



## Review Article

## Potential target plants as anti- sars-cov-2 (Coronavirus): Expectations and challenges

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### ABSTRACT

This review presents the potential target of SARS-CoV-19 therapy and some plants with anti-COVID-19 activity, attained through docking analysis, in vitro and in vivo studies. Furthermore, there are hopes and challenges in identifying new compounds derived from natural ingredients for therapy.

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## 1. Introduction

The corona virus has currently been designated as a pandemic because of the spread to nearly 200 countries worldwide. This disease is also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is caused by a viral infection is termed COVID-19, and is known to attack the respiratory system. Furthermore, the disorders generated advances to acute pneumonia, and possibly death. The spread of the corona virus was initially noticed in December 2019 at Wuhan City, Hubei Province, China.<sup>1</sup> This disease was confirmed capable of instigating respiratory infections, on January 7, 2020, and thus identified as a new type of coronavirus, termed SARS-CoV-2, which was previously 2019-nCoV,<sup>2</sup> and the WHO further named the disease as Coronavirus-2019 (COVID-19) on 11 February 2020.<sup>3</sup> In Indonesia, on March 2, 2020, Indonesia has reported 2 confirmed cases of covid-19. As of March 29, 2020, it has increased to 1285 cases in 30 provinces. The five highest provinces in the covid-19 cases are Jakarta (675), West Java (149), Banten (106), East Java

(90), and Central Java (63).<sup>4</sup>

The typical symptoms of infected patients encompasses coughing, fever, lung damage, and several others, including fatigue, myalgia and diarrhea.<sup>1</sup> Moreover, some anti-viral drugs to be adopted as therapy are currently being researched, and main natural material derived from plants are being exploited as one of the sources of bioactive compounds. This article discusses several possible potential target compounds for remediating SARS-CoV-19 and also some plants currently under investigation for possible therapeutic activities.

## 2. Coronavirus Characteristics

The COVID-19 virus or SARS-CoV-2, is in the group of coronavirus species, with a size of 125 nm, which is slightly larger than influenza viruses, SARS and MERS. This species is an alleged descendant of corona originating from Rhinolophus bats, with 96% homology. In addition, the almost identical gene sequences from 90 cases analyzed from outside of China indicates the possibility of emergence after a solitary species jump from an unknown intermediate host (possibly a mammal) in early December, 2019.<sup>5</sup>

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Corona virus possesses capsules, with round or elliptical particles, which is often pleomorphic, and measuring a diameter of about 50-200nm. Meanwhile, all orders of the Nidovirales viruses are not segmented and are known to have capsules, with positive RNA characterized by very long genomes. The coronavirus is cube-like in structure, with one of the main antigen protein and structure for writing genes, termed protein S (spike protein) located on the surface. This feature plays a major role in the process of attachment and entry into the host cell (the interaction between the S protein and the host cell receptors).<sup>6</sup>

The corona virus family belongs to the order of nidovirales, and further classified into 3 groups, including Group I: which consist of human coronavirus 229E (HCoV-229E), transmissible gastroenteritis virus (TEGV), porcine epidemic diarrhea virus (PEDV), canine coronavirus (CCoV), and feline coronavirus (FIPV). Group II: encompassing human coronavirus OC43 (HCoV-OC43), murine hepatitis virus (MHV), and bovine coronavirus (BCoV), and Group III: comprising turkey coronavirus (TCoV), and avian infectious bronchitis virus (IBV). Conversely, SARS-CoV (Severe acute respiratory syndrome-corona virus-2) in Figure 2 is classified in a new group, due to the demonstration of a cross reaction with group I coronavirus antibodies, despite the disparity in genetic sequences. This virus was first discovered to possess similarities with groups II and III in terms of nucleic acids and proteins sequences in the phylogenetic tree of the coronavirus family. Therefore, the virus was identified as a new corona virus strain with the capacity to cause acute respiratory infections, known as COVID-19 (corona virus disease 2019).<sup>3,7</sup>

The symptoms include fever, dry cough, fatigue, nasal congestion, sore throat and diarrhea. Furthermore, children tend to generally display much milder clinical symptoms compared to adults, with the possibility of showing numerous asymptomatic diseases, following futuristic serological evaluation. In contrast to H1N1, pregnant women have a lower risk of disease severity, as this characteristic is more highly related to age.<sup>1</sup> The elderly (over 80 years of age) are at greatest risk, with the Case Fatality Rate (CFR) of 14.8%, which further increases in those with comorbidities, including cardiovascular abnormalities, diabetes, chronic respiratory diseases, hypertension, and cancer. In addition, the causes of death usually include respiratory failure, shock or failure of many organs.<sup>8</sup>

### 3. Potential Targets for Sars-cov-2 Therapy

Potential anti-coronavirus therapies can be divided into two categories depending on the target, one is acting on the human immune system or human cells, and the other is on coronavirus itself. The therapies acting on the coronavirus itself include preventing the synthesis of viral RNA through acting on the genetic material of the virus, inhibiting virus replication through acting on critical enzymes of virus,

and blocking the virus binding to human cell receptors or inhibiting the virus's self-assembly process through acting on some structural proteins.<sup>9</sup>

The clinical course of the disease involves two triphasic patterns. The first phase is characterized by viral load replication, which occurs with the clinical symptoms of fever, myalgia and also other systemic indications. Furthermore, it is possible for these demonstrations to generally improve after a few days. The second phase features immunopathological imbalances, including oxygen desaturation, the reappearance of fever, and the development of acute pneumonia, alongside a decline in viral load. Moreover, the SARS-CoV-2 infection viral load is recognized 5-6 days after initial symptoms, while the incubation period for SARS is 1-4 days, which takes up 10 days for several patients, with latent period variation of 3-7 days up to 14 days on an average.<sup>10</sup>

#### 3.1. Blocking the ACE2 receptor and the TMPRSS2 protease enzyme target

The first stage of SARS-CoV infection involves the binding of virus to the target receptor of host cells. These include cells of the respiratory, alveolar and vascular endothelial, as well as type II pneumocyte cells and pulmonary macrophages, attained through the target of angiotensin convertase enzyme 2 (ACE-2).<sup>1,11</sup> In addition, SARS-CoV infection has the tendency to induce the down-regulation of ACE-2 within the lung tissue, therefore producing angiotensin II and stimulating angiotensin II type 1A receptors, and consequently increase pulmonary vascular permeability.<sup>10,12</sup>

The spike protein present in the coronavirus membrane surface binds to the ACE-2 receptors of the target cell surface. Therefore, the transmembrane serine protease Type II (TMPRSS2) enzyme binds and cleaves the receptor, and the expression further enhances virus cellular uptake into cells. Ferrario et al (2019) reported on the tendency for ACE Inhibitors and ARB to significantly increase the expression of mRNA heart muscle cells. In addition, out of the 138 hospital patients infected with COVID-19, 31% were hypertensive, 10% possessed diabetes mellitus and 14.5% had cardiovascular disorders.<sup>12</sup> Arbidol can prevent S protein/ACE2 interaction and inhibit membrane fusion of the viral envelope by preventing the binding of viral envelope protein to host cells and preventing viral entry to the target cell. Camostat mesylate inhibits TMPRSS2 and viral cell entry.<sup>11</sup> Chloroquine and hydroxychloroquine can inhibit viral entry and endocytosis by increasing endosomal pH, interfere with ACE2 glycosylation as well as host immunomodulatory effects.<sup>13</sup>

Studies with experimental animals show an increase in the expression of ACE2 mRNA following the administration of ACE Inhibitors and ARBs to rodents, which was different between tissues, including the heart, kidneys and aorta.

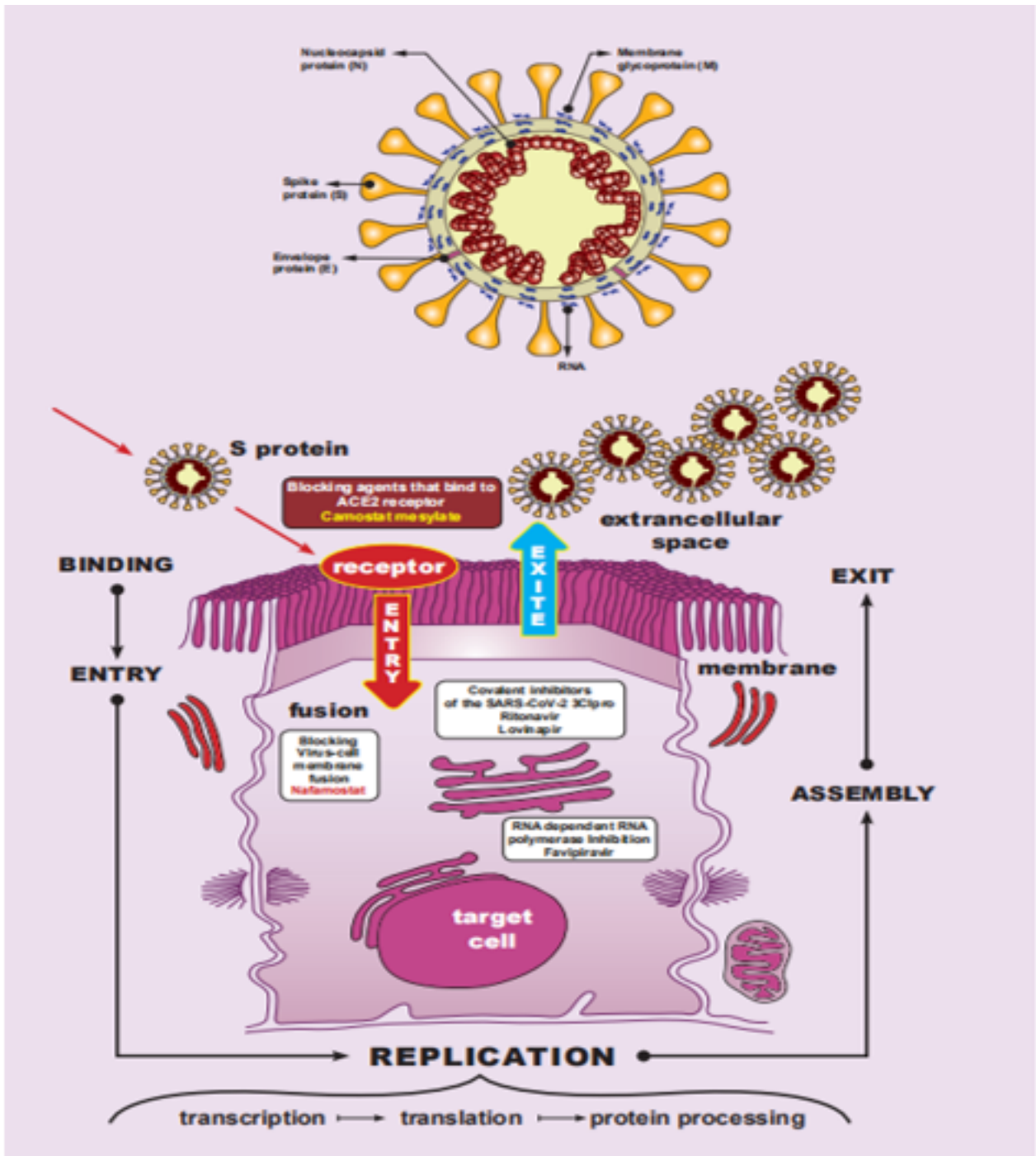


Fig. 1: Potential target of Anti-viral agents against SARS-Cov2 (Coronavirus-19)

Furthermore, the provision of ACE Inhibitors to healthy humans produced a 1.9 fold increase in duodenal ACE2 mRNA expression, compared to controls.<sup>14</sup>

ACE mediates the conversion of angiotensin I to angiotensin II, which interacts with angiotensin II type 1 (AT<sub>1</sub>) receptors. In some pathological conditions, overactivation of AT<sub>1</sub> receptors may lead to damaging events like fibrosis in the liver and lungs, possibly through increasing TGF- $\beta$  expression. Presumably, a drug that would inhibit ACE, such as lisinopril, or block AT<sub>1</sub>, like losartan, would have a beneficial effect of mitigating the heavy fibrosis associated with acute cases of SARS infections by shutting down the ACE-angiotensin II-AT<sub>1</sub> pathway. ACE inhibitors may further play a role in disallowing viral fusion of the coronavirus to the host cell and entry into the cell, denying its pathway to replication.<sup>13,15</sup>

### 3.2. Blocking Virus-cell membrane fusion

After the interaction of the virus with the receptors on the cell surface, the virus RNA genome is released into the cytoplasm.<sup>13,16</sup> Low pH in endosome (5.5) triggers the release of mantle (uncoating) viruses. The acidic condition also causes fusion between the endosome membrane and the membrane.<sup>17</sup> Therefore, the newly formed glycoprotein envelope is inserted into the endoplasmic reticulum membrane or Golgi, followed by the formation of nucleocapsids, which results from the combination of genomic RNA and nucleocapsid proteins. These virus particles then grow into the endoplasmic reticulum Golgi intermediate compartment (ERGIC), and the containing vesicles subsequently connect with the plasma membrane to release the virus.<sup>16,17</sup> Fusion core structure formed by the HR1 and HR2 domains in the SARS-CoV S protein; The fusion core is a six-helix (6-HB) with three HR2  $\alpha$ -helices packed in an oblique antiparallel manner against the hydrophobic grooves on the surface of the central HR1 trimer.<sup>18,19</sup>

To develop specific SARS-CoV-2 fusion inhibitors, it is essential to study the fusion capacity of SARS-CoV-2 compared to that of SARS-CoV. Particularly, SARS-CoV and SARS-CoV-2 have 89.8% sequence identity in their spike (S) proteins S2 subunits, which mediate the membrane fusion process, and both of their S1 subunits utilize human angiotensin-converting enzyme (hACE2) as the receptor to infect human cells.<sup>19,20</sup>

Yamamoto et al reported in 2016 that Nafamostat could inhibit S protein-initiated membrane fusion by a related coronavirus MERS-CoV, which causes Middle Eastern Respiratory Syndrome (MERS). They demonstrated this using a Dual Split Protein (DSP) reporter fusion assay to screen a library of 1,017 US Food and Drug Administration (FDA)-approved drugs and a S protein-fusion assay to test how MERS-CoV infected cultured airway epithelial cell-

derived Calu-3 cells.<sup>21</sup> Nafamostat suppressed SARS-CoV-2 S protein-initiated fusion in 293FT cells (derived from the human fetal kidney) ectopically expressing ACE2 and TMPRSS2. They also performed experiments using Calu-3 cells, where low concentrations in the 1-10 nM range of Nafamostat significantly suppressed membrane fusion.<sup>22,23</sup>

### 3.3. Covalent inhibitors of the SARS-CoV-2 3CLpro

Viruses (including HCoV) require host cellular factors for successful replication during infection. Systematic identification of virus-host protein-protein interactions (PPIs) offers an effective way toward elucidating the mechanisms of viral infection.<sup>24</sup> In SARS-CoV, the 3C-like proteinase (3CLpro) is the main protease, which cleaves the large replicase polyprotein 1a (pp1a) and pp1ab to produce non-structural proteins (NSPs) for the transcription and replication of the virus.<sup>9,19</sup> The viral 3-chymotrypsin-like cysteine protease (3CLpro), which plays a key role in the replication of coronavirus, is a potential drug target for the development of anti-SARS-CoV-2 drugs.<sup>19,25</sup> The 3CLpro, also known as Nsp5, is first automatically cleaved from poly-proteins to produce mature enzymes, and then further cleaves downstream Nsps at 11 sites to release Nsp4-Nsp16<sup>23</sup>. Several natural compounds and derivatives with anti-virus and anti-inflammatory effects also exhibited high binding affinity to 3CLpro, including a series of andrographolide derivatives (chrysin-7-O- $\beta$ -glucuronide from *Scutellaria baicalensis*, betulonal from *Cassine xylocarpa*, 2 $\beta$ -hydroxy-3,4-secofriedelolactone-27-oic acid, isodecortinol and cerevisterol from *Viola diffusa*, hesperidin and neohesperidin from *Citrus aurantium*, kouitchenside I and deacetylcentapicrin from the plants of *Swertia* genus.<sup>8</sup>

### 3.4. RNA dependent RNA polymerase Inhibition

Transcription and replication of the viral RNA genome is carried out in the host cell nucleus, catalized by RdRp enzyme consisting of enzymes PB1, PB2 and PA. The vRNA genome forms a complex with RdRp and NP forms the vRNP as a transcription template (forming mRNA) and replication template (forming the vRNA genome from cRNA).<sup>26</sup>

RNA-dependent RNA polymerase (RdRp) is an important enzyme that catalyzes the replication of RNA from RNA templates. Compared the sequence of RdRp in severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV and SARS-CoV-2 have remarkably similar sequences, and encode structurally similar structures of RdRp. RdRp, also known as nsp12, which catalyzes the synthesis of coronavirus RNA, is an essential enzyme of the coronaviral replication/transcription machinery complex.<sup>27</sup>

Development of some nucleoside-based therapeutics for SARS-CoV infections has been hampered by their removal via a proofreading 3'-5' exoribonuclease (ExoN), but remdesivir, an adenosine nucleoside analog that demonstrates broad-spectrum anti-RdRp activities has been shown to evade ExoN surveillance.<sup>28,29</sup>

The natural products and derivatives with anti-virus, anti-inflammation and anti-tumor effects exhibited high binding affinity to RdRp, such as betulonal from *Cassine xylocarpa*, gnidicin and gniditrin from *Gnidia lamprantha*, 2 $\beta$ ,30 $\beta$ -dihydroxy-3,4-seco-friedelolactone-27-lactone from *Viola diffusa*, 14-deoxy-11,12-didehydroandrographolide from *Andrographis paniculata*, 1,7-dihydroxy-3-methoxyxanthone from *Swerti apseudochinensis*, theaflavin 3,3'-di-O-gallate from *Camellia sinensis*, and andrographolide derivative (R)-((1R,5aS,6R,9aS)-1,5a-dimethyl-7-methylene-3-oxo-6-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl) decahydro-1H-benzo[c]azepin-1-yl) methyl 2-amino-3-phenylpropanoate.<sup>27,28</sup>

#### 4. Drugs for Sars-cov-2 Infection Therapy

The Guidelines have been revised 5 times from the initial edition issued on January 15, 2020, and the latest being the 6<sup>th</sup> edition, released on February 18, 2020. Meanwhile, the fifth publication recommends the use of antivirals, including IFN- $\alpha$ , lopinavir/ritonavir, and ribavirin in the treatment of COVID-19.<sup>30</sup>

Favipiravir is a drug thought to act by interfering with enzymes necessary for viral replication and was approved in China for treatment of COVID-19 in February 2020. The drug is currently undergoing clinical trials as a treatment for COVID-19. The preliminary results from a study of 80 patients (including both the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir.<sup>30</sup>

Chloroquine has been known from the year 1934 as an effective antimalarial treatment. This drug is a substitute of quinine, which is classified as a 9-aminoquinoline. The use of chloroquine as an antimalarial is widely known, while information on the effectiveness and safety during COVID-19 treatment are highly limited. Moreover, this drug is not a first-line antimalarial recommendation in Indonesia because of the issues of resistance, despite the dose-adjusted safety and possible long-term administration. In addition, several in vitro studies showing the anti-virus potential with a broad spectrum have been reported.<sup>31</sup>

Based on testing, the antiviral effect of chloroquine on primate cell culture (Vero E6) infected by the SARS-Cov virus shows effectiveness in reducing the number of those infected<sup>32</sup> show the ability for chloroquine at a concentration of 0.1-1  $\mu$ m to reduce infections by 50%, while a decline of up to 90–94% is obtainable with 33-100  $\mu$ m. In addition, studies have also shown the ability to inhibit the multiplication of the SARS-Cov2 virus, through

the application of standard doses used in humans, as an EC90 of 6.90  $\mu$ M was obtained in Vero E6 cell culture.<sup>33</sup>

Oseltamivir is a neuraminidase enzyme inhibitor, characterized by the ability to inhibit the release of new replicated viruses from host cells. Hence, the absence of this enzyme in SARS-Cov-2 has led to inability to apply this medication as an anti-viral agent against COVID-19.<sup>30,34</sup> Lopinavir is another protease inhibitor; like darunavir, it has been found to inhibit replication of the HIV-1 virus. It is being tested in combination with ritonavir, a compound that increases the half life of lopinavir. The combination (lopinavir/ritonavir) has been approved for treating SARS, MERS, and HIV-1 infections, but has not shown a benefit beyond standard care for COVID-19 patients in the most recently published clinical study.<sup>30,35</sup>

#### 5. Plants for Sars-cov-2 Infection Therapy

Numerous plant extracts possessing antiviral properties have been identified. However, most show strong in vitro activity in cell culture but, with lesser effectiveness during testing on infected animals. In addition, the molecular mechanisms tend to differ with different virus types. For example, the potential therapeutic target for SARS-CoV-2 is mostly in the expression of the ACE2 enzyme, inhibition of replication by influencing some ribosomal proteins, and by boosting the cytokine content of the immune system. Furthermore, some of the plants below are currently used in the testing phase to overcome SARS-CoV-2 infection.



Fig. 2: Chinese Rhubarb extracts(rhubarb)

Wu et al. (2019) conducted a large-scale screening on effective anti-SARS-CoV natural medicines and products, using infected vero cells. Therefore, the ginsenoside-Rb1 isolated from *Panax ginseng* and reserpine isolated from the genus *Rauwolfia* was confirmed capable of inhibiting SARS-CoV virus replication.<sup>8</sup>

Investigation for bioprospecting of natural products can be carried out in three ways. Firstly, the classical method involving phytochemical factors, serendipity and random screening approaches. Second, to use existing molecular databases to screen for molecules that may have therapeutic

**Table 1:** Antivirals included in the Guidelines (version 6) for treatment of COVID-19<sup>30</sup>

Drug	Dosage	Method of administration	Duration of treatment
IFN- $\alpha$	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/ritonavir	200mg/50mg/capsule, 2 capsule each time, 2 times/day	oral	No more than 10 days
Ribavirin	500mg each time, 2 to 3 times/day in combination with IFN- $\alpha$ or lopinavir/ritonavir	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500mg(300 mg for chloroquine) each time, 2 times/day	oral	No more than 10 days
Arbidol	200mg each time, 3 times/day	oral	No more than 10 days

**Table 2:** Antivirals for treatment of COVID-19 in Indonesia

Drug	Dosage	Method of administration	Duration of treatment
Favipiravir	1600 mg for twice a day, followed by 600 mg for twice a day(2nd to 14th day).	oral	No more than 14 days
Chloroquine phosphate	500mg, 2 times/day	oral	No more than 10 days
Hydroxy chloroquine	Initial dose of 400 mg at diagnosis Continue with 400 mg for 12 hours	oral	No more than 10 days
Oseltamivir	Subsequently, 200 mg for twice a day until the 5th day.	oral	No more than 10 days

**Table 3:** Plants to overcome the SARS-CoV-2 infection

No	Simplisia plants	Bioactive compounds and IC50 $\mu\text{g/mL}$	Work mechanism
1.	Chinese Rhubarb extracts (rhubarb)	(IC50: 13.76 $\pm$ 0.03 $\mu\text{g/mL}$ )	The inhibitory effect of SARS-CoV-2 3C-likeprotease (3CL(pro) and RNA polymerase <sup>36-38</sup>
2.	Houttuynia cordata		The inhibitory effect of SARS-CoV-2 3C-likeprotease (3CL(pro) and RNA polymerase <sup>24,39,40</sup>
3.	Isatis indigotica	Sinigrin (IC50: 217 microM) indigo (IC50: 752 microM) beta-sitosterol (IC50: 1210 microM)	The inhibitory effect of SARS-CoV-2 3C-likeprotease (3CL (pro) and RNA polymerase <sup>40,41</sup>
4.	Aloe barbadensis / Aloe vera	Aloe emodin (IC50: 366 $\mu\text{M}$ )	The protease inhibitory effect <sup>40</sup>
5.	Citrus aurantium/ Orange peel	hesperetin (IC50:8.3 $\mu\text{M}$ )	Imunoregulator Reseptor ACE-2 <sup>42</sup>
6.	Camelia sinensis/green tea	epigallocatechin gallate (IC50: 73 $\mu\text{M}$ )	Protease inhibition (Mpro) <sup>36</sup>
8.	Torreya nucifera	amentoflavone (IC50= 8.3IM)	Chymotrypsin-like protease (3CLpro) inhibition <sup>43</sup>
9.	Curcuma domestica L / turmeric	Docking Analysis	Protease inhibition <sup>44</sup>
10.	Glycyrrhizae glabra	glyzyrizin	Inhibits SARS-CoV-2 replication <sup>45</sup>
	Scutellaria lateriflora	Scutellarein 2.71 $\pm$ 0.19 IM	Inhibits nsP13 (protein helicase SARS-CoV) <sup>38,46,47</sup>





**Fig. 3:** *Houttuynia cordata*



**Fig. 6:** *Citrus aurantium*/Orange peel



**Fig. 4:** *Isatis indigotica*



**Fig. 7:** *Camelia sinensis*/green tea



**Fig. 5:** *Aloe barbadensis*/Aloe vera



**Fig. 8:** *Torreya nucifera*



**Fig. 9:** *Curcuma domestica L* /turmeric



**Fig. 10:** *Glycyrrhizae glabra*



**Fig. 11:** *Scutellaria lateriflora*

effect on coronavirus and directly based on the genomic information and pathological characteristics of different coronaviruses to develop new targeted drugs from scratch.

## 6. Conclusion

Up to the time of this report, there are no effective drugs or vaccines available to overcome the SARS-CoV-2 virus infection, which prompts the need to explore bioactive compounds from natural materials, including plants. However, an understanding of the disease pathogenesis

provides explanation for the possible molecular mechanism of a candidate.

Research in molecular virology has opened new avenues in the knowledge and understanding of viral properties, the nature of the obligate parasitism of viruses and, to a certain extent, the mechanisms involved in viral diseases. On the other hand, the search for natural and man-made drugs to inhibit and cure viral infections in man and animals have been marred by failure.

## 7. Source of Funding

None.

## 8. Conflict of Interest

None.

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