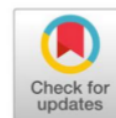


# Modulation of severe acute respiratory syndrome coronavirus (SARS-CoV-2) in receptor, innate immunity and drug antiviral candidate

*By* Indra Lesmana Tarigan



## Review Article

### *Modulation of severe acute respiratory syndrome coronavirus (SARS-CoV-2) in receptor, innate immunity and drug antiviral candidate*

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#### HIGHLIGHTS

- SARS-CoV-2 has a high affinity than SARS-CoV and MERS-CoV due to the changing of some S protein nucleotide.
- High ACE2 expression in respiratory cells that potential high risk for COVID-19 infection by ACE2 receptor.
- There is a screening of drug potential as an antiviral against SARS-CoV-2, chemical synthesis, and natural product.

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#### ABSTRACT

The Coronavirus disease-19 (COVID-19) is a contagious acute respiratory infectious disease caused by SARS-CoV-2 as a global pandemic in 2020. This disease most spreads and causes some severe cases, even death in the world. The main purpose of this review discusses the recent article that was published regarding COVID-19 genomic modulation, the mechanism of innate immunity and the screening of antiviral drug candidates, for treating COVID-19 patients. This review used the latest paper regarding COVID-19 with 63 journals with high impact factors such as Nature, The Lancet, Cells, International Journal of Biological Sciences, Mol Biol Methods, Journal of Microbiology, Immunology, and Infection, Nat. Rev. Microbiol, and other international journals indexed by Scopus, Elsevier, and Springer through in vivo and in vitro studies. The genomic of SARS-CoV-2 consist high similarly to coronaviruses family, albeit possessing a different pathway even has higher affinity, due to changing some nitrogen bases are supposed to have a significant effect on its pneumonia. Herein, we report review article an update on the recent literature of the COVID-19 modulation genome, mechanism of innate immunity, and medical literature. Moreover, we report antiviral drugs that have been developed from synthetic drugs and medicinal compounds from plants. Several studies have been re-analyzed using in vitro, in vivo, and modeling using bioinformatics

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## 1. INTRODUCTION

A novel human coronavirus which is a new evolution of SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) was recognized in Wuhan, China, in December 2019.<sup>1</sup> The virus officially named SARS-CoV-2 by ICTV (International Committee on Taxonomy of Viruses), and pneumonia caused by SARS-CoV-2 has been known as COVID-19 (coronavirus disease 2019).<sup>2</sup> World Health Organization (WHO) was announced on 31 January 2020 that COVID-19 was listed as the Public Health Emergency of International Concern (PHEIC), it's a high risk to multiple countries and requires a coordinated international response<sup>3,6</sup>. The coronavirus has been known to belong to a virus's family that may cause various symptoms such as fever, lung infection, breathing difficulty, and pneumonia<sup>Error! Reference source not found.2,3</sup>. Recently, SARS-CoV-2 became a serious epidemic worldwide due to highly contagious disease. Previously, at the beginning of the coronavirus family was detected in Saudi Arabia in 2012, then attributed to Middle East Respiratory Syndrome Coronavirus (MERS-CoV)<sup>4,5</sup>. SARS-CoV belongs to the family Coronaviridae with an enveloped, positive-stranded RNA virus with ~30,000 nucleotides<sup>Error! Reference source not found.6</sup>. Coronavirus (CoV) is a single strand RNA virus with a diameter of 80-120nm. It is divided into four types;  $\alpha$ -Coronavirus ( $\alpha$ -CoV),  $\beta$ -Coronavirus ( $\beta$ -CoV),  $\delta$ -Coronavirus ( $\delta$ -CoV),  $\gamma$ -Coronavirus ( $\gamma$ -CoV). Based on BLASTP using NCBI, it is known that SARS-CoV-2 like SARS-CoV and MERS-CoV belongs to  $\beta$ -coronavirus, a large class of viruses prevalent in nature. If we compared with SARS and MERS, this virus has high transmissibility and infectivity despite a low mortality rate<sup>6,7,9</sup>. Somehow, phylogenetic trees show that SARS-CoV-2 in Indonesia and similar to the others countries, which derived from the same ancestor of Severe Acute Respiratory Syndrome Coronavirus genome.<sup>6,3</sup>

Albeit, SARS-CoV and MERS-CoV found that has similar case with SARS-CoV-19, it is supposed that the bat is still a probable species of origin for SARS-CoV-2, with 96% whole genome identity with a bat CoV, BatCoV, RaTG12, from *Rhinolophus affinis* from Province of Yunnan<sup>8</sup>. However, SARS-CoV and MERS-CoV usually pass into intermediate host, such as civets or camels, before leaping to human<sup>9, 10</sup>. This fact indicates that the virus was probably transmitted to human by other animals. Considering that the earliest coronavirus disease 2019 (Covid-19) patient reported no exposure at the seafood market<sup>10</sup>. It has been analyzed from genomic database, that Pangolin-CoV is 91.02% and 90.55% identical to SARS-CoV-2 and BatCoV RaTG13, respectively, at the whole genome level<sup>11, Error! Reference source not found.</sup>. The S1 protein of Pangolin-CoV is much more closely related to SARS-CoV-2 than to RaTG13<sup>11, Error! Reference source not found.</sup>. Spike protein can interact with human ACE2 receptor via five key amino acid residues, which is completely consistent between SARS-CoV-2 and Pangolin-CoV, but there is four amino acid mutation in RaTG13<sup>6,11</sup>. Both Pangolin-CoV and RaTG13 are lost the putative furin recognition sequences motif at S1/S2 cleavage site that can be observed in the SARS-CoV-2. Somehow, researchers suggest that Pangolin species are high probably as natural reservoir of SARS-CoV-2 like other Coronavirus.<sup>11, Error! Reference source not found.</sup>

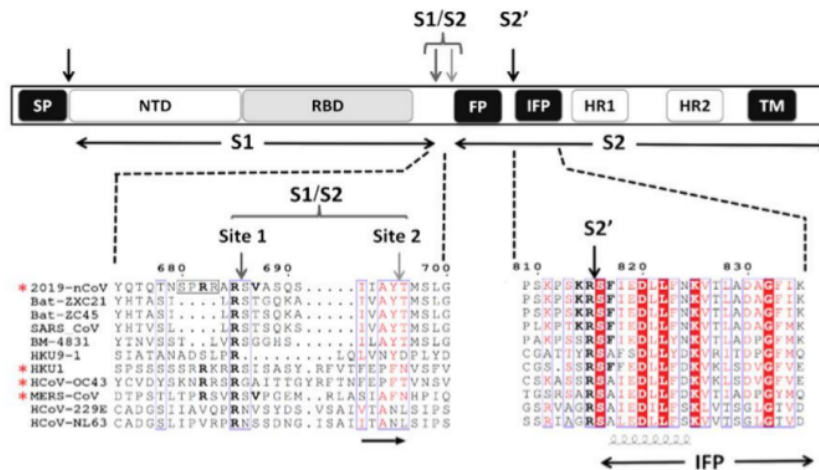


Figure 1. Schematic representation of the COVID-19 contain Spike protein with a focus on the putative maturation sites. The domains were previously characterized in SARS-CoV and MERS-CoV: Signal peptide (SP), N-terminal domain (N-TD), receptor binding domain (RBD), fusion peptide (FP), internal fusion peptide (IFP), heptad repeat  $\frac{1}{2}$  (HR  $\frac{1}{2}$ ), and the transmembrane domain (TM)<sup>Error! Reference source not found.</sup> The SP, S1, S2, and S2' cleavage sites are indicated by arrows. Insertion of furinlike cleavage site is surrounded by a black frame, while red asterisk indicate the presence of canonical furin-like cleavage motif at the S/S2 site<sup>13</sup>.

If we compare, SARS-CoV (2003) infect 8098 individuals which 9% mortality rate, across around 26 countries in the world, but somehow novel coronavirus (2019) infect more than 935.750 individuals people with mortality rate 2.9~4% till date of this paper writ<sup>17</sup> It is shows that the transmission rate of SARS-CoV-2 is higher that SARS-CoV due to **genetic recombination** even at Spike protein in the receptor binding **o<sub>2</sub>main (RBD) region** of SARS-CoV-2 which is have enhanced its transmission ability<sup>11,12</sup>. Scientists and clinicians have learned much of coronavirus disease 2019, COVID-19, and its pathogenesis: not all people exposed to SARS-CoV-2 are infected and not all infected patients develop severe respiratory illness. Accordingly, SARS-CoV-2 infection can be roughly divided into three stages: stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load<sup>Error! Reference source not found.</sup>

Pathogenicity of SARS-CoV-2, uses the SARS-CoV receptor, the **angiotensin-converting enzyme 2 (ACE-2)** for entry and the serine protease TMPRSS2 for S protein priming. Binding of the ACE-2 receptors in the type II pneumocytes in the lungs triggers a cascade of inflammation in the lower respiratory track. It has been demonstrated that when the SARS spike protein binds to the ACE-2 receptor, the complex is proteolytically processed by type 2 transmembr<sup>1</sup> protease TMPRSS2 leading to cleavage of ACE-2 and activation of the spike protein, similar to the mechanism employed by influenza and human metapneumovirus, thus facilitating viral entry into the target cell. It has been suggested that cells in which ACE-2 and TMPRSS2 are simultaneously present are most susceptible to entry by SARS-CoV. Early indications are that SARS-CoV-2 virus also requires ACE-2 and TMPRSS2 to enter cells<sup>13,14</sup>. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines<sup>15</sup>.

Moreover, in this article we report antiviral drugs that have been developed from synthetic drugs and medicinal compounds from plants. Several studies have been re-analyzed using in vitro, in vivo, and modeling using bioinformatics tools.

## 2. REVIEW METHOD

In this article, we reviewed 63 journals related to SARS-CoV-2, ranging from the structure of viruses, schematic to the proteins that make up viruses, the mechanism of

interaction with receptors, the effect of viruses on the immune system, and several drug compounds that have the potential to be used as an anti-viral candidate. We accessed these journals from various primary sources, mainly from the journal website, such as PMC (PubMed Central) system, the National Library of Medicine (NIH), and several other journal sites, especially at this time all of the journals related to COVID-19 can be accessed free of charge. Most of the journals that we use as references in this review, published in 2019 and 2020, are the latest and most updated journals related to COVID-19. Besides, these journals have high impact factors such as Nature (Nature communication, Nature review, Nature medicine), The Lancet, Cells, International Journal of Biological Sciences, Mol Molol Methods. Journal of Microbiology, Immunology, and Infection, Nat. Rev. Microbiol, and other international journals indexed by Scopus, DOAJ, Springer, and Elsevier. Besides, we also review the database of the National Center for Biotechnology Information (NCBI) regarding schematic constituent proteins and RNA sequences to compare with other virus families. We highlight some of the findings from these journals both in vivo and in vitro studies<sup>Error! Reference source not found.</sup> In vivo studies are carried out using either human cells or mice, while in vitro is carried out using bioinformatics tools such as molecular docking, CLC sequences viewers, phylogenetic analysis, computational, Q-UJEL systems, and several other tools<sup>24, Error! Reference source not found.</sup>

### 3. RESULTS AND DISCUSSION

#### Virion genetic structure

Coronavirus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cyro-electron tomography and cyro-electron microscopy<sup>16</sup>. Coronavirus have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative sense RNA viruses. Coronavirus has gene domain, which is domain possessing four protein, such as spike (S), membrane (M), envelope (E), dan nucleocapsid (N) protein, all of which are encoded within 3' end of the viral genome. Protein S (~150 kDa), utilizes an N-terminal domain yang merupakan sekuens signal to gain acces to the ER, and is heavily N-linked glycosylated<sup>17</sup>. Homotrimers of the virus encoded S protein make up the distinctive spike structure on the surface of the virus<sup>18</sup>.

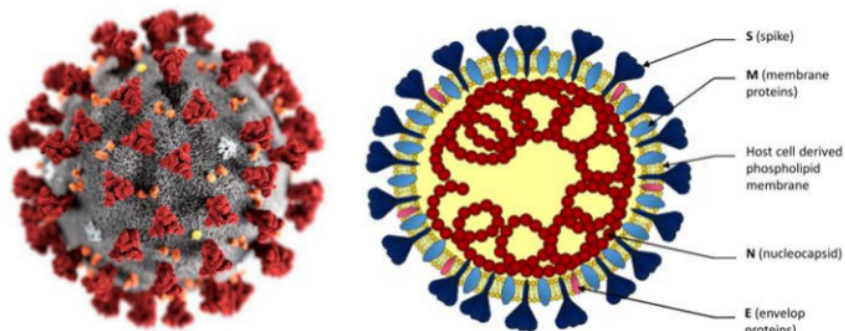


Fig. 18.2. Structure of SARS-CoV-2 (a) Illustration of the SARS-CoV-2 virion Structure, (b) genomic organization of SARS-CoV-2, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins<sup>Error! Reference source not found.</sup>

M protein is the most abundant structural protein in the virion, has small size (~25-30 kDa) protein with 3 transmembrane domain dan is thought give the virion its shape. This protein has a small N-terminal domain, can experience glycosylated ectodomains and a relatively long C-terminal domain endo-domain that extends 6-8 nm into the viral particle<sup>19</sup>. The main difference in the 2019 coronavirus novel (SARS-CoV-2) compared to the coronavirus incorporated in the beta-coronavirus group is the size and sequence of the S (spike) protein. ORF1a, 1b, proteins E, M, and N-terminal domains do not differ much, but in the genetic sequence the S proteins are relatively different<sup>Error! Reference source not found.</sup><sup>20</sup>. Like

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SARS-CoV and MERS-CoV, the SARS-CoV-2 also requires angiotensin-converting enzyme 2 (ACE2) as a receptor to enter the cell<sup>21</sup>.

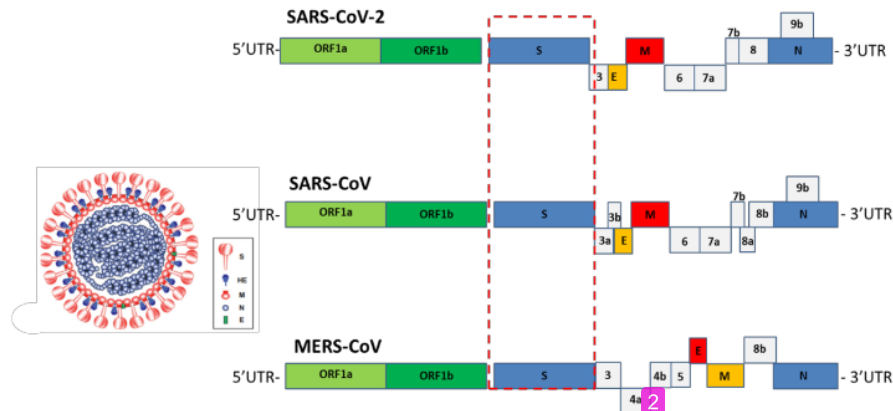


Figure 3. The Schematic of Coronavirus genome organization, including origin replicase complex (ORF), spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins<sup>Error! Reference source not found.</sup>(NCBI database)

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The origin replicase complex (*orf*) *ab* is the largest gene in coronavirus family which encodes the pp1ab protein and 15 non-structural protein (*nsp*). The *orf1a* gene encodes for pp1a protein which also contain 10 *nsp*. All of these *nsp*s are known as viral RNA-dependent RNA-polymerase, via N-terminal extension domain (NTE), together possessing high polymerase activity<sup>22</sup>.

### SARS-CoV-2 interaction with receptor binding domain

Coronavirus has Spike protein that significantly determinant of virus entry into host cells<sup>23</sup>. The virus's envelope spike which is glycoprotein will bind to its receptor, ACE2 for SARS-CoV and SARS-CoV-2, CD209L (a C-type lectin, also known as L-SIGN) for SARS-CoV, DPP4 for MERS-CoV<sup>Error! Reference source not found.,Error! Reference source not found.</sup><sup>23</sup>. When SARS-CoV enter into host cell, it might direct membrane fusion between virus and plasma membrane, then associate with receptor binding, ACE2. The S protein of SARS-CoV-2 consisting of 1255 amino acids (aa) which divided into two subunit, subunit S1 (aa 17-680) and subunit 2 (aa 681-1195). Subunit 1 has function as surface subunit, while subunit 2 as transmembran unit<sup>24,Error! Reference source not found.</sup>.

Receptor ACE2 expression and distribution in human body may indicate the potential infection ways of Coronavirus through the developed single cell RNA sequencing (scRNA-seq) technique dan single-cell transcriptomes based on the public database, the data from researchers show that high ACE2 expression was found in type II alveolar cells of lung, esophagus upper, and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells<sup>Error! Reference source not found.</sup><sup>25</sup>. The epidemic of novel coronavirus 2019 is their ability to associate with respiratory disease and few extrapulmonary sign<sup>26</sup>. That data was confirm, that those organs with high ACE-expressing cells should be considered as potential high risk for COVID-19 infection<sup>27</sup>.

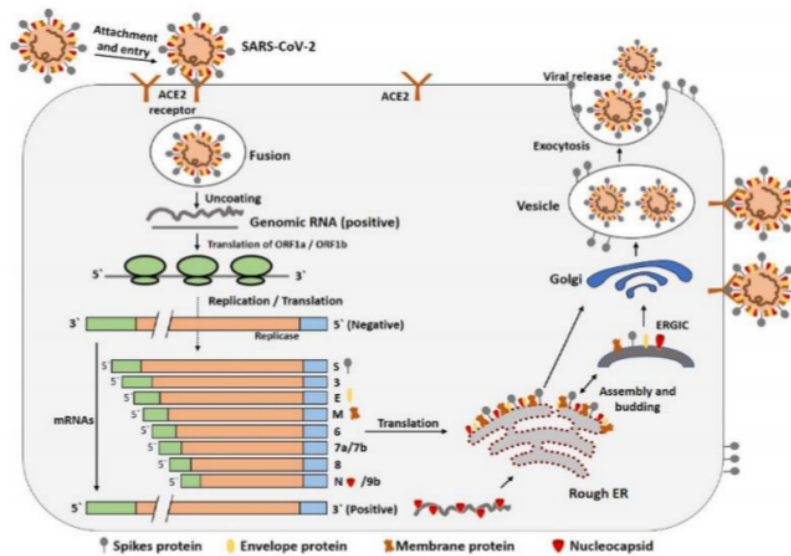


Figure 4. The SARS-CoV life cycle in host cells and its spike (S) protein structure. The life cycle will begins when its S protein bind to the receptor ACE2, then changing of S protein conformation facilitates viral envelope fusion with the cell membrane through the endosomal pathway. After that, SARS-CoV releases RNA into host cell. Genome RNA is translated into viral replicase polyproteins pp1a and pp1a, then cleaved into small product by viral proteinases. At the same time, polymerase translated into relevant viral proteins. Both viral protein and genome RNA are subsequently assembled into virion in the ER and Golgi, which are budding into the lumen of the ERGIC and then transported via vesicles and released out of the cell. (ACE2: Angiotensin-converting enzyme; ER, endoplasmic reticulum; ERGIC, ER-Golgi intermediate compartment<sup>62</sup>.

There, by N domain viral genome bud into membranes of the ERGIC containing viral structural proteins, forming mature virions. Albeit, M protein has protein-protein interaction function for assembly of coronavirus, M and E protein fuction together to produce coronavirus envelopes<sup>28</sup>. ACE2 is receptor used by SARS-CoV-2 that has higher affinity (~10 fold) due to different conformational of Spike protein than other coronaviruses as like SARS-CoV and MERS-CoV. Specifically, the SARS-CoV-2 mechanism can infect humans through S protein, how strong the interaction is for risk human transmission, and how SARS-CoV-2 causes pathological mechanisms of organ damage that remains unknown yet<sup>29</sup>.

### Clinical characteristics of COVID-19

SARS-CoV-2 infection in a person's lungs results in large numbers of lesions. However, it causes viraemia in the body and causes major clinical manifestations such as fever, pharyngalgia, fatigue, diarrhea and other non-specific symptoms. This process includes the incubation phase and the initial phase of the disease. This incubation takes 1–14 days (3–7 regular days). Leukocytes and peripheral blood lymphocytes are not significantly reduced (normal or slightly lower) in this phase. Then, the virus spreads through the bloodstream and especially in the lungs, digestive tract, and heart, possibly concentrated in tissues expressing ACE2 receptors, forming and reducing microthrombus, thereby reducing the risk of damage to major organs<sup>Error! Reference source not found.,30</sup>.

According to medical laboratories in some patients find results, some involve the number of leukocytes, lymphocytes, and eosinophils; percentage of lymphocytes and eosinophils; D-dimer concentration, C-reactive protein (CRP), procalcitonin (PCT), serum amyloid A (SAA), and serum creatine kinase<sup>Error! Reference source not found.</sup>. In several studies, the majority of patients had normal or decreased white blood cell counts, and lymphocytopenia. But in severe patients, the number of neutrophils, D-dimers, blood urea and creatinine levels is significantly higher, and the number of lymphocytes continues to decrease. In addition,

inflammatory factors (interleukin (IL) -6, IL-10, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) increase, indicating the patient's immune status. A number of research data indicate that in plasma patients with severity have increased IL-2 levels, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), 10 kD interferon gamma-induced protein (IP-10), monocyte chemoattractant protein 6 (MCP-1), inflammatory protein macrophage 1- $\alpha$  (MIP- 1 $\alpha$ ), and TNF- $\alpha$ <sup>31,32</sup>.

Clinical diagnosis of COVID-19 is mainly based on epidemiological history, clinical manifestations and some auxiliary examinations, such as nucleic acid detection (RT-PCR), CT scan, immune identification technology (Point-of-care Testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA)) and blood culture. However, the clinical symptoms and signs of patients infected with SARS-CoV-2 are highly atypical, including respiratory symptoms, cough, fever, dyspnea, and viral pneumonia. Therefore, auxiliary examinations are necessary for the diagnosis of COVID-19, just as the epidemiological history<sup>33,34</sup>.

### Mechanism innate immunity of COVID-19

The site of initial infection with SARS-CoV-2 is unknown and the pathogenesis of COVID-19 is still under investigation. Clinically, the immune response caused by SARS-CoV-2 infection occurs in two phases. During the incubation and non-several stages, specific adaptive immune responses are needed to eliminate the virus and to prevent disease progression to a severe stage. The innate immune response that plays a role in SARS-CoV-2 in the lungs involving pro-inflammatory cells such as macrophages and granulocytes because of a binding between the virus with the host cell receptor ACE2 (lung epithelium, macrophages, granulocytes and lymphocytes)<sup>29,35</sup>.

In innate immune response occurs since SARSCoV-2 viral particles and viral genome have been detected in macrocytes and lymphocytes. SARS-CoV-2 uses the entry receptor by binding ACE2 receptor. The early onset of rapid viral replication may cause massive epithelial and endothelial cell apoptosis and vascular leakage, triggering the release of exuberant pro-inflammatory cytokines and chemokines<sup>35,36,37</sup>. In addition, SARS-CoV-2 infection may also cause pyroptosis in macrophages and lymphocytes<sup>34,35</sup>. In SARS-CoV infection, viroporin 3a has also been shown to trigger the activation of NLRP3 (NOD-like receptor protein 3) inflammasome and the secretion of IL-1 $\beta$  in bone marrow-derived macrophages, suggesting the induction of cell pyroptosis, which can cause the release of large amounts of pro-inflammatory factors<sup>34</sup>.

Innate immune responses that play a role in SARS-CoV-19 infection in the lung involve pro-inflammatory cells such as macrophages and granulocytes. These pro-inflammatory cells can recognize the SARS-CoV-2 viral through pathogen associated molecular patterns (PAMPs)<sup>38</sup>. The PAMPs of SARS-CoV-2 viral can be recognized by macrophage cells in the form of RNA at the time of invasion of cells or in the form of dsRNA during replication in cells. SARS-CoV-2 virus RNA and dsRNA are identified by macrophages through their endosomal receptors TLR3 and TLR7 and their cytosolic receptors RIG-1 and MDA-5. Once recognized, there will then be a cascade signaling in the cell which then activates transcription factors in the nucleus such as NF- $\kappa$ B and IRF-3 which mediate the expression of IFN- $\gamma$  and other pro-inflammatory cytokines as a form of initial defense due to viral entry. IFN- $\gamma$  may be used to kill viruses. In contrast, generally the SARS-CoV virals are able to inhibit the formation of IFN- $\gamma$  as a strategy to defend themselves to stay alive in cells. They employ multiple strategies to interfere with the signaling leading to type I IFN production and/or the signaling downstream of IFNAR. This dampening strategy is closely associated with the disease severity. Once type I IFN is secreted, these viruses are equipped with mechanism that inhibit IFN signaling such as decreasing STAT1 phosphorylation. The viral proteins involved in the modulation of this host type I IFN response are both structural proteins (such as M, N) and non-structural proteins (ORF).

However, in COVID-19 patients with severity being able to produce over pro-inflammatory cytokines with very high amounts in peripheral blood namely GM-CSF, IL-1 $\beta$ , IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1 and IL-4, which can potentially cause cytokine storms.



Reference source not found., Error! Reference source not found. The researchers found that in the lungs of Covid-19 patients with severity developed a cytokine storm which made the patient's condition very weak, severe and even death. In several studies, similar getting significant results in COVID-19 patients with severity tended to increase the most visible pro-inflammatory cytokines namely IL-6, IL1, GM-CSF, TNF- $\alpha$  while still the cytokines were known and developed as treatment ta<sup>4</sup>ets<sup>Error! Reference source not found., Error! Reference source not found.</sup>.

The complement system is<sup>4</sup> an important part of the host's immune response to both bacterial and viral infections. The complement system is one way the innate immune system detects and responds to foreign antigens. Because of its potential to damage the host tissue, the complement system is also tightly regulated through several inhibiting proteins that are constitutionally present in the seru<sup>4</sup>. Host factors that encourage complement response related to protective or pathogens in viral infections are not well understood. Of particular concern, C3a, C4a, and C5a anaphylatoxins are produced during activation of the complement signaling cascade; they have strong pro-inflammatory properties an<sup>1</sup> can trigger inflammatory cell recruitment and neutrophil activation<sup>Error! Reference source not found.</sup>. There is still no evidence of complement in SARS-CoV-2 infection and can be used as reference material in suppressing the occurrence of excessive inflammation in severe COVID-19 patients<sup>Error! Reference source not found., Error! Reference source not found., Error! Reference source not found., Error! Reference source not found.</sup>.

### Potential drug to fight SARS-COV-2

The SARS-CoV-2 genome showing drug potential to treat their patient, even by the mechanism, analyze how the SARS-CoV-2 pattern genome, viral mechanism of infecting its host, the researchers have developed the potential of a drug to fight SARS-CoV-2. Especially, tracing from viruses that have high similarly, SARS-CoV and MERS-CoV. The drug compounds developed by the res<sup>9</sup>rchers came from various sources, both natural and synthetic. The researcher<sup>9</sup> so has described the effect of RNA interference on replication of the SARS virus, which by interferons could block colds caused by more weakened members of the coronavirus family. Interferon and  $\alpha$ -ketoamide can form a complex with SARS-CoV-2 that might effective for antiviral candidates by blocking viral re<sup>9</sup>lication<sup>Error! Reference source not found.</sup>. Meanwhile, ribavirin, the nucleoside analog was used as antiviral to be shown to have SARS inhibitory effect in vitro<sup>Error! Reference source not found.</sup>. Interferon and cyclosporine able to reduce the virus replication by increase the immune-suppressive effect of CsA, immunosuppressant agents, while IFN- $\alpha$  is immuno-stimulating protein favoring cell conversion into antiviral agent<sup>Error! Reference source not found., Error! Reference source not found.</sup>.

The screening of the drug candidate mostly carried out by in silico to found several antiviral agents that can be used as drugs to inhibit the development of SARS-CoV-19. Some of them are namely wellferon, alferon, and betaferon (through interferon mechanism), then ribavirin (a nucleoside analogous). In another study, candidate drugs from natural ingredients found by Wang et al (2016) were Scutellarin can reduce the expression and activity of ACE in brain tissue. Hesperidin is a bioflavonoid that can inhibit cleavage activity of the 3-like protease (3CL-Pro) of SARS-CoV based on assays<sup>Error! Reference source not found.</sup>. For some countries have tried to use chloroquine and hydroxychloroquine as a weapon to fight Coronavirus, this is based on previous research shown that the possibility, partly identical involving alkalization by chloroquine of the phagolysosome, seems effective against coronavirus among which is the severe acute respiratory syndrome (SARS)-associate coronavirus. Colson *et al* (2020) finding shows that this drug is also useful<sup>7</sup> an antimalarial, and anti-inflammatory due to infection. There are also some convention treatment of patients with SARS-CoV-2 infection using several type of treatment which is Lopinavir/Ritonavir has anti-HIV inflammatory activity able to inhibit viral RNA replication of SARS, even MERS<sup>Error! Reference source not found., Error! Reference source not found.</sup> like favipiravir (T-750)<sup>Error! Reference source not found., Error! Reference source not found.</sup> by inhibition of virus replication, remdesivir also known has good anti-viral activity as an alternative of treatment SARS-CoV-2<sup>Error! Reference source not found., Error! Reference source not found., Error! Reference source not found.</sup>, *in vitro* effective for controlling infections due to the SARS-CoV-2 (Xiao) virus, although further clinical testing is needed<sup>Error! Reference source not found.</sup>. The mechanism by remdisivir is that it inhibits the synthesis of nucleic acid, but has not yet obtained permission

for marketing in any country<sup>Error! Reference source not found.</sup>, like Oseltamivir<sup>Error! Reference source not found.</sup> and Chloroquine<sup>Error! Reference source not found.</sup>, Error! Reference source not found., Error! Reference source not found.

Some of the natural product has been reported might potential as a drug candidate, as a compound Glycyrrhizin, was an extract from liquorice effects *in vitro* assays on clinical isolates of coronavirus from patients with SARS<sup>Error! Reference source not found.</sup>, Quercetin and TSL-1 from *Toona sinensis* Roer<sup>7</sup> by Inhibit the cellular entry of SARS-CoV<sup>Error! Reference source not found.</sup>, Emodin derived from genus *Rheum* and *Polygonum* it can Inhibit interaction of SARS-CoV spike protein and ACE2<sup>Error! Reference source not found.</sup>, Error! Reference source not found., Baicalin from *Scutellaria baicalensis*, Inhibit Angiotensin-converting enzyme (ACE), also have a role vital function broad therapeutic effect, including anti-apoptosis, anti-inflammation, anti-oxidative stress<sup>Error! Reference source not found.</sup>, Error! Reference source not found., Tetrandrine, fangchinoline, and cepharanthine with mode of action Inhibit the expression of HCoV- OC43 spike and nucleocapsid protein Immunomodulation<sup>Error! Reference source not found.</sup>, Error! Reference source not found., nitazoxamide has been demonstrated by *in vitro* assay for anti-MERS-CoV activity, that could be reached with two daily oral does<sup>Error! Reference source not found.</sup>, Alisporivir uses as a drug additive anti-MERS-CoV activity when used in combination with ribavirin<sup>Error! Reference source not found.</sup>. Moreover, silvestrol is a molecule of the flavaglines family from plants, know can bind to EIF4a and enhances the affinity of EIF4A for mRNA inhibit protein translation by blocking helicase activity<sup>Error! Reference source not found.</sup>, mycophenolate mofetil (MMF) seems synergistic effect with IFN- $\beta$ 1b/MMF was administered to MERS-CoV patients, even had lower APACHE II score<sup>Error! Reference source not found.</sup>, corticosteroids by delayed virus clearance (this may be an extra treatment for reducing viral distribution<sup>Error! Reference source not found.</sup>). Robson *et al* (2020) were conducted an analysis using bioinformatics tools use of steroids derivative compounds, emodin can be an inhibitor of SARS-CoV entry, with some of the binding features, such as ketone group<sup>13</sup> Error! Reference source not found. Recent studies have found that mercaptopurine can also act as an inhibitor of both SARS-CoV and MERS-CoV via targeting papain-like proteases. Melatonin also reported having the potential for antiviral infection through anti-inflammatory activity and antioxidant effects. Melatonin indirectly plays a role in regulating ACE2 expression, which is a key entry receptor involved in viral infections of HCoVs. Specifically, melatonin inhibits calmodulin, which interacts with ACE2 by inhibiting the shedding of its ectodomain, a key infectious process of SARS-CoV<sup>Error! Reference source not found.</sup>, Error! Reference source not found. Furthermore, we need to learn much more, carried out some experiment to verify all of the drug candidates can work effectively as soon as possible to stop COVID pandemic.

#### 4. CONCLUSION

Novel-Coronavirus 2019 (n-CoV-19) possessed high similarity to coronavirus family, especially with SARS and MERS, but somehow has a high affinity than SARS-CoV and MERS-CoV due to change<sup>1</sup> of some S protein nucleotide are supposed to have a significant effect on its pneumonia. SARS-CoV-2 requires angiotensin-converting enzyme 2 (ACE2) as a receptor to enter the cell, which is high ACE2 expression in respiratory cells that potentially high risk for COVID-19 infection. When SARS-CoV-2 enter to host cell, the innate immune response that plays a role in SARS-CoV-2 in the lungs involving pro-inflammatory cells such as macrophages and granulocytes because of a binding between the virus with the host cell receptor ACE2. However in COVID-19 patients with severity being a<sup>11</sup> to produce other pro-inflammatory cytokines with very high amounts in such as GM-CSF, IL-1 $\beta$ , IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1 and IL-4, which can potentially cause cytokine storms. Several antiviral drugs candidates have been developed from synthetic drugs and natural products, drug compounds from plants. Albeit, there are have to verify by several scientific studies, to re-analyzed using *in vitro* and *in vivo* studies, even by modeling using bioinformatics tools.

#### CONFLICT OF INTEREST

All authors state that there is no conflict of interest.

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