Indonesia, masks and hand sanitizers are widely used in preventing the transmission of COVID-19. Medical masks can help to prevent direct exposure to liquid droplets from infected people who are sneezing and always wash or clean their hands with a hand sanitizer. While in other cases with the use of an improper mask can cause an increased risk of transmission of infection which especially infections from people without symptoms and through infected people on surface exposure poses a higher risk of transmission than people who do not properly use a mask.²⁴ This occurs because people who wear a mask can touch the mask itself and the mouth or face part more often than people who do not use masks. This frequent touching of mouth and face part pose higher possibility of reaching of virus to person's respiratory system on exposure of hands with contaminated surfaces (in shops, malls, buses, and other public places) or hand shake with asymptomatic person. So, care should be taken to avoid frequent touching of own face particularly mouth, nose and eyes (whether wearing mask or not).²⁵

The standard procedures which are recommended for preventing the spread of infection are more effective in controlling the spread and keeping things safe. The most important include washing hands after visiting public places will keep the virus (even if it touches a contaminated surface) from being transmitted to other people or infected people by covering their mouths and nose when coughing and sneezing to prevent spread especially if people experience asymptomatic or in the early stages of infection.^{26,27} Besides that, cooking food properly like meat, eggs, and food from animals can destroy the virus. In practice, one must avoid close contact with anyone showing symptoms of respiratory illnesses such as cough, flu, asthma, pneumonia, and tuberculosis. Therefore, this simple precaution can be carried out effectively in controlling the spread and holding the virus itself.

Life cycle of SARS-CoV-2 (COVID-19) virus and infection

Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism consisting of 3 parts, namely entry, replication and release which can be seen in **Figure 3**.

Firstly, infection begins when the viral spike (S) glycoprotein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the host cell protease available, cleavage and activation

allows cell the entry by endocytosis or direct fusion of the viral envelop with the host membrane.²⁸

On entry into the host cell, the virus particle is uncoated, and its genome enters the cell cytoplasm.²⁹ The coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail, which allows the RNA to attach to the host cell's ribosome for translation.³⁰ The host ribosome translates the initial overlapping open reading frame of the virus genome and forms a long polyprotein. The polyprotein has its own proteases which cleave the polyprotein into multiple nonstructural proteins.³¹

Secondly, coronaviruses do replication and transcription of RNA from an RNA strand by the mechanism of SARS-CoV-2 replication in away (Figure 3):³²

1. With their S-protein, coronaviruses bind on cell surface molecules such as metalloprotease amino peptidase having HE-protein can also bind in N-acetyl neuraminic acid as co-receptor.
2. Virus gets into the host cell by fusion of viral and cell membrane or by receptor mediated endocytosis in that the virus is incorporated via an endosome, which is subsequently acidified by proton pump.
3. Coronaviruses have a single positive stranded RNA genome, they can directly produce their proteins and new genomes in the cytoplasm.
4. The negative strand serves as template to transcribe smaller subgenomic positive RNAs which are used to synthesize all other proteins.
5. The protein N binds genomic RNA and the protein M is integrated into the membrane of the endoplasmic reticulum (ER) like the envelope protein S and HE. After binding, assembled nucleocapsids with helical twisted RNA budd into the ER lumen and are encased with its membrane.
6. The viral progeny are finally transported by golgi vesicles to the cell membrane and are exocytosed into the extracellular space.

Thirdly, The replicated positive-sense genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading frame. These mRNAs are translated by the host's ribosomes into the structural proteins and a number of accessory proteins.³¹ RNA translation occurs inside the endoplasmic reticulum. The viral structural proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment. There, the M proteins direct most protein-protein interactions required for assembly of viruses following its binding to the nucleocapsid.³³ Progeny viruses are then released from the host cell by exocytosis through secretory vesicles.³³

Diagnosis

The proper diagnosis for COVID-19 infection must be made first when finding the initial symptoms as described above and the treatment initiative factor. The difference in COVID-19 from the common cold is essential for everyone to know for proper treatment. Sometimes the results of preliminary examinations in infected people do not provide a clear diagnosis of COVID-19 infection. In general, doctors usually consider the patient's travel history by looking at the symptoms that exist such as cough, flu, fever and others. The initial intervention, sputum examination and other diagnostic tests help in determining the right early infection. Possibly the number of days from the first day of infection is taken at the laboratory to recommend individual diagnostic tests such as:

RT-PCR

The standard technique for determination is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab or sputum sample, with results inside a couple of hours to 2 days.³⁴

ELISA

Antibody assays can also be used, using a blood serum sample, with results within a few days.³⁵

CT-Scan

The contamination can likewise be analyzed from a mix of side effects, chance elements, and a chest CT scan demonstrating highlights of pneumonia.³⁶ The fundamental diagnosis reports from medical clinics in China show that the majority of COVID-19 infected patients were determined with pneumonia and trademark CT imaging patterns,³⁷ radiological assessments have become imperative in early determination and appraisal of disease course.³⁸ CT scan of various COVID-19 contaminated patients differed in pattern³⁹ and almost 50% of patients could be discovered of disease from pictures. On admission to emergency clinics, the ground-glass haziness was the most widely recognized radiologic finding on chest figured tomography (CT)³⁹ of 56.4% of patients.⁴⁰ The longitudinal CT discoveries of a COVID-19 infected patient with pneumonia demonstrated sorted out example of CT images in follow up check over the course of treatment. Besides that, it was seen that numerous patients did not have strange radiologic findings.⁴¹

Treatments of COVID-19

There is an urgent demand from WHO and various countries in the world for new COVID-19 disease treatment therapies. The deadly nature of the spread of this virus produces fear in everyone. Infection caused by this disease in the form of acute respiratory disease (SARS) which can cause death and there is no drug that is scientifically proven to kill this new virus. Each country can only do reducing the spread of infectious diseases by physical distancing and maintaining cleanliness of the body. International organizations such as WHO have invited researchers around the world to find vaccines, new drugs and diagnostic development for SARS-CoV-2 and COVID-19. The Director General of WHO has prioritized the main research to prevent the spread of COVID-19 by developing new drug candidate both modern and herbal medicines for therapy and diagnosis that are easily applied to identify active infections, asymptomatic and resolved infections of COVID-19.³

The mechanism of viral infection is the entry of the virus into cells and multiplication using a host cellular mechanism that is characterized by damage to the host cell as a key for the development of new drug compound therapies. To date, there is no definitive and recommended therapy for COVID-19 due to new virus which is caused a viral infection and the curative therapy for COVID-19 is an antiviral. However, all antivirals used in COVID-19 therapy in almost all countries are still in the form of trial and error. Some of them refer to antiviral therapy that was used during the SARS and MERS epidemic several years ago, for example using lopinavir, ritonavir, ribavirin, oseltamivir, and others. These drugs have been used and were quite effective in dealing with SARS and MERS during the past epidemic. Likewise in Indonesia, there are no definitive guidelines for dealing with COVID-19 and only rely on existing drug preparations, for example oseltamivir which is currently widely used in dealing with COVID-19. With the start of the COVID-19 outbreak in China, Indonesia has tried to refer to China

regarding the drugs used, including chloroquine and Avigan. Some prospective drugs are considered to direct current applications or the development of new therapeutic drugs including modern and herbal medicines includes:

Entry inhibitors

The SARS-CoV-2 virus infects the respiratory system and alveoli cells in the lung sac which will become host for the viral infection. In general, viruses enter the host cell by forming a complex between the virus projections (crown such as spikes or lobes) with receptors on the host cell. Whereas the exact structure of the spike⁴² or lobe virus and receptors on host cells for SARS-CoV-2 is not yet fully known but prior experience of coronavirus (β -family) is responsible for SARS infection and has similarities in the form of entry in host cells.⁴³ Recently it has been found that Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for the SARS coronavirus, (SARS-CoV) and (SARS-CoV-2).⁴⁴ Angiotensin-converting enzyme 2 (ACE2) has some homology with angiotensin-converting enzyme (ACE) but not inhibited by ACE inhibitors. A previous SARS case was characterized by an infection that was started by a transmembrane (S) spike in glycoproteins which binds to the host receptor and combines viruses and cell membranes. The identification of the viral / spikes lobes molecular structure will take time, but the development of facilitated heterocyclic drug molecules or existing heterocyclic screening may be able to bind the entry inhibitor drug.⁴⁵

Replication inhibitors

The corona virus is an RNA virus utilizing host cells for genomic replication which encodes the RNA-dependent protein polymerase (RdRp), which allows the viral genome to be transcribed into new RNA copies using host membrane cells. The viral genome replication mechanism serves potential targets for the control of viral infections then nucleoside analogues and potential polymerase inhibitors used as antiviral drugs⁴⁶ can be potentially effective with SARS-CoV-2. RNA polymerase inhibitors such as Remdesivir and Favipiravir (Avigan) (Figure 4A and 4B) which is a nucleotide adenosine analogue antiviral for Ebola virus and other array RNA viruses and have shown promising results in clinical control of SARS-CoV-2 pneumonia in cell culture in vitro and certain clinical cases.⁴⁷ This requires more evaluation further from potential applications with more patients. Many other nucleoside analogues including DNA synthesis inhibitors such as tenofovir, disoproxil, lamivudine and other antivirals have the potential to inhibit the multiplication of SARS-CoV-2 viruses and are being evaluated through molecular docking studies⁴⁸ and testing in infected cell culture.

Avigan is the patent name for favipiravir, also known as T-705, an antiviral drug developed by Toyama Chemical (Fujifilm group) of Japan with activity against many RNA viruses. In Japan, this drug was originally developed as a cold medicine. In February 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel coronavirus) disease. The mechanism of action of favipiravir is by selective inhibition of viral RNA polymerase so that it inhibits viral RNA synthesis (Figure 5).⁴⁹ Other studies have shown that favipiravir induces mutant of RNA transversion mutations, resulting in a viable viral phenotype. Favipiravir is a prodrug that is metabolized by human hypoxanthine guanine phosphoribosyltransferase (HGPRT) into its active form, namely favipiravir-ribofuranos-5-triphosphate (favipiravir-RTP). This drug is available in oral and intravenous formulations. Favipiravir does not inhibit the synthesis of RNA or DNA in mammalian cells and is not toxic to them. In 2014, favipiravir was approved in Japan as a

backup drug against influenza pandemics and to treat a type of virus that was not responsive to antiviral at the time. During this COVID-19 pandemic, in a limited clinical trial with 80 subjects, favopiravir showed an antiviral potential for SARS-CoV-2 that was better than lopinavir / ritonavir.⁵⁰ In March 2020, the Chinese Government stated that favopiravir appeared to be effective in overcoming COVID-19.

Protease inhibitors

In the maturation phase of viral replication in the host cell involves the enzyme protease which is associated with proteins and peptides. Lopinavir and ritonavir (**Figure 4C, 4D**) are anti-HIV drugs that have been approved and a combination of both has shown potential drug compounds in the inhibition of SARS-CoV-2.^{51,52} According to Lim J, et al. stated the treatment of COVID-19 patients in Korea using lopinavir/ritonavir to patients showed interesting results which β -coronavirus was encapsulated and cause a significant decrease and was absent or few coronavirus titers were observed.⁵² This study was conducted in a single patient which detailed analysis is needed to recommend as a candidate for new drug compounds. Molecular docking of potential inhibitors can provide clear information because detailed docking simulation results have shown important input in previous SARS cases and other viral infections.⁵³⁻⁵⁵ However, both of them still need a lot of clinical data to prove the efficacy and safety in the human body.

Heterocyclic anti-viral

Many heterocyclic drug molecules have been used in the treatment of viral infections in the past and are thought to be probably slightly effective in inhibiting SARS-CoV-2. Chloroquine was originally a drug used to treat malaria as an antiparasiticide. This drug is a drug¹⁴ containing a quinoline group (**Figure 4E**) that works by inhibiting the activity of the enzyme heme polymerase which converts heme into hemozoin, resulting in the accumulation of free heme. This accumulation of heme causes death of the Plasmodium parasite that causes malaria.⁵⁶ However, with the decrease in malaria and the emergence of plasmodium resistance to chloroquine, chloroquine is no longer used as an antimalarial drug.

It turns out that chloroquine (and hydroxychloroquine) can also be used for antiviral therapy. Vincent et al (2005) reported that chloroquine⁹ as a strong antiviral effect against the SARS-CoV virus in primate cells. This inhibitory effect is observed when cells are treated with chloroquine both before and after exposure to the virus, which shows that chloroquine has both a preventive and therapeutic effect. In addition, to what is known that chloroquine increases endosomal pH which inhibits viral replication and appears to interact with cellular angiotensin-converting enzyme 2 (ACE2) receptors (**Figure 6**).⁵⁷ These causes inhibitions of the binding of the virus with the receptor which prevent infection and spread of the SARS-CoV-2 virus at concentrations that can cause clinical symptoms. In the SARS-CoV-2 pandemic in China, chloroquine was used at a dose of 500 mg for adult 2 times a day, duration of therapy ≤ 10 days.⁵⁸ Chloroquine (and hydroxychloroquine) is also currently being tried in Malaysia at the same dosage used in China and also in Indonesia.

Meanwhile, there are several other heterocyclic antiviruses that have been used as antivirals such as HIV, H1N1, H1N5 and SARS, all of which will be further investigated to deal with SARS-CoV-2. Oseltamivir (Tamiflu) which has been widely used as a neuraminidase inhibitor for the treatment of influenza and has been recommended for symptoms of COVID-19.⁵⁹ In addition,

other candidate compounds that can be evaluated and potentially have antiviral activity against SARS-CoV-2 are compounds other than heterocyclic based on angiotensin converting enzyme 2 (ACE2) peptides namely 3CLpro inhibitors (3CLpro-1) and vinylsulfone protease inhibitors.⁶⁰ According to Gautret et al. also stated that the combination of hydroxychloroquine and azithromycin as a treatment of COVID-19 showed it is significantly associated with viral load reduction on clinical study even though small sample size.⁶¹

Nano drug delivery systems

Drug delivery systems in the form of nanoparticle preparations have been widely used to improve the bioavailability of drugs in the blood and deliver drugs as antiviral especially nucleoside analogues which are conjugated with potential delivery systems that have been applied in resistant HIV infection drugs.⁶²⁻⁶⁵ Amount of drugs accumulated in the nano delivery system can be used as a new drug in the formulation development which is capable to deliver drugs with a faster therapeutic index for COVID-19.⁶⁶⁻⁶⁸ One example of delivery of nano treatment can be seen in the efficacy of chloroquine against COVID-19 as inhibitor of nanoparticle endocytosis through macrophages. Therefore, chloroquine decreases the accumulation of synthetic nanoparticle of various sizes (14-2,600 nm) and is spherical and discoidal in cell lines.⁶⁹

Biological therapeutics

Antibody therapy is very possible for the treatment of COVID-19 infections. However, the discovery of this vaccine still requires a long time around 1 year and temporarily can use several treatment options to prevent the spread of COVID-19. According to Tian et al reported that SARS-CoV-2 specific human monoclonal antibodies such as CR3022 which are intended to bind strongly to SARS-CoV-2 RBD (KD 6.3 nM).⁷⁰ Reported CR3022 epitope does not overlap with the ACE2 binding site in SARS-CoV-2 RBD. These unique binding results indicate the possibility that CR3022 can be developed as a therapeutic candidate in its own way or in combination with other antibodies. However, in vitro trials and clinical studies are needed to obtain accurate clinical data for the prevention and treatment of COVID-19 infections.⁷⁰

In developing a new vaccine one must pay attention to the similarity of immunogenic structural proteins with COVID-19 such as SARS, MERS which has been used before to be used for SARS-CoV-2.⁷¹ According to Ahmed et al stated that his work had identified a set of B cells and T cell epitopes that derived from spikes (S) and nucleocapsid proteins (N) that can map identically with the SARS-CoV-2 protein.⁷² Reports suggested that the identified epitope has no mutase in the SARS-CoV-2 sequence that was available. So this target immune epitope has the potential to be explored in the fight against the SARS-CoV-2 virus which the glycoprotein spike of SARS-Cov-2 has antigenicity. This is the direction of developing a new vaccine against SARS-CoV-2. However, the final results will depend on in vitro and future clinical trials.⁷²

Herbal drugs

Several anti-SARS agents have been tested for coronavirus-specific therapy, however, an effective SARS antiviral therapy has not yet been established.⁷³⁻⁷⁵ Some modern drugs have shown a broad antiviral activity which is most frequently administered as a SARS-antiviral agent in combination with antibacterial drugs. However, this has little activity against SARS-CoV in vitro having specific monoclonal antibodies, pegylated interferon- α , siRNA, and several protease

inhibitors have also been tested against SARS-CoV.⁷⁶ Therefore, some researchers in the world particularly Indonesia have utilized herbal drugs to test several candidates of active compounds which are derived from plants or herbs.

According to UI and IPB researchers stated that they have conducted research originating from several plants in Indonesia which chemical compounds contained in these plants could potentially prevent COVID-19 infection in the form of molecular docking in silico.⁹⁰ The model of research that has been done can be seen in **Figure 7**. Based on the results of prediction models with machine learning methods (SVM, random forest and MLP neural network) associated with 20644 interactions of protein compounds. The results are 31 herbal compounds with 5 target proteins 3CLPro, PLPro, Spike-ACE2, EIF4 and RdRp. Modeling of structure and ligand based pharmacophores was performed virtual screening with 1,377 compounds from the HerbalDB database.⁷⁷ The results of compound hits from machine learning and pharmacophore mapping were confirmed using molecular docking.

Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin, quercetin, luteolin, kaempferol, isorhamnetin⁷⁸, and hesperidin⁷⁹. Luteolin is known as a furin protein inhibitor⁸⁰ which is assumed as one of the enzymes that break down the Corona virus S (spike) protein as in MERS into units S1 and S2.⁸¹ In the S1 unit, there is a binding domain receptor (RBD) where the ACE2 peptidase binds so that the virus can bind to the h19 cell.⁸¹ The Hesperidin / hesperitin compound in the silico study is known to inhibit the RBD domain binding of the SARS-22 V-2 Spike protein with ACE2 receptors in humans so that it is predicted to potentially inhibit the entry of the SARS-COV-2 virus.⁸² It is also known that luteolin is a neuramidase inhibitor as well as oseltamivir which is currently one of the drugs used in the CDC protocol.

Hesperidin (a form of hesperidin aglycone) and Quercetin are also known to act as inhibitors of 3CLpro virus proteins.^{84,84} Other compounds in guava such as myricetin are known to act as SARS coronavirus helicase inhibitors.⁸⁵ The kaempferol has the potential to be a non-competitive inhibitor of 3CLPro and PLpro as well as quercetin.⁸⁶ Another interesting thing is kaempferol acts as a modulator of autophagy, both as an inducer and inhibitor, both of which can be utilized in strategies to inhibit the SARS-COV-2 virus.

Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived from plants. One of the commonly used condiments for cooking or herbal medicine for Indonesian people is empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. It is not only herbs but also animals such as snakehead fish which can improve immune system in the body due to high protein and amino acids.⁸⁷⁻⁸⁹ According to researchers from UNAIR stated that the approach that can be taken in the public by consuming empon-empon to improve the immune system to avoid COVID-19.

Herbs containing curcumin and turmeric have been consumed and proven by Indonesian people for centuries and to be safe and beneficial to health. For example maintaining health, fitness / vitality, and maintaining liver and digestive health based on empirical experimental evidence. Both ginger and turmeric contain hundreds of bioactive compounds, one of which is curcumin. Various studies have been carried out in the world in vitro and preclinical test showing that

curcumin is anti-inflammatory, antiviral, antibacterial, antifungal and antioxidant based on scientific evidence.

One of the benefits of curcumin obtained from clinical trials is to increase the body's immune system or act as an immune-modulator. Recent research on curcumin against the SARS-CoV-2 virus which is an agent or cause of COVID-19 disease shows that the SARS-CoV-2 receptor is an enzyme called Angiotensin Converting Enzyme-2 (ACE2) found in host cells (human cells especially alveolus cells in the lung). However, the cell entry of the virus not only depends on the binding of the spike virus protein to the receptor on the host cell (ACE2) but also on the priming protein spike by the host cell protease (TMPRSS2). Functionally there are 2 forms of ACE2, the fixed form attached to the cell surface and the free-form soluble form in the blood. The soluble form ACE2 is projected to be one of the SARS-CoV-2 antiviral candidates through a competitive interceptor mechanism that prevents bonding between virus particles and ACE2 on the surface of the host cell. In addition, bio-informatics research published in March 2020 and recent literature has mentioned curcumin as one of the SARS-CoV-2 antiviral candidates, it is expected that curcumin in ginger and turmeric can increase the expression of ACE2 in the form of soluble which can inhibit the bonding between the viral protein and the fixed form ACE2 found on the surface of the host cell.⁹¹

Conclusion

The sudden outbreak of COVID-19 in Wuhan, China made all countries in the world panic because it spread very quickly and killed many people so that WHO issued a statement that this disease is a pandemic that threatens the lives of many people. Therefore, every country has an obligation to protect its people by providing an education protocol to prevent the spread of COVID-19. In many new cases, clinical staff gain infected from patients who visit hospitals so that infected cases increase the spread of the virus through human-to-human transmission, creating an urgent need for the development and approval of a standard therapy protocol including structural details and a complete life cycle of the virus, preventing the spread of the virus, adequate virus testing tools to ensure SARS-CoV-2 infection. Several drugs that have been evaluated for the treatment of COVID-19 show promising results for clinical applications such as chemical and herbal medicines that have been clinically tested in reducing this novel viral infection and assisting a number of patients in safe recovery from COVID-19. Furthermore, as knowledge about SARS-CoV-2 advances, new therapies including vaccines and monoclonal antibodies can be found in the near future. So far, effective treatments for COVID-19 are unknown but potential therapeutics can be found from clinical evaluation of existing antiviral drugs are being researched and continued against new coronaviruses.

Conflict of interests

The authors claim that there is no conflict of interest.

SARS-CoV-2 Disease COVID-19: Infection, Precaution, and Clinical Advances of the Imminent Herbal and Modern Drugs Therapeutics

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1 **Abstract**

2 A recent outbreak of Coronavirus SARS-CoV-2 disease COVID-19 in China and the spread of this
3 infection are very rapid to other countries in the world. All countries worry about the COVID-19
4 pandemic disease which has alarmed the medical and the scientific community mainly because of the
5 lethal nature of this virus infection. COVID-19 is a novel virus that is not yet known the drugs and to
6 cure infected patients causing fear in everyone, social problems in the community and people who are
7 infected. In this case, scientists and researchers have to know the epidemiological cases of COVID-19
8 infection, the characteristics of SARS-CoV-2 transmission and the spread of viruses, the effectiveness
9 of preventive measures, the nature and life cycle of viruses, current literature advances in diagnostic
10 development such as RT-PCR, CT- Scan, Elisa and the development of modern and herbal drugs for
11 the treatment of infected patients which are viewed from the classification of antiviral drugs such as
12 entry inhibitors, replication inhibitors, nucleosides, nucleotides, protease inhibitors, heterocyclic drugs,
13 including biological therapies namely monoclonal antibodies therapy, vaccines development and
14 herbal formulations that have been pre-clinically tested in vitro or in the form of molecular docking
15 and clinical evaluation. Chemical drug molecules with prospective applications in the treatment of
16 COVID-19 have been included in this review.

17 **Keywords:** COVID-19, antiviral, infection, herbal, modern drugs, pandemic

18
19 **Introduction**

20 The spread of infectious diseases in China in December 2019 has emerged with a very high number of
21 deaths and the spread of this infection also involves other countries.¹ Infected people show symptoms
22 of pneumonia which gives symptoms of SARS (Acute Respiratory Syndrome). This infection is
23 caused by a deadly virus in nature and produces the highest number of deaths caused by respiratory
24 infections. The first reported transmission of this infectious disease in China² and has spread to almost
25 all other countries and between continents. The largest numbers of cases of infection were observed in
26 South Korea, Italy, Iran, and several cases in South Africa, USA, and other countries including
27 Indonesia. In recent update from WHO other live updates observing institute, the infection has
28 tainted in excess of 90,000 people worldwide with in excess of 3,000 deaths in various areas and
29 nations. The China, the significant hit nation, alone recorded in excess of 2,500 deaths by end of
30 February 2020.³

31
32 The sudden emergence of the corona virus and its spread is very rapid in all countries where WHO
33 reported that this situation creates a pandemic situation. From the investigation results this virus is
34 found from bats which are commonly consumed by people in China. Early transmission studies report
35 that the relationship between local fish and wild animal markets in China with most initial infections
36 indicates the possibility of virus transmission from animals to humans and then viruses spreading new
37 infections mainly through human to human transmission. This disease which caused by Corona Virus
38 has proven and caused a very high death in the world so that WHO has issued a statement for this virus
39 is a pandemic disease caused by the new corona virus, namely corona virus disease 2019 (COVID-19)
40 or under another name severe acute respiratory syndrome SARS-CoV-2 (**Figure 1**) taken based on the
41 International Virus Taxonomy Committee on 11 February 2020.⁴

42
43 In Indonesia, the case of corona virus until now based on data from the Ministry of Health of the
44 Republic of Indonesia until March 22, 2020 reported that 514 people have been infected with this
45 Covid-19.⁵ Based on these data, the Indonesian government quickly responded and took preventive
46 measures to reduce cases of people infected with COVID-19. Until now there is no drug or vaccine
47 that can be proven to kill or inhibit the Covid-19 corona virus. However, the World Health
48 Organization (WHO) announced that governments and pharmaceutical companies around the world
49 are developing vaccines and drugs to fight the corona virus. More than 20 candidates for the corona
50 virus vaccine are being developed worldwide.⁶ Unfortunately, it seems that the development of the
51 vaccines took at least one year before it was completed and could be distributed throughout the world.

52 Meanwhile, there are several types of corona virus treatment that have entered the stage of clinical
53 testing both modern medicines and herbal medicines.

54

55 The emergence of this coronavirus novel suddenly and continues to spread rapidly which has led
56 experts to think of developing methods of rapid diagnosis for COVID-19 infectious diseases.
57 Specifically in Indonesia, doctors have used several existing medicines both using modern and herbal
58 medicines. Researchers have been directly involved from international and national institutions at the
59 university and ministry of health to understand the mechanism of infection, virulence, pharmacology,
60 and possible drug and vaccine interactions as a beginning of development. This review discusses the
61 literature report on progress regarding diagnostic methods and developmental therapies with the
62 possible use of new compounds of modern and herbal medicines as candidates for new antiviral
63 compounds for COVID-19 infectious diseases.

64

65 **The Coronaviruses**

66 Coronavirus (CoV), a genus of the *Corona viridae* family, is a positive-strand RNA virus with the
67 largest viral genome of all RNA viruses (27–32 kb) causing wide range of diseases mainly related to
68 respiratory system and infection may vary from the common cold to more severe respiratory diseases.⁷
69 Besides that, coronaviruses are enveloped 80 to 160 nm particles which all coronaviruses virion
70 particles contain 4 or 5 structural proteins, spike (S) protein, membrane protein (M), hemagglutinin-
71 eterase (HE) protein, nucleocapsid (N) protein, and small envelope E protein.⁸ In addition, The virion
72 structure of coronaviruses consists of the S glycoprotein forms the large, petal-shaped spikes on the
73 surface of the virion having 180 to 200 KDa molecule that is cotranslationally glycosylated in the
74 endoplasmic reticulum (**Figure 2**).⁸

75

76 There are 2 infectious diseases that occur recently which are caused by Coronavirus namely middle
77 east respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).⁹⁻¹⁰ In
78 the end of 2019 a new coronavirus (nCoV) was discovered is a new strain of coronavirus that has not
79 been found in previous events in humans. For example zoonoses that indicate this virus is found in
80 animals and then transmitted from animals to humans.¹¹ Some of these coronaviruses can cause
81 disease in humans and many other viruses such as dogs and cat viruses are known to only infect
82 animals and recently the corona virus has infected humans and can infect humans spread through
83 human-to-human transmission. This case is thought to occur in a new coronavirus that causes COVID-
84 19 disease.

85

86 **COVID-19 symptoms and infection transmission**

87 COVID-19 can spread rapidly through transmission of infection from humans to other people both in
88 people who have symptoms or are asymptomatic or carrier. In people infected with this virus easily
89 spread through breathing when the patient coughs or sneezes. Transmission in certain cases is usually
90 found in the closest people where transmission so far can be through the air.¹² Meanwhile, in cases
91 without symptoms, people who have the SARS-CoV-2 virus are infected by people who shake hands
92 or surface contamination with their hands such as coughing and sneezing. This manual transmission
93 can also spread if the patient has symptoms. In addition, vertical transmission of the virus from mother
94 to child has not been observed according to research conducted by H. Chen et al in a small group of
95 pregnant women. They suggest the absence of COVID-19 interuterine vertical transmission from
96 unborn mothers. The emergence and the spread of this new virus, focused on the increase in human
97 populations as the main factor. This increase shows that population density increases the likelihood of
98 transmission of new infections due to an increase in humans which causes proximity of the population
99 which rarely results in auto-separation or reduction of infection.¹³

100

101 In summary, these and other researchers have determined that nCoV-2019 is transmitted from person
102 to person when a person comes into contact with the secretions of an infected person. This means the

103 virus is transmitted via coughing, sneezing, shaking hands, touching infected object then touching
104 eyes, mouth or nose, and handling the waste of an infected person.¹⁴

105

106 **Symptoms of patients infected with COVID-19**

107 Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to severe acute
108 respiratory symptoms which marked respiratory infections on COVID-19 patients including runny
109 nose, fever, cough, shortness of breath, sore throat, and mild to moderate upper respiratory tract
110 illness. In severe cases, patients can experience pneumonia, acute respiratory syndrome (SARS),
111 kidney failure and even death in many cases. There are many people who do not show symptoms of
112 being infected with COVID-19 but only as carriers of this virus because that person has a good
113 immune system so this virus cannot infect these patients but can infect others whose immune systems
114 are low.¹⁵

115

116 In clinical research studies conducted by Guan, et al. showed a pattern of various diseases in which the
117 middle-aged infected patients studied were 47 years indicating an infection in people of all ages.¹⁶
118 Furthermore, of the total patients studied, 41.9% were women showing no gender differences in the
119 spread of infection on all patients. The report states that the primary composite endpoint occurred in
120 6% of patients. Whereas in Indonesia, data show similar cases that occur with residents of Wuhan city,
121 there is no gender difference in people infected with COVID-19 which data showed the highest death
122 rates until 20 March 2020 showing 8.4% of patients.^{17,18} Meanwhile, the elderly and young children
123 are most at risk from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal
124 than SARS and MERS. Around 15 to 20% of cases can become severe. The lethal rate is about 1 in 10
125 according to doctors. The nCoV-2019 virus, just as was SARS and MERS, is an enveloped virus. This
126 means the virus is protected by a glycoprotein shell. This is why these viruses are so difficult to treat.¹⁹

127

128 The general symptoms which experienced by some patients are coughing and fever but some patients
129 also do not experience fever symptoms. It means that the patient can infect other patients without
130 symptoms (43.8% at admission and 88.7% during hospitalization) and almost two-thirds of patients
131 experience coughing (67.8%). Blood tests show lymphocytopenia showing the level of lymphocytes is
132 low and abnormal in the majority of patients around 83.2% which are admitted to the hospital. In
133 addition, diarrhea is uncommon in most patients, only about 3.8% of patients experience diarrhea.
134 These symptoms were observed for 2 to 7 days²⁰ in which the incubation period of infection
135 progressed for 4 days with an interquartile range of 2 to 7 days in all patients.²¹

136

137 **Preventive measures**

138 All countries including Indonesia need the preventive measures in overcoming the spread of COVID-
139 19 as a pandemic disease which there is no known availability of emergency medicines or vaccines as
140 therapies for COVID-19. Therefore, handling of infected patients has been recommended as one step
141 to control the rampant spread among people and is difficult to force the isolation of infected patients
142 because this causes many social problems. Like many reports in the Indonesian media, the practice of
143 forced confinement of infected people at home is very difficult to be done by health workers and the
144 police. Isolation is very limited because the availability of medical care equipment is incomplete in
145 hospitals where a better and ethical place of control for treating infected people with COVID-19.²² In
146 this direction, appropriate research studies must be carried out to understand the best approach in
147 infection prevention including assessing whether Indonesia is able to slow the spread of COVID-19 to
148 infected people.²³

149

150 In Indonesia, masks and hand sanitizers are widely used in preventing the transmission of COVID-19.
151 Medical masks can help to prevent direct exposure to liquid droplets from infected people who are
152 sneezing and always wash or clean their hands with a hand sanitizer. While in other cases with the use
153 of an improper mask can cause an increased risk of transmission of infection which especially

154 infections from people without symptoms and through infected people on surface exposure poses a
155 higher risk of transmission than people who do not properly use a mask.²⁴ This occurs because people
156 who wear a mask can touch the mask itself and the mouth or face part more often than people who do
157 not use masks. This frequent touching of mouth and face part pose higher possibility of reaching of
158 virus to person's respiratory system on exposure of hands with contaminated surfaces (in shops, malls,
159 buses, and other public places) or hand shake with asymptomatic person. So, care should be taken to
160 avoid frequent touching of own face particularly mouth, nose and eyes (whether wearing mask or
161 not).²⁵
162

163 The standard procedures which are recommended for preventing the spread of infection are more
164 effective in controlling the spread and keeping things safe. The most important include washing hands
165 after visiting public places will keep the virus (even if it touches a contaminated surface) from being
166 transmitted to other people or infected people by covering their mouths and nose when coughing and
167 sneezing to prevent spread especially if people experience asymptomatic or in the early stages of
168 infection.^{26,27} Besides that, cooking food properly like meat, eggs, and food from animals can destroy
169 the virus. In practice, one must avoid close contact with anyone showing symptoms of respiratory
170 illnesses such as cough, flu, asthma, pneumonia, and tuberculosis. Therefore, this simple precaution
171 can be carried out effectively in controlling the spread and holding the virus itself.
172

173 **Life cycle of SARS-CoV-2 (COVID-19) virus and infection**

174 Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism consisting of 3 parts, namely entry,
175 replication and release which can be seen in **Figure 3**.

176 Firstly, infection begins when the viral spike (S) glycoprotein attaches to its complementary host cell
177 receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike
178 protein. Depending on the host cell protease available, cleavage and activation allows cell
179 the entry by endocytosis or direct fusion of the viral envelop with the host membrane.²⁸

180 On entry into the host cell, the virus particle is uncoated, and its genome enters the cell
181 cytoplasm.²⁹ The coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail,
182 which allows the RNA to attach to the host cell's ribosome for translation.³⁰ The host ribosome
183 translates the initial overlapping open reading frame of the virus genome and forms a long polyprotein.
184 The polyprotein has its own proteases which cleave the polyprotein into multiple nonstructural
185 proteins.³¹

186 Secondly, coronaviruses do replication and transcription of RNA from an RNA strand by the
187 mechanism of SARS-CoV-2 replication in away (**Figure 3**):³²

- 188 1. With their S-protein, coronaviruses bind on cell surface molecules such as metalloprotease amino
189 peptidase having HE-S protein can also bind in N-acetyl neuraminic acid as co-receptor.
- 190 2. Virus gets into the host cell by fusion of viral and cell membrane or by receptor mediated
191 endocytosis in that the virus is incorporated via an endosome, which is subsequently acidified by
192 proton pumps.
- 193 3. Coronaviruses have a single positive stranded RNA genome, they can directly produce their
194 proteins and new genomes in the cytoplasm.
- 195 4. The negative strand serves as template to transcribe smaller subgenomic positive RNAs which are
196 used to synthesize all other proteins.
- 197 5. The protein N binds genomic RNA and the protein M is integrated into the membrane of the
198 endoplasmic reticulum (ER) like the envelope protein S and HE. After binding, assembled
199 nucleocapsids with helical twisted RNA budd into the ER lumen and are encased with its
200 membrane.
- 201 6. The viral progeny are finally transported by golgi vesicles to the cell membrane and are
202 exocytosed into the extracellular space.
203

204 Thirdly, The replicated positive-sense genomic RNA becomes the genome of the progeny_viruses. The
205 mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading
206 frame. These mRNAs are translated by the host's ribosomes into the structural proteins and a number
207 of accessory proteins.³¹ RNA translation occurs inside the endoplasmic reticulum. The viral structural
208 proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment.
209 There, the M proteins direct most protein-protein interactions required for assembly of viruses
210 following its binding to the nucleocapsid.³³ Progeny viruses are then released from the host cell
211 by exocytosis through secretory vesicles.³³

212

213 **Diagnosis**

214 The proper diagnosis for COVID-19 infection must be made first when finding the initial symptoms as
215 described above and the treatment initiative factor. The difference in COVID-19 from the common
216 cold is essential for everyone to know for proper treatment. Sometimes the results of preliminary
217 examinations in infected people do not provide a clear diagnosis of COVID-19 infection. In general,
218 doctors usually consider the patient's travel history by looking at the symptoms that exist such as
219 cough, flu, fever and others. The initial intervention, sputum examination and other diagnostic tests
220 help in determining the right early infection. Possibly the number of days from the first day of
221 infection is taken at the laboratory to recommend individual diagnostic tests such as:

222 ***RT-PCR***

223 The standard technique for determination is by reverse transcription polymerase chain reaction (rRT-
224 PCR) from a nasopharyngeal swab or sputum sample, with results inside a couple of hours to 2 days.³⁴

225

226 ***ELISA***

227 Antibody assays can also be used, using a blood serum sample, with results within a few days.³⁵

228

229 ***CT-Scan***

230 The contamination can likewise be analyzed from a mix of side effects, chance elements, and a chest
231 CT scan demonstrating highlights of pneumonia.³⁶ The fundamental diagnosis reports from medical
232 clinics in China show that the majority of COVID-19 infected patients were determined with
233 pneumonia and trademark CT imaging patterns,³⁷ radiological assessments have become imperative in
234 early determination and appraisal of disease course.³⁸ CT scan of various COVID-19 contaminated
235 patients differed in pattern³⁹ and almost 50% of patients could be discovered of disease from pictures.
236 On admission to emergency clinics, the ground-glass haziness was the most widely recognized
237 radiologic finding on chest figured tomography (CT)³⁹ of 56.4% of patients.⁴⁰ The longitudinal CT
238 discoveries of a COVID-19 infected patient with pneumonia demonstrated sorted out example of CT
239 images in follow up check over the course of treatment. Besides that, it was seen that numerous
240 patients did not have strange radiologic findings.⁴¹

241

242 **Treatments of COVID-19**

243 There is an urgent demand from WHO and various countries in the world for new COVID-19 disease
244 treatment therapies. The deadly nature of the spread of this virus produces fear in everyone. Infection
245 caused by this disease in the form of acute respiratory disease (SARS) which can cause death and there
246 is no drug that is scientifically proven to kill this new virus. Each country can only do reducing the
247 spread of infectious diseases by physical distancing and maintaining cleanliness of the body.
248 International organizations such as WHO have invited researchers around the world to find vaccines,
249 new drugs and diagnostic development for SARS-CoV-2 and COVID-19. The Director General of
250 WHO has prioritized the main research to prevent the spread of COVID-19 by developing new drug
251 candidate both modern and herbal medicines for therapy and diagnosis that are easily applied to
252 identify active infections, asymptomatic and resolved infections of COVID-19.³

253

254 The mechanism of viral infection is the entry of the virus into cells and multiplication using a host
255 cellular mechanism that is characterized by damage to the host cell as a key for the development of
256 new drug compound therapies. To date, there is no definitive and recommended therapy for COVID-
257 19 due to new virus which is caused a viral infection and the curative therapy for COVID-19 is an
258 antiviral. However, all antivirals used in COVID-19 therapy in almost all countries are still in the form
259 of trial and error. Some of them refer to antiviral therapy that was used during the SARS and MERS
260 epidemic several years ago, for example using lopinavir, ritonavir, ribavirin, oseltamivir, and others.
261 These drugs have been used and were quite effective in dealing with SARS and MERS during the past
262 epidemic. Likewise in Indonesia, there are no definitive guidelines for dealing with COVID-19 and
263 only rely on existing drug preparations, for example oseltamivir which is currently widely used in
264 dealing with COVID-19. With the start of the COVID-19 outbreak in China, Indonesia has tried to
265 refer to China regarding the drugs used, including chloroquine and Avigan. Some prospective drugs
266 are considered to direct current applications or the development of new therapeutic drugs including
267 modern and herbal medicines includes:

268

269 *Entry inhibitors*

270 The SARS-CoV-2 virus infects the respiratory system and alveoli cells in the lung sac which will
271 become host for the viral infection. In general, viruses enter the host cell by forming a complex
272 between the virus projections (crown such as spikes or lobes) with receptors on the host cell. Whereas
273 the exact structure of the spike⁴² or lobe virus and receptors on host cells for SARS-CoV-2 is not yet
274 fully known but prior experience of coronavirus (β -family) is responsible for SARS infection and has
275 similarities in the form of entry in host cells.⁴³ Recently it has been found that Angiotensin-converting
276 enzyme 2 (ACE2) is a cellular receptor for the SARS corona virus, (SARS-CoV) and (SARS-CoV-
277 2).⁴⁴ Angiotensin-converting enzyme 2 (ACE2) has some homology with angiotensin-converting
278 enzyme (ACE) but not inhibited by ACE inhibitors. A previous SARS case was characterized by an
279 infection that was started by a transmembrane (S) spike in glycoproteins which binds to the host
280 receptor and combines viruses and cell membranes. The identification of the viral / spikes lobes
281 molecular structure will take time, but the development of facilitated heterocyclic drug molecules or
282 existing heterocyclic screening may be able to bind the entry inhibitor drug.⁴⁵

283

284 *Replication inhibitors*

285 The corona virus is an RNA virus utilizing host cells for genomic replication which encodes the RNA-
286 dependent protein polymerase (RdRp), which allows the viral genome to be transcribed into new RNA
287 copies using host membrane cells. The viral genome replication mechanism serves potential targets for
288 the control of viral infections then nucleoside analogues and potential polymerase inhibitors used as
289 antiviral drugs⁴⁶ can be potentially effective with SARS-CoV-2. RNA polymerase inhibitors such as
290 Remdesivir and Favipiravir (Avigan) (**Figure 4A and 4B**) which is a nucleotide adenosine analogue
291 antiviral for Ebola virus and other array RNA viruses and have shown promising results in clinical
292 control of SARS-CoV-2 pneumonia in cell culture in vitro and certain clinical cases.⁴⁷ This requires
293 more evaluation further from potential applications with more patients. Many other nucleoside
294 analogues including DNA synthesis inhibitors such as tenofovir, disoproxil, lamivudine and other
295 antivirals have the potential to inhibit the multiplication of SARS-CoV-2 viruses and are being
296 evaluated through molecular docking studies⁴⁸ and testing in infected cell culture.

297

298 Avigan is the patent name for favipiravir, also known as T-705, an antiviral drug developed by
299 Toyama Chemical (Fujifilm group) of Japan with activity against many RNA viruses. In Japan, this
300 drug was originally developed as a cold medicine. In February 2020, Favipiravir was used in China for
301 trials of emerging COVID-19 (novel coronavirus) disease. The mechanism of action of favipiravir is
302 by selective inhibition of viral RNA polymerase so that it inhibits viral RNA synthesis (**Figure 5**).⁴⁹
303 Other studies have shown that favipiravir induces mutant of RNA transversion mutations, resulting in
304 a viable viral phenotype. Favipiravir is a product that is metabolized by human hypoxanthine guanine

305 phosphoribosyltransferase (HGPRT) into its active form, namely favipiravir-ribofuranosyl-5-
306 triphosphate (favipiravir-RTP). This drug is available in oral and intravenous formulations. Favipiravir
307 does not inhibit the synthesis of RNA or DNA in mammalian cells and is not toxic to them. In 2014,
308 favipiravir was approved in Japan as a backup drug against influenza pandemics and to treat a type of
309 virus that was not responsive to antiviral at the time. During this COVID-19 pandemic, in a limited
310 clinical trial with 80 subjects, favopiravir showed an antiviral potential for SARS-CoV-2 that was
311 better than lopinavir / ritonavir.⁵⁰ In March 2020, the Chinese Government stated that favipiravir
312 appeared to be effective in overcoming COVID-19.

313

314 **Protease inhibitors**

315 In the maturation phase of viral replication in the host cell involves the enzyme protease which is
316 associated with proteins and peptides. Lopinavir and ritonavir (**Figure 4C, 4D**) are anti-HIV drugs that
317 have been approved and a combination of both has shown potential drug compounds in the inhibition
318 of SARS-CoV-2.^{51,52} According to Lim J, et al. stated the treatment of COVID-19 patients in Korea
319 using lopinavir/ritonavir to patients showed interesting results which β -coronavirus was encapsulated
320 and cause a significant decrease and was absent or few coronavirus titers were observed.⁵² This study
321 was conducted in a single patient which detailed analysis is needed to recommend as a candidate for
322 new drug compounds. Molecular docking of potential inhibitors can provide clear information because
323 detailed docking simulation results have shown important input in previous SARS cases and other
324 viral infections.⁵³⁻⁵⁵ However, both of them still need a lot of clinical data to prove the efficacy and
325 safety in the human body.

326

327 **Heterocyclic anti-viral**

328 Many heterocyclic drug molecules have been used in the treatment of viral infections in the past and
329 are thought to be probably slightly effective in inhibiting SARS-CoV-2. Chloroquine was originally a
330 drug used to treat malaria as an antiplasmodium. This drug is a drug containing a quinoline group
331 (**Figure 4E**) that works by inhibiting the activity of the enzyme heme polymerase which converts
332 heme into hemozoin, resulting in the accumulation of free heme. This accumulation of heme causes
333 death of the Plasmodium parasite that causes malaria.⁵⁶ However, with the decrease in malaria and the
334 emergence of plasmodium resistance to chloroquine, chloroquine is no longer used as an antimalarial
335 drug.

336

337 It turns out that chloroquine (and hydroxychloroquine) can also be used for antiviral therapy. Vincent
338 et al (2005) reported that chloroquine has a strong antiviral effect against the SARS-CoV virus in
339 primate cells. This inhibitory effect is observed when cells are treated with chloroquine both before
340 and after exposure to the virus, which shows that chloroquine has both a preventive and therapeutic
341 effect. In addition, to what is known that chloroquine increases endosomal pH which inhibits viral
342 replication and appears to interact with cellular angiotensin-converting enzyme 2 (ACE2) receptors
343 (**Figure 6**).⁵⁷ These causes inhibitions of the binding of the virus with the receptor which prevent
344 infection and spread of the SARS-CoV-2 virus at concentrations that can cause clinical symptoms. In
345 the SARS-CoV-2 pandemic in China, chloroquine was used at a dose of 500 mg for adult 2 times a
346 day, duration of therapy ≤ 10 days.⁵⁸ Chloroquine (and hydroxychloroquine) is also currently being
347 tried in Malaysia at the same dosage used in China and also in Indonesia.

348

349 Meanwhile, there are several other heterocyclic antiviruses that have been used as antivirals such as
350 HIV, H1N1, H1N5 and SARS, all of which will be further investigated to deal with SARS-CoV-2.
351 Oseltamivir (Tamiflu) which has been widely used as a neuraminidase inhibitor for the treatment of
352 influenza and has been recommended for symptoms of COVID-19.⁵⁹ In addition, other candidate
353 compounds that can be evaluated and potentially have antiviral activity against SARS-CoV-2 are
354 compounds other than heterocyclic based on angiotensin converting enzyme 2 (ACE2) peptides
355 namely 3CLpro inhibitors (3CLpro-1) and vinylsulfone protease inhibitors.⁶⁰

356 According to Gautret et al. also stated that the combination of hydroxychloroquine and azithromycin
357 as a treatment of COVID-19 showed it is significantly associated with viral load reduction on clinical
358 study even though small sample size.⁶¹

359

360 **Nano drug delivery systems**

361 Drug delivery systems in the form of nanoparticle preparations have been widely used to improve the
362 bioavailability of drugs in the blood and deliver drugs as antiviral especially nucleoside analogues
363 which are conjugated with potential delivery systems that have been applied in resistant HIV infection
364 drugs.⁶²⁻⁶⁵ Amount of drugs accumulated in the nano delivery system can be used as a new drug in the
365 formulation development which is capable to deliver drugs with a faster therapeutic index for COVID-
366 19.⁶⁶⁻⁶⁸ One example of delivery of nano treatment can be seen in the efficacy of chloroquine against
367 COVID-19 as inhibitor of nanoparticle endocytosis through macrophages. Therefore, chloroquine
368 decreases the accumulation of synthetic nanoparticle of various sizes (14-2,600 nm) and is spherical
369 and discoidal in cell lines.⁶⁹

370

371 **Biological therapeutics**

372 Antibody therapy is very possible for the treatment of COVID-19 infections. However, the discovery
373 of this vaccine still requires a long time around 1 year and temporarily can use several treatment
374 options to prevent the spread of COVID-19. According to Tian et al reported that SARS-CoV-2
375 specific human monoclonal antibodies such as CR3022 which are intended to bind strongly to SARS-
376 CoV-2 RBD (KD 6.3 nM).⁷⁰ Reported CR3022 epitope does not overlap with the ACE2 binding site in
377 SARS-CoV- 2 RBD. These unique binding results indicate the possibility that CR3022 can be
378 developed as a therapeutic candidate in its own way or in combination with other antibodies. However,
379 in vitro trials and clinical studies are needed to obtain accurate clinical data for the prevention and
380 treatment of COVID-19 infections.⁷⁰

381

382 In developing a new vaccine one must pay attention to the similarity of immunogenic structural
383 proteins with COVID-19 such as SARS, MERS which has been used before to be used for SARS-
384 CoV-2.⁷¹ According to Ahmed et al stated that his work had identified a set of B cells and T cell
385 epitopes that derived from spikes (S) and nucleocapsid proteins (N) that can map identically with the
386 SARS-CoV-2 protein.⁷² Reports suggested that the identified epitope has no mutase in the SARS-
387 CoV-2 sequence that was available. So this target immune epitope has the potential to be explored in
388 the fight against the SARS-CoV-2 virus which the glycoprotein spike of SARS-Cov-2 has antigenicity.
389 This is the direction of developing a new vaccine against SARS-CoV-2. However, the final results will
390 depend on in vitro and future clinical trials.⁷²

391

392 **Herbal drugs**

393 Several anti-SARS agents have been tested for coronavirus-specific therapy, however, an effective
394 SARS antiviral therapy has not yet been established.⁷³⁻⁷⁵ Some modern drugs have shown a broad
395 antiviral activity which is most frequently administered as a SARS-antiviral agent in combination with
396 antibacterial drugs. However, this has little activity against SARS-CoV in vitro having specific
397 monoclonal antibodies, pegylated interferon- α , siRNA, and several protease inhibitors have also been
398 tested against SARS-CoV.⁷⁶ Therefore, some researchers in the world particularly Indonesia have
399 utilized herbal drugs to test several candidates of active compounds which are derived from plants or
400 herbs.

401

402 According to UI and IPB researchers stated that they have conducted research originating from several
403 plants in Indonesia which chemical compounds contained in these plants could potentially prevent
404 COVID-19 infection in the form of molecular docking in silico.⁹⁰ The model of research that has been
405 done can be seen in **Figure 7**. Based on the results of prediction models with machine learning
406 methods (SVM, random forest and MLP neural network) associated with 20644 interactions of protein

407 compounds. The results are 31 herbal compounds with 5 target proteins 3CLPro, PLPro, Spike-ACE2,
408 EIF4 and RdRp. Modeling of structure and ligand based pharmacophores was performed virtual
409 screening with 1,377 compounds from the HerbalDB database.⁷⁷ The results of compound hits from
410 machine learning and pharmacophore mapping were confirmed using molecular docking.

411 Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin, quercetin,
412 luteolin, kaempferol, isorhamnetin⁷⁸, and hesperidin⁷⁹. Luteolin is known as a furin protein inhibitor⁸⁰
413 which is assumed as one of the enzymes that break down the Corona virus S (spike) protein as in
414 MERS into units S1 and S2.⁸¹ In the S1 unit, there is a binding domain receptor (RBD) where the
415 ACE2 peptidase binds so that the virus can bind to the host cell.⁸¹ The Hesperidin / hesperitin
416 compound in the silico study is known to inhibit the RBD domain binding of the SARS-COV-2 Spike
417 protein with ACE2 receptors in humans so that it is predicted to potentially inhibit the entry of the
418 SARS-COV-2 virus.⁸² It is also known that luteolin is a neuramidase inhibitor as well as oseltamivir
419 which is currently one of the drugs used in the CDC protocol.

420
421 Hesperidin (a form of hesperidin aglycone) and Quercetin are also known to act as inhibitors of
422 3CLpro virus proteins.^{84,84} Other compounds in guava such as myricetin are known to act as SARS
423 coronavirus helicase inhibitors.⁸⁵ The kaempferol has the potential to be a non-competitive inhibitor of
424 3CLPro and PLpro as well as quercetin.⁸⁶ Another interesting thing is kaempferol acts as a modulator
425 of autophagy, both as an inducer and inhibitor, both of which can be utilized in strategies to inhibit the
426 SARS-COV-2 virus.

427
428 Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived from
429 plants. One of the commonly used condiments for cooking or herbal medicine for Indonesian people is
430 empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. It is not only herbs
431 but also animals such as snakehead fish which can improve immune system in the body due to high
432 protein and amino acids.⁸⁷⁻⁸⁹ According to researchers from UNAIR stated that the approach that can
433 be taken in the public by consuming empon-empon to improve the immune system to avoid COVID-
434 19.

435
436 Herbs containing curcumin and turmeric have been consumed and proven by Indonesian people for
437 centuries and to be safe and beneficial to health. For example maintaining health, fitness / vitality, and
438 maintaining liver and digestive health based on empirical experimental evidence. Both ginger and
439 turmeric contain hundreds of bioactive compounds, one of which is curcumin. Various studies have
440 been carried out in the world in vitro and preclinical test showing that curcumin is anti-inflammatory,
441 antiviral, antibacterial, antifungal and antioxidant based on scientific evidence.

442
443 One of the benefits of curcumin obtained from clinical trials is to increase the body's immune system
444 or act as an immune-modulator. Recent research on curcumin against the SARS-CoV-2 virus which is
445 an agent or cause of COVID-19 disease shows that the SARS-CoV-2 receptor is an enzyme called
446 Angiotensin Converting Enzyme-2 (ACE2) found in host cells (human cells especially alveolus cells
447 in the lung). However, the cell entry of the virus not only depends on the binding of the spike virus
448 protein to the receptor on the host cell (ACE2) but also on the pad priming protein spike by the host
449 cell protease (TMPRSS2). Functionally there are 2 forms of ACE2, the fixed form attached to the cell
450 surface and the free-form soluble form in the blood. The soluble form ACE2 is projected to be one of
451 the SARS-CoV-2 antiviral candidates through a competitive interceptor mechanism that prevents
452 bonding between virus particles and ACE2 on the surface of the host cell. In addition, bio-informatics
453 research published in March 2020 and recent literature has mentioned curcumin as one of the SARS-
454 CoV-2 antiviral candidates, it is expected that curcumin in ginger and turmeric can increase the
455 expression of ACE2 in the form of soluble which can inhibit the bonding between the viral protein and
456 the fixed form ACE2 found on the surface of the host cell.⁹¹

457

458 **Conclusion**

459 The sudden outbreak of COVID-19 in Wuhan, China made all countries in the world panic because it
460 spread very quickly and killed many people so that WHO issued a statement that this disease is a
461 pandemic that threatens the lives of many people. Therefore, every country has an obligation to protect
462 its people by providing an education protocol to prevent the spread of COVID-19. In many new cases,
463 clinical staff gain infected from patients who visit hospitals so that infected cases increase the spread
464 of the virus through human-to-human transmission, creating an urgent need for the development and
465 approval of a standard therapy protocol including structural details and a complete life cycle of the
466 virus, preventing the spread of the virus, adequate virus testing tools to ensure SARS-CoV-2 infection.
467 Several drugs that have been evaluated for the treatment of COVID-19 show promising results for
468 clinical applications such as chemical and herbal medicines that have been clinically tested in reducing
469 this novel viral infection and assisting a number of patients in safe recovery from COVID-19.
470 Furthermore, as knowledge about SARS-CoV-2 advances, new therapies including vaccines and
471 monoclonal antibodies can be found in the near future. So far, effective treatments for COVID-19 are
472 unknown but potential therapeutics can be found from clinical evaluation of existing antiviral drugs
473 are being researched and continued against new coronaviruses.

474

475 **Conflict of interests**

476 The authors claim that there is no conflict of interest.

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705

706 Table 1. Active compounds having the potential as antiviral SARS-CoV-2⁹⁰

Target	Compounds	Sources
3CLpro	<u>Rhamnetin 3-mannosyl-(1-2)-alloside</u>	<u>Cassia alata</u>
	<u>Kaempferol 3,4'-di-O-methyl ether (Ermanin)</u>	<u>Tanacetum microphyllum</u>
	<u>Cyanidine 3-sophoroside-5-glucoside</u>	<u>Brassica Oleracea ; Ipomoea Batatas; Raphanus Sativus</u>
	<u>Casuarinin</u>	<u>Psidium quajava</u>
	<u>Quercetin 3-(2G-rhamnosylrutinoside)</u>	<u>Clitoria Ternatea</u>
	<u>Peonidine 3-(4'-arabinosylglucoside)</u>	<u>Ipomoea fistulosa</u>
	Hesperidine	<u>Psidium quajava</u> <u>Citrus aurantium</u>
PLpro	<u>Platycodin D</u>	<u>Platycodon grandiflorus</u>
	<u>Baicalin</u>	<u>Scutellaria baicalensis</u>
	<u>Sugetriol-3,9-diacetate</u>	<u>Cyperus rotundus</u>
	<u>Phaitanthrin D</u> <u>2,2-di(3-indolyl)-3-indolone</u>	<u>Isatis indigotica</u>
	<u>((-)-epigallocatechin gallate</u>	<u>Camellia sinensis</u>
	<u>2-(3,4-Dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol</u>	<u>Vitis vinifera</u>
Target	Compounds	Sources
RdRp	<u>Betulonal</u>	<u>Cassine xylocarpa</u>
	<u>Gnidicin</u> <u>Gniditrin</u>	<u>Gnidia lamprantha</u>
	<u>2β,30β-dihydroxy-3,4-seco-friedelolactone-27-lactone</u>	<u>Viola diffusa</u>
	<u>14-deoxy-11,12-didehydroandrographolide</u>	<u>Andrographis paniculata</u>
	<u>1,7-dihydroxy-3-methoxyxanthone</u>	<u>Swerti apseudochinensis</u>
	<u>theaflavin 3,3'-di-O-gallate</u>	<u>Camellia sinensis</u>
	<u>2-(3,4-Dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol</u>	<u>Vitis vinifera</u>
Spike-ACE2	Hesperidine	<u>Psidium quajava</u> <u>Citrus aurantium</u>

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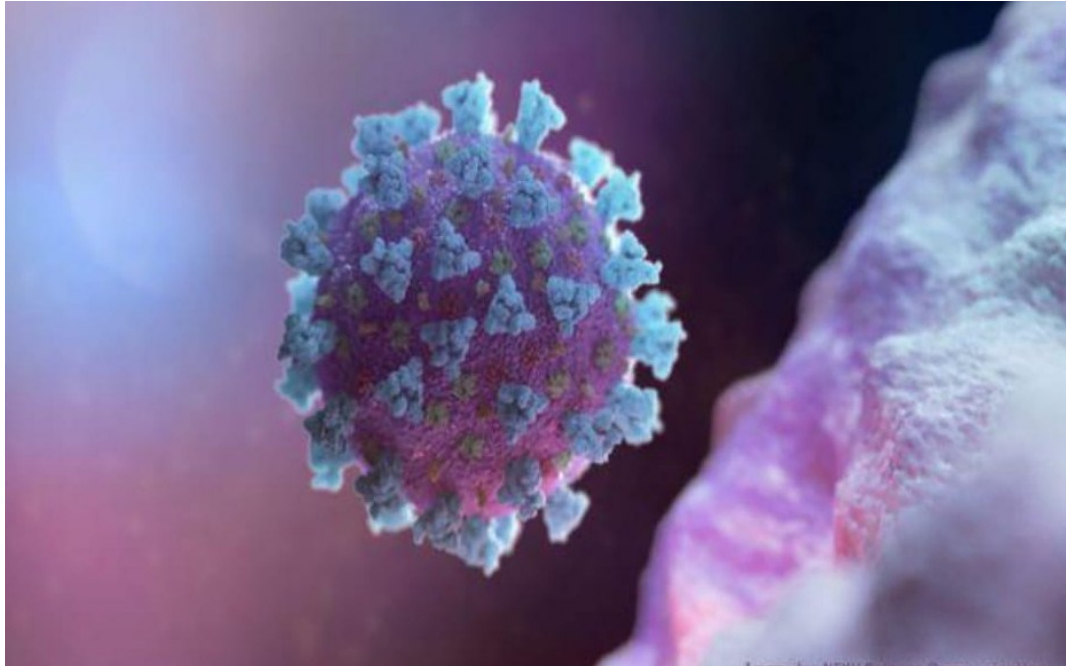


Figure 1. A graphical representation of the structure of coronavirus (SARS-CoV-2).

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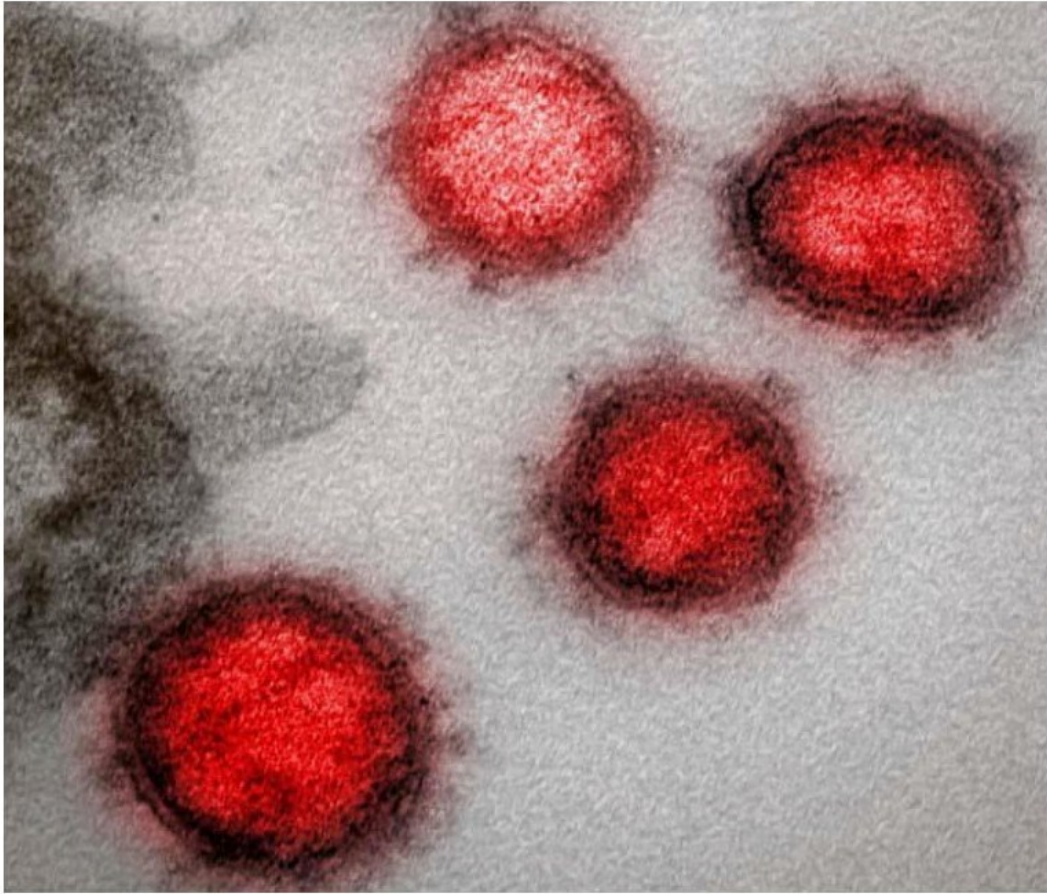


Figure 2. Electron-microscope image of the new coronavirus, now designated SARS-CoV-2. Image reproduced as provided for public domain use by the National Institute of Allergy and Infectious Disease, US. Credit: NIAID-RML/de Wit/Fischer

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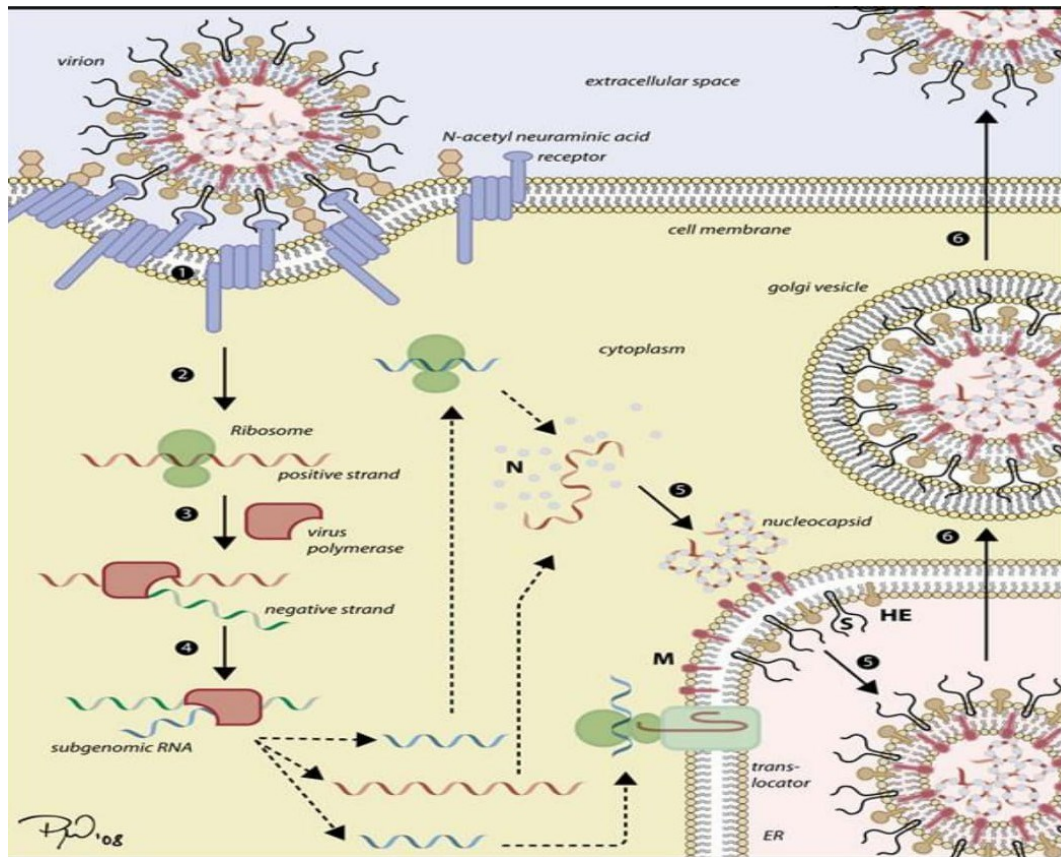


Figure 3. The life cycle of a Coronavirus.

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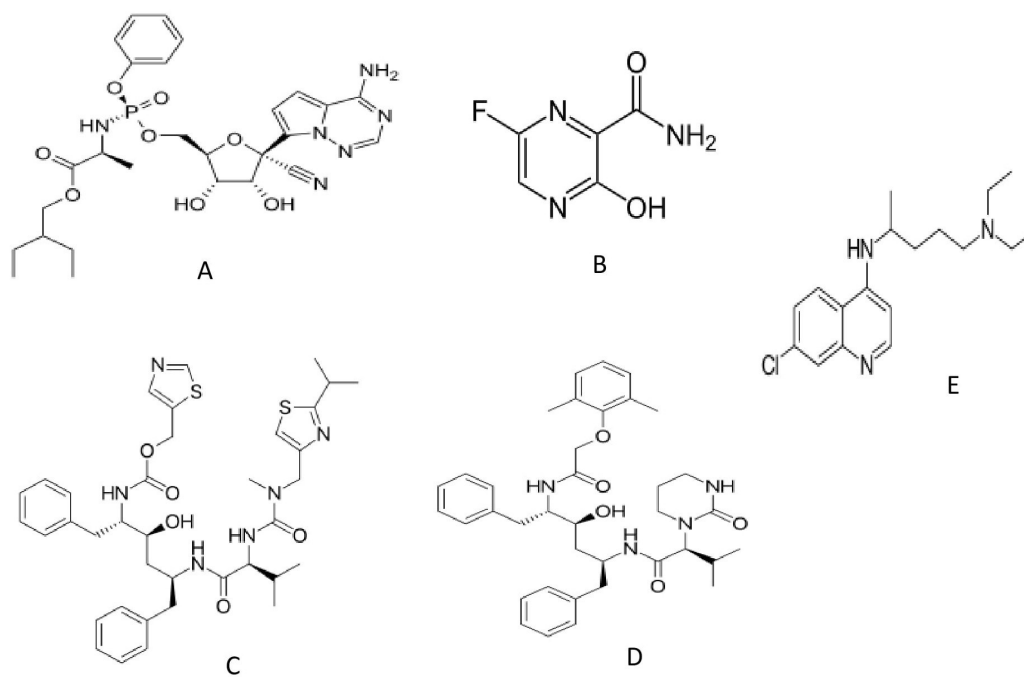


Figure 4. Chemical structures of Ramdesivir (A), Favipiravir (B), Ritonavir (C), Lopinavir (D), Chloroquine (E).

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Acting points of Anti-influenza drugs

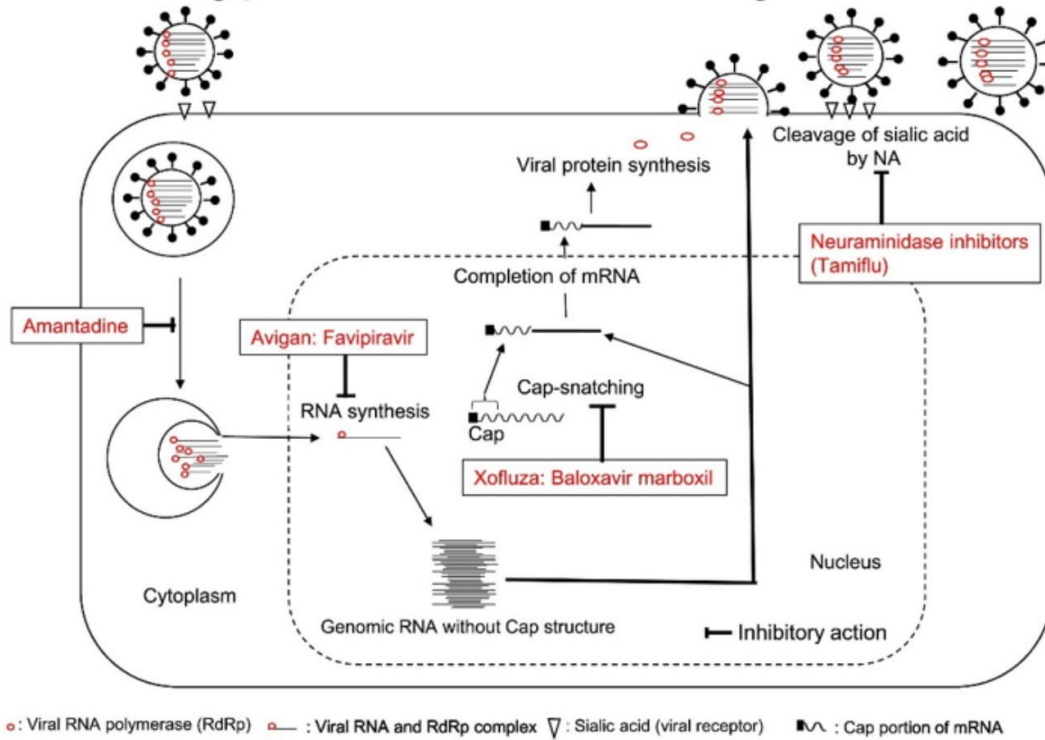


Figure 5. The mechanism of Favipiravir as an antiviral to the SARS-CoV2 virus by inhibiting RNA synthesis, the difference between antiviral and other flu drugs.

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ACE-2 S-Protein Model of 2019 nCoV-Virus

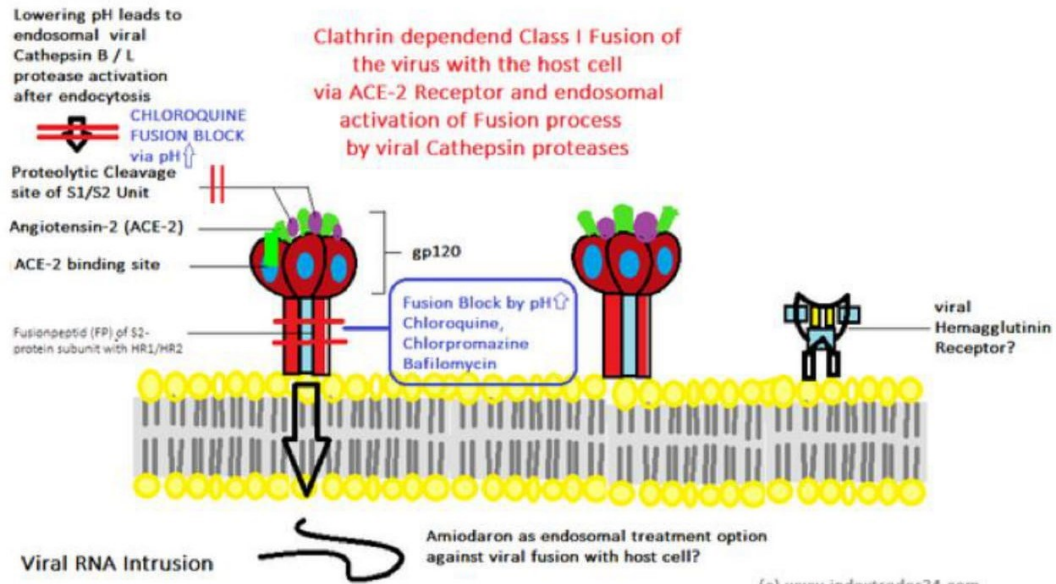


Figure 6. The model describes the mechanism of chloroquine as an antiviral in the SARS-CoV-2 virus. The first binds to the ACE2-cellular receptor which is the site of the binding of the virus, and increases the pH of the endosome thereby inhibiting viral replication.

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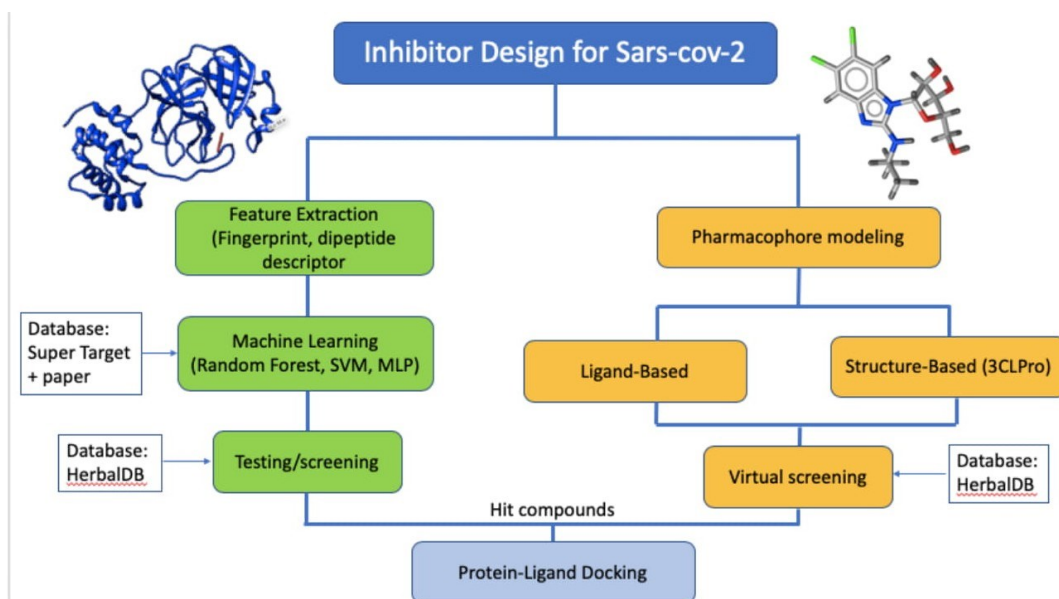
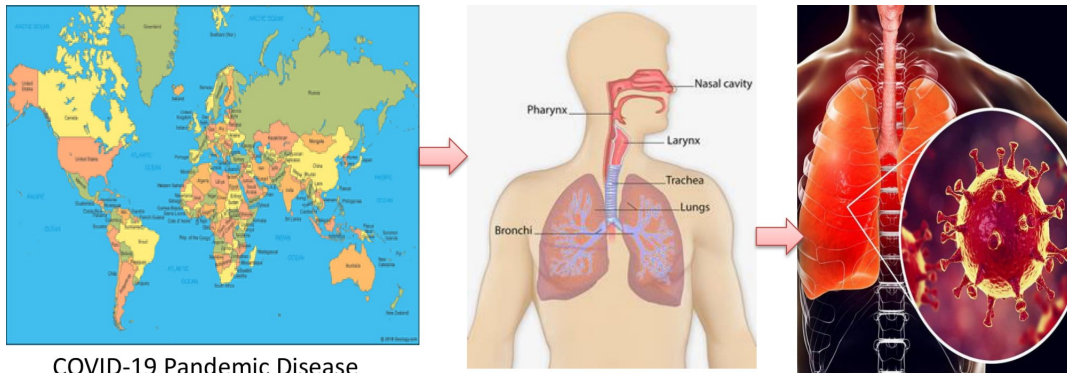


Figure 7. The illustration of molecular docking in inhibiting SARS-CoV-2.

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COVID-19 Pandemic Disease

Transmission

Infection

Diagnosis ?

Diagnosis ?



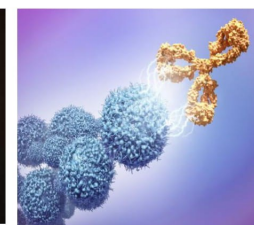
Herbal Medicine



Modern Medicine



Vaccine



Monoclonal Antibody Therapy

Graphical Abstract

Abstract

A recent outbreak of Coronavirus SARS-CoV-2 disease COVID-19 in China and the spread of this infection are very rapid to other countries in the world. All countries worry about the COVID-19 pandemic disease which has alarmed the medical and the scientific community mainly because of the lethal nature of this virus infection. COVID-19 is a novel virus that isn't always to be had the immediate emergency therapy resulting in massive fear of infection which cause social problems in the community and people who are infected. In this case, scientists and researchers have to know the epidemiological cases of COVID-19 infection, the characteristics of SARS-CoV-2 transmission and the spread of viruses, the effectiveness of preventive measures, the nature and life cycle of viruses, current literature advances in diagnostic development such as RT-PCR, CT- Scan, Elisa and the development of modern and herbal drugs for the treatment of infected patients which are viewed from the classification of antiviral drugs such as entry inhibitors, replication inhibitors, nucleosides, nucleotides, protease inhibitors, heterocyclic drugs, including biological therapies namely monoclonal antibodies therapy, vaccines development and herbal formulations that have been pre-clinically tested *in vitro* or in the form of molecular docking and clinical evaluation. Chemical drug molecules with prospective applications in the treatment of COVID-19 have been included in this review.

Keywords: COVID-19, antiviral, infection, herbal, modern drugs, pandemic

Introduction

The spread of infectious diseases in China in December 2019 has emerged with a very high number of deaths and the spread of this infection also involves other countries.¹ Infected people show symptoms of pneumonia which gives symptoms of SARS (Severe Acute Respiratory Syndrome). This infection is caused by a deadly virus in nature and produces the highest number of deaths caused by respiratory infections. The first reported transmission of this infectious disease in China² and has spread to almost all other countries and between continents. The largest numbers of cases of infection were observed in South Korea, Italy, Iran, and several cases in South Africa, USA, and other countries including Indonesia. In recent update from World Health Organization (WHO) and other live updates observing institute, the infection has tainted in excess of 90,000 people worldwide with in excess of 3,000 deaths in various areas and nations. The China, the significant hit nation, alone recorded in excess of 2,500 deaths by end of February 2020.³

The sudden emergence of the corona virus and its spread is very rapid in all countries where WHO reported that this situation creates a pandemic situation. Although not confirmed, the origin of the virus is speculated from completely different animals that are consumed as food in China. Early transmission studies report that the relationship between local fish and wild animal markets in China with most initial infections indicates the possibility of virus transmission from animals to humans and then viruses spreading new infections mainly through human to human transmission. This disease which caused by Coronavirus has proven and caused a very high mortality in the world so that WHO has issued a statement for this virus is a pandemic disease caused by the new coronavirus, namely coronavirus disease 2019 (COVID-19) or under another name severe acute respiratory syndrome SARS-CoV-2 taken based on the International Virus Taxonomy Committee.⁴

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In Indonesia, the cases of corona virus until the end of April 2020 based on data from the Ministry of Health of the Republic of Indonesia have increased rapidly causing high mortality of infected people with this COVID-19.⁵ Based on these data, the Indonesian government quickly responded and took preventive measures to reduce cases of people infected with COVID-19. Until now there is no drug or vaccine that can be proven to kill or inhibit the Covid-19 corona virus. However, WHO announced that governments and pharmaceutical companies around the world are developing vaccines and drugs to fight the corona virus. More than 20 candidates for the corona virus vaccine are being developed worldwide.⁶ Unfortunately, it seems that the development of the vaccines took at least one year before it was completed and could be distributed throughout the world. Meanwhile, there are several types of coronavirus treatments that have entered the stage of clinical testing of modern medicines such as Remdesivir and chloroquine and herbal medicine such as curcumin (*in vitro* study).

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The emergence of this coronavirus novel suddenly and continues to spread rapidly which has led experts to think of developing methods of rapid diagnosis and medicines for COVID-19 infectious diseases. Specifically in Indonesia, doctors have used several existing medicines both using modern and herbal medicines. Researchers have been directly involved from international and national institutions at the university and ministry of health to understand the mechanism of infection, virulence, pharmacology, and possible drug and vaccine interactions as a beginning of development. This review discusses the literature report on progress regarding diagnostic methods and developmental therapies with the possible use of candidate compounds of modern and herbal medicines for COVID-19 infectious diseases in Indonesia.

The Coronaviruses

Coronavirus (CoV), a genus of the *Corona viridae* family, is a positive-strand RNA virus with the largest viral genome of all RNA viruses (27–32 kb) causing wide range of diseases mainly related to respiratory system and infection may vary from the common cold to more severe respiratory diseases.⁷ Besides that, coronaviruses are enveloped 80 to 160 nm particles which all coronaviruses virion particles contain 4 or 5 structural proteins, spike (S) protein, membrane protein (M), hemagglutinin-esterase (HE) protein, nucleocapsid (N) protein, and small envelope E protein.⁸ In addition, The virion structure of coronaviruses consists of the S glycoprotein forms the large, petal-shaped spikes on the surface of the virion having 180 to 200 KDa molecule that is cotranslationally glycosylated in the endoplasmic reticulum (**Figure 1**).⁸

There is current outstanding infections which is caused by Coronavirus namely SARS-CoV-2⁹⁻¹⁰ which at the end of 2019 a new coronavirus (nCoV) is found a new strain of coronavirus and has appeared that was not identified in humans previously. For example zoonoses that indicate this virus is found in animals and then transmitted from animals to humans.¹¹ Some of these coronaviruses can cause disease in humans and many other viruses such as dogs and cat viruses are known to only infect animals and recently the corona virus has infected humans and can infect humans spread through human-to-human transmission. This case is thought to occur in a new coronavirus that causes COVID-19 disease.

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COVID-19 symptoms and infection transmission

COVID-19 can spread rapidly through transmission of infection from humans to other people both in people who have symptoms or are asymptomatic or carrier. In infected people with this virus easily spread through liquid droplet when the patient coughs or sneezes. Transmission in certain cases is usually found in the closest people where transmission so far can be through the air.¹² Meanwhile, Such asymptomatic human beings serve hidden carriers of virus and may similarly contribute in greater transmission of virus to other peoples. This manual transmission can also spread if the patient has symptoms. In addition, vertical transmission of the virus from mother to child has not been observed according to research conducted by Chen H et al. in a small group of pregnant women. They suggest the absence of COVID-19 interuterine vertical transmission from unborn mothers. The emergence and the spread of this new virus, focused on the increase in human populations as the main factor. This increase shows that population density increases the likelihood of transmission of new infections due to an increase in humans which causes proximity of the population which rarely results in auto-separation or reduction of infection.¹³

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In summary, these and other researchers have determined that nCoV-2019 is transmitted from person to person when a person comes into contact with the secretions of an infected person. This means the virus is transmitted via coughing, sneezing, shaking hands, touching infected object then touching eyes, mouth or nose, and handling the waste of an infected person.¹⁴

Symptoms of patients infected with COVID-19

Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to SARS which marked respiratory infections on COVID-19 patients including runny nose, fever, cough, shortness of breath, sore throat, and mild to moderate upper respiratory tract illness. In severe cases, patients can experience pneumonia, SARS, kidney failure and even death in many cases. The patients advanced full signs of the COVID-19 in 2 to 7 days i.e. the median incubation duration of infection development changed into 4 days with an interquartile variety of two to 7 days in all patients.¹⁵

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In clinical research studies conducted by Guan, et al. showed a pattern of various diseases in which the middle-aged infected patients studied were 47 years indicating an infection in people of all ages.¹⁶ Furthermore, of the total patients studied, 41.9% were women showing no gender differences in the spread of infection on all patients. The report states that the primary composite endpoint occurred in 6% of patients. Whereas in Indonesia, data show similar cases that occur with residents of Wuhan city, there is no gender difference in people infected with COVID-19 which data showed the highest death rates until 20 March 2020 showing 8.4% of patients.^{17,18} Meanwhile, the elderly and young children are most at risk from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal than SARS and MERS. Around 15 to 20% of cases can become severe. The lethal rate is about 1 in 10 according to doctors. The nCoV-2019 virus, just as was SARS and MERS, is an enveloped virus. This means the virus is protected by a glycoprotein shell. This is why these viruses are so difficult to treat.¹⁹

The general symptoms which experienced by some patients are coughing and fever but some patients also do not experience fever symptoms. It means that the patient can infect other patients without symptoms (43.8% at admission and 88.7% during hospitalization) and almost two-thirds

of patients experience coughing (67.8%). Blood tests show lymphocytopenia showing the level of lymphocytes is low and abnormal in the majority of patients around 83.2% which are admitted to the hospital. In addition, diarrhea is uncommon in most patients, only about 3.8% of patients experience diarrhea. These symptoms were observed for 2 to 7 days²⁰ in which the incubation period of infection progressed for 4 days with an interquartile range of 2 to 7 days in all patients.²¹

Preventive measures

All countries including Indonesia need the preventive measures in overcoming the spread of COVID-19 as a pandemic disease which there is no known availability of emergency medicines or vaccines as therapies for COVID-19. Therefore, handling of infected patients has been recommended as one step to control the rampant spread among people and is difficult to force the isolation of infected patients because this causes many social problems. Like many reports in the Indonesian media, the practice of forced confinement of infected people at home is very difficult to be done by health workers and the police. The isolation of infected individuals supported with the provision of complete hospital treatment (in hospitals) may be a moral way of control.²² In this direction, appropriate research studies must be carried out to understand the best approach in infection prevention including assessing whether Indonesia is able to slow the spread of COVID-19 to infected people.²³

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In Indonesia, masks and hand sanitizers are widely used in preventing the transmission of COVID-19. Medical masks can help to prevent direct exposure to liquid droplets from infected people who are sneezing and always wash or clean their hands with a hand sanitizer. While in other cases with the use of an improper mask can cause an increased risk of transmission of infection which especially infections from people without symptoms and through infected people on surface exposure poses a higher risk of transmission than people who do not properly use a mask.²⁴ This occurs because people who wear a mask can touch the mask itself and the mouth or face part more often than people who do not use masks. This frequent touching of mouth and face part pose higher possibility of reaching of virus to person's respiratory system on exposure of hands with contaminated surfaces (in shops, malls, buses, and other public places) or hand shake with asymptomatic person. So, care should be taken to avoid frequent touching of own face particularly mouth, nose and eyes (whether wearing mask or not).²⁵

The standard procedures which are recommended for preventing the spread of infection are more effective in controlling the spread and keeping things safe. The most crucial include ordinary hand washing, an exercise easy however very powerful. Washing of palms after any go to public places might hold the virus (although exposed to contaminated surfaces) away from getting transmitted or one getting infected. other practices encompass overlaying mouth and nostril when coughing and sneezing to prevent the unfold especially if the person is asymptomatic or in preliminary degrees of contamination.^{26,27} Besides that, cooking food properly like meat, eggs, and food from animals can destroy the virus. In practice, one must avoid close contact with anyone showing symptoms of respiratory illnesses such as cough, flu, asthma, pneumonia, and tuberculosis. Therefore, this simple precaution can be carried out effectively in controlling the spread and holding the virus itself.

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Life cycle of SARS-CoV-2 (COVID-19) virus and infection

Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism consisting of 3 parts, namely entry, replication and release which can be seen in **Figure 2**.

Firstly, infection begins when the viral spike (S) glycoprotein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the host cell protease available, cleavage and activation allows cell the entry by endocytosis or direct fusion of the viral envelop with the host membrane.²⁸

On entry into the host cell, the virus particle is uncoated, and its genome enters the cell cytoplasm.²⁹ The coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail, which allows the RNA to attach to the host cell's ribosome for translation.³⁰ The host ribosome translates the initial overlapping open reading frame of the virus genome and forms a long polyprotein. The polyprotein has its own proteases which cleave the polyprotein into multiple nonstructural proteins.³¹

Secondly, coronaviruses do replication and transcription of RNA from an RNA strand by the mechanism of SARS-CoV-2 replication by binding on cell surface molecules such as metalloprotease amino peptidase having hemagglutinin esterase (HE-protein) and N-acetyl neuraminic acid as co-receptor. After that, virus gets into the host cell by fusion of viral and cell membrane or by receptor mediated endocytosis in that the virus is incorporated via an endosome, which is subsequently acidified by proton pumps. Meanwhile, virus can produce directly their proteins and new genomes in the cytoplasm particularly single positive stranded RNA gen. Otherwise, the negative strand serves as template to transcribe smaller subgenomic positive RNAs which are used to synthesize all other proteins. After binding, assembled nucleocapsids with helical twisted RNA enter into the ER lumen and are encased with its membrane (**Figure 2**).³²

Thirdly, The replicated positive-sense genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading frame. These mRNAs are translated by the host's ribosomes into the structural proteins and a number of accessory proteins.³¹ RNA translation occurs inside the endoplasmic reticulum. The viral structural proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment. Therefore, the M proteins direct most protein interactions required for assembly of viruses following its binding to the nucleocapsid.³³ Progeny viruses are then released from the host cell by exocytosis through secretory vesicles.³³

Diagnosis

The characteristic proper prognosis of COVID-19 infection is the first line of manage and a finding out aspect inside the initiation of the course of remedy. The difference in COVID-19 from the common cold is essential for everyone to know for proper treatment. Sometimes the results of preliminary examinations in infected people do not provide a clear diagnosis of COVID-19 infection. Therefore, doctors usually ask the symptoms to the patient in detail to determine diagnosis accurately such as cough, flu, fever and others. The initial intervention, sputum examination and other diagnostic tests help in determining the right early infection. Possibly the number of days from the first day of infection is taken at the laboratory to recommend individual diagnostic tests such as:

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RT-PCR

The standard technique for determination is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab or sputum sample, with results inside a couple of hours to 2 days.³⁴ Sample measurement (Swab test) consists of some steps using RT-PCR which is figured out in **Figure 3**.

ELISA

Antibody assays can also be used, using a blood serum sample, with results within a few days.³⁵

CT-Scan

The contamination can likewise be analyzed from a mix of side effects, chance elements, and a chest CT scan demonstrating highlights of pneumonia.³⁶ The fundamental diagnosis reports from medical clinics in China show that the majority of COVID-19 infected patients were determined with pneumonia and trademark CT imaging patterns,³⁷ radiological assessments have become imperative in early determination and appraisal of disease course.³⁸ CT scan of various COVID-19 contaminated patients differed in pattern³⁹ and almost 50% of patients could be discovered of disease from pictures. On admission to emergency clinics, the ground-glass haziness was the most widely recognized radiologic finding on chest figured tomography (CT)³⁹ of 56.4% of patients.⁴⁰ The longitudinal CT discoveries of a COVID-19 infected patient with pneumonia demonstrated sorted out example of CT images in follow up check over the course of treatment. Besides that, it was seen that numerous patients did not have strange radiologic findings.⁴¹

Treatments of COVID-19

There is an urgent demand from WHO and various countries in the world for new COVID-19 disease treatment therapies. The deadly nature of the spread of this virus produces fear in everyone. Infection caused by this disease in the form of SARS which can cause death and there is no drug that is scientifically proven to kill this new virus. Each country can only do reducing the spread of infectious diseases by physical distancing and maintaining cleanliness of the body. International organizations such as WHO have invited researchers around the world to find vaccines, new drugs and diagnostic development for SARS-CoV-2 and COVID-19. The Director General of WHO has prioritized the main research to prevent the spread of COVID-19 by developing new drug candidate both modern and herbal medicines for therapy and diagnosis that are easily applied to identify active infections, asymptomatic and resolved infections of COVID-19.³

The mechanism of viral infection is the entry of the virus into cells and multiplication using a host cellular mechanism that is characterized by damage to the host cell as a key for the development of new drug compound therapies. To date, there is no definitive and recommended therapy for COVID-19 due to new virus which is caused a viral infection and the curative therapy for COVID-19 is an antiviral. However, all antivirals used in COVID-19 therapy in almost all countries are still in the form of trial and error. Some of them refer to antiviral therapy that was used during the SARS and MERS epidemic several years ago, for example using lopinavir, ritonavir, ribavirin, oseltamivir, and others. These drugs have been used and were quite effective in dealing with SARS and MERS during the past epidemic. Likewise in Indonesia, there are no definitive guidelines for dealing with COVID-19 and only rely on existing drug preparations, for example oseltamivir which is currently widely used in dealing with COVID-19.

With the start of the COVID-19 outbreak in China, Indonesia has tried to refer to China regarding the drugs used, including chloroquine and Avigan. Some prospective drugs are considered to direct current applications or the development of new therapeutic drugs including modern and herbal medicines includes:

Entry inhibitors

The SARS-CoV-2 virus infects the respiratory system and alveoli cells in the lung sac which will become host for the viral infection. In general, viruses enter the host cell by forming a complex between the virus projections (crown such as spikes or lobes) with receptors on the host cell. Whereas the exact structure of the spike⁴² or lobe virus and receptors on host cells for SARS-CoV-2 is not yet fully known but prior experience of coronavirus (β -family) is responsible for SARS infection and has similarities in the form of entry in host cells.⁴³ Recently it has been found that Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for the SARS corona virus, (SARS-CoV) and (SARS-CoV-2).⁴⁴ Angiotensin-converting enzyme 2 (ACE2) has some homology with angiotensin-converting enzyme (ACE) but not inhibited by ACE inhibitors. A previous SARS case was characterized by an infection that was started by a transmembrane (S) spike in glycoproteins which binds to the host receptor and combines viruses and cell membranes. The identification of the viral / spikes lobes molecular structure will take time, but the development of facilitated heterocyclic drug molecules or existing heterocyclic screening may be able to bind the entry inhibitor drug.⁴⁵

Replication inhibitors

The corona virus is an RNA virus utilizing host cells for genomic replication which encodes the RNA-dependent protein polymerase (RdRp), which allows the viral genome to be transcribed into new RNA copies using host membrane cells. The viral genome replication mechanism serves potential targets for the control of viral infections then nucleoside analogues and potential polymerase inhibitors used as antiviral drugs⁴⁶ can be potentially effective with SARS-CoV-2. RNA polymerase inhibitors such as Remdesivir and Favipiravir (Avigan) (Figure 4, A and B) are nucleotide adenosine analogue antiviral for Ebola virus and other array RNA viruses which have shown promising results in clinical control of SARS-CoV-2 pneumonia in cell culture *in vitro* and certain clinical cases.⁴⁷ This requires more evaluation further from potential applications with more patients. Many other nucleoside analogues including DNA synthesis inhibitors such as tenofovir, disoproxil, lamivudine and other antivirals have the potential to inhibit the multiplication of SARS-CoV-2 viruses and are being evaluated through molecular docking studies⁴⁸ and testing in infected cell culture.

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Avigan is the patent name for favipiravir, also known as T-705, an antiviral drug developed by Toyama Chemical (Fujifilm group) of Japan with activity against many RNA viruses. In Japan, this drug was originally developed as a cold medicine. In February 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel coronavirus) disease. The action mechanism of favipiravir inhibits synthesis of viral RNA polymerase selectively (Figure 5).⁴⁹ Other studies have shown that favipiravir induces mutant of RNA transversion mutations, resulting in a viable viral phenotype. Favipiravir is a product that is metabolized by human hypoxanthine guanine phosphoribosyltransferase (HGPR) into its active form, namely favipiravir-ribofuranosyl-5-triphosphate (favipiravir-RTP). This drug is available in oral and intravenous formulations. Favipiravir does not inhibit the synthesis of RNA or DNA in mammalian cells and is not toxic to

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them. In 2014, favipiravir was approved in Japan as a backup drug against influenza pandemics and to treat a type of virus that was not responsive to antiviral at the time. During this COVID-19 pandemic, in a limited clinical trial with 80 subjects, favopiravir showed an antiviral potential for SARS-CoV-2 that was better than lopinavir / ritonavir.⁵⁰ In March 2020, the Chinese Government stated that favipiravir appeared to be effective in overcoming COVID-19.

Protease inhibitors

Protease enzymes are involved within the maturation stage of virus replication inside the host mobile and related to protein or peptide translation. Lopinavir and ritonavir (**Figure 4, C and D**) are anti-HIV drugs that have been approved and a combination of both has shown potential drug compounds in the inhibition of SARS-CoV-2.^{51,52} A report of Lim J et.al. concerning the remedy of a COVID-19 affected person in Korea indicated that at the administration of lopinavir/ritonavir (Kaletra, AbbVie) to the patient, apparently, β -coronavirus viral hundreds reduced extensively and on similarly remedy, no or little coronavirus titers were discovered.⁵² This means that a detailed analysis is needed for the recommendation of this drug formulation for the remedy of COVID-19 as a candidate of new drug compounds. Molecular docking of potential inhibitors can provide clear information because detailed docking simulation results have shown important input in previous SARS cases and other viral infections.⁵³⁻⁵⁵ However, both of them still need a lot of clinical data to prove the efficacy and safety in the human body.

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Heterocyclic anti-viral

Many heterocyclic drug molecules have been used in the treatment of viral infections in the past and are thought to be probably slightly effective in inhibiting SARS-CoV-2. Chloroquine was originally a drug used to treat malaria as an antiplasmodium. This drug contains a quinoline group (**Figure 4, E**) and inhibits the activity of the enzyme heme polymerase which converts heme into hemozoin, resulting in the accumulation of free heme. This accumulation of heme causes death of the Plasmodium parasite that causes malaria.⁵⁶ However, with the decrease in malaria and the emergence of plasmodium resistance to Chloroquine, it is no longer used as an antimalarial drug.

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It turns out that chloroquine (and hydroxychloroquine) can also be used for antiviral therapy. Gao et al. (2020) reported that chloroquine has a strong antiviral effect against the SARS-CoV virus in primate cells. This inhibitory effect is observed when cells are treated with chloroquine both before and after exposure to the virus, which shows that chloroquine has both a preventive and therapeutic effect. In addition, to what is known that chloroquine increases endosomal pH which inhibits viral replication and appears to interact with cellular ACE2 receptors (**Figure 6**).⁵⁷ This causes inhibitions of the binding of the virus with the receptor which prevent infection and spread of the SARS-CoV-2 virus at concentrations that can cause clinical symptoms. In the SARS-CoV-2 pandemic in China, chloroquine was used at a dose of 500 mg for adult 2 times a day, duration of therapy ≤ 10 days.⁵⁸ Chloroquine (and hydroxychloroquine) is also currently being tried in Malaysia at the same dosage used in China and also in Indonesia.

Meanwhile, there are several other heterocyclic antiviruses that have been used as antivirals such as HIV, H1N1, H1N5 and SARS, all of which will be further investigated to deal with SARS-CoV-2. Oseltamivir (Tamiflu) which has been widely used as a neuraminidase inhibitor for the treatment of influenza which has been recommended for symptoms of COVID-19.⁵⁹ In addition,

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other candidate compounds that can be evaluated and potentially have antiviral activity against SARS-CoV-2 are compounds other than heterocyclic based on ACE2 peptides namely 3CLpro inhibitors (3CLpro-1) and vinylsulfone protease inhibitors.⁶⁰ According to Mourse et al. also stated that the combination of hydroxychloroquine and azithromycin as a treatment of COVID-19 showing it is significantly associated with viral load reduction on clinical study even though small sample size.⁶¹

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Nano drug delivery systems

Drug delivery systems in the form of nanoparticle preparations have been widely used to improve the bioavailability of drugs in the blood and deliver drugs as antiviral especially nucleoside analogues which are conjugated with potential delivery systems that have been applied in resistant HIV infection drugs.⁶²⁻⁶⁵ Amount of drugs accumulated in the nano delivery system can be used as a new drug in the formulation development which is capable to deliver drugs with a faster therapeutic index for COVID-19.⁶⁶⁻⁶⁸ One example of delivery of nano treatment can be seen in the efficacy of chloroquine against COVID-19 as inhibitor of nanoparticle endocytosis through macrophages. Therefore, chloroquine decreases the accumulation of synthetic nanoparticle of various sizes (14-2,600 nm) and is spherical and discoidal in cell lines.⁶⁹

Biological therapeutics

Antibody therapy is very possible for the treatment of COVID-19 infections. However, the discovery of this vaccine still requires a long time around 1 year and temporarily can use several treatment options to prevent the spread of COVID-19. According to Tian et al reported that SARS-CoV-2 specific human monoclonal antibodies such as CR3022 which are intended to bind strongly to SARS-CoV-2 RBD (KD 6.3 nM).⁷⁰ Reported CR3022 epitope does not overlap with the ACE2 binding site in SARS-CoV-2 RBD. These unique binding results indicate the possibility that CR3022 can be developed as a therapeutic candidate in its own way or in combination with other antibodies. However, *in vitro* trials and clinical studies are needed to obtain accurate clinical data for the prevention and treatment of COVID-19 infections.⁷⁰

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In developing a new vaccine one must pay attention to the similarity of immunogenic structural proteins with COVID-19 such as SARS, MERS which has been used before to be used for SARS-CoV-2.⁷¹ According to Ahmed et al stated that his work had identified a set of B cells and T cell epitopes that derived from spikes (S) and nucleocapsid proteins (N) that can map identically with the SARS-CoV-2 protein.⁷² Reports suggested that the identified epitope has no mutase in the SARS-CoV-2 sequence that was available. So this target immune epitope has the potential to be explored in the fight against the SARS-CoV-2 virus which the glycoprotein spike of SARS-Cov-2 has antigenicity. This is the direction of developing a new vaccine against SARS-CoV-2. However, the final results will depend on *in vitro* and future clinical trials.⁷²

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Herbal drugs

Several anti-SARS agents have been tested for coronavirus-specific therapy, however, an effective SARS antiviral therapy has not yet been established.⁷³⁻⁷⁵ Some modern drugs have shown a broad antiviral activity which is most frequently administered as a SARS-antiviral agent in combination with antibacterial drugs. However, this has little activity against SARS-CoV *in vitro* having specific monoclonal antibodies, pegylated interferon- α , siRNA, and several protease

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inhibitors have also been tested against SARS-CoV.⁷⁶ Therefore, some researchers in the world particularly Indonesia have utilized herbal drugs to test several candidates of active compounds which are derived from plants or herbs.

According to UI and IPB researchers stated that they have conducted research originating from several plants in Indonesia which chemical compounds contained in these plants could potentially prevent COVID-19 infection in the form of molecular docking in silico.⁹⁰ The model of research that has been done can be seen in **Figure 7**. Based on the results of prediction models with machine learning methods (SVM, random forest and MLP neural network) associated with 20644 interactions of protein compounds. The results are 31 herbal compounds with 5 target proteins 3CLPro, PLPro, Spike-ACE2, EIF4 and RdRp. Modeling of structure and ligand based pharmacophores was performed virtual screening with 1,377 compounds from the HerbalDB database.⁷⁷ The results of compound hits from machine learning and pharmacophore mapping were confirmed using molecular docking.

Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin, quercetin, luteolin, kaempferol, isorhamnetin⁷⁸, and hesperidin⁷⁹. Luteolin is known as a furin protein inhibitor⁸⁰ which is assumed as one of the enzymes that breakdown the Corona virus S (spike) protein as in MERS into units S1 and S2.⁸¹ In the S1 unit, there is a receptor binding domain (RBD) where the ACE2 peptidase binds so that the virus can bind to the host cell.⁸¹ The Hesperidin / hesperitin compound in the silico study is known to inhibit the RBD domain binding of the SARS-COV-2 Spike protein with ACE2 receptors in humans so that it is predicted to potentially inhibit the entry of the SARS-COV-2 virus.⁸² It is also known that luteolin is a neuramidase inhibitor as well as oseltamivir which is currently one of the drugs used in the CDC protocol.

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Hesperidin (a form of hesperidin aglycone) and Quercetin are also known to act as inhibitors of 3CLpro virus proteins.^{84,84} Other compounds in guava such as myricetin are known to act as SARS coronavirus helicase inhibitors.⁸⁵ The kaempferol has the potential to be a non-competitive inhibitor of 3CLPro and PLpro as well as quercetin.⁸⁶ Another interesting thing is kaempferol acts as a autophagy modulator which both as an inducer and inhibitor, both of which can be utilized in strategies to inhibit the SARS-COV-2 virus.

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Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived from plants. One of the commonly used condiments for cooking or herbal medicine for Indonesian people is empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. It is not only herbs but also animals such as snakehead fish which can improve immune system in the body due to high protein and amino acids.⁸⁷⁻⁸⁹ According to UNAIR researchers stated that the approach that can be taken in the public by consuming empon-empon to boost the immune system to avoid COVID-19.⁹⁰

Herbs containing curcumin and turmeric have been consumed and proven by Indonesian people for centuries and to be safe and beneficial to health. For example maintaining health, fitness / vitality, and maintaining liver and digestive health based on empirical experimental evidence. Both ginger and turmeric contain hundreds of bioactive compounds, one of which is curcumin. Various studies have been carried out in the world in vitro and preclinical test showing that

curcumin is anti-inflammatory, antiviral, antibacterial, antifungal and antioxidant based on scientific evidence.^{91, 92}

One of the benefits of curcumin obtained from clinical trials is to increase the body's immune system or act as an immune-modulator. Recent research on curcumin against the SARS-CoV-2 virus which is an agent or cause of COVID-19 disease shows that the SARS-CoV-2 receptor is an enzyme ACE2 found in host cells (human cells especially alveolus cells in the lung). However, the cell entry of the virus not only depends on the binding of the spike virus protein to the receptor on the host cell (ACE2) but also on the pad priming protein spike by the host cell protease (TMPRSS2). Functionally there are 2 forms of ACE2, the fixed form attached to the cell surface and the free-form soluble form in the blood. The soluble form ACE2 is projected to be one of the SARS-CoV-2 antiviral candidates through a competitive interceptor mechanism that prevents bonding between virus particles and ACE2 on the surface of the host cell. In addition, bio-informatics research published in March 2020 and recent literature has mentioned curcumin as one of the SARS-CoV-2 antiviral candidates, it is expected that curcumin in ginger and turmeric can increase the expression of ACE2 in the form of soluble which can inhibit the bonding between the viral protein and the fixed form ACE2 found on the surface of the host cell.⁹³

Conclusion

The sudden outbreak of COVID-19 in Wuhan, China made all countries in the world panic because it spread very quickly and killed many people so that WHO issued a statement that this disease is a pandemic that threatens the lives of many people. Therefore, every country has an obligation to protect its people by providing an education protocol to prevent the spread of COVID-19. In many new cases, clinical staff gain infected from patients who visit hospitals so that infected cases increase the spread of the virus through human-to-human transmission, creating an urgent need for the development and approval of a standard therapy protocol including structural details and a complete life cycle of the virus, preventing the spread of the virus, adequate virus testing tools to ensure SARS-CoV-2 infection. Several drugs that have been evaluated for the treatment of COVID-19 show promising results for clinical applications such as chemical and herbal medicines that have been clinically tested in reducing this novel viral infection and assisting a number of patients in safe recovery from COVID-19. Furthermore, as knowledge about SARS-CoV-2 advances, new therapies including vaccines and monoclonal antibodies can be found in the near future. So far, effective treatments for COVID-19 are unknown but potential therapeutics can be found from clinical evaluation of existing antiviral drugs are being researched and continued against new coronaviruses.

Conflict of interests

The authors claim that there is no conflict of interest.

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Table 1. Active compounds having the potential as antiviral SARS-CoV-2⁹⁰

Target	Compounds	Sources
3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	<i>Cassia alata</i>
	Kaempferol 3,4'-di-O-methyl ether (Ermanin)	<i>Tanacetum microphyllum</i>
	Cyanidine 3-sophoroside-5-glucoside	<i>Brassica Oleracea</i> ; <i>Ipomoea Batatas</i> ; <i>Raphanus Sativus</i>
	Casuarinin	<i>Psidium quajava</i>
	Quercetin 3-(2G-rhamnosylrutinoside)	<i>Clitoria Ternatea</i>
	Peonidine 3-(4'-arabinosylglucoside)	<i>Ipomoea fistulosa</i>
	Hesperidine	<i>Psidium quajava</i> <i>Citrus aurantium</i>
PLpro	Platycodin D	<i>Platycodon grandiflorus</i>
	Baicalin	<i>Scutellaria baicalensis</i>
	Sugetriol-3,9-diacetate	<i>Cyperus rotundus</i>
	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	<i>Isatis indiaotica</i>
	(-)-epigallocatechin gallate	<i>Camellia sinensis</i>
	2-(3,4-Dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	<i>Vitis vinifera</i>
Target	Compounds	Sources
RdRp	Betulonal	<i>Cassine xylocarpa</i>
	Gnidicin Gniditrin	<i>Gnidia lamprantha</i>
	2 β ,3 β -dihydroxy-3,4-seco-friedelolactone-27-lactone	<i>Viola diffusa</i>
	14-deoxy-11,12-didehydroandrographolide	<i>Andrographis paniculata</i>
	1,7-dihydroxy-3-methoxyxanthone	<i>Swerti apseudochinensis</i>
	theaflavin 3,3'-di-O-gallate	<i>Camellia sinensis</i>
	2-(3,4-Dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	<i>Vitis vinifera</i>
Spike-ACE2	Hesperidine	<i>Psidium quajava</i> <i>Citrus aurantium</i>

Reviewer 1: [Download File](#)

Comment to Author:

Similarity Check Report: [Download File](#)

From: pharm.sci.tabriz@gmail.com

To: rtungadi@yahoo.com

Date: 4/13/2020 2:42:53 PM

Subject: Your Submission

Body:

Dear Dr. Robert Tungadi

With thanks for your submission entitled "SARS-CoV-2 Disease COVID-19: Infection, Precaution, and Clinical Advances of the Imminent Herbal and Modern Drugs Therapeutics" please find out the reviewers' comments as follow. Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision. If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. The deadline for submission of revision is two months after receiving a decision on manuscript.

Thanks again for your cooperation.

Best Regards,

Ali Shayanfar (Pharm.D, Ph.D.)

Editor

Pharmaceutical Sciences (Indexed in ISI and Scopus)

Reviewer 1:

The manuscript is full of grammatical mistakes and requires proof reading and revision. I have highlighted them and also I have written comments in the attached file.

Reviewer 2:

The authors submitted a paper entitled: "SARS-CoV-2 Disease COVID-19: Infection, Precaution, and Clinical Advances of the Imminent Herbal and Modern Drugs Therapeutics".

Thanks for submitting your article.

The "herbal drugs" section of your manuscript was interesting to us.

Comments and suggestions to the article:

1. The title, structure, and context of your manuscript is so similar to a review article named "Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics" published on March 4, 2020. Please describe the novelty and superiority of your article.
2. Several sentences are exactly adapted from previously published studies, please change them to avoid plagiarism.
3. Please check your manuscript for grammar, proper preposition, missing words and unclear in all sentences. The authors should completely revise the manuscript. If it was only a couple of typos, it could be pointed out here. However, the manuscript seriously suffers from typos, phonetics and especially grammar.
4. If you didn't draw the figures yourself, please attach the obtained permission for using them in your article.
5. You have used numerous repetitive sentences in different sections of your manuscript. Please remove irrelevant statements in each section.
6. All paragraphs in each academic writing should be unified, coherent and relevant. Please revise the whole manuscript.
7. There are too many details about the status of COVID19 in Indonesia, please remove them or if you prepared this review for reporting the status of COVID-19 in Indonesia, you should mention it in the title and introduction part.
8. In "introduction" section:
 - Due to the COVID-19 pandemic, several reviews have been published throughout the world. Please explain the novelty of your manuscript and the new viewpoints discussed in your review.
 - Please ensure that all sentences have appropriate references or edit them to avoid misunderstanding (e.g. the statement "This infection is caused by a deadly virus in nature and produces the highest number of deaths caused by respiratory infections" and "More than 20 candidates for the coronavirus vaccine are being developed worldwide").
 - Please use the correctly defined abbreviations in the manuscript (e.g. SARS is the abbreviation of Severe Acute Respiratory Syndrome, not Acute Respiratory Syndrome).
 - Please choose proper words to describe the concepts of your article (e.g. mortality is a proper alternative for death).

deaths caused by respiratory infections" and "More than 20 candidates for the coronavirus vaccine are being developed worldwide").

- Please use the correctly defined abbreviations in the manuscript (e.g. SARS is the abbreviation of Severe Acute Respiratory Syndrome, not Acute Respiratory Syndrome).
 - Please choose proper words to describe the concepts of your article (e.g. mortality is a proper alternative for death).
9. In "The Coronaviruses" section:
- You used some words which cause misunderstanding, please edit them (e.g. SARS and MERS didn't occur "recently").
10. In "COVID-19 symptoms and infection transmission" section:
- Please ensure that all sentences have appropriate references (e.g. "in cases without symptoms, people who have the SARS-CoV-2 virus are infected by people who shake hands or surface contamination with their hands such as coughing and sneezing").
11. In "Symptoms of patients infected with COVID-19" section:
- Please use the defined abbreviations only for the first time in the manuscript (e.g. there is no need to describe SARS again in this part).
12. In "Life cycle of SARS-CoV-2 (COVID-19) virus and infection" section:
- You have used numerous repetitive sentences. Please do not repeat the descriptions of the figures in the manuscript context.
13. In "diagnosis" section:
- Please ensure that all sentences have appropriate references (e.g. "In general, doctors usually consider the patient's travel history by looking at the symptoms that exist such as cough, flu, fever and others"; Is the travel history still a point to focus on?).
14. In "treatments of COVID19" section:
- Please use the defined abbreviations only for the first time in the manuscript (e.g. there is no need to describe SARS again in this part).
 - Please number the references in the order in the text. (e.g. do not mention the reference 90 before 77).
15. There is no table 1 in your text. Please correct it.

Editor:

1- Please check format of references. Are some of the preprint? (e.g. Ref 90). These journals do not explicitly state that preprints cannot be cited. However, it does suggest they may have concerns about the use of preprints in scholarly communication, and therefore you should use caution.

2- Tables should be cell-based and created in Microsoft Word with the Tables tool with real rows and columns and not aligned with tabs, returns, or spaces. Tables exported from other software as non-editable images are not acceptable. Please make sure the table direction is set "left-to-right." Tables with direction set inversely as right-to-left are not acceptable and should be re-drawn. Right-to-left tables are often

- Please use the defined abbreviations only for the first time in the manuscript (e.g. there is no need to describe SARS again in this part).
- Please number the references in the order in the text. (e.g. do not mention the reference 90 before 77).

15. There is no table 1 in your text. Please correct it.

Editor:

1-Please check format of references. Are some of the preprint? (e.g. Ref 90). These journals do not explicitly state that preprints cannot be cited. However, it does suggest they may have concerns about the use of preprints in scholarly communication, and therefore you should use caution.

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3-Are all figures original? In order to publish all figures as open access, authors must have permission from the rights holder if they wish to include images that have been published elsewhere in non-open-access journals. Graphics downloaded from Web pages should not be used unless the author has a right to re-publish those as open access. The original source and the permission should be indicated in the figure legend, and a citation should be included in the reference list.

4-English should be checked by an expert. Read the article once again and edit the wording, punctuation and grammar errors.

5-Pharmaceutical Sciences scans every manuscript submitted using plagiarism-detecting software (iThenticate). In your manuscript, software has detected plagiarism in some minor sentences (please see the attached file).

1. Plagiarism File: SARS_CoV_2_Disease_COVID_19_Infection_Precaution.pdf (14%) - 4/12/2020 10:16:08 PM

From pharm.sci.tabriz@gmail.com
To rtungadi@yahoo.com
Date 5/25/2020 10:49:36 AM
Subject Your Submission
Body:

Dear Dr. Robert Tungadi

With thanks for your submission entitled "COVID-19: Clinical Characteristics and Molecular Levels of Candidate Compounds of Prospective Herbal and Modern Drugs in Indonesia", please find out the reviewers' comments as follow. Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision. If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

The deadline for submission of revision is two months after receiving a decision on manuscript.

Thanks again for your cooperation.

Best Regards,

Ali Shayanfar (Pharm.D, Ph.D.)

Editor

Pharmaceutical Sciences (Indexed in ISI and Scopus)

Reviewer 1:

Comments to the Author:

The authors re-submitted the paper entitled " COVID-19: Clinical Characteristics and Molecular Levels of Candidate Compounds of Prospective Herbal and Modern Drugs in Indonesia".

Thanks for re-submitting your article.

Comments and suggestions to the article:

The most important points include:

Comments and suggestions to the article:

The most important points include:

- Please apply all the previously requested revisions in the manuscript or send additional explanations in the form of a rebuttal letter. Some of the requested items have not yet been corrected or explained. (e.g. All paragraphs in each academic writing should be unified, coherent, and relevant. Please revise the whole manuscript. In addition, you have used numerous repetitive sentences in different sections of your manuscript. Please remove irrelevant statements in each section. Please check your manuscript for grammar, proper preposition, missing words and unclear in all sentences because, in spite of English language edit certification that you have attached, the manuscript has some scientific errors which most of them are mentioned in detailed suggestions part)
- Please note that Coronavirus disease 2019 (COVID-19) is an infectious disease and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of coronavirus that causes COVID-19. Please use the terms correctly in the whole manuscript.
- The term SARS-Cov-2 is the abbreviation of Severe Acute Respiratory Syndrome Coronavirus 2 so it is not necessary to use "virus" after this term again.

The detailed additional suggestions:

"Abstract" section:

- The abbreviation used in abstract section should be defined separately defined at first mention (e.g. COVID-19, SARS-Cov-2, RT-PCR, CT-Scan).

"Introduction" section:

- The abbreviation should be in parenthesis in front of the complete phrase at first mention in the manuscript and used consistently thereafter. Define COVID-19 and SARS appropriately.
- Coronavirus disease 2019 (COVID-19) is an infectious disease and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of coronavirus that causes COVID-19. Please use the terms correctly (e.g. lines 20-21 and 36-37)
- Please ensure that all sentences have appropriate references or edit them to avoid misunderstanding (e.g. the statement "This disease is caused by a lethal virus in nature and is currently the highest leading cause of mortality all over the world.")
- You have used numerous repetitive sentences in different paragraphs of the introduction. Please merge them. (e.g. lines 31, 36-37, 49-50)

"COVID-19 symptoms and infection transmission" section:

- Change the topic to "COVID-19 transmission" because the symptoms are discussed elsewhere.
- Please ensure that all sentences have appropriate references (e.g. lines 75-77).
- You have used numerous repetitive sentences in different paragraphs of the introduction. Please merge them. (e.g. lines 72-74, 83-85)

"Symptoms of patients infected with COVID-19" section:

- Change the topic to "symptoms and mortality of COVID-19".
- Please merge the first and third paragraphs due to the similar content. In addition, you have used repetitive sentences in these two paragraphs, please remove one of them (e.g. lines 94 and 111).
- It seems that you meant acute respiratory distress syndrome (ARDS) instead of SARS in line 92. Please correct it.
- You mentioned "studies" in line 96, however, only one reference is cited. Correct one of them.

- Please use the correct punctuation mark in line 126. We think that you meant "," instead of "" after "medical masks".
- The contents of second and third paragraphs seem similar, therefore it is recommended to merge them. You can explain the standard procedures first, then describe the preventive measures which are used in Indonesia.

"The life cycle of SARS-CoV-2 (COVID-19) virus and infection" section:

- Please change the topic to "The life cycle of SARS-CoV-2" or "The life cycle of COVID-19 virus". The term SARS-CoV-2 is the abbreviation of Severe Acute Respiratory Syndrome Coronavirus 2 so it is not necessary to use "virus" after this term again.
- Please define the abbreviations used in the manuscript at first mention (e.g. ER lumen in line 165).

"Diagnosis" section:

- The sentence "The proper diagnosis characteristics used to manage COVID-19 is finding out the initiation of the course of remedy" doesn't seem correct. Please rewrite it.
- You mentioned "the initial intervention" as a diagnostic test in the sentence "The initial intervention, sputum examination, and other diagnostic tests help to determine the infection early". Please exactly define what you mean by "initial intervention".
- Please define the abbreviations used in the manuscript at first mention and use them consistently thereafter. (e.g. RT-PCR in line 85, ELISA in line 191 and CT-scan in line 195).

"Treatment of COVID-19" section:

- Please use one of the treatments or therapy in the sentence "produce new COVID-19 treatment therapies" in line 209.
- The sentence "to prevent the spread through the development of modern and herbal medicines for therapy and diagnosis and to easily identify active infections, asymptomatic, and patients" doesn't seem correct. Please rewrite it.
- The first paragraph of this section was discussed in the introduction section. There is no need to repeat them again.

"Entry inhibitors" section:

- Please rewrite the whole "entry inhibitors" section. Some important points are listed as follow:
- COVID-19 is a viral infection. What do you mean by "worse than the viral infection" in the sentence "The SARS-CoV-2 virus infects the respiratory system and alveoli cells in the lung sac, which is worse than the viral infection"? In addition, it is not necessary to use "virus" after the term SARS-CoV-2.
- It seems that the term COVID-19 is unneeded in the sentence "However, the exact structure or lobe of COVID-19 SARS-CoV-2 is not fully determined".
- We think you mean the receptors of host cells. "although prior experience of coronavirus (β -family), shows it has similarities with the host cells of SARS."
- We think you mean the inhibitors of ACE (ACEI) in the sentence "ACE2 has some homology with an angiotensin-converting enzyme (ACE) although it is not inhibited by ACE". In addition, you should cite suitable references for the mentioned sentence."

"Replication inhibitors" section:

- "COVID-19 is an RNA virus that utilizes host cells for genomic replication by encoding the RNA-dependent protein polymerase (RdRp), which allows the viral genome to be transcribed into the host membrane cells" doesn't seem correct. Please rewrite it. In addition, you have defined RdRp abbreviation as RNA-dependent protein polymerase, however, this term is the abbreviation of RNA-dependent RNA polymerase. Please

- In "Remdesivir and Favipiravir (Avigan) has the ability to potentially effective SARS-CoV-2" sentence, we think that you mean "affect" instead of effective.
- In the sentence "Many other nucleoside analogues including DNA synthesis such as tenofovir, disoproxil, lamivudine, and other antivirals have the potential to inhibit the multiplication of SARS-CoV-2 viruses" the mentioned terms seem unnecessary. Additionally, it seems better to bring this part as the last paragraph of the "Replication inhibitors" section.
- You stated that "Avigan is the patent name for favipiravir" but it is the brand name or trade name of the favipiravir. Please correct it.
- You have mentioned that Avigan was developed to treat cold in line 261, however, it was developed for influenza. Please correct it. Also, in the sentence "The action mechanism of favipiravir inhibits..." the mentioned terms seem unnecessary, you can delete them or you should add an appropriate verb.
- The sentences 264-268 does not have any reference. Please add suitable references. Especially you should cite the reference for the sentence "it is not toxic" in line, which doesn't seem rational.
- You have used numerous repetitive sentences in lines 259-263 and 268-270, please merge them.

"Protease inhibitors" section:

- Please describe what you mean by "host mobile" and "important input" in lines 275 and 282 or change the mentioned terms.
- The sentence "In addition, the endosomal pH which inhibits viral replication interacts with cellular ACE2 receptors as shown in Figure 7" doesn't seem correct, however, the figure 7 is correct. The endosomal pH helps viral replication and does not interfere with ACE2 receptors. Please rewrite and correct the sentence.
- It seems that you mean "clinical response" in the sentence "at concentrations that cause clinical symptoms". Please correct it.
- The sentence "other candidate compounds evaluated with antiviral activity against SARS-CoV-2 are heterocyclic based on ACE2 peptides namely 3CLpro inhibitors (3CLpro-1) and vinylsulfone protease inhibitors." doesn't seem correct. ACE2 is the receptor on host cells, however, 3CL-pro is a viral structure. Please rewrite the sentence. Additionally, please correctly define the abbreviations. 3CL-pro is the abbreviation of 3C-like proteinase.
- According to the newly published studies, hydroxychloroquine especially when co-administered with azithromycin. So we suggest to remove the sentence "According to Mourse et al. the combination of hydroxychloroquine and azithromycin to treat the virus, shows that it is significantly associated with viral load reduction on clinical study." or you could add additional sentences and references which shows the controversy regarding the use of hydroxychloroquine.

"Nano drug delivery systems" section:

- This section should be revised completely. Especially the sentences "It is accumulated in the nano delivery system and used as a new drug to deliver drugs with a faster therapeutic index for COVID-19" and "Chloroquine decreases the accumulation of synthetic nanoparticle of various sizes (14-2,600 nm) and is spherical and discoidal in cell lines.

"Biological therapeutics" section:

- Please define the RBD in line 325.
- You have used numerous repetitive sentences in lines 327-328 and 335, please merge them.

"Herbal drugs" section:

- All paragraphs in each academic writing should be unified, coherent, and relevant. Please revise the section.
- The first paragraph was discussed in other parts and is unnecessary, please remove it.
- Please define UI, IPB, PLPro, SVM, EIF4, and UNAIR abbreviations.

- • All paragraphs in each academic writing should be unified, coherent, and relevant. Please revise the section.
- • The first paragraph was discussed in other parts and is unnecessary, please remove it.
- • Please define UI, IPB, PLPro, SVM, EIF4, and UNAIR abbreviations.
- • Remove the s from "ACE2 receptors in humans s" in line 360.
- • Rewrite sentence 373.
- • Please rewrite the whole paragraph "Herbs containing curcumin and turmeric have been consumed and proven by Indonesian for centuries and beneficial to health. For example it is used to maintain fitness vitality, liver, and digestive systems based on empirical experimental evidence. Both ginger and turmeric contain hundreds of bioactive compounds, one of which is curcumin. Various studies have been carried out in the world in vitro and preclinical tests showing that curcumin is anti-inflammatory, antiviral, antibacterial, antifungal, and antioxidant based on scientific evidence."
- • Please remove the line 384-385 because they were discussed in other parts.
- • The lines 383-390 belongs to the "The life cycle of SARS-CoV-2 (COVID-19) virus and infection" section. Please remove them from this part.

"Conclusion" section:

- • Please revise the whole paragraph. Especially the sentences "In conclusion, the sudden outbreak of COVID-19 in Wuhan, China, has led to a worldwide panic due to its rapid spread with the mortality rate." And "there is an urgent need for the development and approval of a standard therapy protocol, including structural details and a complete life cycle of the virus, to prevent the spread." And "However, further knowledge of SARS-CoV-2 advances, new therapies, including vaccines and monoclonal antibodies..."

"Figures and Tables" section:

- • The Figures and Tables should be able to be interpreted independently, so the abbreviated terms should be defined in the caption. Please define all the abbreviations used in the figures/table or the caption of them in the first use, for each figure separately. (e.g. SARS-CoV-2, COVID-19, HE, S, ER, SVM, etc.)

1 Abstract

2 A recent outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease
3 also called Coronavirus disease 2019 (COVID-19) in China, has rapidly spread to other countries
4 of the world. The medical and scientific communities are working tirelessly to produce a vaccine
5 due to the lethal nature of this virus. COVID-19 is a novel virus that requires immediate
6 emergency therapy, thereby leading to massive fear of infection, social problems in the
7 community, and an increase in the number of infected people. Therefore, scientists and
8 researchers need to determine the epidemiological cases of the virus, such as its mode of
9 transmission, effective preventive measures, and the nature of the life cycle. In addition, there
10 need to be current literature advances in diagnostic development such as reverse transcription
11 polymerase chain reaction (RT-PCR), computed tomography scan (CT-Scan), Elisa as well as
12 clinical researches on modern and herbal drugs for the treatment of infected patients. This
13 treatment technique is classified from antiviral drugs such as entry, replication, nucleosides,
14 nucleotides, and protease inhibitors, along with the use of heterocyclic drugs, monoclonal
15 antibodies therapy, vaccine development and herbal formulations that have been pre-clinically
16 tested *in vitro* and molecular docking. Chemical drug molecules with prospective applications in
17 the treatment of COVID-19 have been included in this review.

18 **Keywords:** COVID-19, antiviral, infection, herbal, modern drugs, pandemic

20 Introduction

21 In December 2019, the Chinese city of Wuhan experienced a rapid spread in an infectious
22 disease, which affected the respiratory system, thereby leading to a high mortality rate. This
23 virus, known as Coronavirus disease 2019 (COVID-19), soon spread to other countries and was
24 declared a pandemic by the World Health Organization (WHO).¹ Infected people show
25 symptoms of pneumonia, which is similar to SARS (Severe Acute Respiratory Syndrome). This
26 disease is caused by a lethal virus in nature and is currently the highest leading cause of mortality
27 all over the world.² The first reported case was in China, and within a few months, it has spread
28 to almost all countries and continents in the world.² According to studies, the most significant
29 numbers of cases of infected people are in South Korea, Italy, Iran, South Africa, the USA, and
30 Indonesia. In a recent update by WHO, over 90,000 people all over the world are infected with
31 approximately 3,000 deaths. China alone recorded 2,500 deaths by the end of February 2020.³

33 The WHO declared the virus a pandemic due to its rapid spread in various countries. It is
34 speculated that this virus originated from different animals consumed as food in China. Early
35 transmission studies reported that it originated from local fish and wild animal markets with
36 possible transmission from animals to humans and vice versa. However, this speculation has not
37 been proven. This disease has led to a very high increase in mortality all over the world.⁴

39 In Indonesia, the virus was not in existence till the end of April 2020, based on data from the
40 Ministry of Health. Since its inception, there has been a rapid increase in the mortality rate due to
41 the high number of infected people.⁵ Therefore, based on these data, the Indonesian government
42 quickly responded and took preventive measures to reduce the spread of this virus. Before now,
43 no drug or vaccine has been proven to kill or inhibit the COVID-19 virus. However, WHO
44 announced that over 20 countries and pharmaceutical companies around the world are
45 developing vaccines and drugs to fight the virus.⁶ Unfortunately, this development is going to
46 take at least a year before completion. Meanwhile, several types of modern and herbal COVID-

47 19 treatments have been clinically tested, such as Remdesivir and Chloroquine, as well as
48 curcumin (*in vitro* study).

49
50 The emergence and rapid spread of this virus have hastened the development of diagnosis and
51 medicines for the treatment of this infectious disease. In Indonesia, doctors have used several
52 existing modern and herbal medicines, with national and international health institutions, to
53 understand the mechanism, virulence, and pharmacology of the virus to develop possible drugs
54 and vaccines. This review discusses the literature report on progress regarding diagnostic
55 methods and developmental therapies with the possible use of candidate compounds of modern
56 and herbal medicines for COVID-19 infectious diseases in Indonesia.

57

58 **The Coronaviruses**

59 Coronavirus, a genus of the Coronaviridae family, is a positive-strand and the most significant
60 viral genome of all RNA viruses (27–32 kb), causing a wide range of diseases related to the
61 respiratory system. The symptoms may vary from the common cold, dry cough to more severe
62 respiratory diseases.⁷ Furthermore, it consists of 80 to 160 nm particles, 4 or 5 structural spike
63 (S), membrane (M), hemagglutinin-esterase (HE), nucleocapsid (N), and small envelope E
64 proteins.⁸ In addition, the virion structure consists of S glycoprotein, which forms petal-shaped
65 spikes on the surface with 180 to 200 KDa molecule that is cotranslationally glycosylated in the
66 endoplasmic reticulum as shown in Figure 1.⁸ SARS-CoV-2 was an new strain of the current
67 virus,^{9,10} which was transmitted from animals to human¹¹, however, the new coronavirus infects
68 humans.

69

70 **COVID-19 transmission**

71 COVID-19 spreads rapidly amongst humans with symptoms and asymptomatic carriers. The
72 virus is easily spread when the liquid droplet of an infected person drops on surfaces when the
73 patient coughs or sneezes. Transmission in certain cases is usually through the air, by staying
74 close to an infected person.¹² Meanwhile, asymptomatic patients are hidden carriers of the virus
75 and contribute to a greater transmission of the virus. This manual transmission also spread,
76 assuming the patient has symptoms.³ In addition, vertical transmission of the virus from mother
77 to child has not been observed according to research conducted by Chen H et al. in a small group
78 of pregnant women. They stated that the virus is vertically intrauterine and non-transmittable
79 from mothers to unborn babies. The emergence and the spread of this new virus is due to the
80 increase in human populations which causes proximity.^{13,14}

81

82 **Symptoms and mortality of COVID-19**

83 Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to SARS,
84 which marked respiratory infections on COVID-19 patients. These include runny nose, fever,
85 cough, shortness of breath, sore throat, and mild to moderate upper respiratory tract illness. In
86 severe cases, patients experience pneumonia, SARS, kidney failure, and even death. An infected
87 patient shows full signs of the virus within two to seven days. However, the median incubation
88 duration of infection development changed to 4 days with an interquartile variety of 2 to 7 days
89 in all patients.¹⁵ This is known as the incubation period which progresses for four days with an
90 interquartile range.²¹

91

92 Studies conducted by Guan et al. showed the middle-aged were more prone to infection
93 compared to other categories of people.¹⁶ Approximately 41.9% of the total number of patients
94 were women, therefore, there are gender differences in the spread of the virus. The report also
95 stated that the primary composite endpoint occurred in 6% of patients. In Wuhan city, there is no
96 gender difference in people infected with COVID-19 with the highest mortality rates of 8.4% by
97 20 March 2020.^{17,18} However, research shows that the elderly and young children are most at risk
98 from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal compared
99 to SARS and MERS, this is because approximately 15 to 20% of cases become severe within a
100 limited timeframe. According to doctors, the lethal rate is about 1 in 10 is an enveloped virus
101 which means that it is protected by a glycoprotein shell, thereby, making it difficult to treat.¹⁹

102 103 **Preventive measures**

104 All countries, including Indonesia, need preventive measures to overcome the spread of COVID-
105 19, which currently has no known cure and vaccines. Therefore, handling infected patients has
106 been recommended as one of the steps to control the rampant spread of the virus among people.
107 However, it is difficult to force the isolation of infected patients because this causes many social
108 problems. Like many reports in the Indonesian media, the practice of forced confinement of
109 infected people at home is very difficult for health workers and the police. The isolation of
110 infected individuals supported the provision of complete hospital treatment is one of the moral
111 control methods.²² Therefore, appropriate research studies need to be conducted to understand
112 the best approach in infection prevention including assessing the country's ability to slow the
113 spread of infected people.²³

114
115 In Indonesia, masks and hand sanitizers are widely used in preventing the transmission and
116 spread of COVID-19. Medical masks' continuous washing of hands and the use of sanitizers are
117 some of the methods used to prevent the direct exposure of liquid droplets from infected people.
118 Meanwhile, the improper use of masks causes an increased risk of transmission, which especially
119 infects people without symptoms.²⁴ This is because people that wear masks tend to touch their
120 mouths and face more often. This frequent touching poses a higher possibility of the virus to the
121 person's respiratory system on exposure with contaminated surfaces in shops, malls, buses, and
122 other public places or by shaking hands with an asymptomatic person. Therefore, care is needed
123 to avoid frequent touching of the face particularly mouth, nose and eyes irrespective of the use of
124 a mask.²⁵

125
126 The standard procedures recommended for preventing the spread of infection are more effective
127 in controlling the spread and keeping things safe. The most crucial strategies include washing of
128 hands after visiting public places and frequent exercises. Other practices involve overlaying
129 mouth and nostrils when coughing and sneezing to prevent the spread of the virus, assuming the
130 person is asymptomatic or in preliminary degrees of contamination.^{26,27} Also, proper cooking of
131 foods such as meat, eggs, and animals helps to destroy the virus. In practice, one needs to avoid
132 close contact with anyone showing symptoms of respiratory illnesses such as cough, flu, asthma,
133 pneumonia, and tuberculosis. Therefore, this simple precaution can be effectively carried out in
134 controlling the spread and containing the virus.

135 136 **The life cycle of SARS-CoV-2 (COVID-19) virus and infection**

137 Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism divided into 3 parts, namely
138 entry, replication, and release, as shown in Figure 2.

139 Firstly, the infection starts when the viral spike (S) glycoprotein attached to the complementary
140 host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-
141 attached spike protein. Depending on the availability of the host cell protease, cleavage and
142 activation allow cell entry by endocytosis or direct fusion of the viral envelop with the host
143 membrane.²⁸

144 On entry into the host cell, the virus is uncoated, and its genome enters the cell cytoplasm.²⁹ The
145 coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail, which allows the
146 RNA to attach to the host cell's ribosome for translation, and translates the initial overlapping of
147 the virus genome and forms a long polyprotein.³⁰ The polyprotein consists of
148 proteases which cleaves it into multiple nonstructural proteins.³¹

149 Secondly, coronaviruses replicates and transcripts RNA from the strand by using the SARS-
150 CoV-2 replication mechanism, which binds cell surface molecules such as metalloprotease
151 amino peptidase with hemagglutinin esterase (HE-protein) and N-acetyl neuraminic acid as co-
152 receptor. Furthermore, the virus goes into the host cell by fusion of viral and cell membranes or
153 through the receptor-mediated endocytosis incorporated via an endosome, which is subsequently
154 acidified by proton pumps. Meanwhile, the virus produces direct proteins and new genomes in
155 the cytoplasm, particularly single positive-stranded RNA gen. Otherwise, the negative strand
156 serves as a template used to transcribe smaller subgenomic positive RNAs used to synthesize all
157 other proteins. After binding, assembled nucleocapsids with twisted helical RNA, it enters into
158 the ER lumen and is encased with the membrane as shown in Figure 2.³²

159
160 Thirdly, the replicated positive-sense of genomic RNA becomes the genome of the progeny
161 viruses. The mRNAs are gene transcripts after the initial overlapping reading frame translated by
162 the host's ribosomes into the structural proteins.³¹ RNA translation occurs inside the endoplasmic
163 reticulum, which consists of S, E, and M proteins that move along the secretory pathway into the
164 Golgi intermediate compartment. Therefore, the M proteins are required to assemble and bind
165 the virus into the nucleocapsid.³³ Progeny viruses are released from the host cell
166 by exocytosis through secretory vesicles.³³

167

168 **Diagnosis**

169 The proper diagnosis characteristics used to manage COVID-19 is finding out the initiation of
170 the course of remedy. This is different from the common cold, which is properly treated with the
171 right drugs. Sometimes the results of preliminary examinations in infected people do not provide
172 a clear diagnosis of the infection, therefore, doctors tend to ask the patient to provide a detailed
173 and accurate diagnosis of their disease such as cough, flu, fever, and so on. The initial
174 intervention, sputum examination, and other diagnostic tests help to determine the infection
175 early. Also, the number of days from the infected date is noted at the laboratory to recommend
176 individual diagnostic tests as follows:

177

178 ***RT-PCR***

179 This is a standard technique for determining the virus by reverse transcription-polymerase chain
180 reaction (rRT-PCR) from a nasopharyngeal swab. A sputum sample is used to obtain the
181 required results within hours to 2 days.³⁴ Sample measurements (Swab test) consist of some steps
182 using RT-PCR, as shown in Figure 3.

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ELISA

Antibody assays are used to test infected people using their blood serum sample, with the results released with few days.³⁵

CT-Scan

The contamination is analyzed from a mixture of side effects, chance elements, and a chest CT scan demonstrating highlights of pneumonia.³⁶ The fundamental diagnosis reports from medical clinics in China show that majority of COVID-19 infected patients were determined using pneumonia and trademark CT imaging patterns.³⁷ Furthermore, radiological assessments have become imperative in early determination and appraisal of disease course.³⁸ CT scan of various COVID-19 contaminated patients differed in pattern³⁹, and almost 50% of patients were discovered from pictures. On admission to emergency clinics, the ground-glass haziness was the most widely recognized radiologic finding on chest figured tomography (CT)³⁹ of 56.4% of patients.⁴⁰ The longitudinal CT discovered infected patients with pneumonia with follow up checks over the course of treatment. Besides that, it was seen that numerous patients did not have strange radiologic findings.⁴¹

Treatments of COVID-19

The deadly nature of the spread of this virus increases fears in everyone. Therefore, there is an urgent demand from WHO and various countries to produce new COVID-19 treatment therapies. Infection caused by this disease is similar to SARS, and there is no drug that is scientifically proven for treatment. Countries only tend to reduce the spread by physical distancing and maintaining cleanliness. International organizations such as WHO have invited scientists from all over the world to work on developing vaccines, drugs, and diagnostic for SARS-CoV-2 and COVID-19. The Director-General of WHO has prioritized the main research to prevent the spread through the development of modern and herbal medicines for therapy and diagnosis and to easily identify active infections, asymptomatic and patients.³

The mechanism of viral infection is the entry of the virus into cells and multiplication using a host cellular method characterized by damages to the host cell as a key for the development of new drug compound therapies. Currently, there is no definitive and recommended therapy for COVID-19 because it is a new virus, and making a vaccine required numerous clinical analyses and tests. However, all antivirals used in COVID-19 therapy in almost all countries are still in the form of trial and error. Some countries have referred to the antiviral therapy used during the occurrence of the SARS and MERS epidemic several years ago, such as lopinavir, ritonavir, ribavirin, oseltamivir, etc. These drugs have been used and were quite effective in dealing with SARS and MERS during the epidemic.³ Similarly, there are no definitive guidelines for dealing with COVID-19 in Indonesia, as the country also relies on an existing drug such as oseltamivir. Indonesia has tried reaching out to China regarding the drugs used to treat their infected citizens, including the purchase of Chloroquine and Avigan. Some prospective drugs are considered to direct current applications or the development of new therapeutic drugs, including modern and herbal medicines.

Entry inhibitors

228 The SARS-CoV-2 virus infects the respiratory system and alveoli cells in the lung sac, which is
229 worse than the viral infection. In general, viruses enter the host cell by forming complex
230 projections such as spikes or lobes with receptors. However, the exact structure⁴² or lobe of
231 COVID-19 SARS-CoV-2 is not fully determined, although prior experience of coronavirus (β -
232 family), shows it has similarities with the host cells of SARS.⁴³ Recently it has been found that
233 Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-
234 CoV) and (SARS-CoV-2).⁴⁴ ACE2 has some homology with an angiotensin-converting enzyme
235 (ACE) although it is not inhibited by ACE. A previous SARS case was characterized by an
236 infection that was started by the transmembrane (S) spike in the glycoproteins binding the host
237 receptor and combines viruses to cell membranes. The identification of the viral / spikes lobes
238 molecular structure is time-consuming, while the development of facilitated heterocyclic drug
239 molecules or existing heterocyclic screening has the ability to bind the entry inhibitor drug.⁴⁵

240

241 ***Replication inhibitors***

242 COVID-19 is an RNA virus that utilizes host cells for genomic replication by encoding the
243 RNA-dependent protein polymerase (RdRp), which allows the viral genome to be transcribed
244 into the host membrane cells. The viral genome replication mechanism serves potential targets
245 for the control of viral infections, while antiviral drugs such as Remdesivir and Favipiravir
246 (Avigan)⁴⁶ has the ability to potentially effective SARS-CoV-2 as shown in Figures 4A and B.
247 The nucleotide adenosine analogue antiviral for Ebola and RNA viruses have shown some
248 promising results in the clinical control of this virus.⁴⁷ However, further evaluation is needed for
249 potential applications with more patients. Many other nucleoside analogues including DNA
250 synthesis such as tenofovir, disoproxil, lamivudine, and other antivirals have the potential to
251 inhibit the multiplication of SARS-CoV-2 viruses and are being evaluated through molecular
252 docking studies and testing in infected cell culture⁴⁸. The action mechanism of Remdesivir as
253 antiviral drug as shown in Figure 5.

254

255 Avigan is the patent name for favipiravir, also known as T-705, which is an antiviral drug
256 developed by Toyama Chemical, a Fujifilm group, located in Japan with activity against many
257 RNA viruses. In Japan, this drug was originally developed to treat cold, however, in February
258 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel coronavirus)
259 disease. The action mechanism of favipiravir inhibits the synthesis of viral RNA polymerase
260 selectively, as shown in Figure 6.⁴⁹ Further studies have shown that favipiravir induces mutant of
261 RNA transversion, resulting in a viable viral phenotype. This product is metabolized by human
262 hypoxanthine-guanine phosphoribosyltransferase (HGPRT) known as favipiravir-ribofuransyl-
263 5-triphosphate (favipiravir-RTP). This drug is available in oral and intravenous formulations and
264 does not inhibit the synthesis of RNA or DNA in mammalian cells, and it is not toxic. In 2014,
265 favipiravir was approved in Japan as a backup drug against influenza pandemics and to treat
266 viruses that were not responsive to antiviral at the time. During this COVID-19 pandemic, in a
267 limited clinical trial with 80 subjects, favipiravir showed an antiviral potential for SARS-CoV-2
268 that was better than lopinavir/ritonavir.⁵⁰ In March 2020, the Chinese Government stated that
269 favipiravir appeared to be effective in overcoming COVID-19.

270

271 ***Protease inhibitors***

272 Protease enzymes are involved within the maturation stage of virus replication inside the host
273 mobile and related to protein or peptide translation. Figures 4C and D, shows that Lopinavir and

274 ritonavir are approved anti-HIV drugs, and a combination of both aids in the inhibition of SARS-
275 CoV-2.^{51,52} A research carried out by Lim J et.al. on the remedy used to treat persons affected
276 with COVID-19 in Korea indicated that the administration of lopinavir/ritonavir (Kaletra,
277 AbbVie) extensively reduced the virus.⁵² This means that a detailed analysis is needed for the
278 recommendation of this drug and the formation of new drug compounds. Molecular docking of
279 potential inhibitors provide clear information because detailed docking simulation results have
280 shown important input in previous SARS cases and other viral infections.⁵³⁻⁵⁵ However, a lot of
281 clinical data needs to be conducted to prove the efficacy and safety of the human body.

282

283 *Heterocyclic antiviral*

284 Over the decades, many heterocyclic drug molecules have been used in the treatment of viral
285 infections, and these drugs are thought to be probably slightly effective in inhibiting SARS-CoV-
286 2. An example is Chloroquine, which was originally an antiplasmodium used to treat malaria.
287 This drug contains a quinoline group as shown in Figure 4E and inhibits the activity of the
288 enzyme heme polymerase into hemozoin. This accumulation kills the Plasmodium parasite
289 responsible for malaria.⁵⁶ However, with the decrease in malaria and the emergence of
290 plasmodium resistance to Chloroquine, this drug is no longer used. Also, Chloroquine and
291 hydroxychloroquine are used for antiviral therapy. Gao et al. (2020) stated that Chloroquine has
292 a strong antiviral effect against the virus in primate cells. This inhibitory effect is observed when
293 cells are treated with Chloroquine both before and after exposure, which shows that it has a
294 preventive and therapeutic effect. In addition, the endosomal pH which inhibits viral replication
295 interacts with cellular ACE2 receptors as shown in Figure 7.^{57,59} This inhibits the receptor which
296 prevent infection and spread of the SARS-CoV-2 at concentrations that cause clinical symptoms.
297 In the SARS-CoV-2 pandemic in China, Chloroquine was used at a dose of 500 mg for adult 2
298 times a day, for 10 days.⁵⁸ Chloroquine and hydroxychloroquine are also currently being tried in
299 Malaysia at the same dosage used in China and Indonesia.

300

301 There are several heterocyclic antiviruses previously used as antivirals such as HIV, H1N1,
302 H1N5, and SARS, which are further examined for the treatment of COVID-19. Oseltamivir
303 (Tamiflu) has been widely used as a neuraminidase inhibitor for the treatment of influenza was
304 also recommended.⁵⁹ In addition, other candidate compounds evaluated with antiviral activity
305 against SARS-CoV-2 are heterocyclic based on ACE2 peptides namely 3CLpro inhibitors
306 (3CLpro-1) and vinyulfone protease inhibitors.⁶⁰ According to Mourse et al. the combination of
307 hydroxychloroquine and azithromycin to treat the virus, shows that it is significantly associated
308 with viral load reduction on clinical study.⁶¹

309

310 **Nano drug delivery systems**

311 Drug delivery systems in the form of nanoparticle preparations have been widely used to
312 improve the bioavailability in the blood. The use of antiviral especially nucleoside analogues in
313 conjugate with potential delivery systems that have been applied in resistant HIV infection
314 drugs.⁶²⁻⁶⁵ It is accumulated in the nano delivery system and used as a new drug to deliver drugs
315 with a faster therapeutic index for COVID-19.⁶⁶⁻⁶⁸ One example of delivery of nano treatment is
316 seen in the efficacy of Chloroquine against COVID-19 as an inhibitor of nanoparticle
317 endocytosis through macrophages. Therefore, Chloroquine decreases the accumulation of
318 synthetic nanoparticle of various sizes (14-2,600 nm) and is spherical and discoidal in cell
319 lines.⁶⁹

320

321 **Biological therapeutics**

322 Antibody therapy can be used for the treatment of COVID-19 infections. However, this vaccine
323 still requires approximately 1 year before it can be globally utilized to prevent the spread of the
324 virus. According to Tian et al. specific human monoclonal antibodies such as CR3022 are
325 intended to bind strongly to SARS-CoV-2 RBD (KD 6.3 nM) and overlap the ACE2 binding
326 site.⁷⁰ These unique results indicate the possibility of developing a therapeutic vaccine with a
327 combination of other antibodies. However, *in vitro* trials and clinical studies are needed to obtain
328 accurate clinical data for the prevention and treatment of COVID-19 infections.⁷⁰

329

330 In developing a new vaccine one must pay attention to the similarity of immunogenic structural
331 proteins similar to SARS, MERS for SARS-CoV-2.⁷¹ Ahmed et al. used a set of B and T cell
332 epitopes derived from spikes (S) and nucleocapsid proteins (N) to identically map the SARS-
333 CoV-2 protein.⁷² Reports suggested that the identified epitope has no available mutase sequence.
334 Therefore, this target immune epitope has the potential to be explored in the fight against the
335 SARS-CoV-2. However, the final results depend on *in vitro* and future clinical trials.⁷²

336

337 **Herbal drugs**

338 Several anti-SARS agents have been tested for coronavirus-specific therapy, however, none is
339 effective.⁷³⁻⁷⁵ Some modern drugs have shown a broad antiviral activity, which is most
340 frequently administered as a SARS-antiviral agent in combination with antibacterial drugs.
341 However, this has little activity against SARS-CoV *in vitro* with specific monoclonal antibodies,
342 pegylated interferon- α , siRNA, and several protease inhibitors.⁷⁶ Therefore, various studies have
343 been conducted on the use of herbal drugs to test several patients in Indonesia.

344

345 The chemical compounds contained in UI and IPB, which originated from several plants in
346 Indonesia, they have the potential ability to prevent COVID-19 infection in the form of
347 molecular docking *in silico*. The model of research that has been conducted is shown in Figure 8.
348 Based on the results of prediction models with machine learning methods, namely SVM, random
349 forest, and MLP neural network is associated with 20644 interactions of protein compounds. The
350 results are 31 herbal compounds with 5 target proteins 3CLPro, PLPro, Spike-ACE2, EIF4, and
351 RdRp. Modeling of structure and ligand based pharmacophores was used to carry out virtual
352 screening with 1,377 compounds from the HerbalDB database.⁷⁷ The results of compound hit
353 from machine learning, and pharmacophore mapping was confirmed using molecular docking.

354

355 Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin,
356 quercetin, luteolin, kaempferol, isorhamnetin⁷⁸, and hesperidin⁷⁹. Luteolin is a furin protein
357 inhibitor⁸⁰ and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein
358 in MERS into units of S1 and S2.⁸¹ In the S1 unit, there is a receptor-binding domain (RBD)
359 where the ACE2 peptidase binds the virus in the host cell.⁸¹ The Hesperidin/hesperitin compound
360 in the *in silico* study inhibits the RBD domain binding of the SARS-COV-2 Spike protein with
361 ACE2 receptors in humans s.⁸² It is also known that luteolin is a neuramidase inhibitor as well as
362 oseltamivir which is currently one of the drugs used in the CDC protocol.

363

364 Hesperidin a form of hesperidin aglycone and Quercetin is also known to act as inhibitors of
365 3CLpro virus proteins.^{83,84} Other compounds in guava such as myricetin act as SARS

366 coronavirus helicase inhibitors.⁸⁵ The kaempferol has the potential to be a non-competitive
367 inhibitor of 3CLPro and PLpro as well as quercetin.⁸⁶ It also acts as a autophagy modulator,
368 inducer and inhibitor, of the virus.

369
370 Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived
371 from plants. One of the commonly used condiments for cooking or herbal medicine in Indonesia
372 is empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. Furthermore,
373 animals such as snakehead fish also improve immune system in the body due to high protein and
374 amino acids.⁸⁷⁻⁸⁹ According to UNAIR researchers stated that the approach that can be taken in
375 the public by consuming empon-empon to boost the immune system to avoid COVID-19.⁹⁰

376
377 Herbs containing curcumin and turmeric have been consumed and proven by Indonesian for
378 centuries and beneficial to health. For example it is used to maintain fitness vitality, liver, and
379 digestive systems based on empirical experimental evidence. Both ginger and turmeric contain
380 hundreds of bioactive compounds, one of which is curcumin. Various studies have been carried
381 out in the world in vitro and preclinical tests showing that curcumin is anti-inflammatory,
382 antiviral, antibacterial, antifungal, and antioxidant based on scientific evidence.^{91, 92}

383
384 One of the benefits of curcumin obtained from clinical trials is to increase the body's immune
385 system. Recent research on curcumin against the virus shows that the SARS-CoV-2 receptor is
386 an enzyme ACE2 found in host cells of human especially alveolus lungs. However, the cell entry
387 of the virus depends on the binding of the spike virus protein, the receptor on the host cell
388 (ACE2) and pad priming protein spike (TMPRSS2). There are 2 forms of ACE2, the fixed
389 attached to the cell surface and the free-form soluble in the blood. The soluble ACE2 is projected
390 to be one of the SARS-CoV-2 antiviral candidates through a competitive interceptor mechanism,
391 which prevents bonding between virus particles on the surface of the host cell. In addition, bio-
392 informatics research published in March 2020 and recent literature has mentioned curcumin as
393 one of the SARS-CoV-2 antiviral candidates. The curcumin in ginger and turmeric increase the
394 expression of ACE2 in the form of soluble which inhibit the bonding between the viral protein
395 and the fixed form ACE2 found on the surface of the host cell.⁹³

396
397 **Conclusion**

398 In conclusion, the sudden outbreak of COVID-19 in Wuhan, China, has led to a worldwide panic
399 due to its rapid spread with the mortality rate. The WHO, in 2020, declared the virus a
400 pandemic, therefore, every country has an obligation to protect its people by educating them with
401 the right preventive measures. In many new cases, clinical staffs are infected from patients that
402 visit the hospitals, thereby increasing the spread of the virus through human-to-human
403 transmission. Hence there is an urgent need for the development and approval of a standard
404 therapy protocol, including structural details and a complete life cycle of the virus, to prevent the
405 spread. Several drugs have been clinically evaluated for the treatment of COVID-19, which
406 showed promising results and assisted a number of patients to recover safely. However, further
407 knowledge of SARS-CoV-2 advances, new therapies, including vaccines and monoclonal
408 antibodies, are needed for proper treatment in the near future. Although the effective treatments
409 for COVID-19 are unknown, there is continuous research on the potential of therapeutics in
410 evaluating the existing antiviral drugs such as modern and herbal medicines.

411

412 **Conflict of interests**

413 The authors claim that there is no conflict of interest.

414

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- 660
- 661

662 **Table 1.** Active compounds having the potential as antiviral SARS-CoV-2⁹⁰

663	Target	Compounds	Sources
664	3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	<i>Cassia alata</i> ,30
665		Kaempferol 3,4'-di-O-methyl ether (Ermanin)	<i>Tanacetum microphyllum</i>
666		Cyanidine 3-sophoroside-5-glucoside	<i>Brassica oleracea</i> ; <i>Ipomoea</i>
667			<i>batatas</i> ; <i>Raphanus sativus</i>
668		Casuarinin	<i>Psidium guajava</i>
669		Quercetin 3-(2G-rhamnosylrutinoside)	<i>Clitoria ternatea</i>
670		Peonidine 3-(4'-arabinosylglucoside)	<i>Ipomoea fistulosa</i>
671		Hesperidine	<i>Psidium guajava</i>
672			<i>Citrus aurantium</i>
673		PLpro	Platycodin D
674	Baicalin		<i>Scutellaria baicalensis</i>
675	Sugetriol-3,9-diacetate		<i>Cyperus rotundus</i>
676	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone		<i>Isatis indigotica</i>
677	(-)-epigallocatechin gallate		<i>Camellia sinensis</i>
678	2-93,4-Dihydroxyphenyl)-2-[2-(3,4-		
679	Dihydroxyphenyl)-3,4-dihydro-5,7-dihidroksi-2H-		<i>Vitis vinifera</i>
680	1-benzopyran-3-yl]-3,4-dihydro-2H-1-benzopyran-		
681	3,4,5,7-tetrol		
682	RdRp.	Betulanol	<i>Cassine xylocarpa</i>
683		Gnidicin	<i>Gnidia lamprantha</i>
684		2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	<i>Viola diffusa</i>
685		14-deoxy-11,12-didehydroandrographolide	<i>Andrographis paniculata</i>
686		1,7-dihydroxy-3-methoxyxanthone	<i>Swerti apseudochinensis</i>
687		Theaflacin 3,3'-di-O-gallate	<i>Camelia sinensis</i>
688		2-(3,4-dihydrophenyl)-2-[(2-3,4-dihydroxyphenyl)-	
689		3,4-dihydro-5-7-dihydroxy-2H-1-benzopyran-	<i>Vitis vinifera</i>
690		3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	
691		Spike-ACE2	Hesperidine
692			<i>Citrus aurantium</i>
693			

1 Abstract

2 A recent outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease
3 also called Coronavirus disease 2019 (COVID-19) in China, has rapidly spread to other countries
4 of the world. The medical and scientific communities are working tirelessly to produce a vaccine
5 due to the lethal nature of this virus. COVID-19 is a novel virus that requires immediate
6 emergency therapy, thereby leading to massive fear of infection, social problems in the
7 community, and an increase in the number of infected people. Therefore, scientists and
8 researchers need to determine the epidemiological cases of the virus, such as its mode of
9 transmission, effective preventive measures, and the nature of the life cycle. In addition, there
10 need to be current literature advances in diagnostic development such as reverse transcription
11 polymerase chain reaction (RT-PCR), computed tomography scan (CT-Scan), Elisa as well as
12 clinical researches on modern and herbal drugs for the treatment of infected patients. This
13 treatment technique is classified from antiviral drugs such as entry, replication, nucleosides,
14 nucleotides, and protease inhibitors, along with the use of heterocyclic drugs, monoclonal
15 antibodies therapy, vaccine development and herbal formulations that have been pre-clinically
16 tested *in vitro* and molecular docking. Chemical drug molecules with prospective applications in
17 the treatment of COVID-19 have been included in this review.

18 **Keywords:** COVID-19, antiviral, infection, herbal, modern drugs, pandemic

20 Introduction

21 In December 2019, the Chinese city of Wuhan experienced a rapid spread in an infectious
22 disease, which affected the respiratory system, thereby leading to a high mortality rate. This
23 virus, known as Coronavirus disease 2019 (COVID-19), soon spread to other countries and was
24 declared a pandemic by the World Health Organization (WHO).¹ Infected people show
25 symptoms of pneumonia, which is similar to SARS (Severe Acute Respiratory Syndrome). This
26 disease is caused by a lethal virus in nature and is currently the highest leading cause of mortality
27 all over the world.² The first reported case was in China, and within a few months, it has spread
28 to almost all countries and continents in the world.² According to studies, the most significant
29 numbers of cases of infected people are in South Korea, Italy, Iran, South Africa, the USA, and
30 Indonesia. In a recent update by WHO, over 90,000 people all over the world are infected with
31 approximately 3,000 deaths. China alone recorded 2,500 deaths by the end of February 2020.³

33 The WHO declared the virus a pandemic due to its rapid spread in various countries. It is
34 speculated that this virus originated from different animals consumed as food in China. Early
35 transmission studies reported that it originated from local fish and wild animal markets with
36 possible transmission from animals to humans and vice versa. However, this speculation has not
37 been proven. This disease has led to a very high increase in mortality all over the world.⁴

39 In Indonesia, the virus was not in existence till the end of April 2020, based on data from the
40 Ministry of Health. Since its inception, there has been a rapid increase in the mortality rate due to
41 the high number of infected people.⁵ Therefore, based on these data, the Indonesian government
42 quickly responded and took preventive measures to reduce the spread of this virus. Before now,
43 no drug or vaccine has been proven to kill or inhibit the COVID-19 virus. However, WHO
44 announced that over 20 countries and pharmaceutical companies around the world are
45 developing vaccines and drugs to fight the virus.⁶ Unfortunately, this development is going to
46 take at least a year before completion. Meanwhile, several types of modern and herbal COVID-

47 19 treatments have been clinically tested, such as Remdesivir and Chloroquine, as well as
48 curcumin (*in vitro* study).

49
50 The emergence and rapid spread of this virus have hastened the development of diagnosis and
51 medicines for the treatment of this infectious disease. In Indonesia, doctors have used several
52 existing modern and herbal medicines, with national and international health institutions, to
53 understand the mechanism, virulence, and pharmacology of the virus to develop possible drugs
54 and vaccines. This review discusses the literature report on progress regarding diagnostic
55 methods and developmental therapies with the possible use of candidate compounds of modern
56 and herbal medicines for COVID-19 infectious diseases in Indonesia.

57

58 **The Coronaviruses**

59 Coronavirus, a genus of the Coronaviridae family, is a positive-strand and the most significant
60 viral genome of all RNA viruses (27–32 kb), causing a wide range of diseases related to the
61 respiratory system. The symptoms may vary from the common cold, dry cough to more severe
62 respiratory diseases.⁷ Furthermore, it consists of 80 to 160 nm particles, 4 or 5 structural spike
63 (S), membrane (M), hemagglutinin-esterase (HE), nucleocapsid (N), and small envelope E
64 proteins.⁸ In addition, the virion structure consists of S glycoprotein, which forms petal-shaped
65 spikes on the surface with 180 to 200 KDa molecule that is cotranslationally glycosylated in the
66 endoplasmic reticulum as shown in Figure 1.⁸ SARS-CoV-2 was an new strain of the current
67 virus,^{9,10} which was transmitted from animals to human¹¹, however, the new coronavirus infects
68 humans.

69

70 **COVID-19 transmission**

71 COVID-19 spreads rapidly amongst humans with symptoms and asymptomatic carriers. The
72 virus is easily spread when the liquid droplet of an infected person drops on surfaces when the
73 patient coughs or sneezes. Transmission in certain cases is usually through the air, by staying
74 close to an infected person.¹² Meanwhile, asymptomatic patients are hidden carriers of the virus
75 and contribute to a greater transmission of the virus. This manual transmission also spread,
76 assuming the patient has symptoms.³ In addition, vertical transmission of the virus from mother
77 to child has not been observed according to research conducted by Chen H et al. in a small group
78 of pregnant women. They stated that the virus is vertically intrauterine and non-transmittable
79 from mothers to unborn babies. The emergence and the spread of this new virus is due to the
80 increase in human populations which causes proximity.^{13,14}

81

82 **Symptoms and mortality of COVID-19**

83 Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to acute
84 respiratory distress syndrome (ARDS), which marked respiratory infections on COVID-19
85 patients. These include runny nose, fever, cough, shortness of breath, sore throat, and mild to
86 moderate upper respiratory tract illness. In severe cases, patients experience pneumonia, SARS,
87 kidney failure, and even death. An infected patient shows full signs of the virus within two to
88 seven days. However, the median incubation duration of infection development changed to 4
89 days with an interquartile variety of 2 to 7 days in all patients.¹⁵ This is known as the incubation
90 period which progresses for four days with an interquartile range.²¹

91

92 **Study** conducted by Guan et al. showed the middle-aged were more prone to infection compared
93 to other categories of people.¹⁶ Approximately 41.9% of the total number of patients were
94 women, therefore, there are gender differences in the spread of the virus. The report also stated
95 that the primary composite endpoint occurred in 6% of patients. In Wuhan city, **there was** no
96 gender difference in people infected with COVID-19 with the highest mortality rates of 8.4% by
97 20 March 2020.^{17,18} However, research shows that the elderly and young children are most at risk
98 from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal compared
99 to SARS and MERS, this is because approximately 15 to 20% of cases become severe within a
100 limited timeframe. According to doctors, the lethal rate is about 1 in 10 which caused by
101 enveloped virus meaning that it is protected by a glycoprotein shell, thereby, making it difficult
102 to treat.¹⁹

103

104 **Preventive measures**

105 All countries, including Indonesia, need preventive measures to overcome the spread of COVID-
106 19, which currently has no known cure and vaccines. Therefore, handling infected patients has
107 been recommended as one of the steps to control the rampant spread of the virus among people.
108 However, it is difficult to force the isolation of infected patients because this causes many social
109 problems. Like many reports in the Indonesian media, the practice of forced confinement of
110 infected people at home is very difficult for health workers and the police. The isolation of
111 infected individuals supported the provision of complete hospital treatment is one of the moral
112 control methods.²² Therefore, appropriate research studies need to be conducted to understand
113 the best approach in infection prevention including assessing the country's ability to slow the
114 spread of infected people.²³

115

116 In Indonesia, the standard procedures recommended for preventing the spread of infection are
117 more effective in controlling the spread and keeping things safe. The most crucial strategies
118 include washing of hands after visiting public places and frequent exercises.^{24,25} Other practices
119 involve overlaying mouth and nostrils when coughing and sneezing to prevent the spread of the
120 virus, assuming the person is asymptomatic or in preliminary degrees of contamination.^{26,27} Also,
121 proper cooking of foods such as meat, eggs, and animals helps to destroy the virus. In practice,
122 one needs to avoid close contact with anyone showing symptoms of respiratory illnesses such as
123 cough, flu, asthma, pneumonia, and tuberculosis. Therefore, this simple precaution can be
124 effectively carried out in controlling the spread and containing the virus.

125

126

127 **The life cycle of SARS-CoV-2 and infection**

128 Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism divided into 3 parts, namely
129 entry, replication, and release, as shown in Figure 2.

130 Firstly, the infection starts when the viral spike (S) glycoprotein attached to the complementary
131 host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-
132 attached spike protein. Depending on the availability of the host cell protease, cleavage and
133 activation allow cell entry by endocytosis or direct fusion of the viral envelop with the host
134 membrane.²⁸

135 On entry into the host cell, the virus is uncoated, and its genome enters the cell cytoplasm.²⁹ The
136 coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail, which allows the
137 RNA to attach to the host cell's ribosome for translation, and translates the initial overlapping of

138 the virus genome and forms a long polyprotein.³⁰ The polyprotein consists of
139 proteases which cleaves it into multiple nonstructural proteins.³¹

140 Secondly, coronaviruses replicates and transcripts RNA from the strand by using the SARS-
141 CoV-2 replication mechanism, which binds cell surface molecules such as metalloprotease
142 amino peptidase with hemagglutinin esterase (HE-protein) and N-acetyl neuraminic acid as co-
143 receptor. Furthermore, the virus goes into the host cell by fusion of viral and cell membranes or
144 through the receptor-mediated endocytosis incorporated via an endosome, which is subsequently
145 acidified by proton pumps. Meanwhile, the virus produces direct proteins and new genomes in
146 the cytoplasm, particularly single positive-stranded RNA gen. Otherwise, the negative strand
147 serves as a template used to transcribe smaller subgenomic positive RNAs used to synthesize all
148 other proteins. After binding, assembled nucleocapsids with twisted helical RNA, it enters into
149 the **endoplasmic reticulum** (ER) lumen and is encased with the membrane as shown in Figure
150 2.³²

151
152 Thirdly, the replicated positive-sense of genomic RNA becomes the genome of the progeny
153 viruses. The mRNAs are gene transcripts after the initial overlapping reading frame translated by
154 the host's ribosomes into the structural proteins.³¹ RNA translation occurs inside the endoplasmic
155 reticulum, which consists of S, E, and M proteins that move along the secretory pathway into the
156 Golgi intermediate compartment. Therefore, the M proteins are required to assemble and bind
157 the virus into the nucleocapsid.³³ Progeny viruses are released from the host cell
158 by exocytosis through secretory vesicles.³³

159

160 **Diagnosis**

161 **The proper diagnosis characteristics used to manage COVID-19 is the first line of control and a**
162 **deciding factor in the initiation of the course of treatment.** This is different from the common
163 cold, which is properly treated with the right drugs. Sometimes the results of preliminary
164 examinations in infected people do not provide a clear diagnosis of the infection, therefore,
165 doctors tend to ask the patient to provide a detailed and accurate diagnosis of their disease such
166 as cough, flu, fever, and so on. **The identifying and providing effective support,** sputum
167 examination, and other diagnostic tests help to determine the infection early. Also, the number of
168 days from the infected date is noted at the laboratory to recommend individual diagnostic tests as
169 follows:

170

171 ***Reverse transcription-polymerase chain reaction (RT-PCR)***

172 This is a standard technique for determining the virus by rRT-PCR from a nasopharyngeal swab.
173 A sputum sample is used to obtain the required results within hours to 2 days.³⁴ Sample
174 measurements (Swab test) consist of some steps using RT-PCR, as shown in Figure 3.

175

176 ***Enzyme-linked immunosorbent assay (ELISA)***

177 Antibody assays are used to test infected people using their blood serum sample, with the results
178 released with few days.³⁵

179

180 ***Computerized-Tomography (CT-Scan)***

181 The contamination is analyzed from a mixture of side effects, chance elements, and a chest CT
182 scan demonstrating highlights of pneumonia.³⁶ The fundamental diagnosis reports from medical
183 clinics in China show that majority of COVID-19 infected patients were determined using

184 pneumonia and trademark CT imaging patterns.³⁷ Furthermore, radiological assessments have
185 become imperative in early determination and appraisal of disease course.³⁸ CT scan of various
186 COVID-19 contaminated patients differed in pattern³⁹, and almost 50% of patients were
187 discovered from pictures. On admission to emergency clinics, the ground-glass haziness was the
188 most widely recognized radiologic finding on chest figured tomography (CT)³⁹ of 56.4% of
189 patients.⁴⁰ The longitudinal CT discovered infected patients with pneumonia with follow up
190 checks over the course of treatment. Besides that, it was seen that numerous patients did not have
191 strange radiologic findings.⁴¹

192

193 **Treatments of COVID-19**

194 The mechanism of viral infection is the entry of the virus into cells and multiplication using a
195 host cellular method characterized by damages to the host cell as a key for the development of
196 new drug compound therapies. Currently, there is no definitive and recommended therapy for
197 COVID-19 because it is a new virus, and making a vaccine required numerous clinical analyses
198 and tests. One of examples of treatment therapy i.e. convalescent plasma therapy which is the
199 administration of plasma from a recovered Covid-19 patient to a Covid-19 patient who is still
200 suffering from illness, so antibodies (immunity) in the plasma of the cured patient can help
201 patients who are still ill to cope with the disease.^{3,41} However, all antivirals used in COVID-19
202 therapy in almost all countries are still in the form of trial and error. Some countries have
203 referred to the antiviral therapy used during the occurrence of the SARS and MERS epidemic
204 several years ago, such as lopinavir, ritonavir, ribavirin, oseltamivir, etc. These drugs have been
205 used and were quite effective in dealing with SARS and MERS during the epidemic.³ Similarly,
206 there are no definitive guidelines for dealing with COVID-19 in Indonesia, as the country also
207 relies on an existing drug such as oseltamivir. Indonesia has tried reaching out to China
208 regarding the drugs used to treat their infected citizens, including the purchase of Chloroquine
209 and Avigan. Some prospective drugs are considered to direct current applications or the
210 development of new therapeutic drugs, including modern and herbal medicines.

211

212 ***Entry inhibitors***

213 The SARS-CoV-2 infects the respiratory system and alveoli cells in the lung sacs would be the
214 **host for viral infection**. In general, viruses enter the host cell by forming complex projections
215 such as spikes or lobes with receptors. However, the exact structure or lobe of SARS-CoV-2 is
216 not fully determined,⁴² although prior experience of coronavirus (β -family), shows it has
217 similarities with the receptor of host cells of SARS.⁴³ Recently it has been found that
218 Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-
219 CoV) and (SARS-CoV-2).⁴⁴ ACE2 has some homology with an angiotensin-converting enzyme
220 (ACE) although it is not inhibited by **ACE inhibitors**.⁵ A previous SARS case was characterized
221 by an infection that was started by the transmembrane (S) spike in the glycoproteins binding the
222 host receptor and combines viruses to cell membranes. The identification of the viral / spikes
223 lobes molecular structure is time-consuming, while the development of facilitated heterocyclic
224 drug molecules or existing heterocyclic screening has the ability to bind the entry inhibitor
225 drug.⁴⁵

226

227 ***Replication inhibitors***

228 COVID-19 is an RNA virus that utilizes host cells for genomic replication by encoding the
229 **RNA-dependent RNA polymerase (RdRp)**, which allows the viral genome to be transcribed into

230 new RNA copies using the host cell's machinery. The viral genome replication mechanism
231 serves potential targets for the control of viral infections, while antiviral drugs such as
232 Remdesivir and Favipiravir (Avigan)⁴⁶ has the ability to potentially affect SARS-CoV-2 as
233 shown in Figures 4A and B. The nucleotide adenosine analogue antiviral for Ebola and RNA
234 viruses have shown some promising results in the clinical control of this virus.⁴⁷ However,
235 further evaluation is needed for potential applications with more patients. The action mechanism
236 of Remdesivir as antiviral drug as shown in Figure 5.

237
238 Favipiravir is the brand name for Avigan, also known as T-705, which is an antiviral drug
239 developed by Toyama Chemical, a Fujifilm group, located in Japan with activity against many
240 RNA viruses. In Japan, this drug was originally developed to treat influenza, however, in
241 February 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel
242 coronavirus) disease. The action mechanism of favipiravir can inhibit replication and translation
243 of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses, as shown in Figure
244 6.⁴⁸ Further studies have shown that favipiravir induces mutant of RNA transversion, resulting in
245 a viable viral phenotype. This product is metabolized by human hypoxanthine-guanine
246 phosphoribosyltransferase (HGPRT) known as favipiravir-ribofuranosyl-5-triphosphate
247 (favipiravir-RTP). During this COVID-19 pandemic, in a limited clinical trial with 80 subjects,
248 favipiravir showed an antiviral potential for SARS-CoV-2 that was better than
249 lopinavir/ritonavir.⁴⁹ Many other nucleoside analogues including DNA synthesis such as
250 tenofovir, disoproxil, lamivudine, and other antivirals have the potential to inhibit the
251 multiplication of SARS-CoV-2 and are being evaluated through molecular docking studies and
252 testing in infected cell culture.⁵⁰

253 254 **Protease inhibitors**

255 Protease enzymes are involved within the maturation stage of virus replication inside the host
256 cell and related to protein or peptide translation. Figures 4C and D, shows that Lopinavir and
257 ritonavir are approved anti-HIV drugs, and a combination of both aids in the inhibition of SARS-
258 CoV-2.^{51,52} A research carried out by Lim J et.al. on the remedy used to treat persons affected
259 with COVID-19 in Korea indicated that the administration of lopinavir/ritonavir (Kaletra,
260 AbbVie) extensively reduced the virus.⁵² This means that a detailed analysis is needed for the
261 recommendation of this drug and the formation of new drug compounds. Molecular docking of
262 potential inhibitors provide clear information because detailed docking simulation results have
263 shown essential input in previous SARS cases and other viral infections.⁵³⁻⁵⁵ However, a lot of
264 clinical data needs to be conducted to prove the efficacy and safety of the human body.

265 266 **Heterocyclic antiviral**

267 Over the decades, many heterocyclic drug molecules have been used in the treatment of viral
268 infections, and these drugs are thought to be probably slightly effective in inhibiting SARS-CoV-
269 2. An example is Chloroquine, which was originally an antiplasmodium used to treat malaria.
270 This drug contains a quinoline group as shown in Figure 4E and inhibits the activity of the
271 enzyme heme polymerase into hemozoin. This accumulation kills the Plasmodium parasite
272 responsible for malaria.⁵⁶ However, with the decrease in malaria and the emergence of
273 plasmodium resistance to Chloroquine, this drug is no longer used. Also, Chloroquine and
274 hydroxychloroquine are used for antiviral therapy. Gao et al. (2020) stated that Chloroquine has
275 a strong antiviral effect against the virus in primate cells. This inhibitory effect is observed when

276 cells are treated with Chloroquine both before and after exposure, which shows that it has a
277 preventive and therapeutic effect. In addition, Chloroquine and hydroxychloroquine are weak
278 bases that are known to elevate the pH of acidic intracellular organelles, such as
279 endosomes/lysosomes, essential for membrane fusion inhibiting SARS-CoV-2 entry through
280 changing the glycosylation of ACE2 receptor and spike protein, shown in Figure 7.^{57,59} This
281 inhibits the receptor which prevent infection and spread of the SARS-CoV-2 at concentrations
282 that cause clinical response. In the SARS-CoV-2 pandemic in China, Chloroquine was used at a
283 dose of 500 mg for adult 2 times a day, for 10 days.⁵⁸ Chloroquine and hydroxychloroquine are
284 also currently being tried in Malaysia at the same dosage used in China and Indonesia.

285
286 There are several heterocyclic antiviruses previously used as antivirals such as HIV, H1N1,
287 H1N5, and SARS, which are further examined for the treatment of COVID-19. Oseltamivir
288 (Tamiflu) has been widely used as a neuraminidase inhibitor for the treatment of influenza was
289 also recommended.⁵⁹ In addition, other candidate compounds evaluated with antiviral activity
290 against SARS-CoV-2 are heterocyclic based on ACE2 peptides namely 3C-like protease
291 (3CLpro and 3CLpro-1) inhibitors and vinylsulfone protease inhibitors.^{60,61}

292
293 **Nano drug delivery systems**
294 Drug delivery systems in the form of nanoparticle preparations have been widely used to
295 improve the bioavailability in the blood and enhance the transport and efficacy antiviral drugs
296 especially nucleoside analogues on conjugation with potential delivery systems that have been
297 proven in drug-resistant HIV infection.⁶²⁻⁶⁵ The wide variety of available nano delivery system
298 can be used with the new developed drug formulation which could be efficacious in delivering
299 the drugs with faster therapeutic indices for COVID-19.⁶⁶⁻⁶⁸

300
301 **Biological therapeutics**
302 Antibody therapy can be used for the treatment of COVID-19 infections. However, this vaccine
303 still requires approximately 1 year before it can be globally utilized to prevent the spread of the
304 virus. According to Tian et al. specific human monoclonal antibodies such as CR3022 are
305 intended to bind strongly to SARS-CoV-2 receptor binding domain (RBD) (KD 6.3 nM) and
306 overlap the ACE2 binding site.⁷⁰ These unique results indicate the possibility of developing a
307 therapeutic vaccine with a combination of other antibodies. However, *in vitro* trials and clinical
308 studies are needed to obtain accurate clinical data for the prevention and treatment of COVID-19
309 infections.⁷⁰

310
311 In developing a new vaccine one must pay attention to the similarity of immunogenic structural
312 proteins similar to SARS, MERS for SARS-CoV-2.⁷¹ Ahmed et al. used a set of B and T cell
313 epitopes derived from spikes (S) and nucleocapsid proteins (N) to identically map the SARS-
314 CoV-2 protein.⁷² Reports suggested that the identified epitope has no available mutase sequence.
315 Therefore, this target immune epitope has the potential to be explored in the fight against the
316 SARS-CoV-2. However, the final results depend on *in vitro* and future clinical trials.⁷²

317
318 **Herbal drugs**
319 The herbal formulations used as alternative medication has been a success in presenting the
320 remedy to a number of infections in conjunction with symptom specific remedy using herbs.⁷³⁻⁷⁵
321 The initial lead from herbal medicinal drug has been successful in developing final applicable

322 formulations like Praneem (a natural extract of neem tree) as microbicide for HIV therapy.⁷⁶
323 Therefore, various studies have been conducted on the use of herbal drugs to test the active
324 compounds of some herbal in Indonesia by molecular docking in silico.

325
326 According to University of Indonesia (UI) and Institute of Bogor Agriculture (IPB) researchers,
327 they stated that some chemical compounds which originated from several plants in Indonesia
328 have the potential ability to prevent COVID-19 infection in the form of molecular docking in
329 silico. The model of research that has been conducted is shown in Figure 8. Based on the results
330 of prediction models with machine learning methods, namely SVM (support vector machine),
331 random forest, and MLP (multilayer perceptron) neural network is associated with 20644
332 interactions of protein compounds. The results are 31 herbal compounds with 5 target proteins
333 3CLPro (Chymotrypsin-like protease), PLPro (Papain-like protease), Spike-ACE2, EIF4
334 (Eukaryotic initiation factor-4), and RdRp. Modeling of structure and ligand based
335 pharmacophores was used to carry out virtual screening with 1,377 compounds from the
336 HerbalDB database.⁷⁷ The results of compound hit from machine learning, and pharmacophore
337 mapping was confirmed using molecular docking.

338
339 Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin,
340 quercetin, luteolin, kaempferol, isorhamnetin⁷⁸, and hesperidin⁷⁹. Luteolin is a furin protein
341 inhibitor⁸⁰ and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein
342 in MERS into units of S1 and S2.⁸¹ In the S1 unit, there is a receptor-binding domain (RBD)
343 where the ACE2 peptidase binds the virus in the host cell.⁸¹ The Hesperidin/hesperitin compound
344 in the silico study inhibits the RBD of the SARS-COV-2 Spike protein which is also known as
345 luteolin having a neuramidase inhibitor as well as oseltamivir which is currently one of the drugs
346 used in the CDC protocol.⁸²

347
348 Hesperidin a form of hesperidin aglycone and Quercetin is also known to act as inhibitors of
349 3CLpro virus proteins.^{83,84} Other compounds in guava such as myricetin act as SARS
350 coronavirus helicase inhibitors.⁸⁵ The kaempferol has the potential to be a non-competitive
351 inhibitor of 3CLPro and PLpro as well as quercetin.⁸⁶ It also acts as a autophagy modulator,
352 inducer and inhibitor, of the virus.

353
354 Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived
355 from plants. One of the commonly used condiments for cooking or herbal medicine in Indonesia
356 is empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. Furthermore,
357 animals such as snakehead fish also improve immune system in the body due to high protein and
358 amino acids.⁸⁷⁻⁸⁹ According to UNAIR (University of Airlangga) researchers stated that the
359 approach that can be taken in the public by consuming empon-empon to boost the immune
360 system to avoid COVID-19.⁹⁰

361
362 Turmeric containing curcumin have been consumed and proven by people for centuries and
363 beneficial to health. For example it is used to maintain fitness vitality, liver, and digestive
364 systems based on empirical experimental evidence. Various studies have been carried out in vitro
365 and preclinical tests showing that curcumin is anti-inflammatory, antiviral, antibacterial,
366 antifungal, and antioxidant based on scientific evidence.^{91, 92}

367 One of the benefits of curcumin obtained from clinical trials is to increase the body's immune
368 system. Recent research on curcumin against the virus shows that the SARS-CoV-2 receptor is
369 an enzyme ACE2 found in host cells of human especially alveolus lungs. However, the cell entry
370 of the virus depends on the binding of the spike virus protein, the receptor on the host cell
371 (ACE2) and pad priming protein spike (TMPRSS2).⁹³

372

373 **Conclusion**

374 The surging spread of the virus through human-to-human transmission has created a change in
375 human life that must meet health protocol standards including therapy protocols to combat
376 COVID-19. Few existing drugs had been evaluated for the remedy of SARS-CoV-2 and shown
377 promising good effects in clinical applications. The chemical and herbal drugs for the
378 management of viral infection symptoms have been on the frontline to mitigate this novel viral
379 infectious disease and have helped the number of patients in safe healing from COVID-19.
380 Several drugs have been clinically evaluated for the treatment of COVID-19, which showed
381 promising results and assisted a number of patients to recover safely. There is continuous
382 research on the potential of therapeutics in evaluating the existing antiviral drugs such as modern
383 and herbal medicines.

384

385 **Conflict of interests**

386 The authors claim that there is no conflict of interest.

387

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633
- 634

635 **Table 1.** Active compounds having the potential as antiviral SARS-CoV-2⁹⁰

636	Target	Compounds	Sources
637	3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	<i>Cassia alata</i> ,30
638		Kaempferol 3,4'-di-O-methyl ether (Ermanin)	<i>Tanacetum microphyllum</i>
639		Cyanidine 3-sophoroside-5-glucoside	<i>Brassica oleracea</i> ; <i>Ipomoea</i>
640			<i>batatas</i> ; <i>Raphanus sativus</i>
641		Casuarinin	<i>Psidium guajava</i>
642		Quercetin 3-(2G-rhamnosylrutinoside)	<i>Clitoria ternatea</i>
643		Peonidine 3-(4'-arabinosylglucoside)	<i>Ipomoea fistulosa</i>
644		Hesperidine	<i>Psidium guajava</i>
645			<i>Citrus aurantium</i>
646	PLpro	Platycodin D	<i>Platycodon grandiflorus</i>
647		Baicalin	<i>Scutellaria baicalensis</i>
648		Sugetriol-3,9-diacetate	<i>Cyperus rotundus</i>
649		Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	<i>Isatis indigotica</i>
650		(-)-epigallocatechin gallate	<i>Camellia sinensis</i>
651		2-93,4-Dihydroxyphenyl)-2-[2-(3,4-	
652	Dihydroxyphenyl)-3,4-dihydro-5,7-dihidroksi-2H-	<i>Vitis vinifera</i>	
653	1-benzopyran-3-yl]-3,4-dihydro-2H-1-benzopyran-		
654	3,4,5,7-tetrol		
655	RdRp.	Betulanol	<i>Cassine xylocarpa</i>
656		Gnidicin	<i>Gnidia lamprantha</i>
657		2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	<i>Viola diffusa</i>
658		14-deoxy-11,12-didehydroandrographolide	<i>Andrographis paniculata</i>
659		1,7-dihydroxy-3-methoxyxanthone	<i>Swerti apseudochinensis</i>
660		Theaflacin 3,3'-di-O-gallate	<i>Camelia sinensis</i>
661		2-(3,4-dihydroxyphenyl)-2-[(2-3,4-dihydroxyphenyl)-	
662		3,4-dihydro-5-7-dihydroxy-2H-1-benzopyran-	<i>Vitis vinifera</i>
663	3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol		
664	Spike-ACE2	Hesperidine	<i>Psidium guajava</i>
665			<i>Citrus aurantium</i>
666			

Dear Editor

I have revised all comments and corrections from reviewer.

Please see revision in the table below:

Title: COVID-19: Clinical Characteristics and Molecular Levels of Candidate Compounds of Prospective Herbal and Modern Drugs in Indonesia

No.	Corrections	Revision (high light yellow color)
1.	“Abstract section”: abbreviation COVID-19, SARS-CoV-2, RT-PCR, CT-Scan	Line 2, 3, 10, 11
2.	“Introduction section”: Define COVID-19 and SARS appropriately,	Line 23, 24, 27. 66 – 68. Already merge some paragraph and rewrite some sentences.
3.	“COVID-19 symptoms and infection transmission section”: Change the topic to “COVID-19 transmission” Please ensure that all sentences have appropriate references	Line 70 Line 76 Already merge some sentences
4.	- “Symptoms of patients infected with COVID-19 section”: - Please merge the first and third paragraphs due to the similar content - Acute respiratory distress syndrome (ARDS) instead of SARS - Rewrite some sentences - Should be singular - Should be past tense	Already change topic line 82 Already merge into one paragraph Line 84 Line 88 – 90 Line 92 Line 95
5.	“Preventive measures” section: - The contents of second and third paragraphs seem similar, therefore it is recommended to merge them	Line 116 – 124
6.	“The life cycle of SARS-CoV-2 (COVID-19) virus and infection” section: - change the topic to “The life cycle of SARS-CoV-2 - Abbreviation ER lumen	Line 127 Line 149
7.	“Diagnosis” section: - The sentence “The proper diagnosis characteristics used to manage COVID-19 is finding out the initiation of the course of remedy.” doesn’t seem correct - Exactly define what do you mean by “initial intervention”. - Abbreviation RT-PCR, CT-Scan, Elisa	Line 161 – 162 Line 166 Line 171, 176, 180
8.	“Treatment of COVID-19” section: - Rewrite and merge paragraph 1 and 2	Line 194 – 210
9.	“Entry inhibitors” section: - Rewrite and merge sentences	Line 213 – 214

	- Correct “although it is not inhibited by <u>ACE</u> ”	Line 220
10.	“Replication inhibitors” section: - Abbreviation RdRp - Change effective - it is the brand name or trade name of the favipiravir? - Correct “cold” - Rewrite the mechanism of favipiravir	Line 229 Line 232 Line 238 Line 240 Line 242 – 243
11.	“Protease inhibitors” section: - Correct “host mobile” and “important input”	Line 256, 263
12.	“Heterocyclic antiviral” section: - Rewrite endosomal pH - Correct “clinical response”	Line 277 – 280 Line 282
13.	“Nano drug delivery systems” section: Rewrite of this section	Line 294 – 299
14.	“Biological therapeutics” section: Abbreviation of RBD and merge some sentences	Line 305,
15.	“Herbal drugs” section: - Define UI, IPB, PLPro, SVM, EIF4, and UNAIR abbreviations. - Rewrite herbal drugs	Line 333 – 334 Line 319 -324; 326 – 329; 343 – 346; 362 – 366
16.	“Conclusion” section: Rewrite conclusion	Line 374 – 383

Dear Editor

I have revised some corrections about figures and references.
Please see revision in the table below:

Title: COVID-19: Clinical Characteristics and Molecular Levels of Candidate Compounds of Prospective Herbal and Modern Drugs in Indonesia

No.	Corrections	Revision (Comments)
1.	Figure 1	I have made my own image for figure 1 by using application of Biorender
2.	Figure 2	I have made my own image for figure 2 by using application of Biorender
3.	Figure 6	I have made my own image for figure 6 by using application of Biorender
4.	Figure 8	I delete figure 8 because I have made narrative structure in the text.
5.	Ref. 90	Line 614
6.	Ref. 93	Line 625

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Robert Tungadi <robert.tungadi@ung.ac.id> kepada Pharmaceutical
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I have checked the proof of the article and find minor corrections on page 147 at table 1 especially the part of SFP concentrations. Please find the attached file Thank you for your attention

Kind regards
Robert

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1 **Abstract**

2 A recent outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease
3 also called Coronavirus disease 2019 (COVID-19) in China, has rapidly spread to other countries
4 of the world. The medical and scientific communities are working tirelessly to produce a vaccine
5 due to the lethal nature of this virus. COVID-19 is a novel virus that requires immediate
6 emergency therapy, thereby leading to massive fear of infection, social problems in the
7 community, and an increase in the number of infected people. Therefore, scientists and
8 researchers need to determine the epidemiological cases of the virus, such as its mode of
9 transmission, effective preventive measures, and the nature of the life cycle. In addition, there
10 need to be current literature advances in diagnostic development such as reverse transcription
11 polymerase chain reaction (RT-PCR), computed tomography scan (CT-Scan), Elisa as well as
12 clinical researches on modern and herbal drugs for the treatment of infected patients. This
13 treatment technique is classified from antiviral drugs such as entry, replication, nucleosides,
14 nucleotides, and protease inhibitors, along with the use of heterocyclic drugs, monoclonal
15 antibodies therapy, vaccine development and herbal formulations that have been pre-clinically
16 tested *in vitro* and molecular docking. Chemical drug molecules with prospective applications in
17 the treatment of COVID-19 have been included in this review.

18 **Keywords:** COVID-19, antiviral, infection, herbal, modern drugs, pandemic

19

20 **Introduction**

21 In December 2019, the Chinese city of Wuhan experienced a rapid spread in an infectious
22 disease, which affected the respiratory system, thereby leading to a high mortality rate. This
23 virus, known as Coronavirus disease 2019 (COVID-19), soon spread to other countries and was
24 declared a pandemic by the World Health Organization (WHO).¹ Infected people show
25 symptoms of pneumonia, which is similar to SARS (Severe Acute Respiratory Syndrome). This
26 disease is caused by a lethal virus in nature and is currently the highest leading cause of mortality
27 all over the world.² The first reported case was in China, and within a few months, it has spread
28 to almost all countries and continents in the world.² According to studies, the most significant
29 numbers of cases of infected people are in South Korea, Italy, Iran, South Africa, the USA, and
30 Indonesia. In a recent update by WHO, over 90,000 people all over the world are infected with
31 approximately 3,000 deaths. China alone recorded 2,500 deaths by the end of February 2020.³

32

33 The WHO declared the virus a pandemic due to its rapid spread in various countries. It is
34 speculated that this virus originated from different animals consumed as food in China. Early
35 transmission studies reported that it originated from local fish and wild animal markets with
36 possible transmission from animals to humans and vice versa. However, this speculation has not
37 been proven. This disease has led to a very high increase in mortality all over the world.⁴

38

39 In Indonesia, the virus was not in existence till the end of April 2020, based on data from the
40 Ministry of Health. Since its inception, there has been a rapid increase in the mortality rate due to
41 the high number of infected people.⁵ Therefore, based on these data, the Indonesian government
42 quickly responded and took preventive measures to reduce the spread of this virus. Before now,
43 no drug or vaccine has been proven to kill or inhibit the COVID-19 virus. However, WHO
44 announced that over 20 countries and pharmaceutical companies around the world are
45 developing vaccines and drugs to fight the virus.⁶ Unfortunately, this development is going to
46 take at least a year before completion. Meanwhile, several types of modern and herbal COVID-

47 19 treatments have been clinically tested, such as Remdesivir and Chloroquine, as well as
48 curcumin (*in vitro* study).

49
50 The emergence and rapid spread of this virus have hastened the development of diagnosis and
51 medicines for the treatment of this infectious disease. In Indonesia, doctors have used several
52 existing modern and herbal medicines, with national and international health institutions, to
53 understand the mechanism, virulence, and pharmacology of the virus to develop possible drugs
54 and vaccines. This review discusses the literature report on progress regarding diagnostic
55 methods and developmental therapies with the possible use of candidate compounds of modern
56 and herbal medicines for COVID-19 infectious diseases in Indonesia.

57

58 **The Coronaviruses**

59 Coronavirus, a genus of the Coronaviridae family, is a positive-strand and the most significant
60 viral genome of all RNA viruses (27–32 kb), causing a wide range of diseases related to the
61 respiratory system. The symptoms may vary from the common cold, dry cough to more severe
62 respiratory diseases.⁷ Furthermore, it consists of 80 to 160 nm particles, 4 or 5 structural spike
63 (S), membrane (M), hemagglutinin-esterase (HE), nucleocapsid (N), and small envelope E
64 proteins.⁸ In addition, the virion structure consists of S glycoprotein, which forms petal-shaped
65 spikes on the surface with 180 to 200 KDa molecule that is cotranslationally glycosylated in the
66 endoplasmic reticulum as shown in Figure 1.⁸ SARS-CoV-2 was a new strain of the current
67 virus,^{9,10} which was transmitted from animals to human¹¹, however, the new coronavirus infects
68 humans.

69

70 **COVID-19 transmission**

71 COVID-19 spreads rapidly amongst humans with symptoms and asymptomatic carriers. The
72 virus is easily spread when the liquid droplet of an infected person drops on surfaces when the
73 patient coughs or sneezes. Transmission in certain cases is usually through the air, by staying
74 close to an infected person.¹² Meanwhile, asymptomatic patients are hidden carriers of the virus
75 and contribute to a greater transmission of the virus. This manual transmission also spread,
76 assuming the patient has symptoms.³ In addition, vertical transmission of the virus from mother
77 to child has not been observed according to research conducted by Chen H et al. in a small group
78 of pregnant women. They stated that the virus is vertically intrauterine and non-transmittable
79 from mothers to unborn babies. The emergence and the spread of this new virus is due to the
80 increase in human populations which causes proximity.^{13,14}

81

82 **Symptoms and mortality of COVID-19**

83 Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to acute
84 respiratory distress syndrome (ARDS), which marked respiratory infections on COVID-19
85 patients. These include runny nose, fever, cough, shortness of breath, sore throat, and mild to
86 moderate upper respiratory tract illness. In severe cases, patients experience pneumonia, SARS,
87 kidney failure, and even death. An infected patient shows full signs of the virus within two to
88 seven days. However, the median incubation duration of infection development changed to 4
89 days with an interquartile variety of 2 to 7 days in all patients.¹⁵ This is known as the incubation
90 period which progresses for four days with an interquartile range.²¹

91

92 Study conducted by Guan et al. showed the middle-aged were more prone to infection compared
93 to other categories of people.¹⁶ Approximately 41.9% of the total number of patients were
94 women, therefore, there are gender differences in the spread of the virus. The report also stated
95 that the primary composite endpoint occurred in 6% of patients. In Wuhan city, there was no
96 gender difference in people infected with COVID-19 with the highest mortality rates of 8.4% by
97 20 March 2020.^{17,18} However, research shows that the elderly and young children are most at risk
98 from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal compared
99 to SARS and MERS, this is because approximately 15 to 20% of cases become severe within a
100 limited timeframe. According to doctors, the lethal rate is about 1 in 10 which caused by
101 enveloped virus meaning that it is protected by a glycoprotein shell, thereby, making it difficult
102 to treat.¹⁹

103

104 **Preventive measures**

105 All countries, including Indonesia, need preventive measures to overcome the spread of COVID-
106 19, which currently has no known cure and vaccines. Therefore, handling infected patients has
107 been recommended as one of the steps to control the rampant spread of the virus among people.
108 However, it is difficult to force the isolation of infected patients because this causes many social
109 problems. Like many reports in the Indonesian media, the practice of forced confinement of
110 infected people at home is very difficult for health workers and the police. The isolation of
111 infected individuals supported the provision of complete hospital treatment is one of the moral
112 control methods.²² Therefore, appropriate research studies need to be conducted to understand
113 the best approach in infection prevention including assessing the country's ability to slow the
114 spread of infected people.²³

115

116 In Indonesia, the standard procedures recommended for preventing the spread of infection are
117 more effective in controlling the spread and keeping things safe. The most crucial strategies
118 include washing of hands after visiting public places and frequent exercises.^{24,25} Other practices
119 involve overlaying mouth and nostrils when coughing and sneezing to prevent the spread of the
120 virus, assuming the person is asymptomatic or in preliminary degrees of contamination.^{26,27} Also,
121 proper cooking of foods such as meat, eggs, and animals helps to destroy the virus. In practice,
122 one needs to avoid close contact with anyone showing symptoms of respiratory illnesses such as
123 cough, flu, asthma, pneumonia, and tuberculosis. Therefore, this simple precaution can be
124 effectively carried out in controlling the spread and containing the virus.

125

126 **The life cycle of SARS-CoV-2 and infection**

127 Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism divided into 3 parts, namely
128 entry, replication, and release, as shown in Figure 2. Firstly, the infection starts when the viral
129 spike (S) glycoprotein attached to the complementary host cell receptor. After attachment, a
130 protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on
131 the availability of the host cell protease, cleavage and activation allow cell
132 entry by endocytosis or direct fusion of the viral envelop with the host membrane.²⁸

133 On entry into the host cell, the virus is uncoated, and its genome enters the cell cytoplasm.²⁹ The
134 coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail, which allows the
135 RNA to attach to the host cell's ribosome for translation, and translates the initial overlapping of
136 the virus genome and forms a long polyprotein.³⁰ The polyprotein consists of
137 proteases which cleaves it into multiple nonstructural proteins.³¹

138 Secondly, coronaviruses replicates and transcripts RNA from the strand by using the SARS-
139 CoV-2 replication mechanism, which binds cell surface molecules such as metalloprotease
140 amino peptidase with hemagglutinin esterase (HE-protein) and N-acetyl neuraminic acid as co-
141 receptor. Furthermore, the virus goes into the host cell by fusion of viral and cell membranes or
142 through the receptor-mediated endocytosis incorporated via an endosome, which is subsequently
143 acidified by proton pumps. Meanwhile, the virus produces direct proteins and new genomes in
144 the cytoplasm, particularly single positive-stranded RNA gen. Otherwise, the negative strand
145 serves as a template used to transcribe smaller subgenomic positive RNAs used to synthesize all
146 other proteins. After binding, assembled nucleocapsids with twisted helical RNA, it enters into
147 the endoplasmic reticulum (ER) lumen and is encased with the membrane as shown in Figure
148 2.³²

149
150 Thirdly, the replicated positive-sense of genomic RNA becomes the genome of the progeny
151 viruses. The mRNAs are gene transcripts after the initial overlapping reading frame translated by
152 the host's ribosomes into the structural proteins.³¹ RNA translation occurs inside the endoplasmic
153 reticulum, which consists of S, E, and M proteins that move along the secretory pathway into the
154 Golgi intermediate compartment. Therefore, the M proteins are required to assemble and bind
155 the virus into the nucleocapsid.³³ Progeny viruses are released from the host cell
156 by exocytosis through secretory vesicles.³³

157

158 **Diagnosis**

159 The proper diagnosis characteristics used to manage COVID-19 is the first line of control and a
160 deciding factor in the initiation of the course of treatment. This is different from the common
161 cold, which is properly treated with the right drugs. Sometimes the results of preliminary
162 examinations in infected people do not provide a clear diagnosis of the infection, therefore,
163 doctors tend to ask the patient to provide a detailed and accurate diagnosis of their disease such
164 as cough, flu, fever, and so on. The identifying and providing effective support, sputum
165 examination, and other diagnostic tests help to determine the infection early. Also, the number of
166 days from the infected date is noted at the laboratory to recommend individual diagnostic tests as
167 follows:

168

169 ***Reverse transcription-polymerase chain reaction (RT-PCR)***

170 This is a standard technique for determining the virus by rRT-PCR from a nasopharyngeal swab.
171 A sputum sample is used to obtain the required results within hours to 2 days.³⁴ Sample
172 measurements (Swab test) consist of some steps using RT-PCR, as shown in Figure 3.

173

174 **Enzyme-linked immunosorbent assay (ELISA)**

175 Antibody assays are used to test infected people using their blood serum sample, with the results
176 released with few days.³⁵

177

178 ***Computerized-Tomography (CT-Scan)***

179 The contamination is analyzed from a mixture of side effects, chance elements, and a chest CT
180 scan demonstrating highlights of pneumonia.³⁶ The fundamental diagnosis reports from medical
181 clinics in China show that majority of COVID-19 infected patients were determined using
182 pneumonia and trademark CT imaging patterns.³⁷ Furthermore, radiological assessments have
183 become imperative in early determination and appraisal of disease course.³⁸ CT scan of various

184 COVID-19 contaminated patients differed in pattern³⁹, and almost 50% of patients were
185 discovered from pictures. On admission to emergency clinics, the ground-glass haziness was the
186 most widely recognized radiologic finding on chest figured tomography (CT)³⁹ of 56.4% of
187 patients.⁴⁰ The longitudinal CT discovered infected patients with pneumonia with follow up
188 checks over the course of treatment. Besides that, it was seen that numerous patients did not have
189 strange radiologic findings.⁴¹

190

191 **Treatments of COVID-19**

192 The mechanism of viral infection is the entry of the virus into cells and multiplication using a
193 host cellular method characterized by damages to the host cell as a key for the development of
194 new drug compound therapies. Currently, there is no definitive and recommended therapy for
195 COVID-19 because it is a new virus, and making a vaccine required numerous clinical analyses
196 and tests. One of examples of treatment therapy i.e. convalescent plasma therapy which is the
197 administration of plasma from a recovered Covid-19 patient to a Covid-19 patient who is still
198 suffering from illness, so antibodies (immunity) in the plasma of the cured patient can help
199 patients who are still ill to cope with the disease.^{3,41} However, all antivirals used in COVID-19
200 therapy in almost all countries are still in the form of trial and error. Some countries have
201 referred to the antiviral therapy used during the occurrence of the SARS and MERS epidemic
202 several years ago, such as lopinavir, ritonavir, ribavirin, oseltamivir, etc. These drugs have been
203 used and were quite effective in dealing with SARS and MERS during the epidemic.³ Similarly,
204 there are no definitive guidelines for dealing with COVID-19 in Indonesia, as the country also
205 relies on an existing drug such as oseltamivir. Indonesia has tried reaching out to China
206 regarding the drugs used to treat their infected citizens, including the purchase of Chloroquine
207 and Avigan. Some prospective drugs are considered to direct current applications or the
208 development of new therapeutic drugs, including modern and herbal medicines.

209

210 ***Entry inhibitors***

211 The SARS-CoV-2 infects the respiratory system and alveoli cells in the lung sacs would be the
212 host for viral infection. In general, viruses enter the host cell by forming complex projections
213 such as spikes or lobes with receptors. However, the exact structure or lobe of SARS-CoV-2 is
214 not fully determined,⁴² although prior experience of coronavirus (β -family), shows it has
215 similarities with the receptor of host cells of SARS.⁴³ Recently it has been found that
216 Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-
217 CoV) and (SARS-CoV-2).⁴⁴ ACE2 has some homology with an angiotensin-converting enzyme
218 (ACE) although it is not inhibited by ACE inhibitors.⁵ A previous SARS case was characterized
219 by an infection that was started by the transmembrane (S) spike in the glycoproteins binding the
220 host receptor and combines viruses to cell membranes. The identification of the viral / spikes
221 lobes molecular structure is time-consuming, while the development of facilitated heterocyclic
222 drug molecules or existing heterocyclic screening has the ability to bind the entry inhibitor
223 drug.⁴⁵

224

225 ***Replication inhibitors***

226 COVID-19 is an RNA virus that utilizes host cells for genomic replication by encoding the
227 RNA-dependent RNA polymerase (RdRp), which allows the viral genome to be transcribed into
228 new RNA copies using the host cell's machinery. The viral genome replication mechanism
229 serves potential targets for the control of viral infections, while antiviral drugs such as

230 Remdesivir and Favipiravir (Avigan)⁴⁶ has the ability to potentially affect SARS-CoV-2 as
231 shown in Figures 4A and B. The nucleotide adenosine analogue antiviral for Ebola and RNA
232 viruses have shown some promising results in the clinical control of this virus.⁴⁷ However,
233 further evaluation is needed for potential applications with more patients. The action mechanism
234 of Remdesivir as antiviral drug as shown in Figure 5.

235
236 Favipiravir is the brand name for Avigan, also known as T-705, which is an antiviral drug
237 developed by Toyama Chemical, a Fujifilm group, located in Japan with activity against many
238 RNA viruses. In Japan, this drug was originally developed to treat influenza, however, in
239 February 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel
240 coronavirus) disease. The action mechanism of favipiravir can inhibit replication and translation
241 of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses, as shown in Figure
242 6.⁴⁸ Further studies have shown that favipiravir induces mutant of RNA transversion, resulting in
243 a viable viral phenotype. This product is metabolized by human hypoxanthine-guanine
244 phosphoribosyltransferase (HGPRT) known as favipiravir-ribofuranosyl-5-triphosphate
245 (favipiravir-RTP). During this COVID-19 pandemic, in a limited clinical trial with 80 subjects,
246 favipiravir showed an antiviral potential for SARS-CoV-2 that was better than
247 lopinavir/ritonavir.⁴⁹ Many other nucleoside analogues including DNA synthesis such as
248 tenofovir, disoproxil, lamivudine, and other antivirals have the potential to inhibit the
249 multiplication of SARS-CoV-2 and are being evaluated through molecular docking studies and
250 testing in infected cell culture.⁵⁰

251 252 **Protease inhibitors**

253 Protease enzymes are involved within the maturation stage of virus replication inside the host
254 cell and related to protein or peptide translation. Figures 4C and D, shows that Lopinavir and
255 ritonavir are approved anti-HIV drugs, and a combination of both aids in the inhibition of SARS-
256 CoV-2.^{51,52} A research carried out by Lim J et.al. on the remedy used to treat persons affected
257 with COVID-19 in Korea indicated that the administration of lopinavir/ritonavir (Kaletra,
258 AbbVie) extensively reduced the virus.⁵² This means that a detailed analysis is needed for the
259 recommendation of this drug and the formation of new drug compounds. Molecular docking of
260 potential inhibitors provide clear information because detailed docking simulation results have
261 shown essential input in previous SARS cases and other viral infections.⁵³⁻⁵⁵ However, a lot of
262 clinical data needs to be conducted to prove the efficacy and safety of the human body.

263 264 ***Heterocyclic antiviral***

265 Over the decades, many heterocyclic drug molecules have been used in the treatment of viral
266 infections, and these drugs are thought to be probably slightly effective in inhibiting SARS-CoV-
267 2. An example is Chloroquine, which was originally an antiplasmodium used to treat malaria.
268 This drug contains a quinoline group as shown in Figure 4E and inhibits the activity of the
269 enzyme heme polymerase into hemozoin. This accumulation kills the Plasmodium parasite
270 responsible for malaria.⁵⁶ However, with the decrease in malaria and the emergence of
271 plasmodium resistance to Chloroquine, this drug is no longer used. Also, Chloroquine and
272 hydroxychloroquine are used for antiviral therapy. Gao et al. (2020) stated that Chloroquine has
273 a strong antiviral effect against the virus in primate cells. This inhibitory effect is observed when
274 cells are treated with Chloroquine both before and after exposure, which shows that it has a
275 preventive and therapeutic effect. In addition, Chloroquine and hydroxychloroquine are weak

276 bases that are known to elevate the pH of acidic intracellular organelles, such as
277 endosomes/lysosomes, essential for membrane fusion inhibiting SARS-CoV-2 entry through
278 changing the glycosylation of ACE2 receptor and spike protein, shown in Figure 7.^{57,59} This
279 inhibits the receptor which prevent infection and spread of the SARS-CoV-2 at concentrations
280 that cause clinical response. In the SARS-CoV-2 pandemic in China, Chloroquine was used at a
281 dose of 500 mg for adult 2 times a day, for 10 days.⁵⁸ Chloroquine and hydroxychloroquine are
282 also currently being tried in Malaysia at the same dosage used in China and Indonesia.

283
284 There are several heterocyclic antiviruses previously used as antivirals such as HIV, H1N1,
285 H1N5, and SARS, which are further examined for the treatment of COVID-19. Oseltamivir
286 (Tamiflu) has been widely used as a neuraminidase inhibitor for the treatment of influenza was
287 also recommended.⁵⁹ In addition, other candidate compounds evaluated with antiviral activity
288 against SARS-CoV-2 are heterocyclic based on ACE2 peptides namely 3C-like protease
289 (3CLpro and 3CLpro-1) inhibitors and vinylsulfone protease inhibitors.^{60,61}

290
291 **Nano drug delivery systems**
292 Drug delivery systems in the form of nanoparticle preparations have been widely used to
293 improve the bioavailability in the blood and enhance the transport and efficacy antiviral drugs
294 especially nucleoside analogues on conjugation with potential delivery systems that have been
295 proven in drug-resistant HIV infection.⁶²⁻⁶⁵ The wide variety of available nano delivery system
296 can be used with the new developed drug formulation which could be efficacious in delivering
297 the drugs with faster therapeutic indices for COVID-19.⁶⁶⁻⁶⁸

298
299 **Biological therapeutics**
300 Antibody therapy can be used for the treatment of COVID-19 infections. However, this vaccine
301 still requires approximately 1 year before it can be globally utilized to prevent the spread of the
302 virus. According to Tian et al. specific human monoclonal antibodies such as CR3022 are
303 intended to bind strongly to SARS-CoV-2 receptor binding domain [= (RBD) (KD 6.3 nM) and
304 overlap the ACE2 binding site.⁷⁰ These unique results indicate the possibility of developing a
305 therapeutic vaccine with a combination of other antibodies. However, *in vitro* trials and clinical
306 studies are needed to obtain accurate clinical data for the prevention and treatment of COVID-19
307 infections.⁷⁰

308
309 In developing a new vaccine one must pay attention to the similarity of immunogenic structural
310 proteins similar to SARS, MERS for SARS-CoV-2.⁷¹ Ahmed et al. used a set of B and T cell
311 epitopes derived from spikes (S) and nucleocapsid proteins (N) to identically map the SARS-
312 CoV-2 protein.⁷² Reports suggested that the identified epitope has no available mutase sequence.
313 Therefore, this target immune epitope has the potential to be explored in the fight against the
314 SARS-CoV-2. However, the final results depend on *in vitro* and future clinical trials.⁷²

315
316 **Herbal drugs**
317 The herbal formulations used as alternative medication has been a success in presenting the
318 remedy to a number of infections in conjunction with symptom specific remedy using herbs.⁷³⁻⁷⁵
319 The initial lead from herbal medicinal drug has been successful in developing final applicable
320 formulations like Praneem (a natural extract of neem tree) as microbicide for HIV therapy.⁷⁶

321 Therefore, various studies have been conducted on the use of herbal drugs to test the active
322 compounds of some herbal in Indonesia by molecular docking in silico.

323
324 According to University of Indonesia (UI) and Institute of Bogor Agriculture (IPB) researchers,
325 they stated that some chemical compounds which originated from several plants in Indonesia
326 have the potential ability to prevent COVID-19 infection in the form of molecular docking in
327 silico. Based on the results of prediction models with machine learning methods, namely SVM
328 (support vector machine), random forest, and MLP (multilayer perceptron) neural network is
329 associated with 20,644 interactions of protein compounds. The results are 31 herbal compounds
330 with 5 target proteins 3CLPro (Chymotrypsin-like protease), PLPro (Papain-like protease), Spike-
331 ACE2, EIF4 (Eukaryotic initiation factor-4), and RdRp. Modeling of structure and ligand based
332 pharmacophores was used to carry out virtual screening with 1,377 compounds from the
333 HerbalDB database.^{77,90} The results of compound hit from machine learning, and pharmacophore
334 mapping was confirmed using molecular docking.

335
336 Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin,
337 quercetin, luteolin, kaempferol, isorhamnetin⁷⁸, and hesperidin⁷⁹. Luteolin is a furin protein
338 inhibitor⁸⁰ and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein
339 in MERS into units of S1 and S2.⁸¹ In the S1 unit, there is a receptor-binding domain (RBD)
340 where the ACE2 peptidase binds the virus in the host cell.⁸¹ The Hesperidin/hesperitin compound
341 in the silico study inhibits the RBD of the SARS-COV-2 Spike protein which is also known as
342 luteolin having a neuramidase inhibitor as well as oseltamivir which is currently one of the drugs
343 used in the CDC protocol.⁸²

344
345 Hesperidin a form of hesperidin aglycone and Quercetin is also known to act as inhibitors of
346 3CLpro virus proteins.^{83,84} Other compounds in guava such as myricetin act as SARS
347 coronavirus helicase inhibitors.⁸⁵ The kaempferol has the potential to be a non-competitive
348 inhibitor of 3CLPro and PLpro as well as quercetin.⁸⁶ It also acts as a autophagy modulator,
349 inducer and inhibitor, of the virus.

350
351 Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived
352 from plants. One of the commonly used condiments for cooking or herbal medicine in Indonesia
353 is empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. Furthermore,
354 animals such as snakehead fish also improve immune system in the body due to high protein and
355 amino acids.⁸⁷⁻⁸⁹ According to UNAIR (University of Airlangga) researchers stated that the
356 approach that can be taken in the public by consuming empon-empon to boost the immune
357 system to avoid COVID-19.⁹⁰

358
359 Turmeric containing curcumin have been consumed and proven by people for centuries and
360 beneficial to health. For example it is used to maintain fitness vitality, liver, and digestive
361 systems based on empirical experimental evidence. Various studies have been carried out in vitro
362 and preclinical tests showing that curcumin is anti-inflammatory, antiviral, antibacterial,
363 antifungal, and antioxidant based on scientific evidence.^{91,92}

364 One of the benefits of curcumin obtained from clinical trials is to increase the body's immune
365 system. Recent research on curcumin against the virus shows that the SARS-CoV-2 receptor is
366 an enzyme ACE2 found in host cells of human especially alveolus lungs. However, the cell entry

367 of the virus depends on the binding of the spike virus protein, the receptor on the host cell
368 (ACE2) and pad priming protein spike (TMPRSS2).⁹³
369

370 **Conclusion**

371 The surging spread of the virus through human-to-human transmission has created a change in
372 human life that must meet health protocol standards including therapy protocols to combat
373 COVID-19. Few existing drugs had been evaluated for the remedy of SARS-CoV-2 and shown
374 promising good effects in clinical applications. The chemical and herbal drugs for the
375 management of viral infection symptoms have been on the frontline to mitigate this novel viral
376 infectious disease and have helped the number of patients in safe healing from COVID-19.
377 Several drugs have been clinically evaluated for the treatment of COVID-19, which showed
378 promising results and assisted a number of patients to recover safely. There is continuous
379 research on the potential of therapeutics in evaluating the existing antiviral drugs such as modern
380 and herbal medicines.

381

382 **Conflict of interests**

383 The authors claim that there is no conflict of interest.

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- 631

632 **Table 1.** Active compounds having the potential as antiviral SARS-CoV-2⁹⁰

633	Target	Compounds	Sources
634	3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	<i>Cassia alata</i> ,30
635		Kaempferol 3,4'-di-O-methyl ether (Ermanin)	<i>Tanacetum microphyllum</i>
636		Cyanidine 3-sophoroside-5-glucoside	<i>Brassica oleracea</i> ; <i>Ipomoea</i>
637			<i>batatas</i> ; <i>Raphanus sativus</i>
638		Casuarinin	<i>Psidium guajava</i>
639		Quercetin 3-(2G-rhamnosylrutinoside)	<i>Clitoria ternatea</i>
640		Peonidine 3-(4'-arabinosylglucoside)	<i>Ipomoea fistulosa</i>
641		Hesperidine	<i>Psidium guajava</i>
642			<i>Citrus aurantium</i>
643		PLpro	Platycodin D
644	Baicalin		<i>Scutellaria baicalensis</i>
645	Sugetriol-3,9-diacetate		<i>Cyperus rotundus</i>
646	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone		<i>Isatis indigotica</i>
647	(-)-epigallocatechin gallate		<i>Camellia sinensis</i>
648	2-93,4-Dihydroxyphenyl)-2-[2-(3,4-		
649	Dihydroxyphenyl)-3,4-dihydro-5,7-dihidroksi-2H-		<i>Vitis vinifera</i>
650	1-benzopyran-3-yl]-3,4-dihydro-2H-1-benzopyran-		
651	3,4,5,7-tetrol		
652	RdRp.	Betulanol	<i>Cassine xylocarpa</i>
653		Gnidicin	<i>Gnidia lamprantha</i>
654		2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	<i>Viola diffusa</i>
655		14-deoxy-11,12-didehydroandrographolide	<i>Andrographis paniculata</i>
656		1,7-dihydroxy-3-methoxyxanthone	<i>Swerti apseudochinensis</i>
657		Theaflacin 3,3'-di-O-gallate	<i>Camelia sinensis</i>
658		2-(3,4-dihydrophenyl)-2-[(2-3,4-dihydroxyphenyl)-	
659		3,4-dihydro-5-7-dihydroxy-2H-1-benzopyran-	<i>Vitis vinifera</i>
660		3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	
661		Spike-ACE2	Hesperidine
662			<i>Citrus aurantium</i>

663



COVID-19: Clinical Characteristics and Molecular Levels of Candidate Compounds of Prospective Herbal and Modern Drugs in Indonesia

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Abstract

A recent outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease also called Coronavirus disease 2019 (COVID-19) in China, has rapidly spread to other countries of the world. The medical and scientific communities are working tirelessly to produce a vaccine due to the lethal nature of this virus. COVID-19 is a novel virus that requires immediate emergency therapy, thereby leading to massive fear of infection, social problems in the community, and an increase in the number of infected people. Therefore, scientists and researchers need to determine the epidemiological cases of the virus, such as its mode of transmission, effective preventive measures, and the nature of the life cycle. In addition, there need to be current literature advances in diagnostic development such as reverse transcription polymerase chain reaction (RT-PCR), computed tomography scan (CT-Scan), Elisa as well as clinical researches on modern and herbal drugs for the treatment of infected patients. This treatment technique is classified from antiviral drugs such as entry, replication, nucleosides, nucleotides, and protease inhibitors, along with the use of heterocyclic drugs, monoclonal antibodies therapy, vaccine development and herbal formulations that have been pre-clinically tested in vitro and molecular docking. Chemical drug molecules with prospective applications in the treatment of COVID-19 have been included in this review.

Introduction

In December 2019, the Chinese city of Wuhan experienced a rapid spread in an infectious disease, which affected the respiratory system, thereby leading to a high mortality rate. This virus, known as Coronavirus disease 2019 (COVID-19), soon spread to other countries and was declared a pandemic by the World Health Organization (WHO).¹ Infected people show symptoms of pneumonia, which is similar to SARS (Severe Acute Respiratory Syndrome). This disease is caused by a lethal virus in nature and is currently the highest leading cause of mortality all over the world.² The first reported case was in China, and within a few months, it has spread to almost all countries and continents in the world.² According to studies, the most significant numbers of cases of infected people are in South Korea, Italy, Iran, South Africa, the USA, and Indonesia. In a recent update by WHO, over 90,000 people all over the world are infected with approximately 3,000 deaths. China alone recorded 2,500 deaths by the end of February 2020.³ The WHO declared the virus a pandemic due to its rapid spread in various countries. It is speculated that this virus originated from different animals consumed as food in China. Early transmission studies reported that it originated from local fish and wild animal markets with possible transmission from animals to humans and vice versa. However, this speculation has not been proven. This

disease has led to a very high increase in mortality all over the world.⁴

In Indonesia, the virus was not in existence till the end of April 2020, based on data from the Ministry of Health. Since its inception, there has been a rapid increase in the mortality rate due to the high number of infected people.⁵ Therefore, based on these data, the Indonesian government quickly responded and took preventive measures to reduce the spread of this virus. Before now, no drug or vaccine has been proven to kill or inhibit the COVID-19 virus. However, WHO announced that over 20 countries and pharmaceutical companies around the world are developing vaccines and drugs to fight the virus.⁶ Unfortunately, this development is going to take at least a year before completion. Meanwhile, several types of modern and herbal COVID-19 treatments have been clinically tested, such as Remdesivir and Chloroquine, as well as curcumin (in vitro study).

The emergence and rapid spread of this virus have hastened the development of diagnosis and medicines for the treatment of this infectious disease. In Indonesia, doctors have used several existing modern and herbal medicines, with national and international health institutions, to understand the mechanism, virulence, and pharmacology of the virus to develop possible drugs and vaccines. This

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review discusses the literature report on progress regarding diagnostic methods and developmental therapies with the possible use of candidate compounds of modern and herbal medicines for COVID-19 infectious diseases in Indonesia.

The Coronaviruses

Coronavirus, a genus of the Coronaviridae family, is a positive-strand and the most significant viral genome of all RNA viruses (27–32 kb), causing a wide range of diseases related to the respiratory system. The symptoms may vary from the common cold, dry cough to more severe respiratory diseases.⁷ Furthermore, it consists of 80 to 160 nm particles, 4 or 5 structural spike (S), membrane (M), hemagglutinin-esterase (HE), nucleocapsid (N), and small envelope E proteins.⁸ In addition, the virion structure consists of S glycoprotein, which forms petal-shaped spikes on the surface with 180 to 200 kDa molecule that is cotranslationally glycosylated in the endoplasmic reticulum as shown in **Figure 1**.⁸ SARS-CoV-2 was a new strain of the current virus,^{9,10} which was transmitted from animals to human¹¹, however, the new coronavirus infects humans.

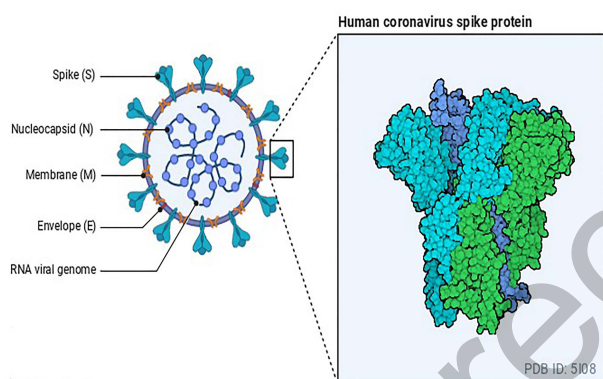


Figure 1. Structure of new coronavirus and protein visualization, now designated severe acute respiratory syndrome coronavirus-2, (SARS-CoV-2)

COVID-19 Transmission

COVID-19 spreads rapidly amongst humans with symptoms and asymptomatic carriers. The virus is easily spread when the liquid droplet of an infected person drops on surfaces when the patient coughs or sneezes. Transmission in certain cases is usually through the air, by staying close to an infected person.¹² Meanwhile, asymptomatic patients are hidden carriers of the virus and contribute to a greater transmission of the virus. This manual transmission also spread, assuming the patient has symptoms.³ In addition, vertical transmission of the virus from mother to child has not been observed according to research conducted by Chen H et al. in a small group of pregnant women. They stated that the virus is vertically intrauterine and non-transmittable from mothers to unborn babies. The emergence and the spread of this new virus is due to the increase in human populations which causes proximity.^{13,14}

Symptoms and Mortality of COVID-19

Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to acute respiratory distress syndrome (ARDS), which marked respiratory infections on COVID-19 patients. These include runny nose, fever, cough, shortness of breath, sore throat, and mild to moderate upper respiratory tract illness. In severe cases, patients experience pneumonia, SARS, kidney failure, and even death. An infected patient shows full signs of the virus within two to seven days. However, the median incubation duration of infection development changed to 4 days with an interquartile variety of 2 to 7 days in all patients.¹⁵ This is known as the incubation period which progresses for four days with an interquartile range.¹⁶ Study conducted by Guan et al. showed the middle-aged were more prone to infection compared to other categories of people.¹⁷ Approximately 41.9% of the total number of patients were women, therefore, there are gender differences in the spread of the virus. The report also stated that the primary composite endpoint occurred in 6% of patients. In Wuhan city, there was no gender difference in people infected with COVID-19 with the highest mortality rates of 8.4% by 20 March 2020.^{18,19} However, research shows that the elderly and young children are most at risk from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal compared to SARS and MERS, this is because approximately 15 to 20% of cases become severe within a limited timeframe. According to doctors, the lethal rate is about 1 in 10 which caused by enveloped virus meaning that it is protected by a glycoprotein shell, thereby, making it difficult to treat.^{20,21}

Preventive Measures

All countries, including Indonesia, need preventive measures to overcome the spread of COVID-19, which currently has no known cure and vaccines. Therefore, handling infected patients has been recommended as one of the steps to control the rampant spread of the virus among people. However, it is difficult to force the isolation of infected patients because this causes many social problems. Like many reports in the Indonesian media, the practice of forced confinement of infected people at home is very difficult for health workers and the police. The isolation of infected individuals supported the provision of complete hospital treatment is one of the moral control methods.²² Therefore, appropriate research studies need to be conducted to understand the best approach in infection prevention including assessing the country's ability to slow the spread of infected people.²³

In Indonesia, the standard procedures recommended for preventing the spread of infection are more effective in controlling the spread and keeping things safe. The most crucial strategies include washing of hands after visiting public places and frequent exercises.^{24,25} Other practices involve overlaying mouth and nostrils when coughing and sneezing to prevent the spread of the virus, assuming the person is asymptomatic or in preliminary degrees of

contamination.^{26,27} Also, proper cooking of foods such as meat, eggs, and animals helps to destroy the virus. In practice, one needs to avoid close contact with anyone showing symptoms of respiratory illnesses such as cough, flu, asthma, pneumonia, and tuberculosis. Therefore, this simple precaution can be effectively carried out in controlling the spread and containing the virus.

The Life Cycle of SARS-CoV-2 and Infection

Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism divided into 3 parts, namely entry, replication, and release, as shown in **Figure 2**. Firstly, the infection starts when the viral spike (S) glycoprotein attached to the complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the availability of the host cell protease, cleavage and activation allow cell entry by endocytosis or direct fusion of the viral envelop with the host membrane.²⁸

On entry into the host cell, the virus is uncoated, and its genome enters the cell cytoplasm.²⁹ The coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail, which allows the RNA to attach to the host cell's ribosome for translation, and translates the initial overlapping of the virus genome and forms a long polyprotein.³⁰ The polyprotein consists of proteases which cleaves it into multiple nonstructural proteins.²⁹

Secondly, coronaviruses replicates and transcribes RNA from the strand by using the SARS-CoV-2 replication mechanism, which binds cell surface molecules such as metalloprotease amino peptidase with hemagglutinin esterase (HE-protein) and N-acetyl neuraminic acid as co-receptor. Furthermore, the virus goes into the host

cell by fusion of viral and cell membranes or through the receptor-mediated endocytosis incorporated via an endosome, which is subsequently acidified by proton pumps. Meanwhile, the virus produces direct proteins and new genomes in the cytoplasm, particularly single positive-stranded RNA gen. Otherwise, the negative strand serves as a template used to transcribe smaller subgenomic positive RNAs used to synthesize all other proteins. After binding, assembled nucleocapsids with twisted helical RNA, it enters into the endoplasmic reticulum (ER) lumen and is encased with the membrane as shown in **Figure 2**.³¹ Thirdly, the replicated positive-sense of genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts after the initial overlapping reading frame translated by the host's ribosomes into the structural proteins.³² RNA translation occurs inside the endoplasmic reticulum, which consists of S, E, and M proteins that move along the secretory pathway into the Golgi intermediate compartment. Therefore, the M proteins are required to assemble and bind the virus into the nucleocapsid.³³ Progeny viruses are released from the host cell by exocytosis through secretory vesicles.²⁹

Diagnosis

The proper diagnosis characteristics used to manage COVID-19 is the first line of control and a deciding factor in the initiation of the course of treatment. This is different from the common cold, which is properly treated with the right drugs. Sometimes the results of preliminary examinations in infected people do not provide a clear diagnosis of the infection, therefore, doctors tend to ask the patient to provide a detailed and accurate diagnosis of their disease such as cough, flu, fever, and so on. The identifying and providing effective support, sputum examination, and

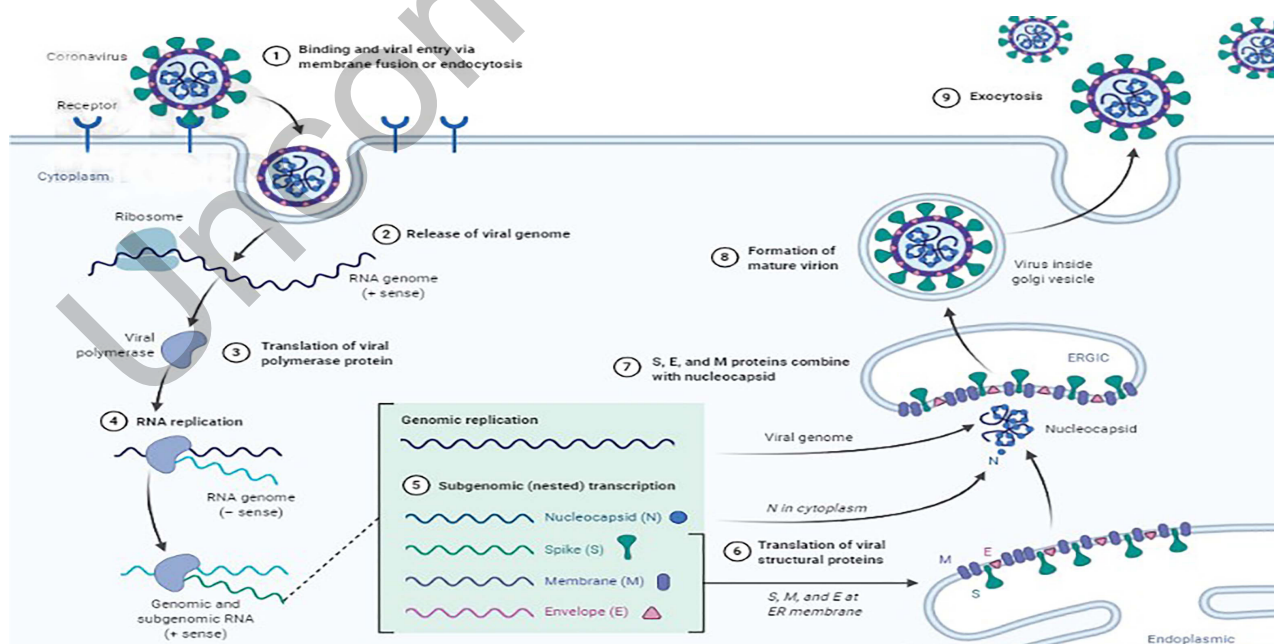


Figure 2. The life cycle of coronavirus including the viral spike (S) glycoprotein attach to the complementary host cell receptor via membrane fusion or endocytosis then release of viral genome, translation of viral polymerase protein, RNA replication, subgenomic transcription and translation of viral structural proteins. S, E, and M protein combine with nucleocapsid forming mature virion and exocytosis.

other diagnostic tests help to determine the infection early. Also, the number of days from the infected date is noted at the laboratory to recommend individual diagnostic tests as follows:

Reverse transcription-polymerase chain reaction (RT-PCR)

This is a standard technique for determining the virus by rRT-PCR from a nasopharyngeal swab. A sputum sample is used to obtain the required results within hours to 2 days.³² Sample measurements (Swab test) consist of some steps using RT-PCR, as shown in Figure 3.

Enzyme-linked immunosorbent assay (ELISA)

Antibody assays are used to test infected people using their blood serum sample, with the results released with few days.³³

Computerized-Tomography (CT-Scan)

The contamination is analyzed from a mixture of side effects, chance elements, and a chest CT scan demonstrating highlights of pneumonia.³⁴ The fundamental diagnosis reports from medical clinics in China show that majority of COVID-19 infected patients were determined using pneumonia and trademark CT imaging patterns.³⁵ Furthermore, radiological assessments have become imperative in early determination and appraisal of disease course.³⁶ CT scan of various COVID-19 contaminated patients differed in pattern³⁷, and almost 50% of patients were discovered from pictures. On admission to emergency

clinics, the ground-glass haziness was the most widely recognized radiologic finding on chest figured tomography (CT)³⁷ of 56.4% of patients.³⁸ The longitudinal CT discovered infected patients with pneumonia with follow up checks over the course of treatment. Besides that, it was seen that numerous patients did not have strange radiologic findings.³⁹

Treatments of COVID-19

The mechanism of viral infection is the entry of the virus into cells and multiplication using a host cellular method characterized by damages to the host cell as a key for the development of new drug compound therapies. Currently, there is no definitive and recommended therapy for COVID-19 because it is a new virus, and making a vaccine required numerous clinical analyses and tests. One of examples of treatment therapy i.e. convalescent plasma therapy which is the administration of plasma from a recovered COVID-19 patient to a Covid-19 patient who is still suffering from illness, so antibodies (immunity) in the plasma of the cured patient can help patients who are still ill to cope with the disease.^{3,39} However, all antivirals used in COVID-19 therapy in almost all countries are still in the form of trial and error. Some countries have referred to the antiviral therapy used during the occurrence of the SARS and MERS epidemic several years ago, such as lopinavir, ritonavir, ribavirin, oseltamivir, etc. These drugs have been used and were quite effective in dealing with SARS and MERS during the epidemic.³ Similarly, there are no definitive guidelines for dealing with COVID-19 in Indonesia, as the country also relies on an existing drug

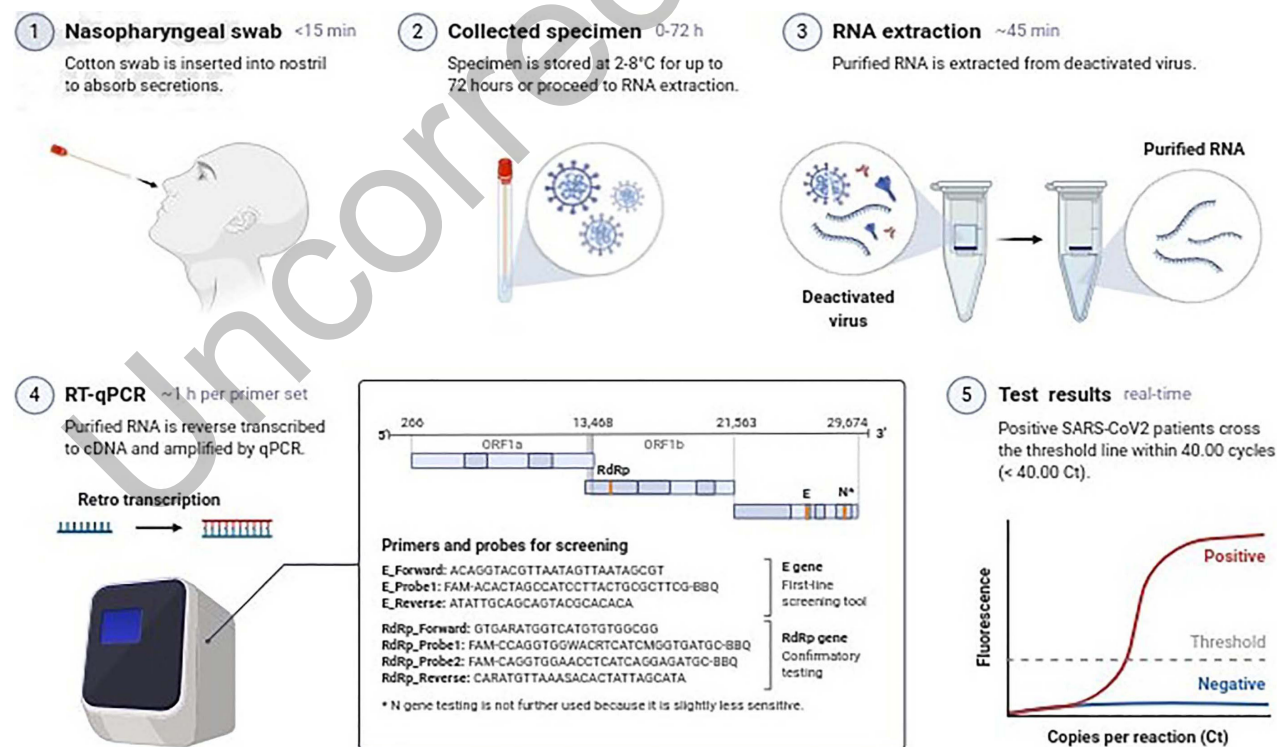


Figure 3. The steps of coronavirus disease 2019 (COVID-19) diagnostic test through reverse transcription polymerase chain reaction (RT-PCR) by nasopharyngeal swab using cotton swab, collecting specimen, extracting RNA, operating RT-PCR, and showing positive or negative results. Created with BioRender.com.

such as oseltamivir. Indonesia has tried reaching out to China regarding the drugs used to treat their infected citizens, including the purchase of Chloroquine and Avigan. Some prospective drugs are considered to direct current applications or the development of new therapeutic drugs, including modern and herbal medicines.

Entry inhibitors

The SARS-CoV-2 infects the respiratory system and alveoli cells in the lung sacs would be the host for viral infection. In general, viruses enter the host cell by forming complex projections such as spikes or lobes with receptors. However, the exact structure or lobe of SARS-CoV-2 is not fully determined,⁴⁰ although prior experience of coronavirus (β -family), shows it has similarities with the receptor of host cells of SARS.⁴¹ Recently it has been found that Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-CoV) and (SARS-CoV-2).⁴² ACE2 has some homology with an angiotensin-converting enzyme (ACE) although it is not inhibited by ACE inhibitors.³ A previous SARS case was characterized by an infection that was started by the transmembrane (S) spike in the glycoproteins binding the host receptor and combines viruses to cell membranes. The identification of the viral / spikes lobes molecular structure is time-consuming, while the development of facilitated heterocyclic drug molecules or existing heterocyclic screening has the ability to bind the entry inhibitor drug.⁴³

Replication inhibitors

COVID-19 is an RNA virus that utilizes host cells for

genomic replication by encoding the RNA-dependent RNA polymerase (RdRp), which allows the viral genome to be transcribed into new RNA copies using the host cell's machinery. The viral genome replication mechanism serves potential targets for the control of viral infections, while antiviral drugs (Figure 4) such as Remdesivir and Favipiravir (Avigan)⁴⁴ has the ability to potentially affect SARS-CoV-2 as shown in Figures 4A and B. The nucleotide adenosine analogue antiviral for Ebola and RNA viruses have shown some promising results in the clinical control of this virus.⁴⁵ However, further evaluation is needed for potential applications with more patients. The action mechanism of Remdesivir as antiviral drug as shown in Figure 5.

Favipiravir is the brand name for Avigan, also known as T-705, which is an antiviral drug developed by Toyama Chemical, a Fujifilm group, located in Japan with activity against many RNA viruses. In Japan, this drug was originally developed to treat influenza, however, in February 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel coronavirus) disease. The action mechanism of favipiravir can inhibit replication and translation of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses, as shown in Figure 6.⁴⁶ Further studies have shown that favipiravir induces mutant of RNA transversion, resulting in a viable viral phenotype. This product is metabolized by human hypoxanthine-guanine phosphoribosyltransferase (HGPRT) known as favipiravir-ribofuranosyl-5-triphosphate (favipiravir-RTP). During this COVID-19 pandemic, in a limited clinical trial with 80 subjects, favipiravir showed an

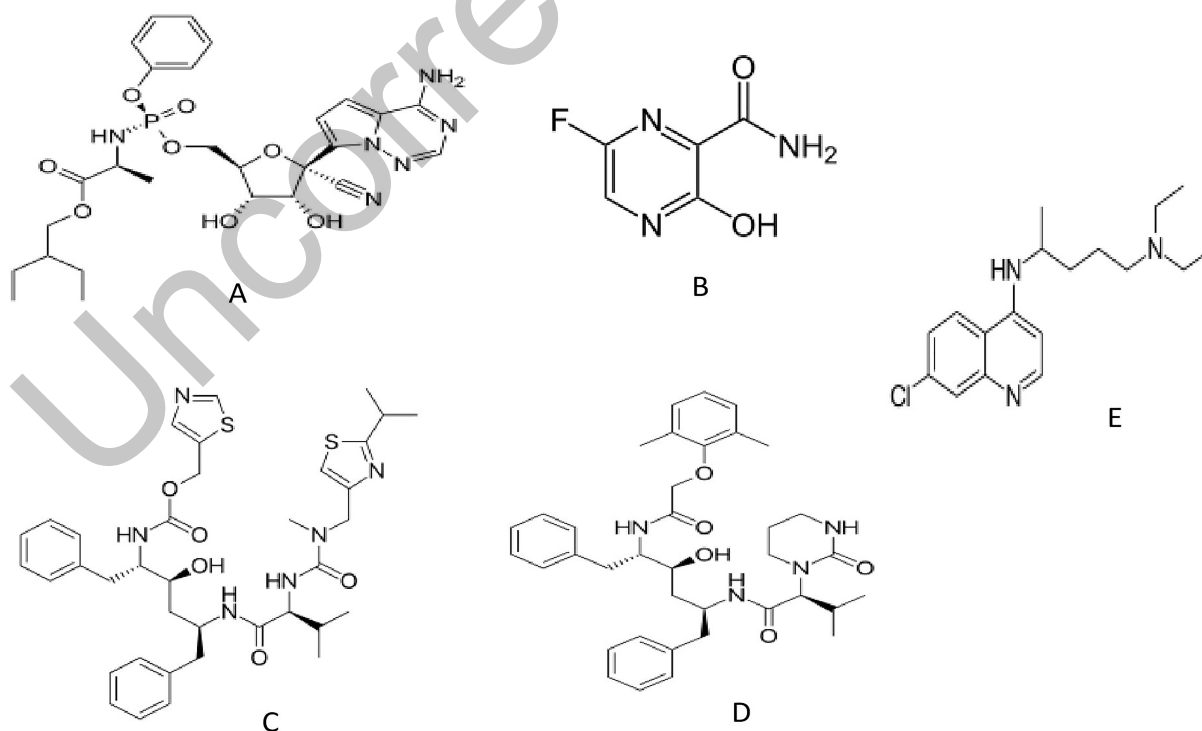


Figure 4. Chemical structures of Remdesivir (A), Favipiravir (B), Ritonavir (C), Lopinavir (D), Chloroquine (E)

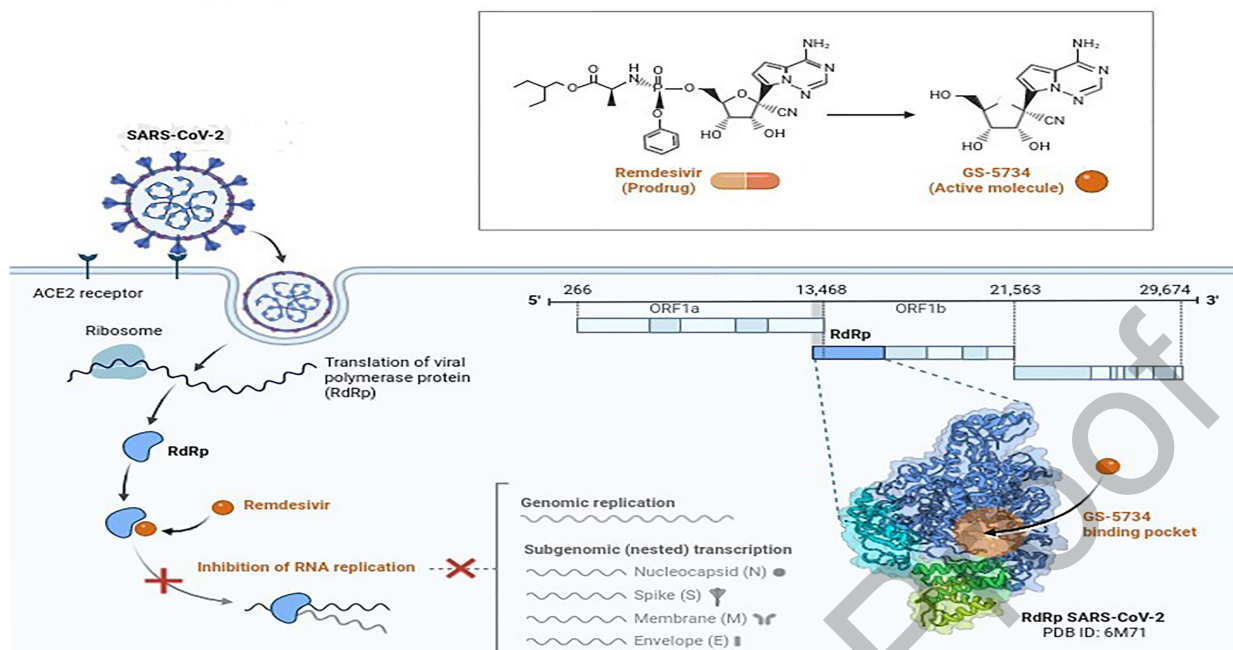


Figure 5. The action mechanism of Remdesivir against coronavirus by changing Remdesivir as prodrug into active molecule GS-5734, binding drug target molecule (RdRp), and inhibiting RNA replication in membrane cell. *Created with BioRender.com.*

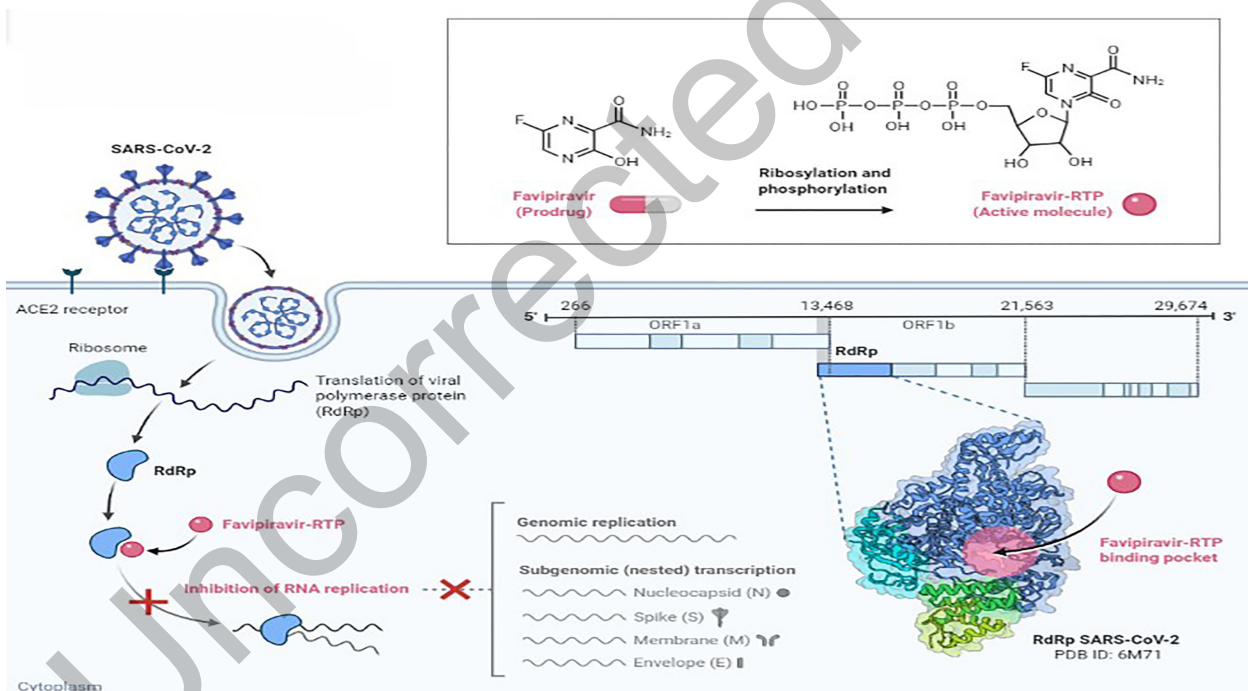


Figure 6. The action mechanism of Favipiravir as a potential repurposed drug candidate for COVID-19 which can inhibit replication and translation of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses. *Created with BioRender.com.*

antiviral potential for SARS-CoV-2 that was better than lopinavir/ritonavir.⁴⁷ Many other nucleoside analogues including DNA synthesis such as tenofovir, disoproxil, lamivudine, and other antivirals have the potential to inhibit the multiplication of SARS-CoV-2 and are being evaluated through molecular docking studies and testing in infected cell culture.⁴⁸

Protease inhibitors

Protease enzymes are involved within the maturation

stage of virus replication inside the host cell and related to protein or peptide translation. Figures 4C and D, shows that Lopinavir and ritonavir are approved anti-HIV drugs, and a combination of both aids in the inhibition of SARS-CoV-2.^{49,50} A research carried out by Lim J et.al.⁵¹ on the remedy used to treat persons affected with COVID-19 in Korea indicated that the administration of lopinavir/ritonavir (Kaletra, AbbVie) extensively reduced the virus. This means that a detailed analysis is needed for the recommendation of this drug and the formation of

new drug compounds. Molecular docking of potential inhibitors provide clear information because detailed docking simulation results have shown essential input in previous SARS cases and other viral infections.⁵¹⁻⁵³ However, a lot of clinical data needs to be conducted to prove the efficacy and safety of the human body.

Heterocyclic antiviral

Over the decades, many heterocyclic drug molecules have been used in the treatment of viral infections, and these drugs are thought to be probably slightly effective in inhibiting SARS-CoV-2. An example is Chloroquine, which was originally an antiplasmodium used to treat malaria. This drug contains a quinoline group as shown in Figure 4E and inhibits the activity of the enzyme heme polymerase into hemozoin. This accumulation kills the Plasmodium parasite responsible for malaria.⁵⁴ However, with the decrease in malaria and the emergence of plasmodium resistance to Chloroquine, this drug is no longer used. Also, Chloroquine and hydroxychloroquine are used for antiviral therapy. Gao et al. (2020) stated that Chloroquine has a strong antiviral effect against the virus in primate cells. This inhibitory effect is observed when cells are treated with Chloroquine both before and after exposure, which shows that it has a preventive and therapeutic effect. In addition, Chloroquine and hydroxychloroquine are weak bases that are known to elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes, essential for membrane fusion inhibiting SARS-CoV-2 entry through changing the glycosylation of ACE2 receptor and spike protein, shown in Figure 7.⁵⁵⁻⁵⁷ This inhibits the receptor which prevent infection and spread of the SARS-CoV-2 at concentrations that cause clinical response. In the SARS-

CoV-2 pandemic in China, Chloroquine was used at a dose of 500 mg for adult 2 times a day, for 10 days.⁵⁶ Chloroquine and hydroxychloroquine are also currently being tried in Malaysia at the same dosage used in China and Indonesia. There are several heterocyclic antiviruses previously used as antivirals such as HIV, H1N1, H1N5, and SARS, which are further examined for the treatment of COVID-19. Oseltamivir (Tamiflu) has been widely used as a neuraminidase inhibitor for the treatment of influenza was also recommended.⁵⁷ In addition, other candidate compounds evaluated with antiviral activity against SARS-CoV-2 are heterocyclic based on ACE2 peptides namely 3C-like protease (3CLpro and 3CLpro-1) inhibitors and vinyulfone protease inhibitors.^{58,59}

Nano Drug Delivery Systems

Drug delivery systems in the form of nanoparticle preparations have been widely used to improve the bioavailability in the blood and enhance the transport and efficacy antiviral drugs especially nucleoside analogues on conjugation with potential delivery systems that have been proven in drug-resistant HIV infection.⁶⁰⁻⁶³ The wide variety of available nano delivery system can be used with the new developed drug formulation which could be efficacious in delivering the drugs with faster therapeutic indices for COVID-19.⁶³⁻⁶⁷

Biological Therapeutics

Antibody therapy can be used for the treatment of COVID-19 infections. However, this vaccine still requires approximately 1 year before it can be globally utilized to prevent the spread of the virus. According to Tian et al. specific human monoclonal antibodies such as CR3022 are

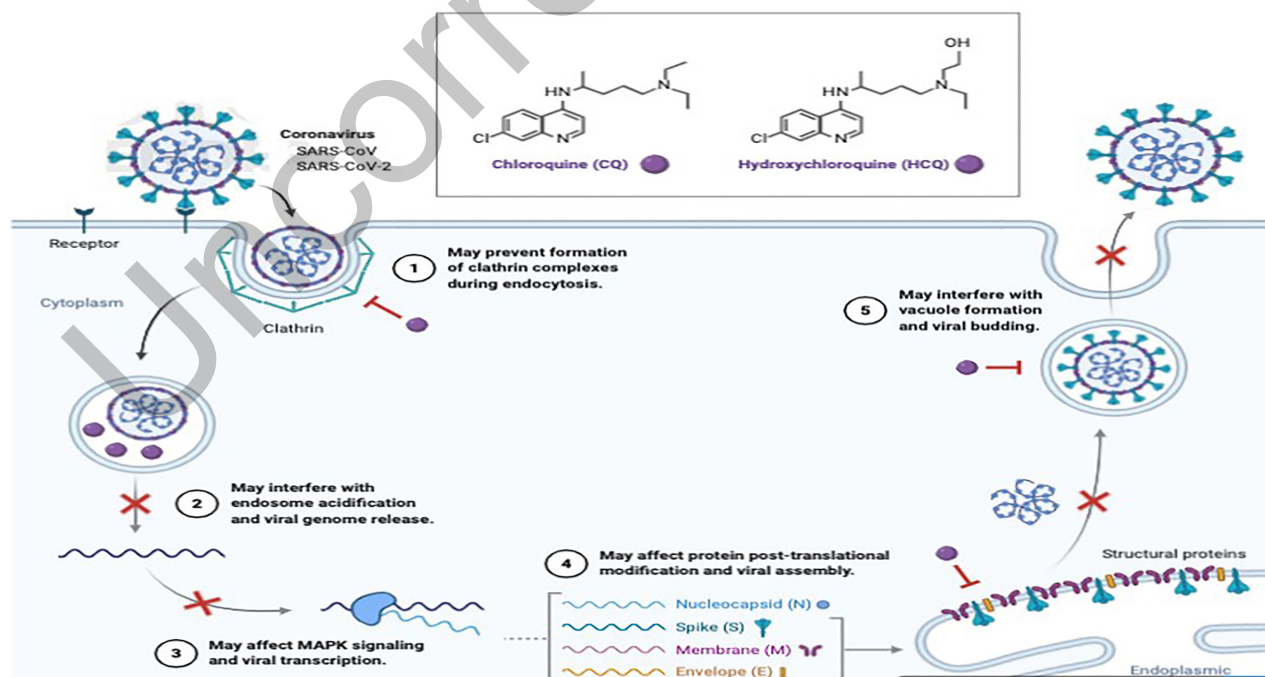


Figure 7. The molecular mechanism of chloroquine in membrane cell by preventing the formation of clathrin complexes in the cytoplasm during endocytosis, interfering with endosome acidification and viral genome release, affecting MAPK signaling and viral transcription, affecting protein post-translational modification, and interfering vacuole formation and viral budding. [Created with BioRender.com.](#)

intended to bind strongly to SARS-CoV-2 receptor binding domain (= RBD) (KD 6.3 nM) and overlap the ACE2 binding site.⁶⁸ These unique results indicate the possibility of developing a therapeutic vaccine with a combination of other antibodies. However, *in vitro* trials and clinical studies are needed to obtain accurate clinical data for the prevention and treatment of COVID-19 infections.⁶⁸

In developing a new vaccine one must pay attention to the similarity of immunogenic structural proteins similar to SARS, MERS for SARS-CoV-2.⁶⁹ Ahmed et al. used a set of B and T cell epitopes derived from spikes (S) and nucleocapsid proteins (N) to identically map the SARS-CoV-2 protein.⁷⁰ Reports suggested that the identified epitope has no available mutase sequence. Therefore, this target immune epitope has the potential to be explored in the fight against the SARS-CoV-2. However, the final results depend on *in vitro* and future clinical trials.⁷⁰

Herbal drugs

The herbal formulations used as alternative medication has been a success in presenting the remedy to a number of infections in conjunction with symptom specific remedy using herbs.⁷¹⁻⁷³ The initial lead from herbal medicinal drug has been successful in developing final applicable formulations like Praneem (a natural extract of neem tree) as microbicide for HIV therapy.⁷⁴ Therefore, various

studies have been conducted on the use of herbal drugs to test the active compounds of some herbal in Indonesia by molecular docking in silico (Table 1).

According to University of Indonesia (UI) and Institute of Bogor Agriculture (IPB) researchers, they stated that some chemical compounds which originated from several plants in Indonesia have the potential ability to prevent COVID-19 infection in the form of molecular docking in silico. Based on the results of prediction models with machine learning methods, namely SVM (support vector machine), random forest, and MLP (multilayer perceptron) neural network is associated with 20,644 interactions of protein compounds. The results are 31 herbal compounds with 5 target proteins 3CLPro (Chymotrypsin-like protease), PLPro (Papain-like protease), Spike-ACE2, EIF4 (Eukaryotic initiation factor-4), and RdRp. Modeling of structure and ligand based pharmacophores was used to carry out virtual screening with 1,377 compounds from the HerbalDB database.⁷⁵ The results of compound hit from machine learning, and pharmacophore mapping was confirmed using molecular docking.

Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin, quercetin, luteolin, kaempferol, isorhamnetin⁷⁶, and hesperidin.⁷⁷ Luteolin is a furin protein inhibitor⁷⁸ and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein

Table 1. Active compounds having the potential as antiviral SARS-CoV-2⁸¹

Target	Compounds	Sources
3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	<i>Cassia alata</i> , ³⁰
	Kaempferol 3,4'-di-O-methyl ether (Ermanin)	<i>Tanacetum microphyllum</i>
	Cyanidine 3-sophoroside-5-glucoside	<i>Brassica oleracea</i> , <i>Ipomoea batatas</i> , <i>Raphanus sativus</i>
	Casuarinin	<i>Psidium guajava</i>
	Quercetin 3-(2G-rhamnosylrutinoside)	<i>Clitoria ternatea</i>
	Peonidine 3-(4'-arabinosyl)glucoside)	<i>Ipomoea fistulosa</i>
	Hesperidine	<i>Psidium guajava</i> , <i>Citrus aurantium</i>
PLpro	Platycodin D	<i>Platycodon grandiflorus</i>
	Baicalin	<i>Scutellaria baicalensis</i>
	Sugetriol-3,9-diacetate	<i>Cyperus rotundus</i>
	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	<i>Isatis indigotica</i>
	(-)-epigallocatechin gallate	<i>Camellia sinensis</i>
	2-(3,4-Dihydroxyphenyl)-2-[[2-(3,4-Dihydroxyphenyl)-3,4-dihydro-5,7-dihydroksi-2H-1-benzopyran-3-yl]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	<i>Vitis vinifera</i>
RdRp.	Betulanol	<i>Cassine xylocarpa</i>
	Gnidicin	<i>Gnidia lamprantha</i>
	2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	<i>Viola diffusa</i>
	14-deoxy-11,12-didehydroandrographolide	<i>Andrographis paniculata</i>
	1,7-dihydroxy-3-methoxyxanthone	<i>Swerti apseudochinensis</i>
	Theaflacin 3,3'-di-O-gallate	<i>Camellia sinensis</i>
	2-(3,4-dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5-7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	<i>Vitis vinifera</i>
Hesperidine	<i>Psidium guajava</i> , <i>Citrus aurantium</i>	

in MERS into units of S1 and S2.^{79,80} In the S1 unit, there is a receptor-binding domain (RBD) where the ACE2 peptidase binds the virus in the host cell.⁸⁰ The Hesperidin/hesperitin compound in the silico study inhibits the RBD of the SARS-COV-2 Spike protein which is also known as luteolin having a neuramidase inhibitor as well as oseltamivir which is currently one of the drugs used in the CDC protocol.⁸¹ Hesperidin a form of hesperidin aglycone and Quercetin is also known to act as inhibitors of 3CLpro virus proteins.^{82,83} Other compounds in guava such as myricetin act as SARS coronavirus helicase inhibitors.⁸⁴ The kaempferol has the potential to be a non-competitive inhibitor of 3CLPro and PLpro as well as quercetin.⁸⁵ It also acts as a autophagy modulator, inducer and inhibitor, of the virus.

Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived from plants. One of the commonly used condiments for cooking or herbal medicine in Indonesia is empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. Furthermore, animals such as snakehead fish also improve immune system in the body due to high protein and amino acids.⁸⁶⁻⁸⁸ According to UNAIR (University of Airlangga) researchers stated that the approach that can be taken in the public by consuming empon-empon to boost the immune system to avoid COVID-19.⁷⁹

Turmeric containing curcumin have been consumed and proven by people for centuries and beneficial to health. For example it is used to maintain fitness vitality, liver, and digestive systems based on empirical experimental evidence. Various studies have been carried out in vitro and preclinical tests showing that curcumin is anti-inflammatory, antiviral, antibacterial, antifungal, and antioxidant based on scientific evidence.^{89,90}

One of the benefits of curcumin obtained from clinical trials is to increase the body's immune system. Recent research on curcumin against the virus shows that the SARS-CoV-2 receptor is an enzyme ACE2 found in host cells of human especially alveolus lungs. However, the cell entry of the virus depends on the binding of the spike virus protein, the receptor on the host cell (ACE2) and pad priming protein spike (TMPRSS2).⁹⁰

Conclusion

The surging spread of the virus through human-to-human transmission has created a change in human life that must meet health protocol standards including therapy protocols to combat COVID-19. Few existing drugs had been evaluated for the remedy of SARS-CoV-2 and shown promising good effects in clinical applications. The chemical and herbal drugs for the management of viral infection symptoms have been on the frontline to mitigate this novel viral infectious disease and have helped the number of patients in safe healing from COVID-19. Several drugs have been clinically evaluated for the treatment of COVID-19, which showed promising results and assisted a number of patients to recover safely. There is continuous research on the potential of therapeutics in evaluating the existing

antiviral drugs such as modern and herbal medicines.

Conflict of Interest

The authors claim that there is no conflict of interest

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COVID-19: Clinical Characteristics and Molecular Levels of Candidate Compounds of Prospective Herbal and Modern Drugs in Indonesia

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Abstract

A recent outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease also called Coronavirus disease 2019 (COVID-19) in China, has rapidly spread to other countries of the world. The medical and scientific communities are working tirelessly to produce a vaccine due to the lethal nature of this virus. COVID-19 is a novel virus that requires immediate emergency therapy, thereby leading to massive fear of infection, social problems in the community, and an increase in the number of infected people. Therefore, scientists and researchers need to determine the epidemiological cases of the virus, such as its mode of transmission, effective preventive measures, and the nature of the life cycle. In addition, there need to be current literature advances in diagnostic development such as reverse transcription polymerase chain reaction (RT-PCR), computed tomography scan (CT-Scan), Elisa as well as clinical researches on modern and herbal drugs for the treatment of infected patients. This treatment technique is classified from antiviral drugs such as entry, replication, nucleosides, nucleotides, and protease inhibitors, along with the use of heterocyclic drugs, monoclonal antibodies therapy, vaccine development and herbal formulations that have been pre-clinically tested in vitro and molecular docking. Chemical drug molecules with prospective applications in the treatment of COVID-19 have been included in this review.

Introduction

In December 2019, the Chinese city of Wuhan experienced a rapid spread in an infectious disease, which affected the respiratory system, thereby leading to a high mortality rate. This virus, known as Coronavirus disease 2019 (COVID-19), soon spread to other countries and was declared a pandemic by the World Health Organization (WHO).¹ Infected people show symptoms of pneumonia, which is similar to SARS (Severe Acute Respiratory Syndrome). This disease is caused by a lethal virus in nature and is currently the highest leading cause of mortality all over the world.² The first reported case was in China, and within a few months, it has spread to almost all countries and continents in the world.² According to studies, the most significant numbers of cases of infected people are in South Korea, Italy, Iran, South Africa, the USA, and Indonesia. In a recent update by WHO, over 90,000 people all over the world are infected with approximately 3,000 deaths. China alone recorded 2,500 deaths by the end of February 2020.³ The WHO declared the virus a pandemic due to its rapid spread in various countries. It is speculated that this virus originated from different animals consumed as food in China. Early transmission studies reported that it

originated from local fish and wild animal markets with possible transmission from animals to humans and vice versa. However, this speculation has not been proven. This disease has led to a very high increase in mortality all over the world.⁴

In Indonesia, the virus was not in existence till the end of April 2020, based on data from the Ministry of Health. Since its inception, there has been a rapid increase in the mortality rate due to the high number of infected people.⁵ Therefore, based on these data, the Indonesian government quickly responded and took preventive measures to reduce the spread of this virus. Before now, no drug or vaccine has been proven to kill or inhibit the COVID-19 virus. However, WHO announced that over 20 countries and pharmaceutical companies around the world are developing vaccines and drugs to fight the virus.⁶ Unfortunately, this development is going to take at least a year before completion. Meanwhile, several types of modern and herbal COVID-19 treatments have been clinically tested, such as Remdesivir and Chloroquine, as well as curcumin (in vitro study).

The emergence and rapid spread of this virus have hastened

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the development of diagnosis and medicines for the treatment of this infectious disease. In Indonesia, doctors have used several existing modern and herbal medicines, with national and international health institutions, to understand the mechanism, virulence, and pharmacology of the virus to develop possible drugs and vaccines. This review discusses the literature report on progress regarding diagnostic methods and developmental therapies with the possible use of candidate compounds of modern and herbal medicines for COVID-19 infectious diseases in Indonesia.

The Coronaviruses

Coronavirus, a genus of the Coronaviridae family, is a positive-strand and the most significant viral genome of all RNA viruses (27–32 kb), causing a wide range of diseases related to the respiratory system. The symptoms may vary from the common cold, dry cough to more severe respiratory diseases.⁷ Furthermore, it consists of 80 to 160 nm particles, 4 or 5 structural spike (S), membrane (M), hemagglutinin-esterase (HE), nucleocapsid (N), and small envelope E proteins.⁸ In addition, the virion structure consists of S glycoprotein, which forms petal-shaped spikes on the surface with 180 to 200 KDa molecule that is cotranslationally glycosylated in the endoplasmic reticulum as shown in Figure 1.⁸ SARS-CoV-2 was a new strain of the current virus,^{9,10} which was transmitted from animals to human¹¹, however, the new coronavirus infects humans.

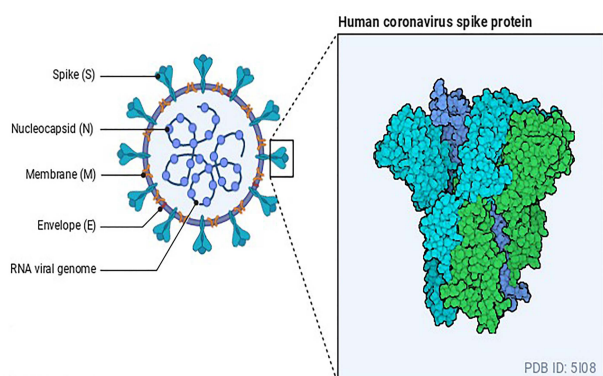


Figure 1. Structure of new coronavirus and protein visualization, now designated severe acute respiratory syndrome coronavirus-2, (SARS-CoV-2)

COVID-19 Transmission

COVID-19 spreads rapidly amongst humans with symptoms and asymptomatic carriers. The virus is easily spread when the liquid droplet of an infected person drops on surfaces when the patient coughs or sneezes. Transmission in certain cases is usually through the air, by staying close to an infected person.¹² Meanwhile, asymptomatic patients are hidden carriers of the virus and contribute to a greater transmission of the virus. This manual transmission also spread, assuming the patient has symptoms.³ In addition, vertical transmission of the virus from mother to child has not been observed according to research conducted by Chen H et al. in a small group of

pregnant women. They stated that the virus is vertically intrauterine and non-transmittable from mothers to unborn babies. The emergence and the spread of this new virus is due to the increase in human populations which causes proximity.^{13,14}

Symptoms and Mortality of COVID-19

Symptoms of COVID-19 are indicated by the occurrence of respiratory distress similar to acute respiratory distress syndrome (ARDS), which marked respiratory infections on COVID-19 patients. These include runny nose, fever, cough, shortness of breath, sore throat, and mild to moderate upper respiratory tract illness. In severe cases, patients experience pneumonia, SARS, kidney failure, and even death. An infected patient shows full signs of the virus within two to seven days. However, the median incubation duration of infection development changed to 4 days with an interquartile variety of 2 to 7 days in all patients.¹⁵ This is known as the incubation period which progresses for four days with an interquartile range.¹⁶

Study conducted by Guan et al. showed the middle-aged were more prone to infection compared to other categories of people.¹⁷ Approximately 41.9% of the total number of patients were women, therefore, there are gender differences in the spread of the virus. The report also stated that the primary composite endpoint occurred in 6% of patients. In Wuhan city, there was no gender difference in people infected with COVID-19 with the highest mortality rates of 8.4% by 20 March 2020.^{18,19} However, research shows that the elderly and young children are most at risk from the infection. This is similar to SARS, though it appears nCoV-2019 is less lethal compared to SARS and MERS, this is because approximately 15 to 20% of cases become severe within a limited timeframe. According to doctors, the lethal rate is about 1 in 10 which caused by enveloped virus meaning that it is protected by a glycoprotein shell, thereby, making it difficult to treat.^{20,21}

Preventive Measures

All countries, including Indonesia, need preventive measures to overcome the spread of COVID-19, which currently has no known cure and vaccines. Therefore, handling infected patients has been recommended as one of the steps to control the rampant spread of the virus among people. However, it is difficult to force the isolation of infected patients because this causes many social problems. Like many reports in the Indonesian media, the practice of forced confinement of infected people at home is very difficult for health workers and the police. The isolation of infected individuals supported the provision of complete hospital treatment is one of the moral control methods.²² Therefore, appropriate research studies need to be conducted to understand the best approach in infection prevention including assessing the country's ability to slow the spread of infected people.²³

In Indonesia, the standard procedures recommended for preventing the spread of infection are more effective in

controlling the spread and keeping things safe. The most crucial strategies include washing of hands after visiting public places and frequent exercises.^{24,25} Other practices involve overlaying mouth and nostrils when coughing and sneezing to prevent the spread of the virus, assuming the person is asymptomatic or in preliminary degrees of contamination.^{26,27} Also, proper cooking of foods such as meat, eggs, and animals helps to destroy the virus. In practice, one needs to avoid close contact with anyone showing symptoms of respiratory illnesses such as cough, flu, asthma, pneumonia, and tuberculosis. Therefore, this simple precaution can be effectively carried out in controlling the spread and containing the virus.

The Life Cycle of SARS-CoV-2 and Infection

Novel Coronavirus 2019 (COVID-19) has a life cycle mechanism divided into 3 parts, namely entry, replication, and release, as shown in Figure 2. Firstly, the infection starts when the viral spike (S) glycoprotein attached to the complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the availability of the host cell protease, cleavage and activation allow cell entry by endocytosis or direct fusion of the viral envelop with the host membrane.²⁸

On entry into the host cell, the virus is uncoated, and its genome enters the cell cytoplasm.²⁹ The coronavirus RNA genome has a 5'-methylated cap and a 3'-polyadenylated tail, which allows the RNA to attach to the host cell's ribosome for translation, and translates the initial overlapping of the virus genome and forms a long polyprotein.³⁰ The polyprotein consists of proteases which cleaves it into multiple nonstructural proteins.²⁹

Secondly, coronaviruses replicates and transcribes RNA from the strand by using the SARS-CoV-2 replication mechanism, which binds cell surface molecules such as metalloprotease amino peptidase with hemagglutinin esterase (HE-protein) and N-acetyl neuraminic acid as co-receptor. Furthermore, the virus goes into the host cell by fusion of viral and cell membranes or through the receptor-mediated endocytosis incorporated via an endosome, which is subsequently acidified by proton pumps. Meanwhile, the virus produces direct proteins and new genomes in the cytoplasm, particularly single positive-stranded RNA gen. Otherwise, the negative strand serves as a template used to transcribe smaller subgenomic positive RNAs used to synthesize all other proteins. After binding, assembled nucleocapsids with twisted helical RNA, it enters into the endoplasmic reticulum (ER) lumen and is encased with the membrane as shown in Figure 2.³¹ Thirdly, the replicated positive-sense of genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts after the initial overlapping reading frame translated by the host's ribosomes into the structural proteins.³² RNA translation occurs inside the endoplasmic reticulum, which consists of S, E, and M proteins that move along the secretory pathway into the Golgi intermediate compartment. Therefore, the M proteins are required to assemble and bind the virus into the nucleocapsid.³³ Progeny viruses are released from the host cell by exocytosis through secretory vesicles.²⁹

Diagnosis

The proper diagnosis characteristics used to manage COVID-19 is the first line of control and a deciding factor in the initiation of the course of treatment. This is different from the common cold, which is properly treated with

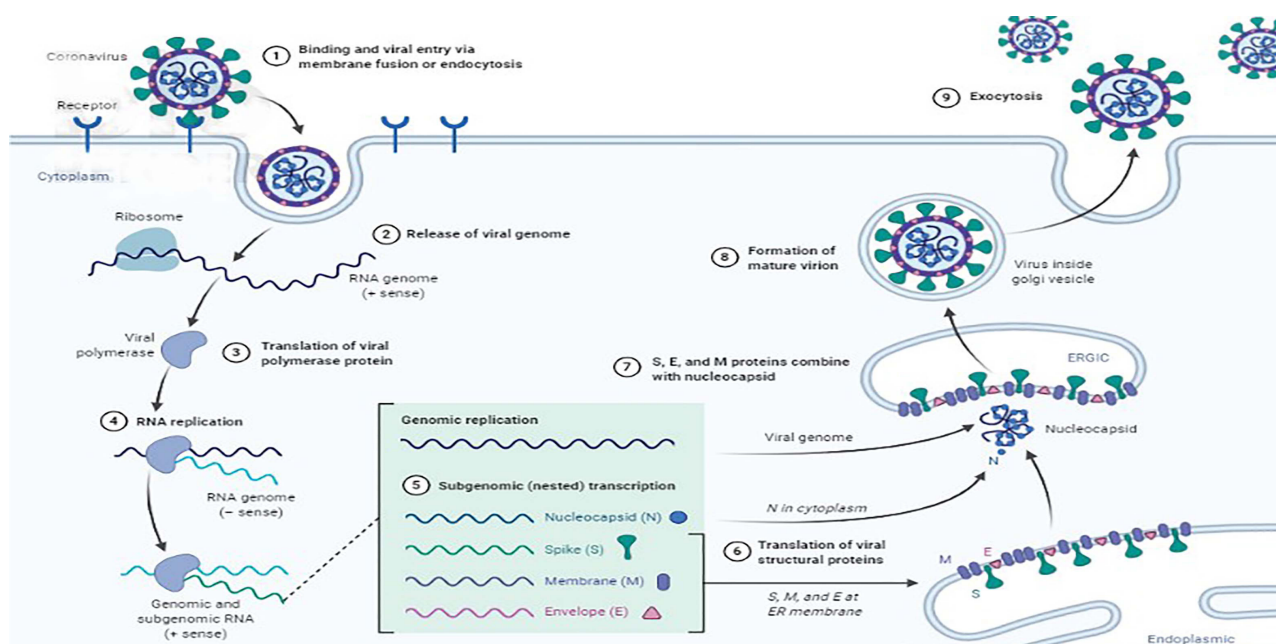


Figure 2. The life cycle of coronavirus including the viral spike (S) glycoprotein attach to the complementary host cell receptor via membrane fusion or endocytosis then release of viral genome, translation of viral polymerase protein, RNA replication, subgenomic transcription and translation of viral structural proteins. S, E, and M protein combine with nucleocapsid forming mature virion and exocytosis.

the right drugs. Sometimes the results of preliminary examinations in infected people do not provide a clear diagnosis of the infection, therefore, doctors tend to ask the patient to provide a detailed and accurate diagnosis of their disease such as cough, flu, fever, and so on. The identifying and providing effective support, sputum examination, and other diagnostic tests help to determine the infection early. Also, the number of days from the infected date is noted at the laboratory to recommend individual diagnostic tests as follows:

Reverse transcription-polymerase chain reaction (RT-PCR)

This is a standard technique for determining the virus by rRT-PCR from a nasopharyngeal swab. A sputum sample is used to obtain the required results within hours to 2 days.³² Sample measurements (Swab test) consist of some steps using RT-PCR, as shown in Figure 3.

Enzyme-linked immunosorbent assay (ELISA)

Antibody assays are used to test infected people using their blood serum sample, with the results released with few days.³³

Computerized-Tomography (CT-Scan)

The contamination is analyzed from a mixture of side effects, chance elements, and a chest CT scan demonstrating highlights of pneumonia.³⁴ The fundamental diagnosis reports from medical clinics in China show that majority of COVID-19 infected patients were determined using

pneumonia and trademark CT imaging patterns.³⁵ Furthermore, radiological assessments have become imperative in early determination and appraisal of disease course.³⁶ CT scan of various COVID-19 contaminated patients differed in pattern³⁷, and almost 50% of patients were discovered from pictures. On admission to emergency clinics, the ground-glass haziness was the most widely recognized radiologic finding on chest figured tomography (CT)³⁷ of 56.4% of patients.³⁸ The longitudinal CT discovered infected patients with pneumonia with follow up checks over the course of treatment. Besides that, it was seen that numerous patients did not have strange radiologic findings.³⁹

Treatments of COVID-19

The mechanism of viral infection is the entry of the virus into cells and multiplication using a host cellular method characterized by damages to the host cell as a key for the development of new drug compound therapies. Currently, there is no definitive and recommended therapy for COVID-19 because it is a new virus, and making a vaccine required numerous clinical analyses and tests. One of examples of treatment therapy i.e. convalescent plasma therapy which is the administration of plasma from a recovered COVID-19 patient to a Covid-19 patient who is still suffering from illness, so antibodies (immunity) in the plasma of the cured patient can help patients who are still ill to cope with the disease.^{3,39} However, all antivirals used in COVID-19 therapy in almost all countries are still in the form of trial and error. Some countries have referred to the antiviral therapy used during the occurrence of

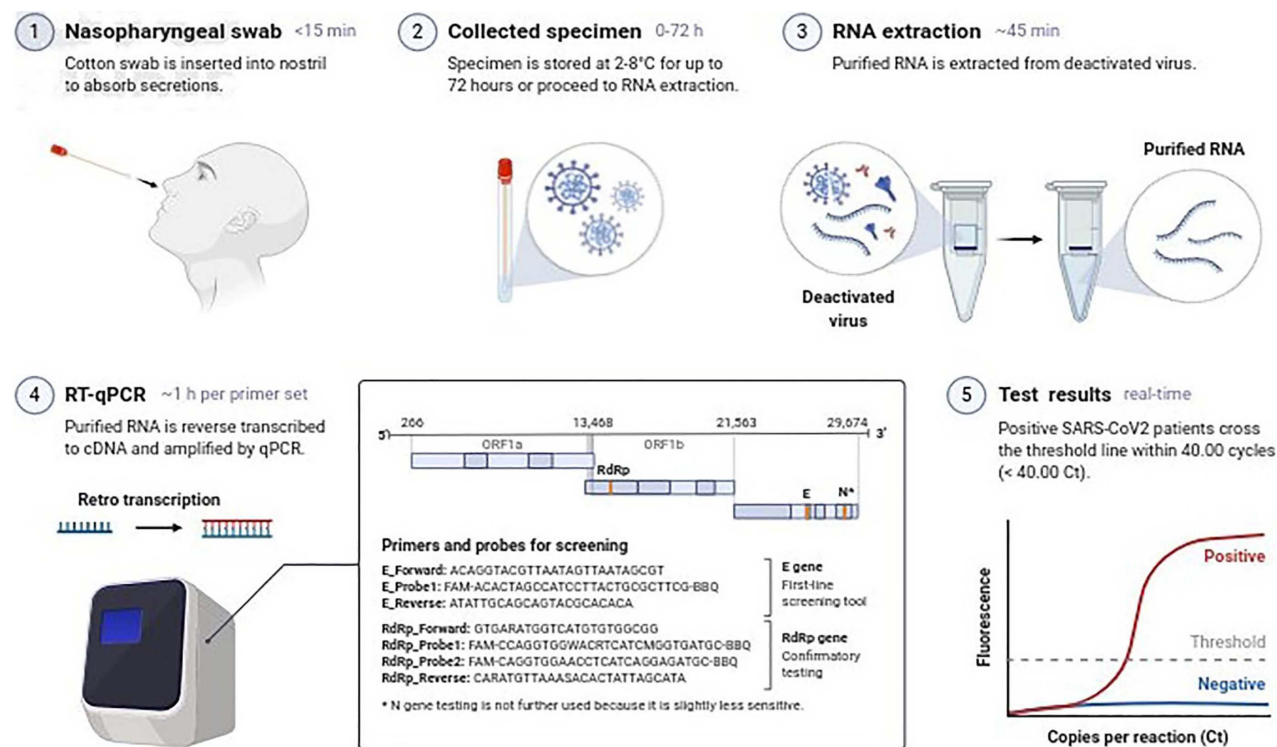


Figure 3. The steps of coronavirus disease 2019 (COVID-19) diagnostic test through reverse transcription polymerase chain reaction (RT-PCR) by nasopharyngeal swab using cotton swab, collecting specimen, extracting RNA, operating RT-PCR, and showing positive or negative results.

the SARS and MERS epidemic several years ago, such as lopinavir, ritonavir, ribavirin, oseltamivir, etc. These drugs have been used and were quite effective in dealing with SARS and MERS during the epidemic.³ Similarly, there are no definitive guidelines for dealing with COVID-19 in Indonesia, as the country also relies on an existing drug such as oseltamivir. Indonesia has tried reaching out to China regarding the drugs used to treat their infected citizens, including the purchase of Chloroquine and Avigan. Some prospective drugs are considered to direct current applications or the development of new therapeutic drugs, including modern and herbal medicines.

Entry inhibitors

The SARS-CoV-2 infects the respiratory system and alveoli cells in the lung sacs would be the host for viral infection. In general, viruses enter the host cell by forming complex projections such as spikes or lobes with receptors. However, the exact structure or lobe of SARS-CoV-2 is not fully determined,⁴⁰ although prior experience of coronavirus (β -family), shows it has similarities with the receptor of host cells of SARS.⁴¹ Recently it has been found that Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-CoV) and (SARS-CoV-2).⁴² ACE2 has some homology with an angiotensin-converting enzyme (ACE) although it is not inhibited by ACE inhibitors.³ A previous SARS case was characterized by an infection that was started by the transmembrane (S) spike in the glycoproteins binding the host receptor and combines viruses to cell membranes. The identification of the viral / spikes lobes molecular structure

is time-consuming, while the development of facilitated heterocyclic drug molecules or existing heterocyclic screening has the ability to bind the entry inhibitor drug.⁴³

Replication inhibitors

COVID-19 is an RNA virus that utilizes host cells for genomic replication by encoding the RNA-dependent RNA polymerase (RdRp), which allows the viral genome to be transcribed into new RNA copies using the host cell's machinery. The viral genome replication mechanism serves potential targets for the control of viral infections, while antiviral drugs (Figure 4) such as Remdesivir and Favipiravir (Avigan)⁴⁴ has the ability to potentially affect SARS-CoV-2 as shown in Figures 4A and B. The nucleotide adenosine analogue antiviral for Ebola and RNA viruses have shown some promising results in the clinical control of this virus.⁴⁵ However, further evaluation is needed for potential applications with more patients. The action mechanism of Remdesivir as antiviral drug as shown in Figure 5.

Favipiravir is the brand name for Avigan, also known as T-705, which is an antiviral drug developed by Toyama Chemical, a Fujifilm group, located in Japan with activity against many RNA viruses. In Japan, this drug was originally developed to treat influenza, however, in February 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel coronavirus) disease. The action mechanism of favipiravir can inhibit replication and translation of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses, as shown in Figure 6.⁴⁶ Further studies have shown that favipiravir induces mutant

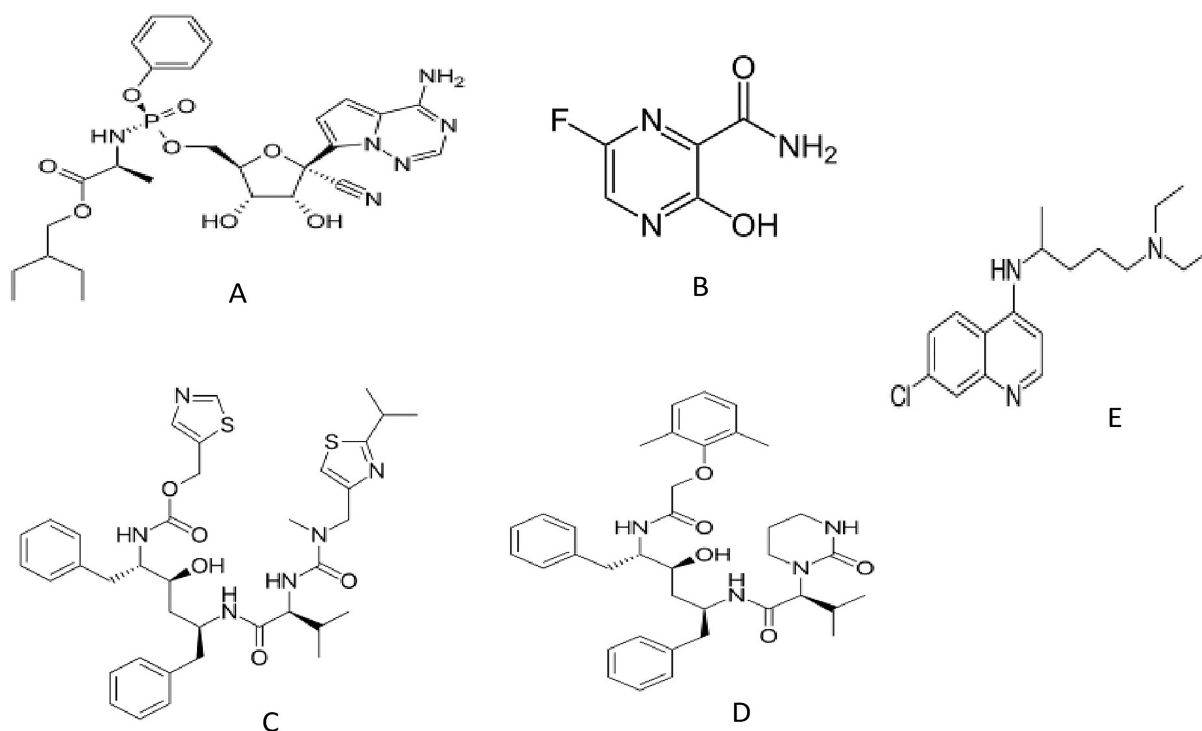


Figure 4. Chemical structures of Remdesivir (A), Favipiravir (B), Ritonavir (C), Lopinavir (D), Chloroquine (E)

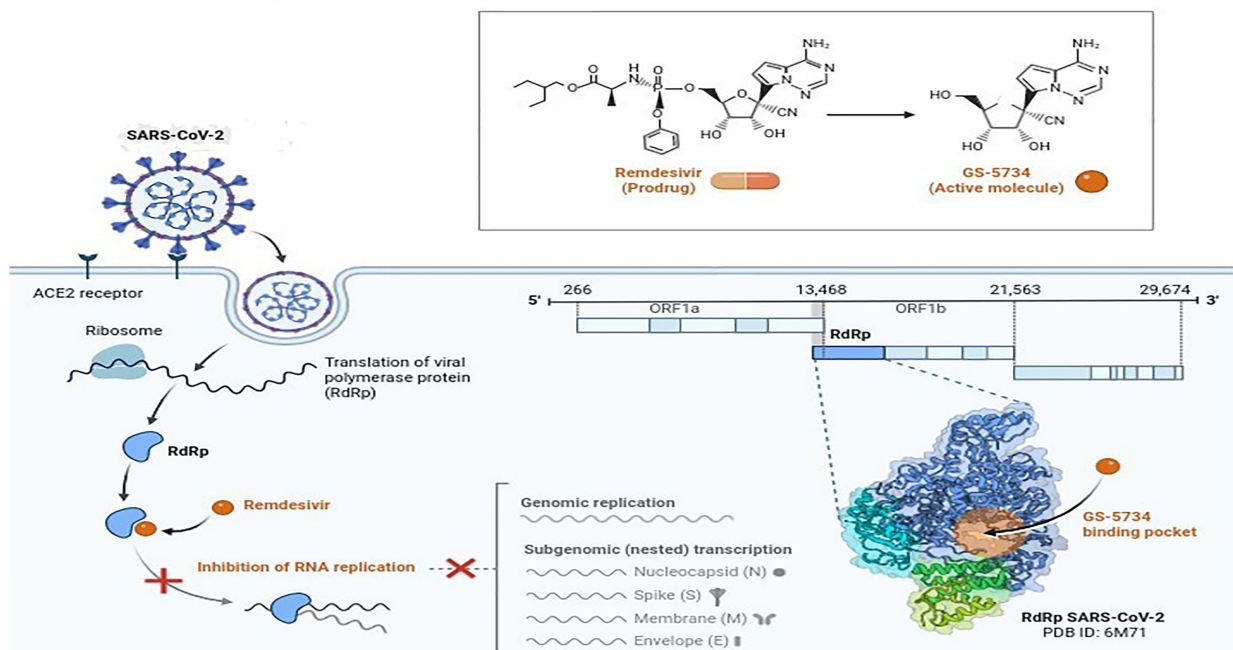


Figure 5. The action mechanism of Remdesivir against coronavirus by changing Remdesivir as prodrug into active molecule GS-5734, binding drug target molecule (RdRp), and inhibiting RNA replication in membrane cell.

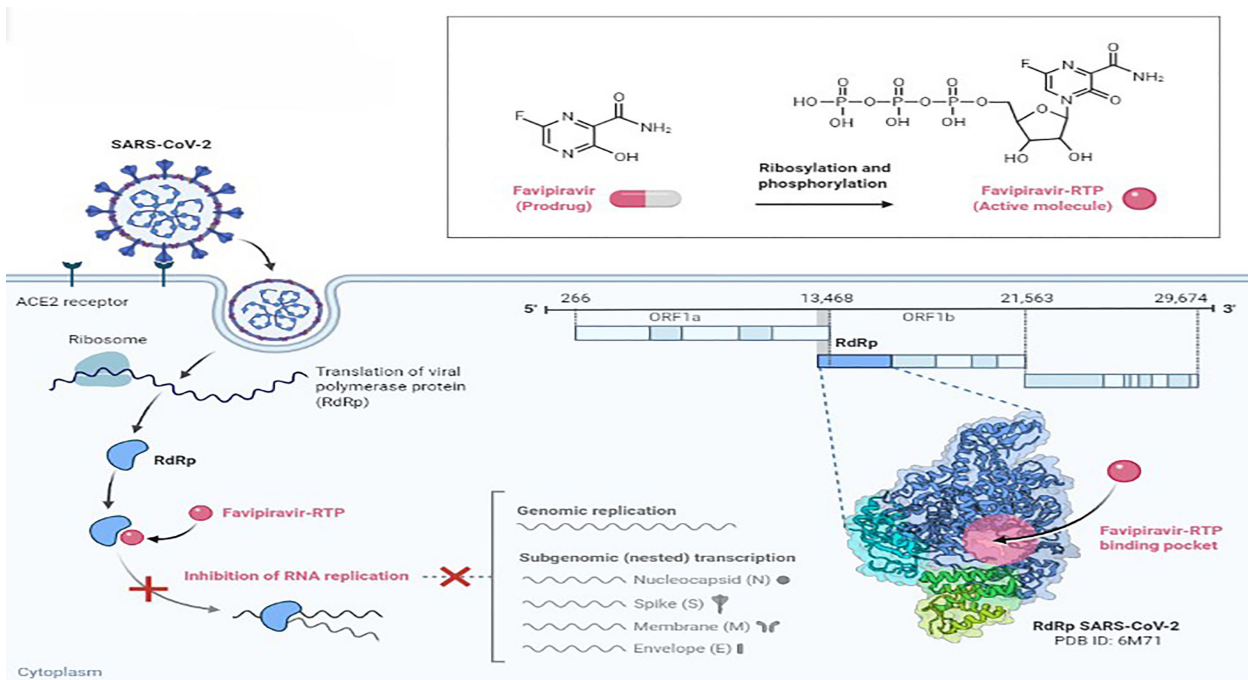


Figure 6. The action mechanism of Favipiravir as a potential repurposed drug candidate for COVID-19 which can inhibit replication and translation of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses.

of RNA transversion, resulting in a viable viral phenotype. This product is metabolized by human hypoxanthine-guanine phosphoribosyltransferase (HGPRT) known as favipiravir-ribofuranosyl-5-triphosphate (favipiravir-RTP). During this COVID-19 pandemic, in a limited clinical trial with 80 subjects, favipiravir showed an antiviral potential for SARS-CoV-2 that was better than lopinavir/ritonavir.⁴⁷ Many other nucleoside analogues including DNA synthesis such as tenofovir, disoproxil, lamivudine, and other antivirals have the potential to

inhibit the multiplication of SARS-CoV-2 and are being evaluated through molecular docking studies and testing in infected cell culture.⁴⁸

Protease inhibitors

Protease enzymes are involved within the maturation stage of virus replication inside the host cell and related to protein or peptide translation. Figures 4C and D, shows that Lopinavir and ritonavir are approved anti-HIV drugs, and a combination of both aids in the inhibition of SARS-

CoV-2.^{49,50} A research carried out by Lim J et.al.⁵¹ on the remedy used to treat persons affected with COVID-19 in Korea indicated that the administration of lopinavir/ritonavir (Kaletra, AbbVie) extensively reduced the virus. This means that a detailed analysis is needed for the recommendation of this drug and the formation of new drug compounds. Molecular docking of potential inhibitors provide clear information because detailed docking simulation results have shown essential input in previous SARS cases and other viral infections.⁵¹⁻⁵³ However, a lot of clinical data needs to be conducted to prove the efficacy and safety of the human body.

Heterocyclic antiviral

Over the decades, many heterocyclic drug molecules have been used in the treatment of viral infections, and these drugs are thought to be probably slightly effective in inhibiting SARS-CoV-2. An example is Chloroquine, which was originally an antiplasmodium used to treat malaria. This drug contains a quinoline group as shown in Figure 4E and inhibits the activity of the enzyme heme polymerase into hemozoin. This accumulation kills the Plasmodium parasite responsible for malaria.⁵⁴ However, with the decrease in malaria and the emergence of plasmodium resistance to Chloroquine, this drug is no longer used. Also, Chloroquine and hydroxychloroquine are used for antiviral therapy. Gao et al. (2020) stated that Chloroquine has a strong antiviral effect against the virus in primate cells. This inhibitory effect is observed when cells are treated with Chloroquine both before and after exposure, which shows that it has a preventive and therapeutic effect. In addition, Chloroquine and hydroxychloroquine are weak bases that are known to elevate the pH of acidic intracellular

organelles, such as endosomes/lysosomes, essential for membrane fusion inhibiting SARS-CoV-2 entry through changing the glycosylation of ACE2 receptor and spike protein, shown in Figure 7.⁵⁵⁻⁵⁷ This inhibits the receptor which prevent infection and spread of the SARS-CoV-2 at concentrations that cause clinical response. In the SARS-CoV-2 pandemic in China, Chloroquine was used at a dose of 500 mg for adult 2 times a day, for 10 days.⁵⁶ Chloroquine and hydroxychloroquine are also currently being tried in Malaysia at the same dosage used in China and Indonesia. There are several heterocyclic antiviruses previously used as antivirals such as HIV, H1N1, H1N5, and SARS, which are further examined for the treatment of COVID-19. Oseltamivir (Tamiflu) has been widely used as a neuraminidase inhibitor for the treatment of influenza was also recommended.⁵⁷ In addition, other candidate compounds evaluated with antiviral activity against SARS-CoV-2 are heterocyclic based on ACE2 peptides namely 3C-like protease (3CLpro and 3CLpro-1) inhibitors and vinyulfone protease inhibitors.⁵⁸

Nano Drug Delivery Systems

Drug delivery systems in the form of nanoparticle preparations have been widely used to improve the bioavailability in the blood and enhance the transport and efficacy antiviral drugs especially nucleoside analogues on conjugation with potential delivery systems that have been proven in drug-resistant HIV infection.⁵⁹⁻⁶² The wide variety of available nano delivery system can be used with the new developed drug formulation which could be efficacious in delivering the drugs with faster therapeutic indices for COVID-19.⁶²⁻⁶⁶

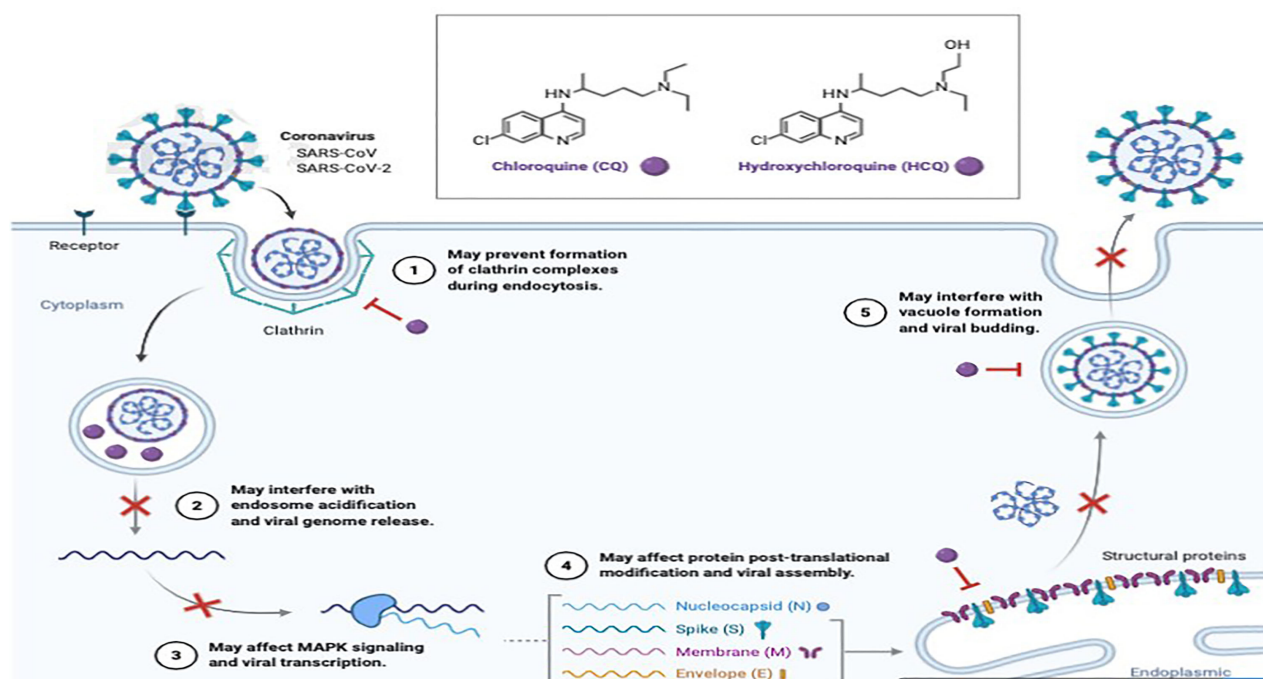


Figure 7. The molecular mechanism of chloroquine in membrane cell by preventing the formation of clathrin complexes in the cytoplasm during endocytosis, interfering with endosome acidification and viral genome release, affecting MAPK signaling and viral transcription, affecting protein post-translational modification, and interfering vacuole formation and viral budding.

Biological Therapeutics

Antibody therapy can be used for the treatment of COVID-19 infections. However, this vaccine still requires approximately 1 year before it can be globally utilized to prevent the spread of the virus. According to Tian et al. specific human monoclonal antibodies such as CR3022 are intended to bind strongly to SARS-CoV-2 receptor binding domain (= RBD) (KD 6.3 nM) and overlap the ACE2 binding site.⁶⁷ These unique results indicate the possibility of developing a therapeutic vaccine with a combination of other antibodies. However, *in vitro* trials and clinical studies are needed to obtain accurate clinical data for the prevention and treatment of COVID-19 infections.⁶⁷

In developing a new vaccine one must pay attention to the similarity of immunogenic structural proteins similar to SARS, MERS for SARS-CoV-2.⁶⁸ Ahmed et al. used a set of B and T cell epitopes derived from spikes (S) and nucleocapsid proteins (N) to identically map the SARS-CoV-2 protein.⁶⁹ Reports suggested that the identified epitope has no available mutase sequence. Therefore, this target immune epitope has the potential to be explored in the fight against the SARS-CoV-2. However, the final results depend on *in vitro* and future clinical trials.⁶⁹

Herbal drugs

The herbal formulations used as alternative medication has been a success in presenting the remedy to a number of

infections in conjunction with symptom specific remedy using herbs.⁷⁰⁻⁷² The initial lead from herbal medicinal drug has been successful in developing final applicable formulations like Praneem (a natural extract of neem tree) as microbicide for HIV therapy.⁷³ Therefore, various studies have been conducted on the use of herbal drugs to test the active compounds of some herbal in Indonesia by molecular docking in silico (Table 1).

According to University of Indonesia (UI) and Institute of Bogor Agriculture (IPB) researchers, they stated that some chemical compounds which originated from several plants in Indonesia have the potential ability to prevent COVID-19 infection in the form of molecular docking in silico. Based on the results of prediction models with machine learning methods, namely SVM (support vector machine), random forest, and MLP (multilayer perceptron) neural network is associated with 20,644 interactions of protein compounds. The results are 31 herbal compounds with 5 target proteins 3CLPro (Chymotrypsin-like protease), PLPro (Papain-like protease), Spike-ACE2, EIF4 (Eukaryotic initiation factor-4), and RdRp. Modeling of structure and ligand based pharmacophores was used to carry out virtual screening with 1,377 compounds from the HerbalDB database.⁷⁴ The results of compound hit from machine learning, and pharmacophore mapping was confirmed using molecular docking.

Table 1. Active compounds having the potential as antiviral SARS-CoV-2⁸¹

Target	Compounds	Sources
3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	<i>Cassia alata</i>
	Kaempferol 3,4'-di-O-methyl ether (Ermanin)	<i>Tanacetum microphyllum</i>
	Cyanidine 3-sophoroside-5-glucoside	<i>Brassica oleracea, Ipomoea batatas, Raphanus sativus</i>
	Casuarinin	<i>Psidium guajava</i>
	Quercetin 3-(2G-rhamnosylrutinoside)	<i>Clitoria ternatea</i>
	Peonidine 3-(4'-arabinosylglucoside)	<i>Ipomoea fistulosa</i>
	Hesperidine	<i>Psidium guajava, Citrus aurantium</i>
PLpro	Platycodin D	<i>Platycodon grandiflorus</i>
	Baicalin	<i>Scutellaria baicalensis</i>
	Sugetriol-3,9-diacetate	<i>Cyperus rotundus</i>
	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	<i>Isatis indigotica</i>
	(-)-epigallocatechin gallate	<i>Camellia sinensis</i>
	2,4-Dihydroxyphenyl)-2-[2-(3,4-Dihydroxyphenyl)-3,4-dihydro-5,7-dihydroksi-2H-1-benzopyran-3-yl]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	<i>Vitis vinifera</i>
RdRp.	Betulanol	<i>Cassine xylocarpa</i>
	Gnidicin	<i>Gnidia lamprantha</i>
	2-β-dihydroxy-3,4-seo-friedelolactone-27-lactone	<i>Viola diffusa</i>
	14-deoxy-11,12-didehydroandrographolide	<i>Andrographis paniculata</i>
	1,7-dihydroxy-3-methoxyxanthone	<i>Swerti apseudochinensis</i>
	Theaflacin 3,3'-di-O-gallate	<i>Camellia sinensis</i>
	2-(3,4-dihydroxyphenyl)-2-[(2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl)oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	<i>Vitis vinifera</i>
Hesperidine	<i>Psidium guajava, Citrus aurantium</i>	

Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin, quercetin, luteolin, kaempferol, isorhamnetin⁷⁵, and hesperidin.⁷⁶ Luteolin is a furin protein inhibitor⁷⁷ and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein in MERS into units of S1 and S2.^{78,79} In the S1 unit, there is a receptor-binding domain (RBD) where the ACE2 peptidase binds the virus in the host cell.⁷⁹ The Hesperidin/hesperitin compound in the silico study inhibits the RBD of the SARS-COV-2 Spike protein which is also known as luteolin having a neuramidase inhibitor as well as oseltamivir which is currently one of the drugs used in the CDC protocol.⁸⁰ Hesperidin a form of hesperidin aglycone and Quercetin is also known to act as inhibitors of 3CLpro virus proteins.^{81,82} Other compounds in guava such as myricetin act as SARS coronavirus helicase inhibitors.⁸³ The kaempferol has the potential to be a non-competitive inhibitor of 3CLPro and PLpro as well as quercetin.⁸⁴ It also acts as a autophagy modulator, inducer and inhibitor, of the virus.

Meanwhile, Indonesia is also famous for its variety of cooking condiments which are derived from plants. One of the commonly used condiments for cooking or herbal medicine in Indonesia is empon-empon consisting of ginger, turmeric, galangal, curcuma and lemongrass. Furthermore, animals such as snakehead fish also improve immune system in the body due to high protein and amino acids.⁸⁵⁻⁸⁷ According to UNAIR (University of Airlangga) researchers stated that the approach that can be taken in the public by consuming empon-empon to boost the immune system to avoid COVID-19.⁷⁸

Turmeric containing curcumin have been consumed and proven by people for centuries and beneficial to health. For example it is used to maintain fitness vitality, liver, and digestive systems based on empirical experimental evidence. Various studies have been carried out in vitro and preclinical tests showing that curcumin is anti-inflammatory, antiviral, antibacterial, antifungal, and antioxidant based on scientific evidence.^{88, 89}

One of the benefits of curcumin obtained from clinical trials is to increase the body's immune system. Recent research on curcumin against the virus shows that the SARS-CoV-2 receptor is an enzyme ACE2 found in host cells of human especially alveolus lungs. However, the cell entry of the virus depends on the binding of the spike virus protein, the receptor on the host cell (ACE2) and pad priming protein spike (TMPRSS2).⁸⁹

Conclusion

The surging spread of the virus through human-to-human transmission has created a change in human life that must meet health protocol standards including therapy protocols to combat COVID-19. Few existing drugs had been evaluated for the remedy of SARS-CoV-2 and shown promising good effects in clinical applications. The chemical and herbal drugs for the management of viral infection symptoms have been on the frontline to mitigate this novel viral infectious disease and have helped the number of

patients in safe healing from COVID-19. Several drugs have been clinically evaluated for the treatment of COVID-19, which showed promising results and assisted a number of patients to recover safely. There is continuous research on the potential of therapeutics in evaluating the existing antiviral drugs such as modern and herbal medicines.

Conflict of Interest

The authors claim that there is no conflict of interest

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