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

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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 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 China[2] 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.

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, coronavirus 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-eterase (HE) protein, nucleocapsid (N) protein, and 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]

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 interauterine 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 symptoms 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 days[20] 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 6operly 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, 1nfection 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 pumps.
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 pattern[39] 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 antivirus. 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 spike[42] 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 (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 drugs[46] 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 studies[48] 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 product that is metabolized by human hypoxanthine guanine phosphoribosyltransferase (HGPRT) 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 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

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 antiplasmodium. This drug is a drug 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 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 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 vinysulfone 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, isorhamnetin[78], and hesperidin[79]. Luteolin is known as a furin protein inhibitor[80] 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 h 19 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 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 antivirus 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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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 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 China[2] 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 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.

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-eterase (HE) protein, nucleocapsid (N) protein, and 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]

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 interauterine 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 symptoms 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 days[20] 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 pumps.
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 pattern[39] 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 produ 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 antivirus. 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 spike[42] 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 drugs[46] 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 studies[48] 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 product that is metabolized by human hypoxanthine guanine

phosphoribosyltransferase (HGPRT) 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 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

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 antiplasmodium. This drug is a drug 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 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 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 vinysulfone 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, isorhamnetin[78], and hesperidin[79]. Luteolin is known as a furin protein inhibitor[80] 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 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.

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 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 antivirus 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.

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Table 1. Active compounds having the potential as antiviral SARS-CoV-2[90]

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

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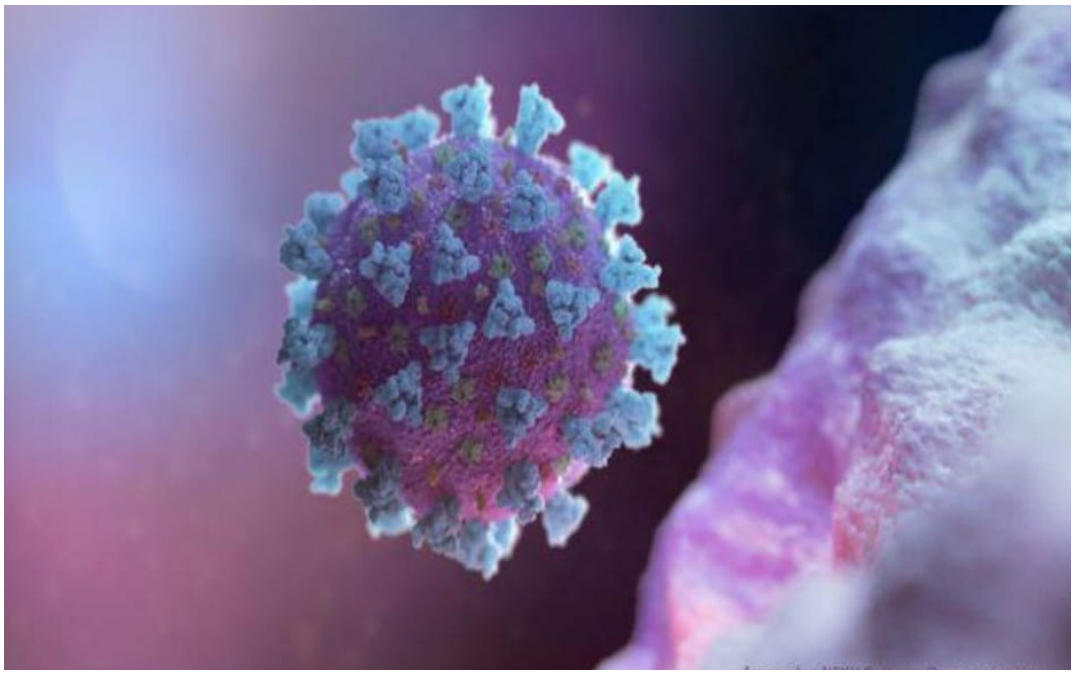

Figure 1. A graphical representation of the structure of coronavirus (SARS-CoV-2).

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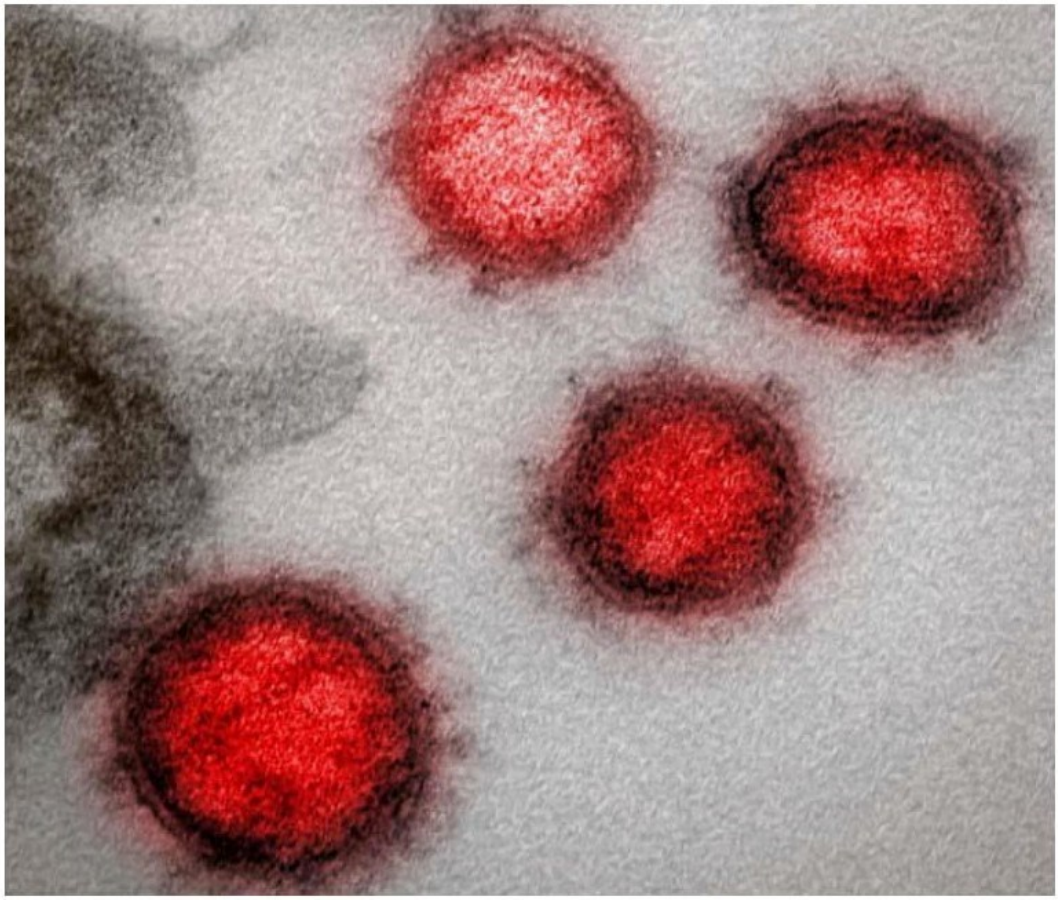

Figure 2. Electron-microscope image of the new coronavirus, now designated SARS-CoV-2. Image reproduced as provided for public domain use by the National Institute of Allergy and Infectious Disease, US. Credit: NIAID-RML/de Wit/Fischer

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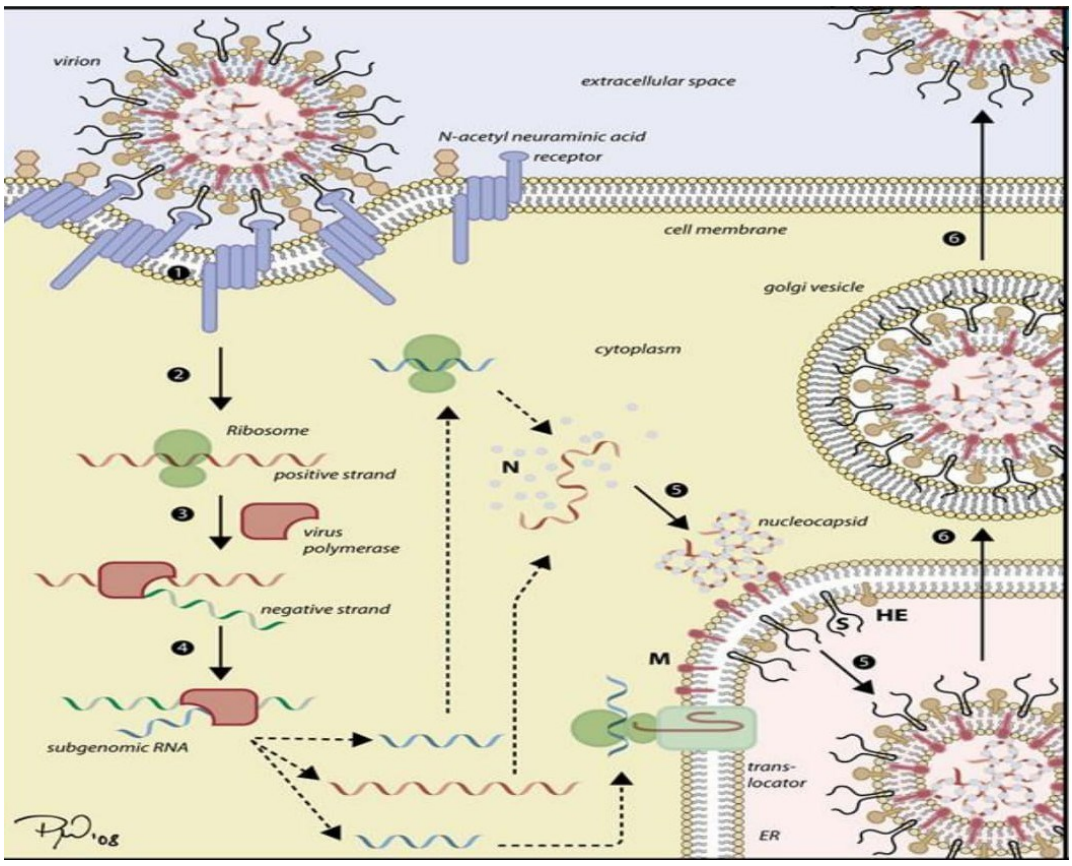

Figure 3. The life cycle of a Coronavirus.

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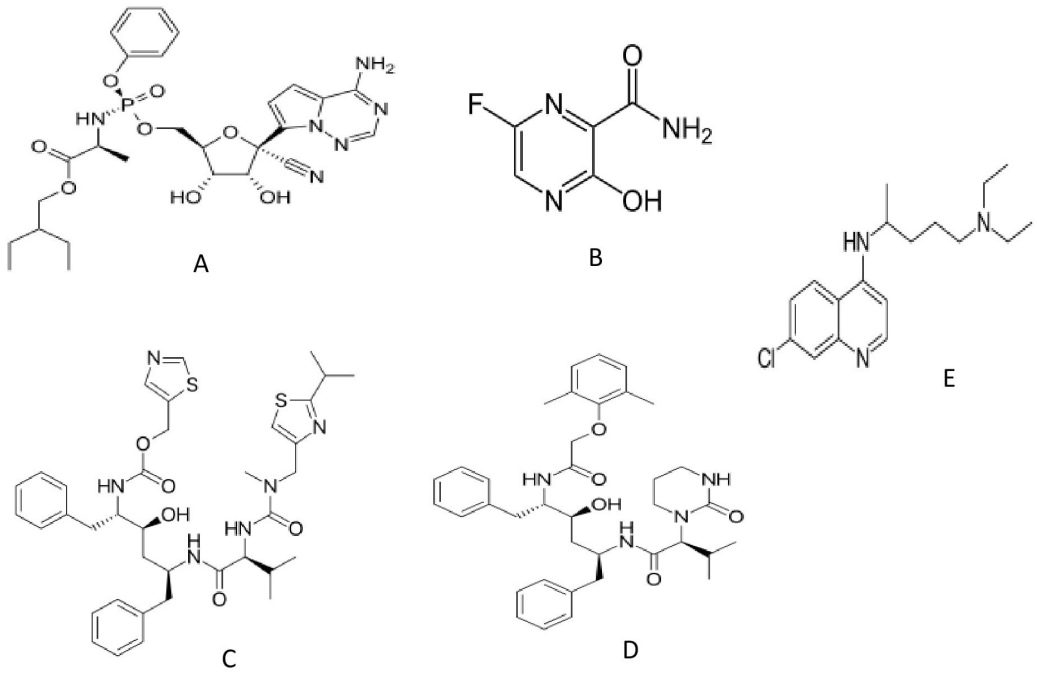

Figure 4. Chemical structures of Ramdesivir (A), Favipiravir (B), Ritonavir (C), Lopinavir (D), Chloroquine (E).

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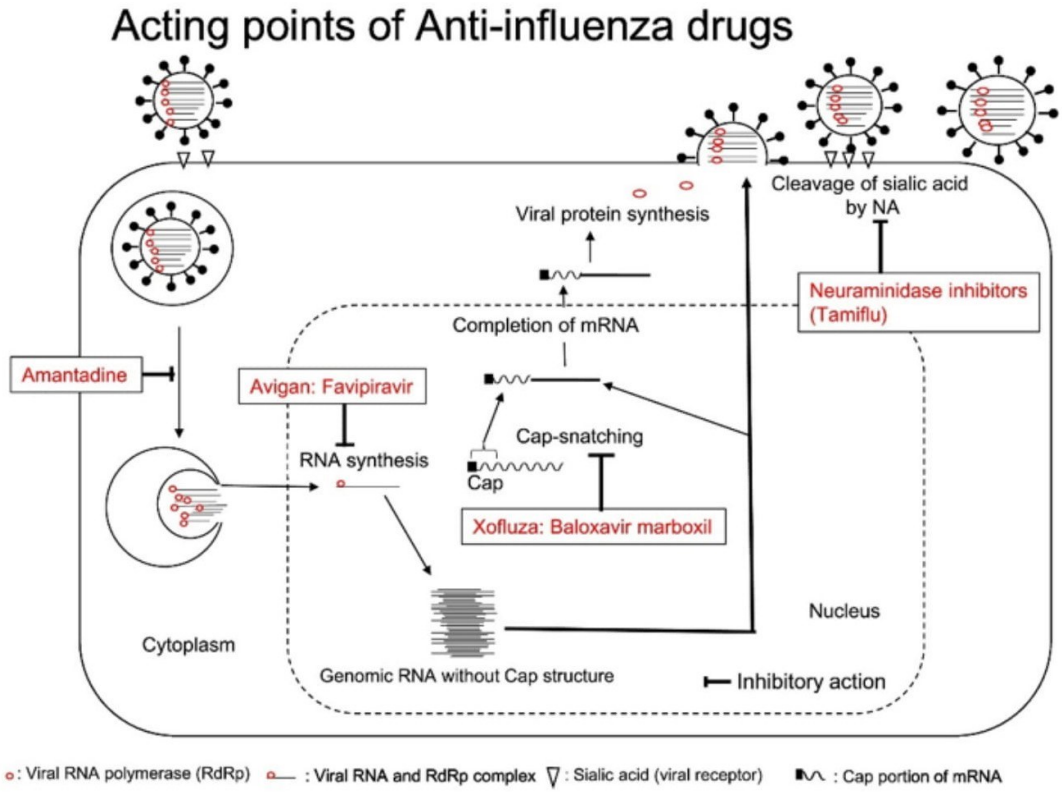

Figure 5. The mechanism of Favipiravir as an antiviral to the SARS-CoV2 virus by inhibiting RNA synthesis, the difference between antiviral and other flu drugs.

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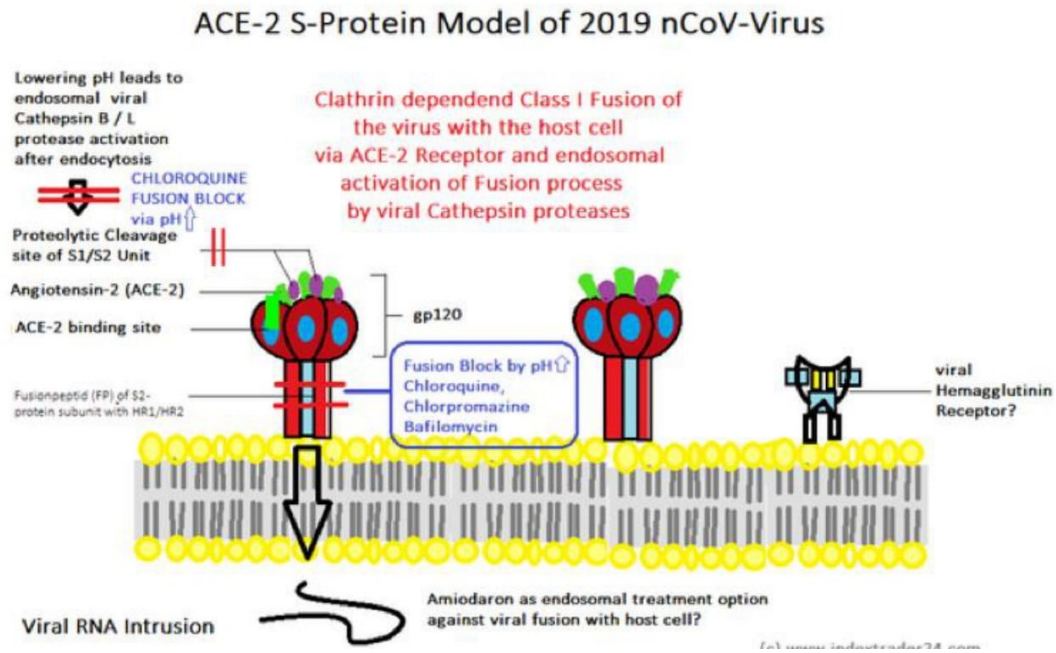

Figure 6. The model describes the mechanism of chloroquine as an antiviral in the SARS-CoV-2 virus. The first binds to the ACE2-cellular receptor which is the site of the binding of the virus, and increases the pH of the endosome thereby inhibiting viral replication.

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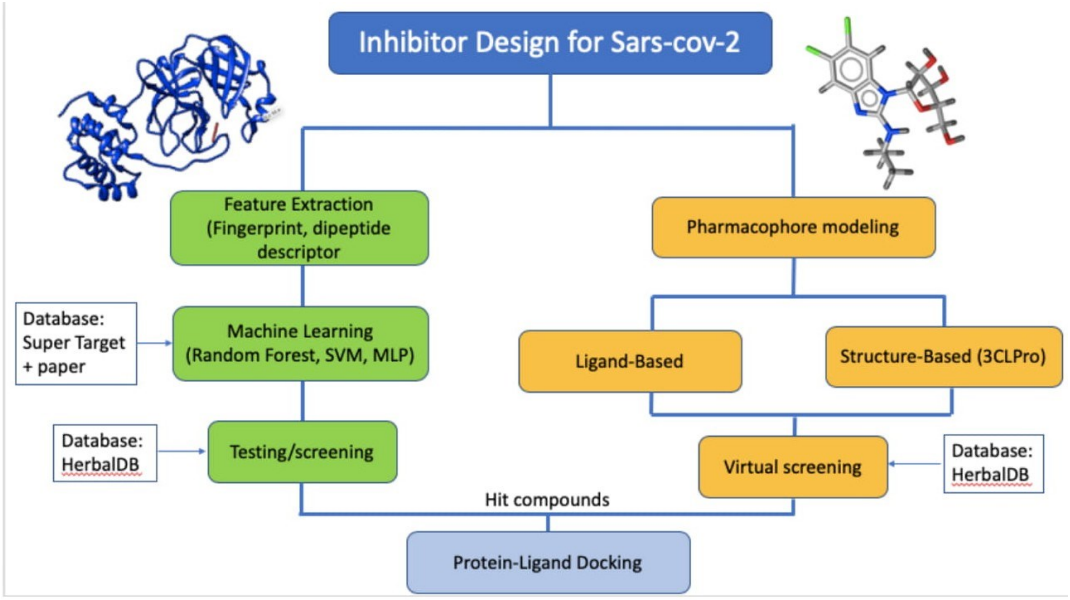

Figure 7. The illustration of molecular docking in inhibiting SARS-CoV-2.

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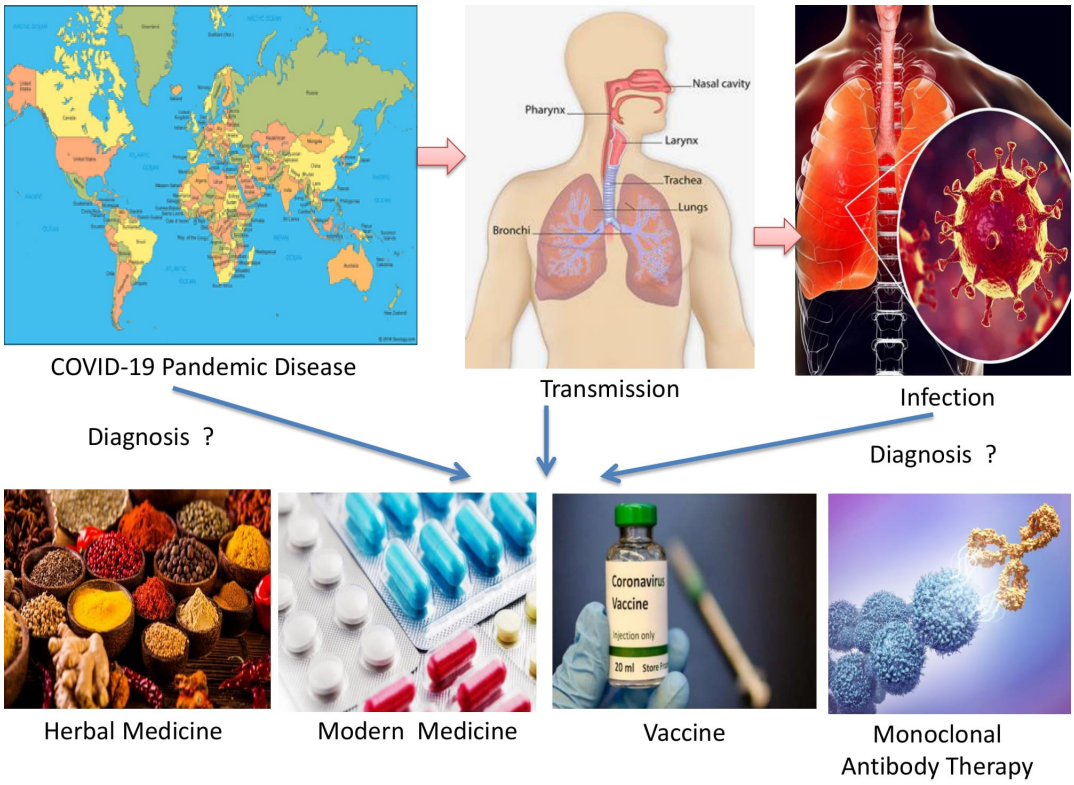

Graphical Abstract

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

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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 China[2] 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]

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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-eterase (HE) protein, nucleocapsid (N) protein, and 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 1**).[8]

There is current outstanding infections which is caused by Coronavirus namely SARS-CoV-2[9-10] 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 interauterine 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 days[20] 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 pattern[39] 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 antivirus. 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 spike[42] 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 drugs[46] 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 studies[48] 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 (HGPRT) 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 vinysulfone 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

Comment [T25]: Already change italic

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, isorhamnetin[78], and hesperidin[79]. Luteolin is known as a furin protein inhibitor[80] 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.

Comment [T26]: Already change this sentence

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.

Comment [T27]: Already rewrite this sentences

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 antivirus 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-2[90]

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

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.

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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 measured 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". Pleas exactly define what do 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 vinysulfone 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.)

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 san (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.

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

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 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 € 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 an new strain of the current virus, [9,10] which was transmitted from animals to human[11], however, the new coronavirus infects humans.

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 SARS, 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.[21]

Studies conducted by Guan et al. showed the middle-aged were more prone to infection compared to other categories of people. [16] 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 is no gender difference in people infected with COVID-19 with the highest mortality rates of 8.4% by 20 March 2020.[17,18] 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 10is an enveloped virus which means that it is protected by a glycoprotein shell, thereby, making it difficult to treat.[19]

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

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. 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 (COVID-19) virus 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.[31]

Secondly, coronaviruses replicates and transcripts 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 ER lumen and is encased with the membrane as shown in Figure 2.[32]

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.[31] 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.[33]

Diagnosis

The proper diagnosis characteristics used to manage COVID-19 is finding out the initiation of the course of remedy. 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 initial intervention, 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:

RT-PCR

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

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 pattern[39], 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

The SARS-CoV-2 virus infects the respiratory system and alveoli cells in the lung sac, which is worse than the viral infection. In general, viruses enter the host cell by forming complex projections such as spikes or lobes with receptors. However, the exact structure [42] or lobe of COVID-19 SARS-CoV-2 is not fully determined, although prior experience of coronavirus (β-family), shows it has similarities with the host cells of SARS.[43] Recently it has been found that Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-CoV) and (SARS-CoV-2).[44] ACE2 has some homology with an angiotensin-converting enzyme (ACE) although it is not inhibited by ACE. 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.[45]

Replication inhibitors

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. The viral genome replication mechanism serves potential targets for the control of viral infections, while antiviral drugs such as Remdesivir and Favipiravir (Avigan) [46] has the ability to potentially effective 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.[47] However, further evaluation is needed for potential applications with more patients. 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 and are being evaluated through molecular docking studies and testing in infected cell culture [48]. The action mechanism of Remdesivir as antiviral drug as shown in Figure 5.

Avigan is the patent name for favipiravir, 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 cold, however, in February 2020, Favipiravir was used in China for trials of emerging COVID-19 (novel coronavirus) disease. The action mechanism of favipiravir inhibits the synthesis of viral RNA polymerase selectively, as shown in Figure 6.[49] 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). This drug is available in oral and intravenous formulations and does not inhibit the synthesis of RNA or DNA in mammalian cells, and it is not toxic. In 2014, favipiravir was approved in Japan as a backup drug against influenza pandemics and to treat viruses that were not responsive to antiviral at the time. 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.[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. 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.[51,52] A research carried out by Lim J et.al. 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. [52] 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 important input in previous SARS cases and other viral infections.[53-55] 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.[56] 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, the endosomal pH which inhibits viral replication interacts with cellular ACE2 receptors as shown in Figure 7.[57,59] This inhibits the receptor which prevent infection and spread of the SARS-CoV-2 at concentrations that 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, for 10 days.[58] 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.[59] In addition, other candidate compounds evaluated with antiviral activity against SARS-CoV-2 are heterocyclic based on ACE2 peptides namely 3CLpro inhibitors (3CLpro-1) and vinysulfone protease inhibitors.[60] 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.[61]

Nano drug delivery systems

Drug delivery systems in the form of nanoparticle preparations have been widely used to improve the bioavailability in the blood. The use of antiviral especially nucleoside analogues in conjugate with potential delivery systems that have been applied in resistant HIV infection drugs.[62-65] 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.[66-68] One example of delivery of nano treatment is seen in the efficacy of Chloroquine against COVID-19 as an 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 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 RBD (KD 6.3 nM) and overlap the ACE2 binding site.[70] 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.[70]

In developing a new vaccine one must pay attention to the similarity of immunogenic structural proteins similar to SARS, MERS for SARS-CoV-2.[71] 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.[72] 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.[72]

Herbal drugs

Several anti-SARS agents have been tested for coronavirus-specific therapy, however, none is effective.[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* with specific monoclonal antibodies, pegylated interferon-α, siRNA, and several protease inhibitors.[76] Therefore, various studies have been conducted on the use of herbal drugs to test several patients in Indonesia.

The chemical compounds contained in UI and IPB, which originated from several plants in Indonesia, they have the potential ability to prevent COVID-19 infection in the form of molecular docking in silico. The model of research that has been conducted is shown in Figure 8. Based on the results of prediction models with machine learning methods, namely SVM, random forest, and MLP neural network is 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 used to carry out virtual screening with 1,377 compounds from the HerbalDB database.[77] 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, isorhamnetin[78], and hesperidin[79]. Luteolin is a furin protein inhibitor[80] and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein in MERS into units of S1 and S2.[81] In the S1 unit, there is a receptor-binding domain (RBD) where the ACE2 peptidase binds the virus in the host cell.[81] The Hesperidin/hesperitin compound in the silico study inhibits the RBD domain binding of the SARS-COV-2 Spike protein with ACE2 receptors in humans s.[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 is also known to act as inhibitors of 3CLpro virus proteins.[83,84] Other compounds in guava such as myricetin 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] 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.[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 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.[91, 92]

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). There are 2 forms of ACE2, the fixed attached to the cell surface and the free-form soluble in the blood. The soluble ACE2 is projected to be one of the SARS-CoV-2 antivirus candidates through a competitive interceptor mechanism, which prevents bonding between virus particles 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. The curcumin in ginger and turmeric increase the expression of ACE2 in the form of soluble which inhibit the bonding between the viral protein and the fixed form ACE2 found on the surface of the host cell.[93]

Conclusion

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. The WHO, in 2020, declared the virus a pandemic, therefore, every country has an obligation to protect its people by educating them with the right preventive measures. In many new cases, clinical staffs are infected from patients that visit the hospitals, thereby increasing the spread of the virus through human-to-human transmission. Hence 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. 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. However, further knowledge of SARS-CoV-2 advances, new therapies, including vaccines and monoclonal antibodies, are needed for proper treatment in the near future. Although the effective treatments for COVID-19 are unknown, there is continuous research on the potential of therapeutics in evaluating the existing antiviral drugs such as modern and herbal medicines.

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-2[90]

Target	Compounds	Sources
3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	*Cassia alata,30*
	Kaempherol 3,4'-di-O-methyl ether (Ermanin)	*Tanacetum microphyllum*
	Cyanidine 3-sophoroside-5-glucoside	*Brassica oleracea; Ipomoea batatas; Raphanus sativus*
	Casuarinin	*Psidium guajava*
	Quercetin 3-(2G-rhamnosylrutinoside)	*Clitoria ternatea*
	Peonidine 3-(4'-arabinosylglucoside)	*Ipomoea fistulosa*
	Hesperidine	*Psidium guajava*
		Citrus aurantium
PLpro	Platycodin D	*Platycodon grandiflorus*
	Baicalin	*Scutellaria baicalensis*
	Sugetriol-3,9-diacetate	*Cyperus rotundus*
	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	*Isatis indigotica*
	(-)-epigallocatechin gallate	*Camellia sinensis*
	2-93,4-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	*Vitis vinifera*
RdRp.	Betulanol	*Cassine xylocarpa*
	Gnidicin	*Gnidia lamprantha*
	2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	*Viola diffusa*
	14-deoxy-11,12-didehydroandrographolide	*Andrographis paniculata*
	1,7-dihyroxy-3-methoxyxanthone	*Swerti apseudochinensis*
	Theaflacin 3,3'-di-O-gallate	*Camelia sinensis*
	2-(3,4-dihydrophenyl)-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	*Vitis vinifera*
Spike-ACE2	Hesperidine	*Psidium guajava*
		Citrus aurantium

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 san (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.

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

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 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 € 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 an new strain of the current virus, [9,10] which was transmitted from animals to human[11], however, the new coronavirus infects humans.

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.[21]

Study conducted by Guan et al. showed the middle-aged were more prone to infection compared to other categories of people. [16] 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.[17,18] 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.[19]

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.[31]

Secondly, coronaviruses replicates and transcripts 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.[32]

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.[31] 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.[33]

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 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.[34] 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.[35]

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.[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 pattern[39], 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 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.[3,41] 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

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,[42] although prior experience of coronavirus (β-family), shows it has similarities with the receptor of host cells of SARS.[43] Recently it has been found that Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-CoV) and (SARS-CoV-2).[44] 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.[45]

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 such as Remdesivir and Favipiravir (Avigan) [46] 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.[47] 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.[48] 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 antiviral potential for SARS-CoV-2 that was better than lopinavir/ritonavir.[49] 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.[50]

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.[51,52] A research carried out by Lim J et.al. 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. [52] 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.[53-55] 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.[56] 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.[57,59] 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.[58] 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.[59] 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 vinysulfone protease inhibitors.[60,61]

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.[62-65] 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.[66-68]

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.[70] 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.[70]

In developing a new vaccine one must pay attention to the similarity of immunogenic structural proteins similar to SARS, MERS for SARS-CoV-2.[71] 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.[72] 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.[72]

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.[73-75] 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.[76] 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.

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. The model of research that has been conducted is shown in Figure 8. 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 20644 interactions of protein compounds. The results are 31 herbal compounds with 5 target proteins 3CLPro (Chymotripsin-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.[77] 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, isorhamnetin[78], and hesperidin[79]. Luteolin is a furin protein inhibitor[80] and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein in MERS into units of S1 and S2.[81] In the S1 unit, there is a receptor-binding domain (RBD) where the ACE2 peptidase binds the virus in the host cell.[81] 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.[82]

Hesperidin a form of hesperidin aglycone and Quercetin is also known to act as inhibitors of 3CLpro virus proteins.[83,84] Other compounds in guava such as myricetin 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] 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.[87-89] 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.[90]

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.[91, 92]

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).[93]

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 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-2[90]

Target	Compounds	Sources
3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	*Cassia alata,30*
	Kaempherol 3,4'-di-O-methyl ether (Ermanin)	*Tanacetum microphyllum*
	Cyanidine 3-sophoroside-5-glucoside	*Brassica oleracea; Ipomoea batatas; Raphanus sativus*
	Casuarinin	*Psidium guajava*
	Quercetin 3-(2G-rhamnosylrutinoside)	*Clitoria ternatea*
	Peonidine 3-(4'-arabinosylglucoside)	*Ipomoea fistulosa*
	Hesperidine	*Psidium guajava*
		Citrus aurantium
PLpro	Platycodin D	*Platycodon grandiflorus*
	Baicalin	*Scutellaria baicalensis*
	Sugetriol-3,9-diacetate	*Cyperus rotundus*
	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	*Isatis indigotica*
	(-)-epigallocatechin gallate	*Camellia sinensis*
	2-93,4-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	*Vitis vinifera*
RdRp.	Betulanol	*Cassine xylocarpa*
	Gnidicin	*Gnidia lamprantha*
	2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	*Viola diffusa*
	14-deoxy-11,12-didehydroandrographolide	*Andrographis paniculata*
	1,7-dihyroxy-3-methoxyxanthone	*Swerti apseudochinensis*
	Theaflacin 3,3'-di-O-gallate	*Camelia sinensis*
	2-(3,4-dihydrophenyl)-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	*Vitis vinifera*
Spike-ACE2	Hesperidine	*Psidium guajava*
		Citrus aurantium

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 ACE”	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

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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
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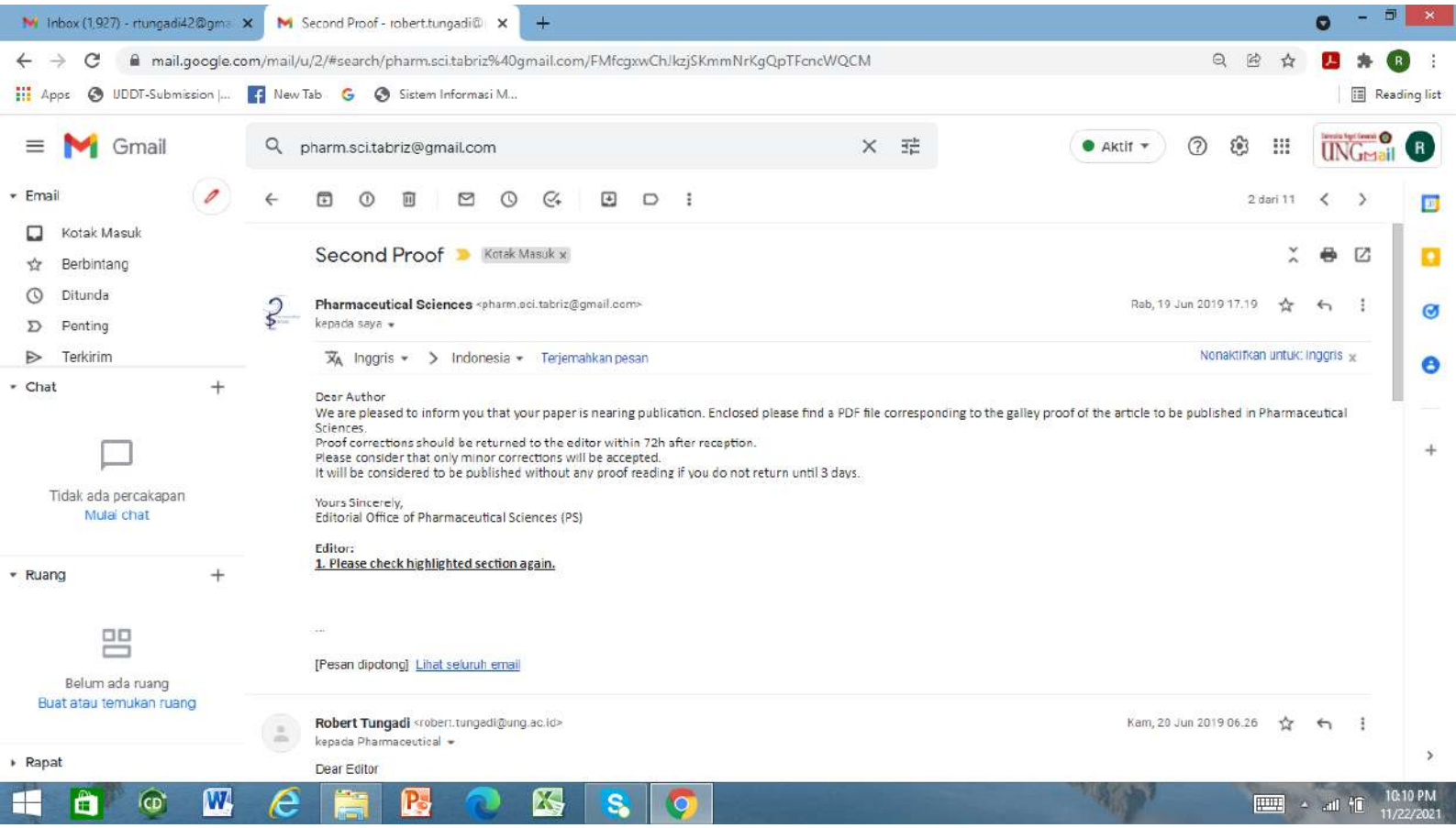
4.	Figure 8	I delete figure 8 because I have made narrative structure in the text.
5.	Ref. 90	Line 614
6.	Ref. 93	Line 625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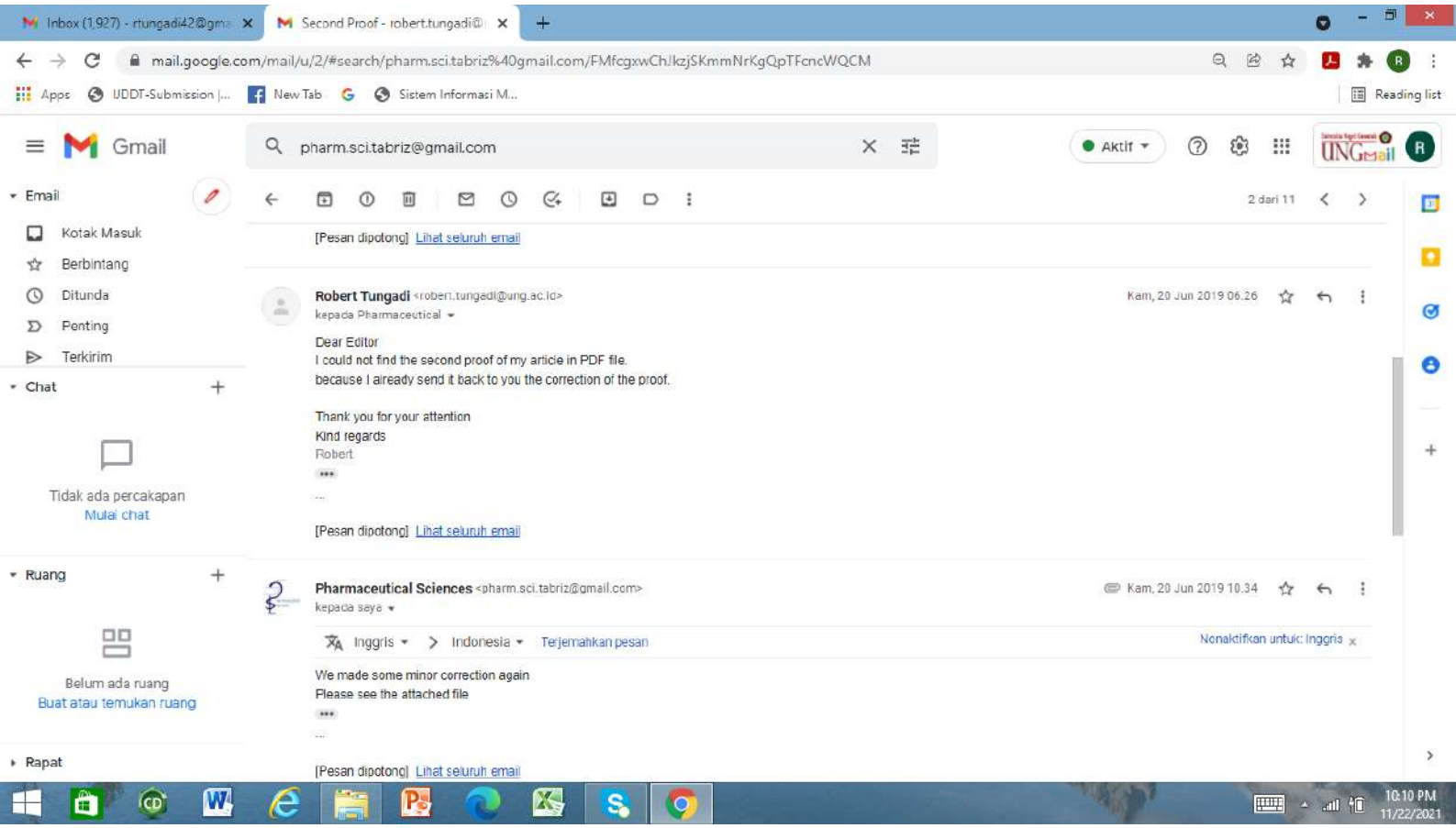
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Abstract

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 san (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.

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

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 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 € 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 an new strain of the current virus, [9,10] which was transmitted from animals to human[11], however, the new coronavirus infects humans.

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.[21]

Study conducted by Guan et al. showed the middle-aged were more prone to infection compared to other categories of people. [16] 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.[17,18] 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.[19]

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.[31]

Secondly, coronaviruses replicates and transcripts 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.[32]

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.[31] 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.[33]

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 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.[34] 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.[35]

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.[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 pattern[39], 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 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.[3,41] 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

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,[42] although prior experience of coronavirus (β-family), shows it has similarities with the receptor of host cells of SARS.[43] Recently it has been found that Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS coronavirus, (SARS-CoV) and (SARS-CoV-2).[44] 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.[45]

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 such as

Remdesivir and Favipiravir (Avigan) [46] 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.[47] 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.[48] 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 antiviral potential for SARS-CoV-2 that was better than lopinavir/ritonavir.[49] 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.[50]

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.[51,52] A research carried out by Lim J et.al. 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. [52] 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.[53-55] 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.[56] 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.[57,59] 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.[58] 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.[59] 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 vinysulfone protease inhibitors.[60,61]

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.[62-65] 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.[66-68]

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.[70] 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.[70]

In developing a new vaccine one must pay attention to the similarity of immunogenic structural proteins similar to SARS, MERS for SARS-CoV-2.[71] 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.[72] 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.[72]

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.[73-75] 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.[76]

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.

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 (Chymotripsin-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.[77,90] 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, isorhamnetin[78], and hesperidin[79]. Luteolin is a furin protein inhibitor[80] and assumed as one of the enzymes that breakdown the Coronavirus S (spike) protein in MERS into units of S1 and S2.[81] In the S1 unit, there is a receptor-binding domain (RBD) where the ACE2 peptidase binds the virus in the host cell.[81] 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.[82]

Hesperidin a form of hesperidin aglycone and Quercetin is also known to act as inhibitors of 3CLpro virus proteins.[83,84] Other compounds in guava such as myricetin 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] 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.[87-89] 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.[90]

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.[91, 92]
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).[93]

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 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-2[90]

Target	Compounds	Sources
3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	*Cassia alata,30*
	Kaempherol 3,4'-di-O-methyl ether (Ermanin)	*Tanacetum microphyllum*
	Cyanidine 3-sophoroside-5-glucoside	*Brassica oleracea; Ipomoea batatas; Raphanus sativus*
	Casuarinin	*Psidium guajava*
	Quercetin 3-(2G-rhamnosylrutinoside)	*Clitoria ternatea*
	Peonidine 3-(4'-arabinosylglucoside)	*Ipomoea fistulosa*
	Hesperidine	*Psidium guajava*
		Citrus aurantium
PLpro	Platycodin D	*Platycodon grandiflorus*
	Baicalin	*Scutellaria baicalensis*
	Sugetriol-3,9-diacetate	*Cyperus rotundus*
	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	*Isatis indigotica*
	(-)-epigallocatechin gallate	*Camellia sinensis*
	2-93,4-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	*Vitis vinifera*
RdRp.	Betulanol	*Cassine xylocarpa*
	Gnidicin	*Gnidia lamprantha*
	2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	*Viola diffusa*
	14-deoxy-11,12-didehydroandrographolide	*Andrographis paniculata*
	1,7-dihyroxy-3-methoxyxanthone	*Swerti apseudochinensis*
	Theaflacin 3,3'-di-O-gallate	*Camelia sinensis*
	2-(3,4-dihydrophenyl)-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	*Vitis vinifera*
Spike-ACE2	Hesperidine	*Psidium guajava*
		Citrus aurantium

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Review Article

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

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-Pandemic

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 san (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 € 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 an new strain of the current virus,[9,10] which was transmitted from animals to human[11], however, the new coronavirus infects humans.

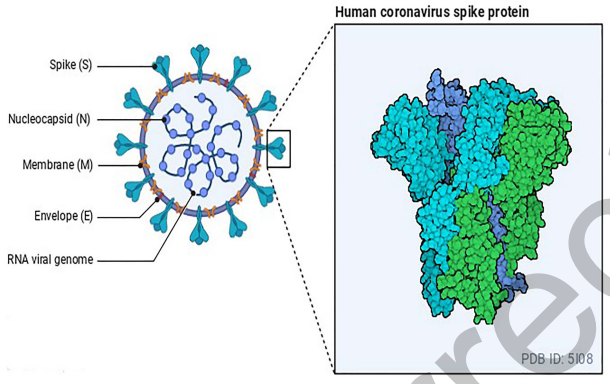

Figure 1. Structure of new coronavirus and protein visualization, now designated severe acute respiratory syndrome coronavirus-2, (SARS-CoV-2)

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 transcripts 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

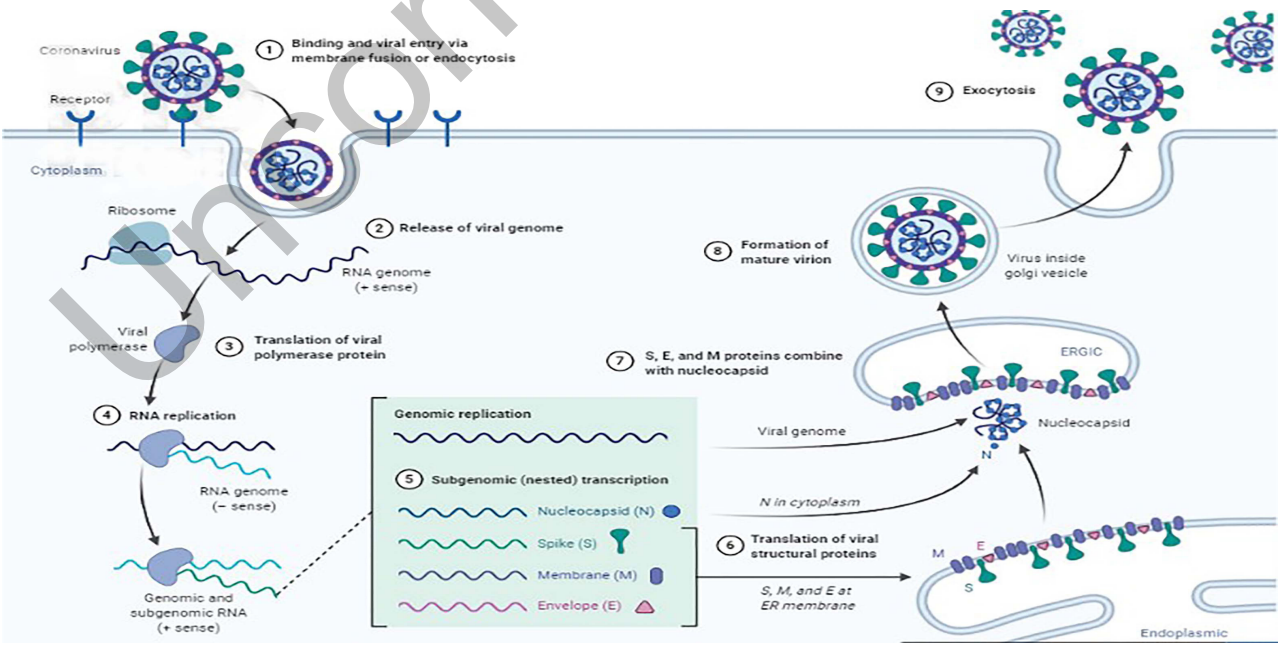

Figure 2. The life cycle of coronavirus including the viral spike (S) glycoprotein attach to the complementary host cell receptor via membrane fusion or endocytosis then release of viral genome, translation of viral polymerase protein, RNA replication, subgenomic transcription and translation of viral 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 pattern[37], 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

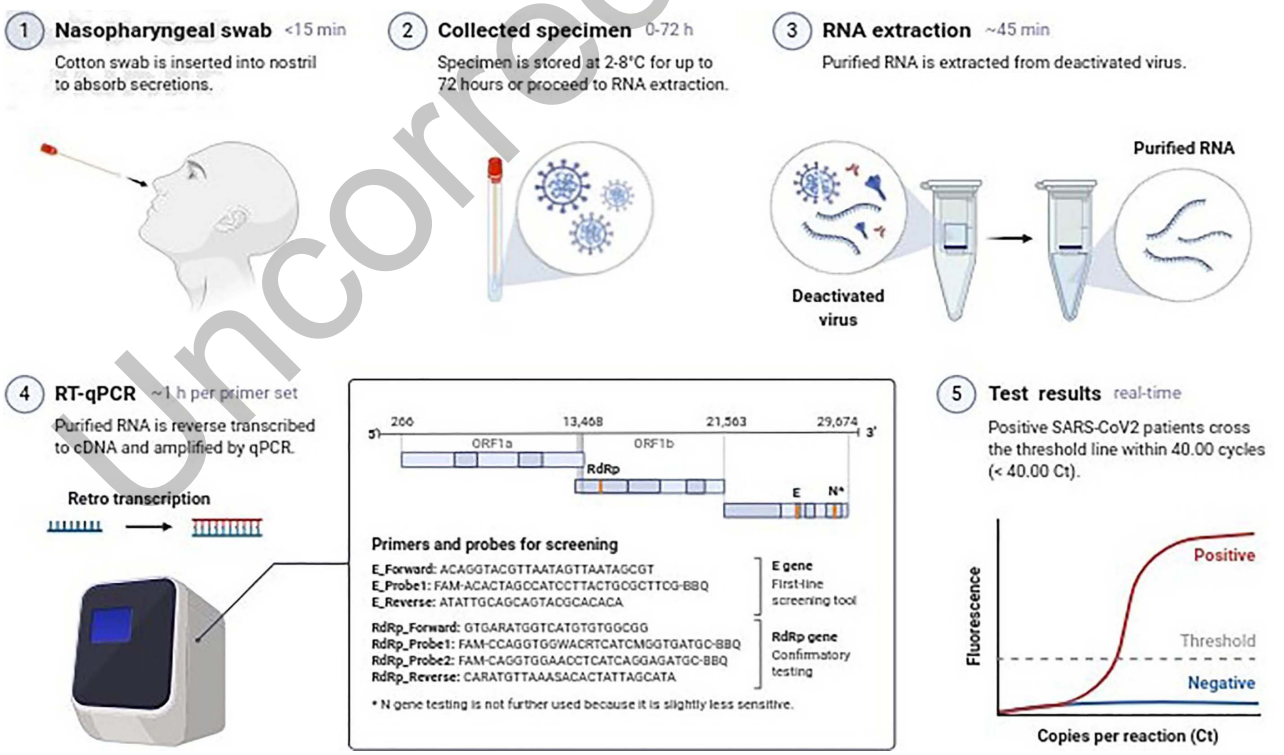

Figure 3. The steps of coronavirus disease 2019 (COVID-19) diagnostic test through reverse transcription polymerase chain reaction (RT-PCR) by nasophangeal swab using cotton swab, collecting specimen, extracting RNA, operating RT-PCR, and showing positive or negative results. Created with BioRender.com.

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

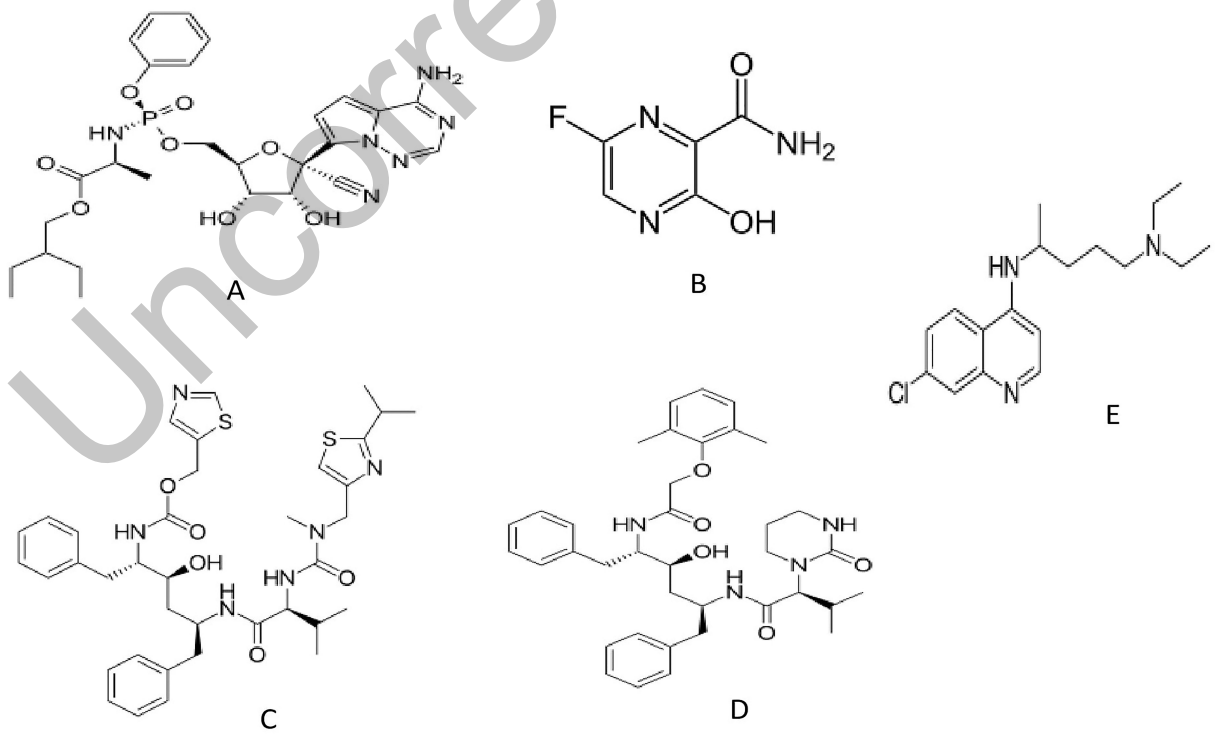

Figure 4. Chemical structures of Remdesivir (A), Favipiravir (B), Ritonavir (C), Lopinavir (D), Chloroquine (E)

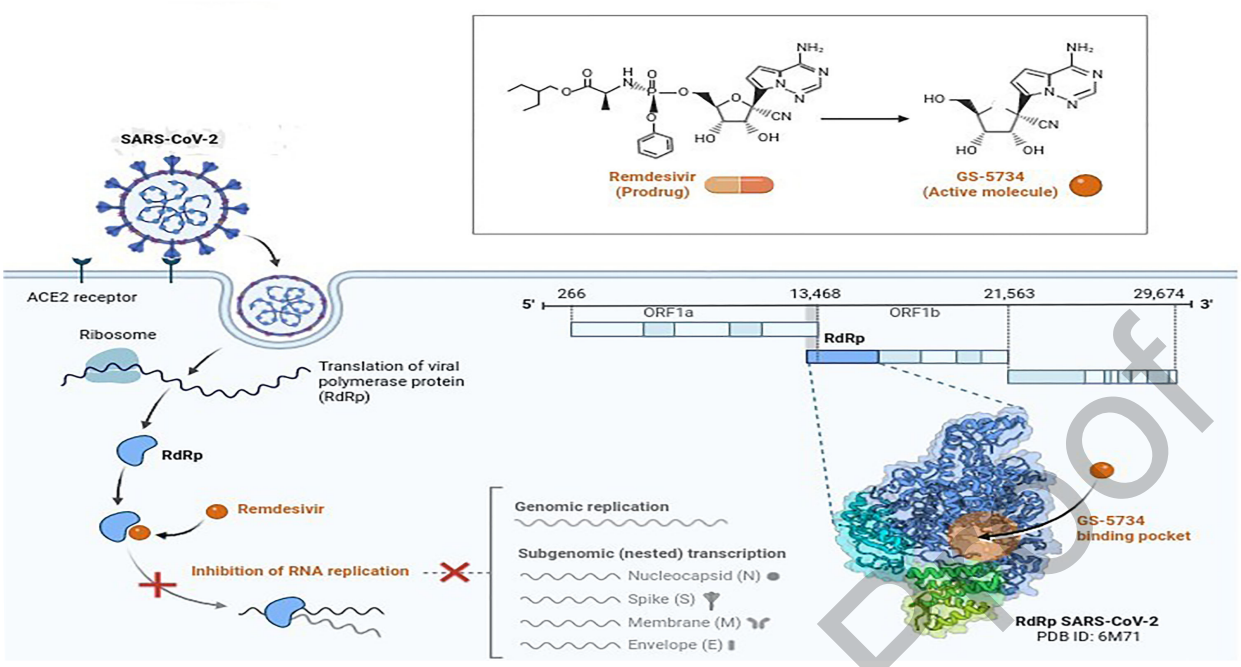

Figure 5. The action mechanism of Remdesivir against coronavirus by changing Remdesivir as prodrug into active molecule GS-5734, binding drug target molecule (RdRp), and inhibiting RNA replication in membrane cell. Created with BioRender.com.

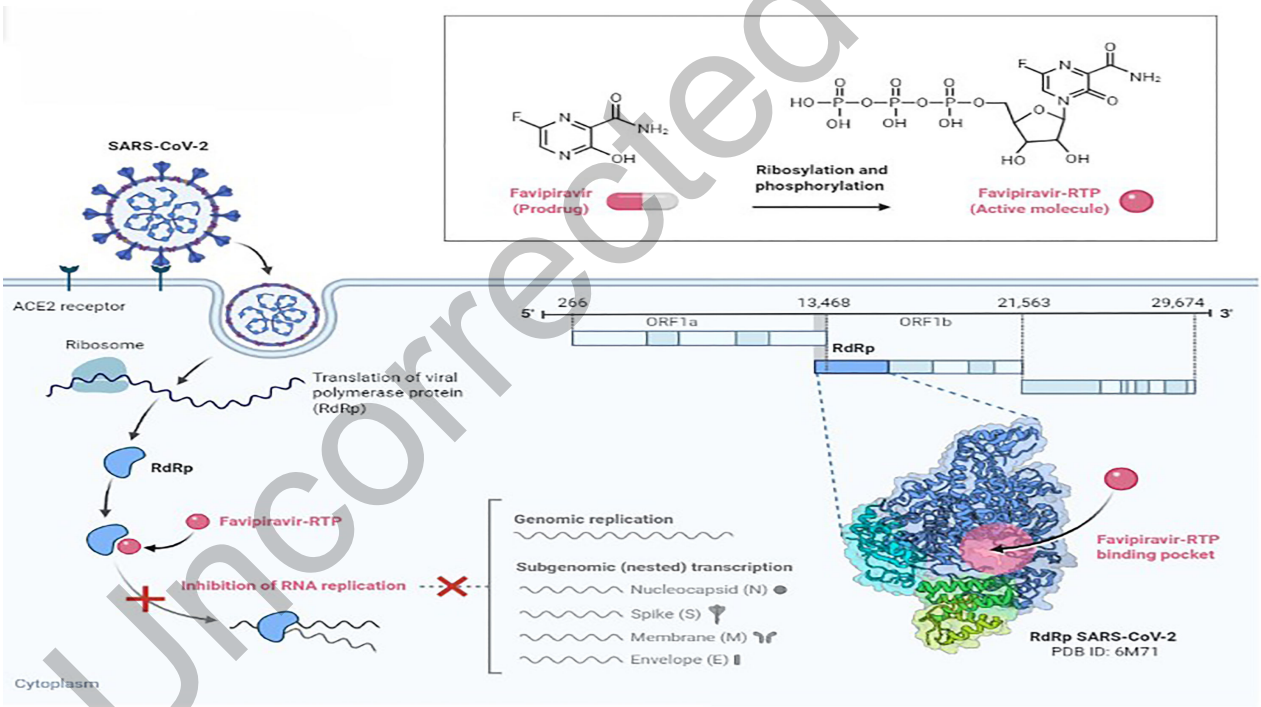

Figure 6. The action mechanism of Favipiravir as a potential repurposed drug candidate for COVID-19 which can inhibit replication and translation of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Created with BioRender.com.

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 vinysulfone 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

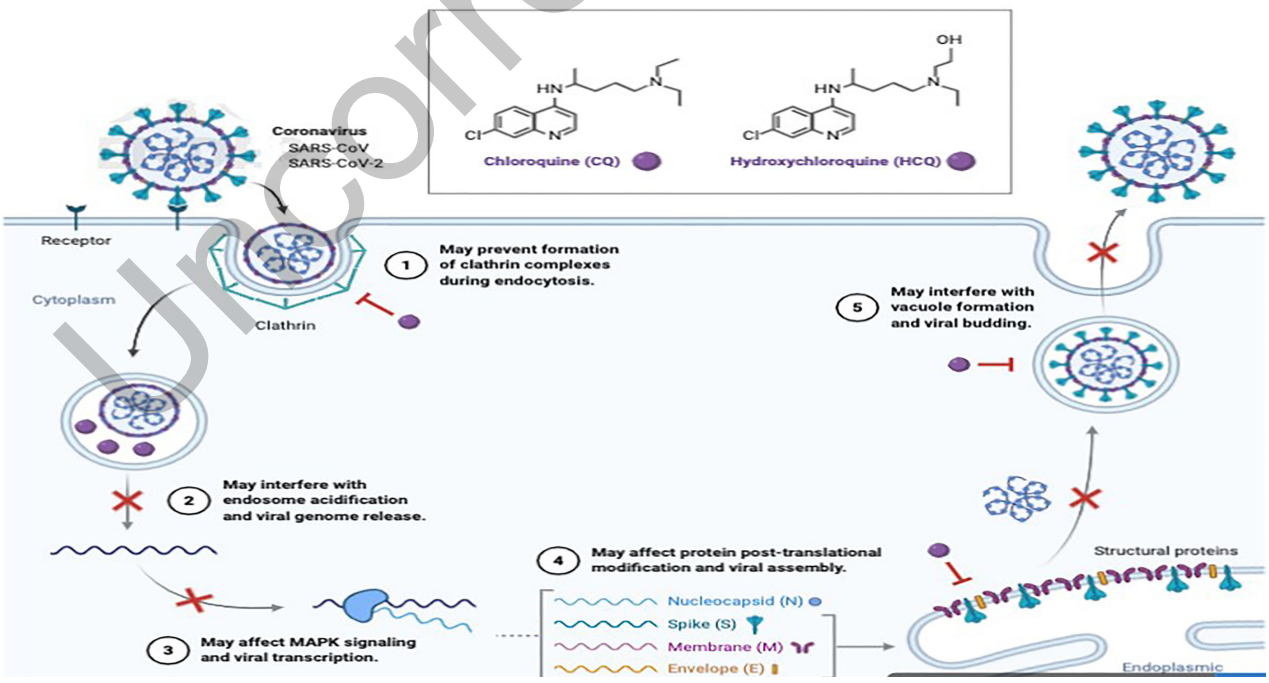

Figure 7. The molecular mechanism of chloroquine in membrane cell by preventing the formation of clathrin complexes in the cytoplasm during endocytosis, interfering with endosome acidification and viral genome release, affecting MAPK signaling and viral transcription, affecting protein post-translational 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 (Chymotripsin-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, isorhamnetin[76], and hesperidin.[77] Luteolin is a furin protein inhibitor[78] 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-2[81]

Target	Compounds	Sources
3CLpro	Rhamnetin 3-mannosyl-(1-2)-alloside	*Cassia alata*,30
	Kaempherol 3,4'-di-O-methyl ether (Ermanin)	*Tanacetum microphyllum*
	Cyanidine 3-sophoroside-5-glucoside	*Brassica oleracea, Ipomoea batatas, Raphanus sativus*
	Casuarinin	*Psidium guajava*
	Quercetin 3-(2G-rhamnosylrutinoside)	*Clitoria ternatea*
	Peonidine 3-(4'-arabinosylglucoside)	*Ipomoea fistulosa*
	Hesperidine	*Psidium guajava, Citrus aurantium*
PLpro	Platycodin D	*Platycodon grandiflorus*
	Baicalin	*Scutellaria baicalensis*
	Sugetriol-3,9-diacetate	*Cyperus rotundus*
	Phaitanthrin D 2,2-di(3-indolyl)-3-indolone	*Isatis indigotica*
	(-)-epigallocatechin gallate	*Camellia sinensis*
	2-93,4-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	*Vitis vinifera*
RdRp.	Betulanol	*Cassine xylocarpa*
	Gnidicin	*Gnidia lamprantha*
	2-β,30β-dihydroxy-3,4-seo-friedelolactone-27-lactone	*Viola diffusa*
	14-deoxy-11,12-didehydroandrographolide	*Andrographis paniculata*
	1,7-dihyroxy-3-methoxyxanthone	*Swerti apseudochinensis*
	Theaflacin 3,3'-di-O-gallate	*Camelia sinensis*
	2-(3,4-dihydrophenyl)-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	*Vitis vinifera*
	Hesperidine	*Psidium guajava, Citrus aurantium*

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 interes

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Review Article

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 san (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 € 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 an new strain of the current virus,[9,10] which was transmitted from animals to human[11], however, the new coronavirus infects humans.

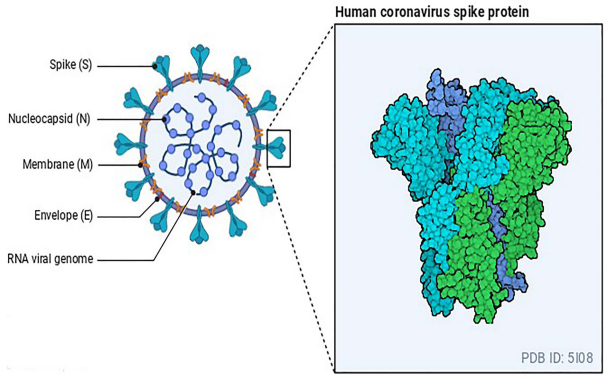

Figure 1. Structure of new coronavirus and protein visualization, now designated severe acute respiratory syndrome coronavirus-2, (SARS-CoV-2)

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 transcripts 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

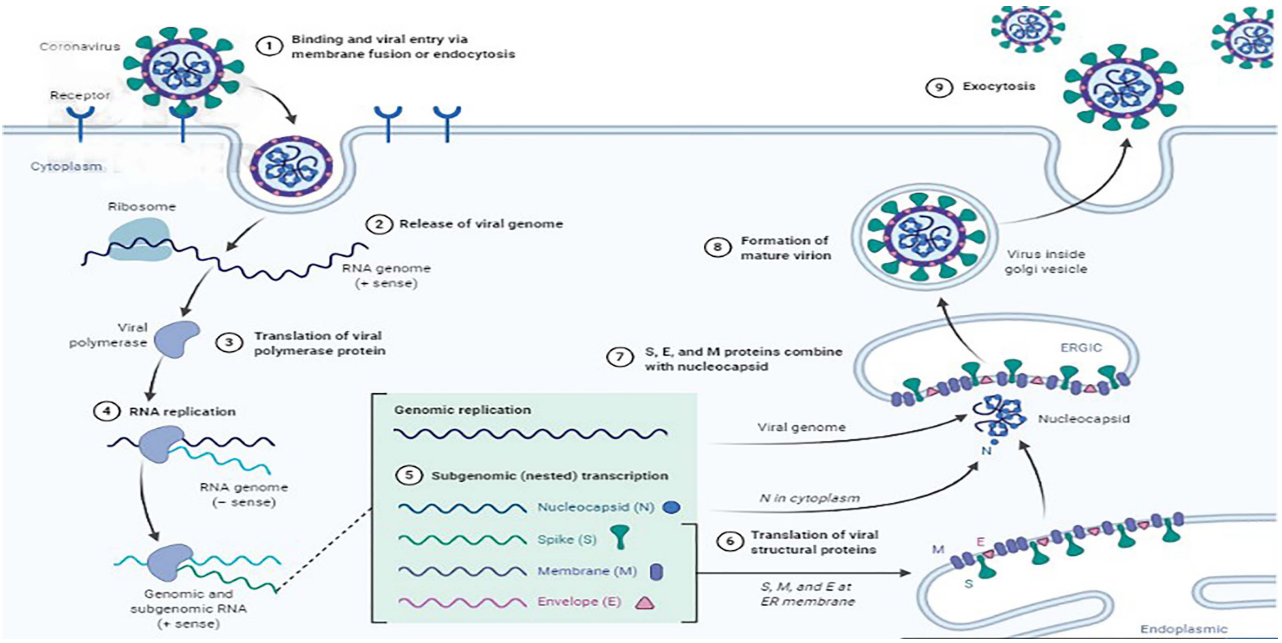

Figure 2. The life cycle of coronavirus including the viral spike (S) glycoprotein attach to the complementary host cell receptor via membrane fusion or endocytosis then release of viral genome, translation of viral polymerase protein, RNA replication, subgenomic transcription and translation of viral 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 pattern[37], 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

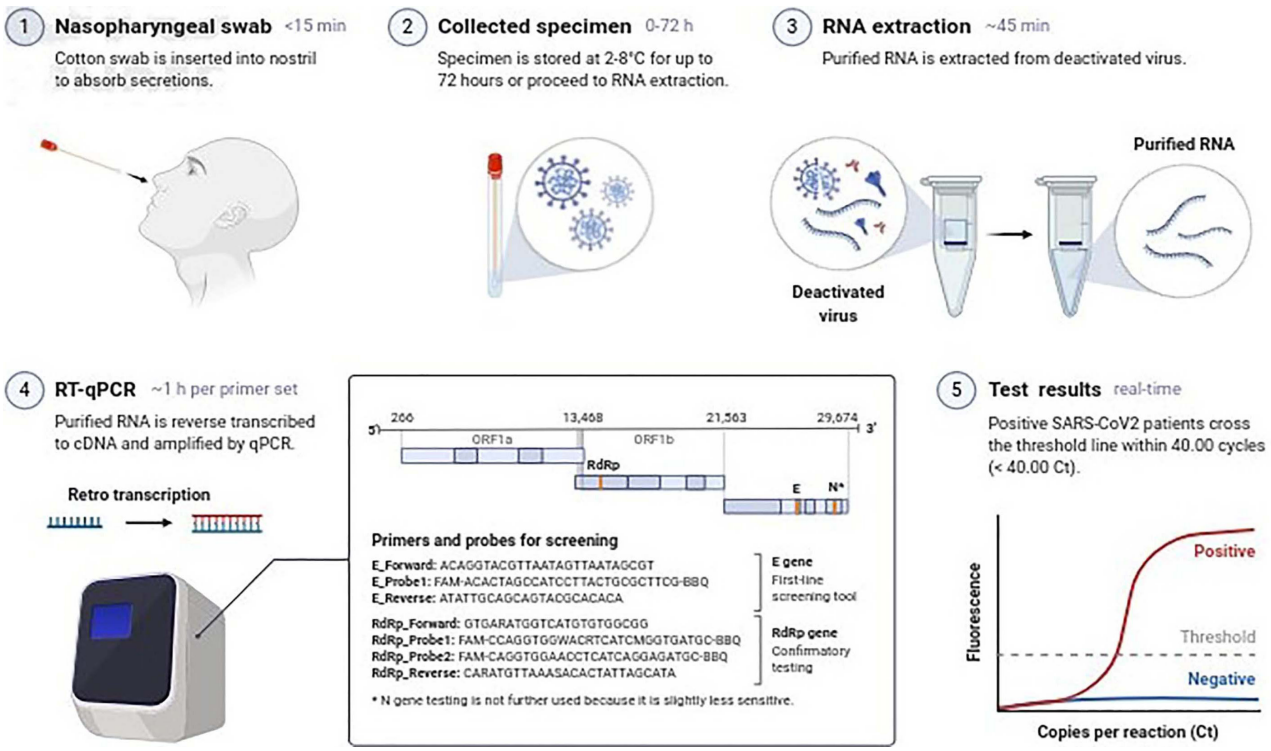

Figure 3. The steps of coronavirus disease 2019 (COVID-19) diagnostic test through reverse transcription polymerase chain reaction (RT-PCR) by nasophangeal swab using cotton swab, collecting specimen, extracting RNA, operating RT-PCR, and showing positive or negative results.

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

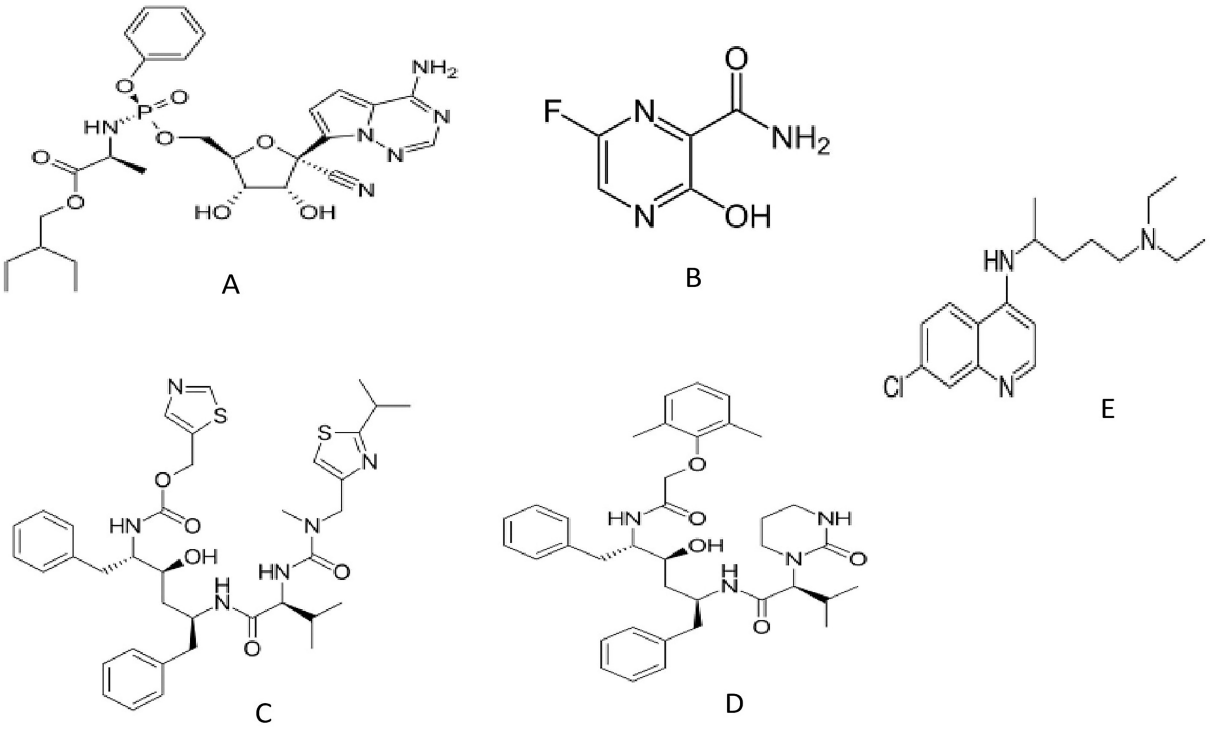

Figure 4. Chemical structures of Remdesivir (A), Favipiravir (B), Ritonavir (C), Lopinavir (D), Chloroquine (E)

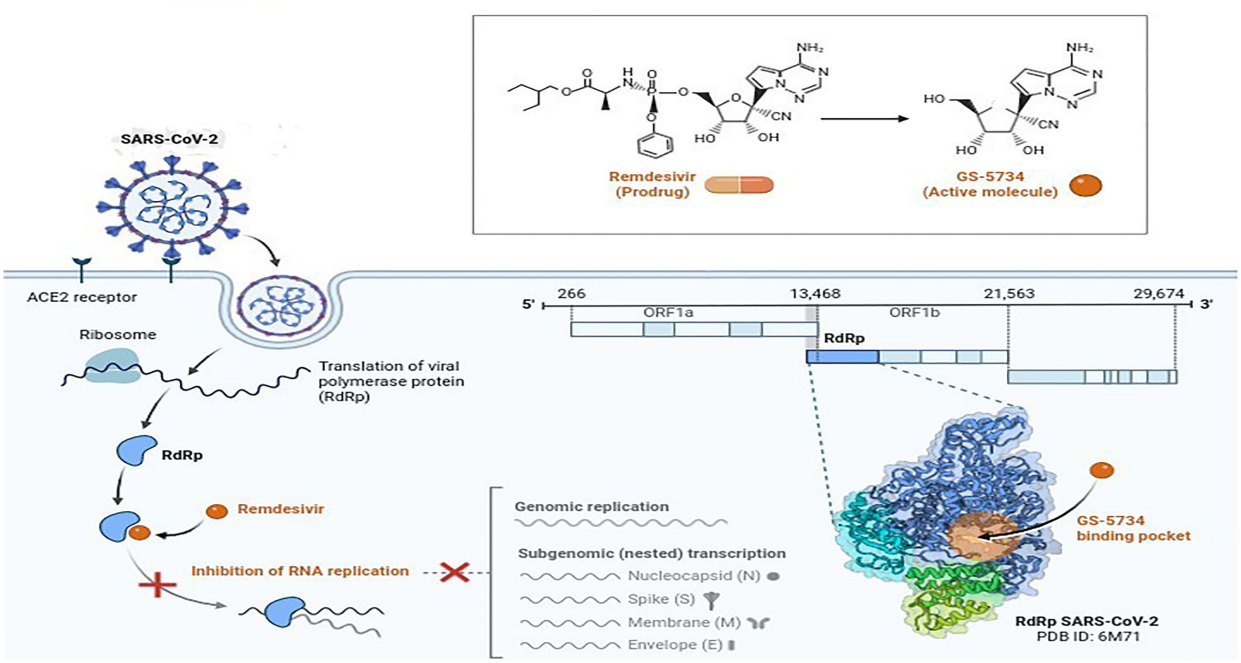

Figure 5. The action mechanism of Remdesivir against coronavirus by changing Remdesivir as prodrug into active molecule GS-5734, binding drug target molecule (RdRp), and inhibiting RNA replication in membrane cell.

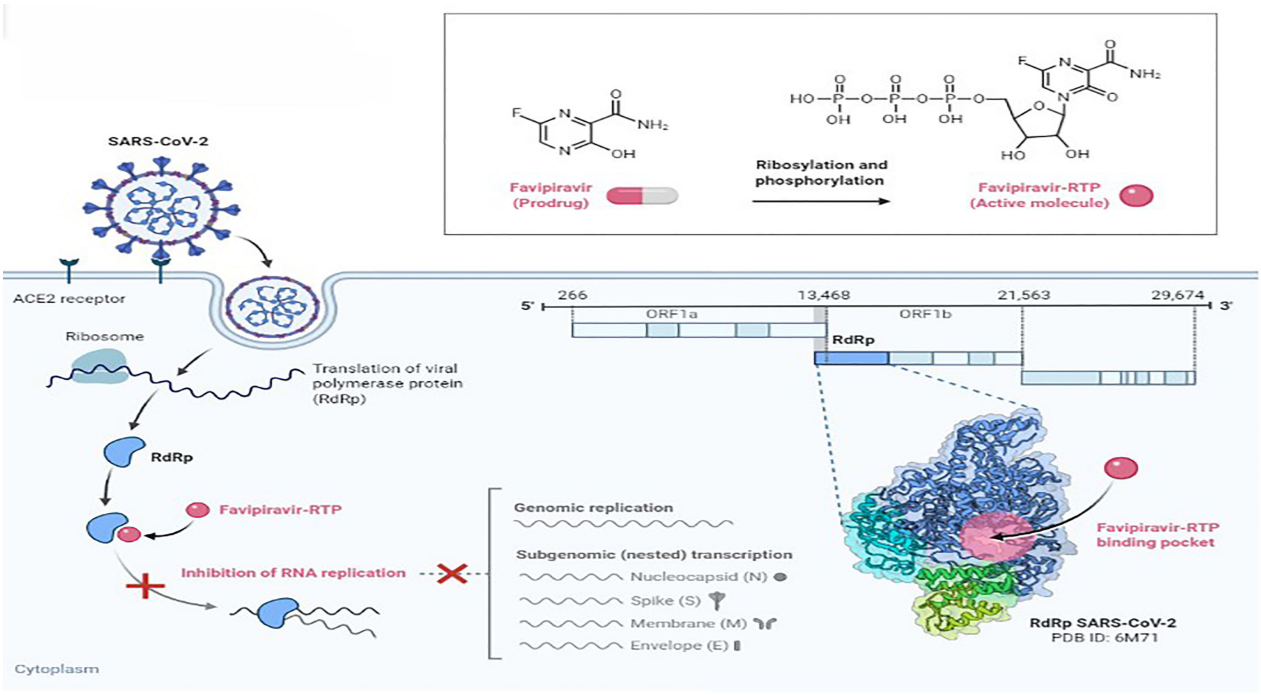

Figure 6. The action mechanism of Favipiravir as a potential repurposed drug candidate for COVID-19 which can inhibit replication and translation of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses.

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 vinysulfone 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]

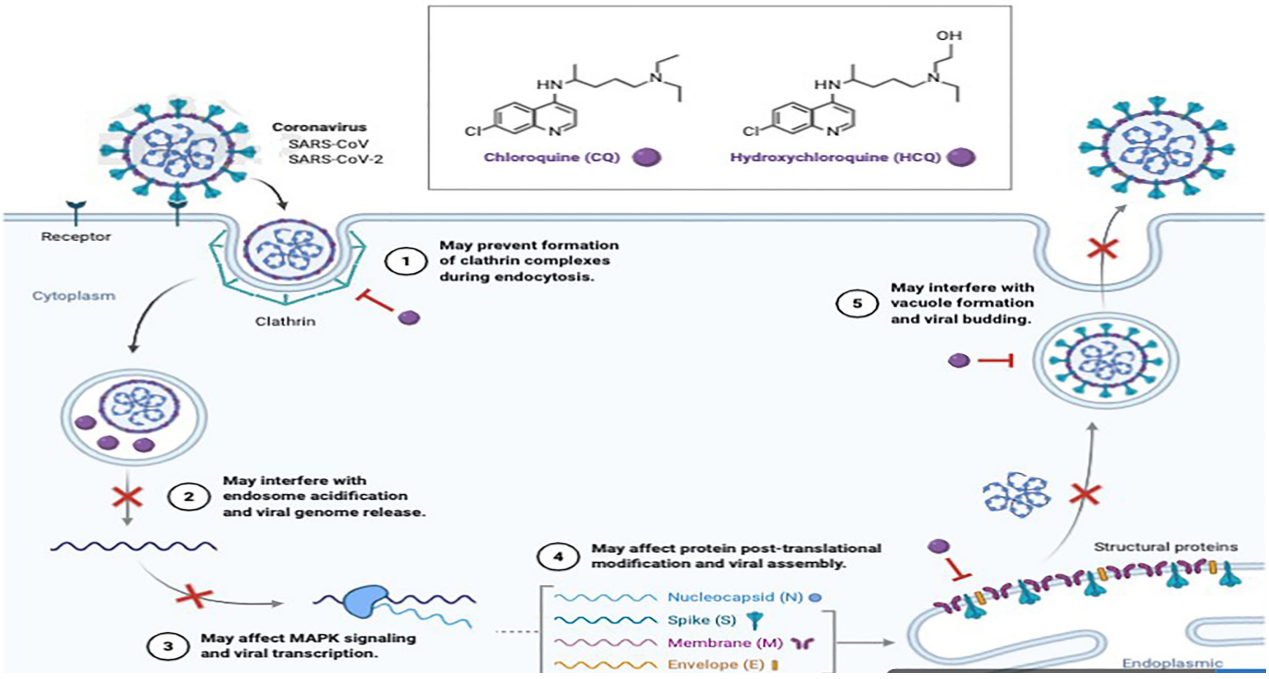

Figure 7. The molecular mechanism of chloroquine in membrane cell by preventing the formation of clathrin complexes in the cytoplasm during endocytosis, interfering with endosome acidification and viral genome release, affecting MAPK signaling and viral transcription, affecting protein post-translational 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 (Chymotripsin-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-2[81]

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

Guava (*Psidium guajava*) with pink flesh contains active compounds including myricetin, quercetin, luteolin, kaempferol, isorhamnetin[75], and hesperidin.[76] Luteolin is a furin protein inhibitor[77] 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 interes

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