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Review Article

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

Robert Tungadi[1*], Teti Sutriyati Tuloli[1], Widysusanti Abdulkadir[1], Nurain Thomas[1], Madania[1], Ani Mustapa Hasan[2], Zulfiayu Sapiun[3]

[1]*Department of Pharmacy, Faculty of Sport and Health, State University of Gorontalo, Gorontalo, Indonesia.*

[2]*Department of Biology, Faculty of Mathematics and Natural Sciences, State University of Gorontalo, Gorontalo, Indonesia*

[3]*Department of Pharmacy, Health Polytechnic of Gorontalo, Gorontalo, 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

*Corresponding Author: Robert Tungadi, E-mail: robert.tungadi@ung.ac.id

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.

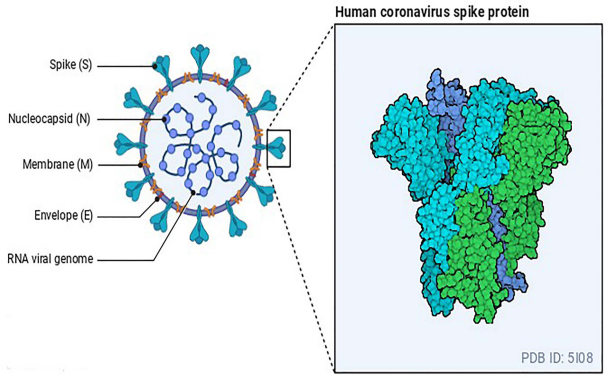

Figure 1. Structure of new coronavirus and protein visualization, now designated severe acute respiratory syndrome coronavirus-2, (SARS-CoV-2)

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

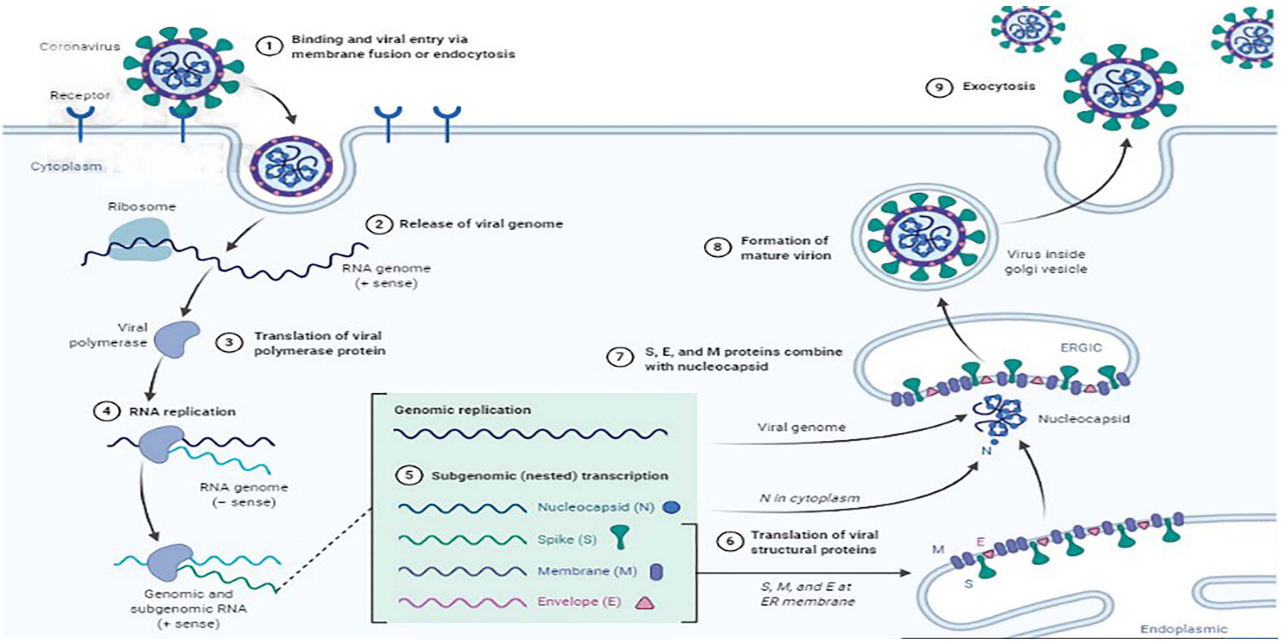

Figure 2. The life cycle of coronavirus including the viral spike (S) glycoprotein attach to the complementary host cell receptor via membrane fusion or endocytosis then release of viral genome, translation of viral polymerase protein, RNA replication, subgenomic transcription and translation of viral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

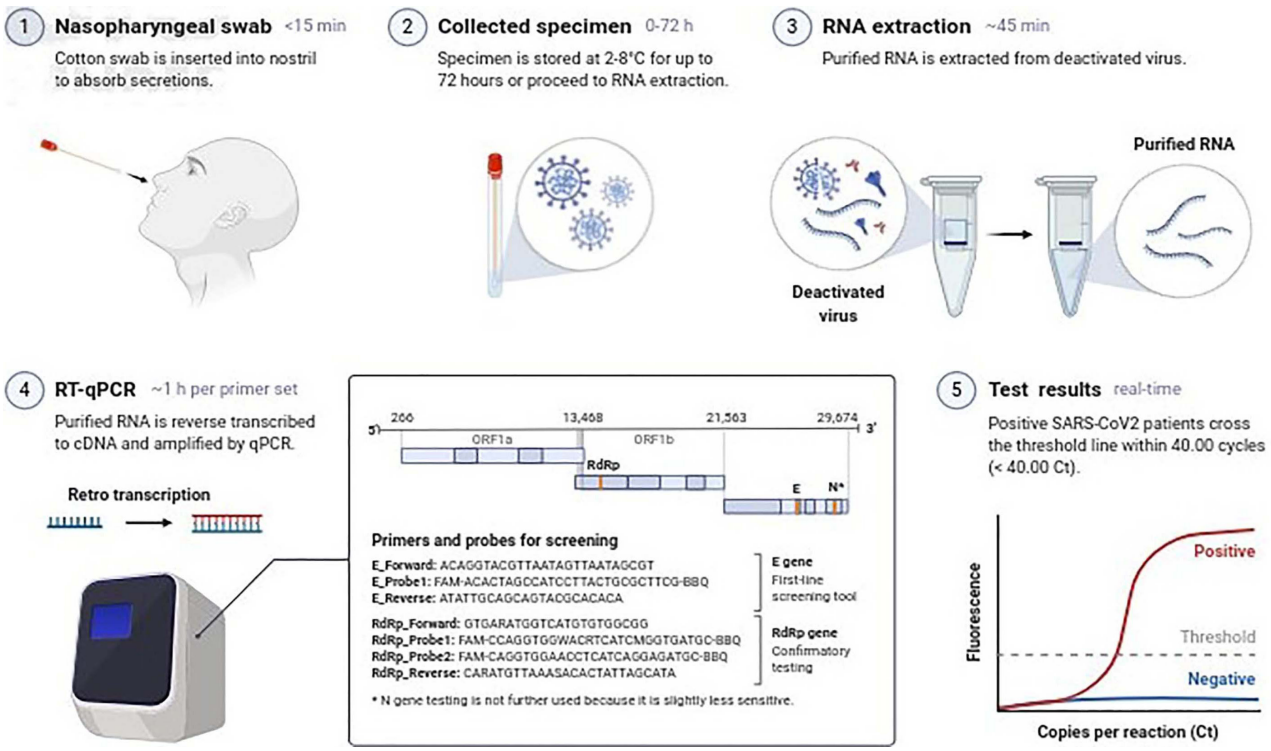

Figure 3. The steps of coronavirus disease 2019 (COVID-19) diagnostic test through reverse transcription polymerase chain reaction (RT-PCR) by nasophangeal swab using cotton swab, collecting specimen, extracting RNA, operating RT-PCR, and showing positive or negative results.

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

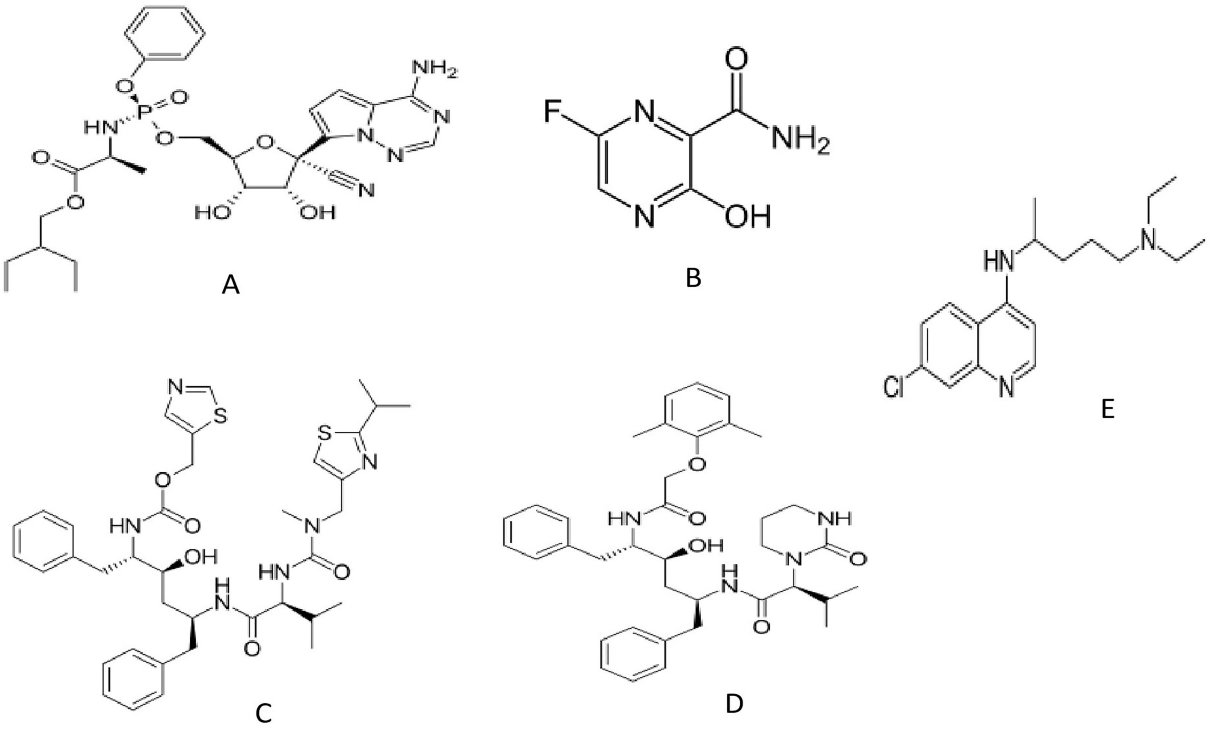

Figure 4. Chemical structures of Remdesivir (A), Favipiravir (B), Ritonavir (C), Lopinavir (D), Chloroquine (E)

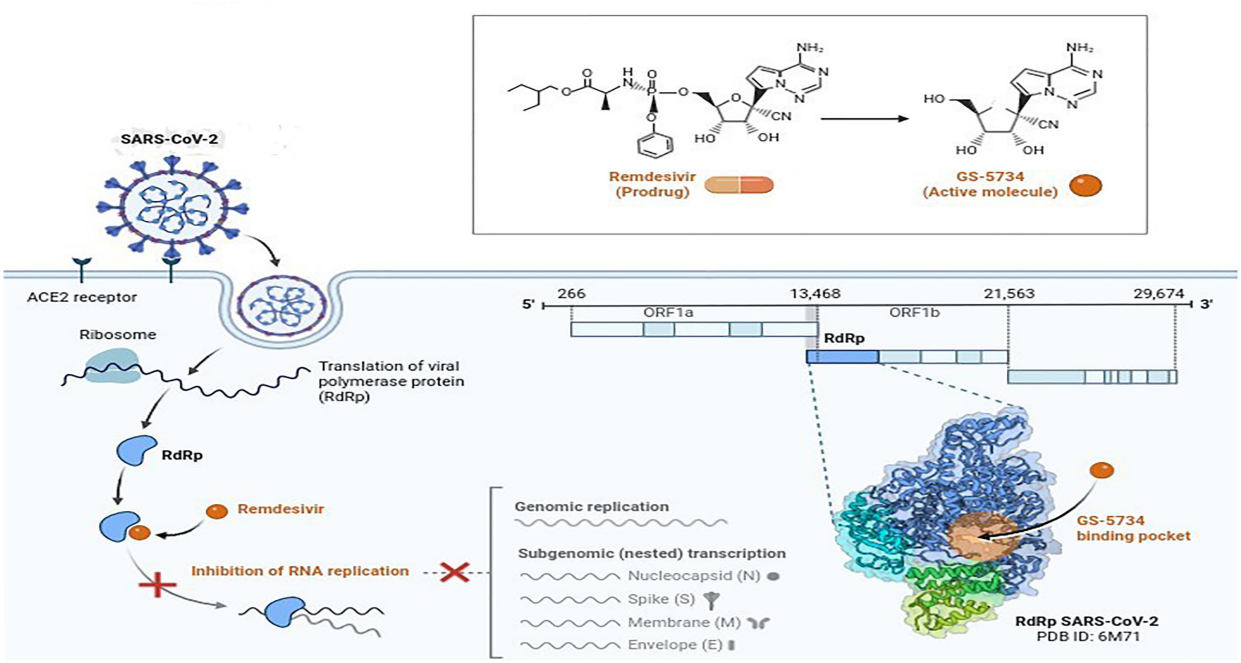

Figure 5. The action mechanism of Remdesivir against coronavirus by changing Remdesivir as prodrug into active molecule GS-5734, binding drug target molecule (RdRp), and inhibiting RNA replication in membrane cell.

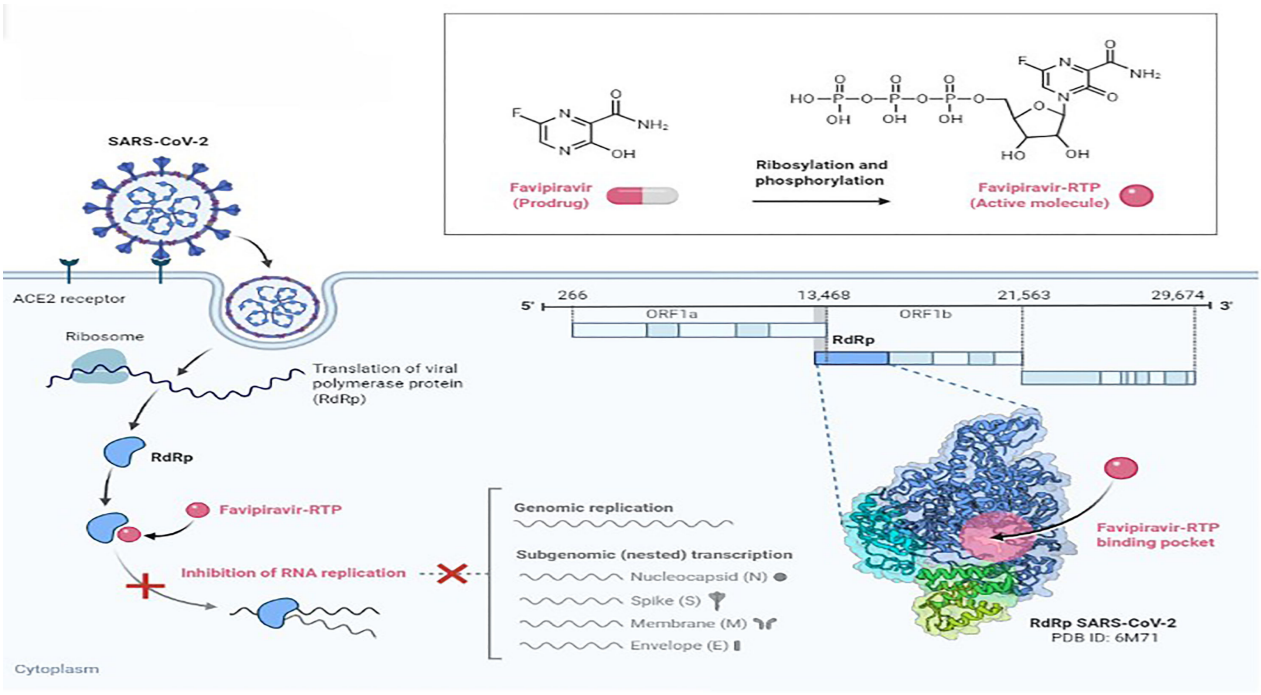

Figure 6. The action mechanism of Favipiravir as a potential repurposed drug candidate for COVID-19 which can inhibit replication and translation of virus by the RNA-dependent RNA polymerase (RdRp) of RNA viruses.

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]

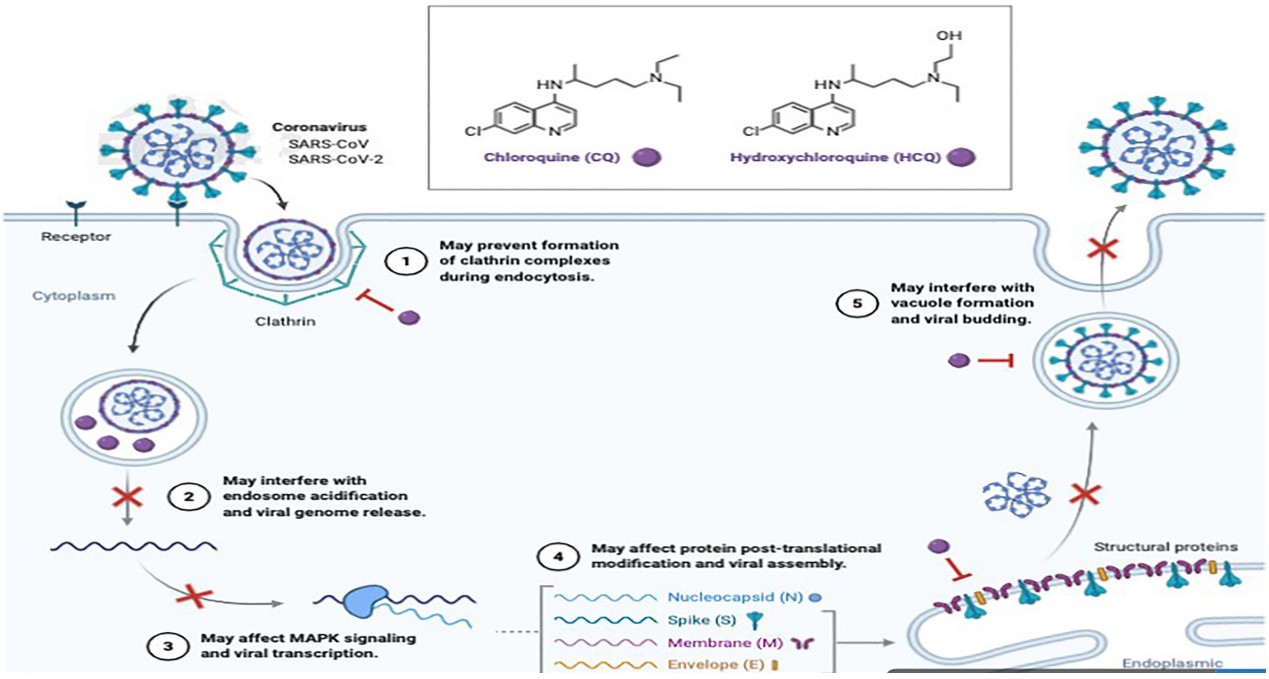

Figure 7. The molecular mechanism of chloroquine in membrane cell by preventing the formation of clathrin complexes in the cytoplasm during endocytosis, interfering with endosome acidification and viral genome release, affecting MAPK signaling and viral transcription, affecting protein post-translational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