Review Article

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

Indra Lasmana Tarigan\textsuperscript{1a}, Kartika Arum\textsuperscript{2b}

\textsuperscript{1} Department of Chemistry, Faculty of Science and Technology, Universitas Jambi, Indonesia
\textsuperscript{2} Department of Health Analysis, STIKes Karya Putra Bangsa, Tulungagung, Indonesia

\textsuperscript{a}E-mail address: indratarigan@unja.ac.id
\textsuperscript{b}E-mail address: arumkartika77@gmail.com

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 anti-viral 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 primary 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 anti-viral 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 anti-viral 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 modelling using bioinformatics tools.

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*Corresponding Author:
Indra Lasmana Tarigan
Department of Chemistry, Faculty of Science and Technology, Universitas Jambi, Indonesia
E-mail: indratarigan@unja.ac.id
Phone: +62 821 4226 5676
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. 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). World Health Organization (WHO) was announced on 31 January 2020 that COVID-19 was list as the Public Health Emergency of International Concern (PHEIC), it’s a might risk to multiple countries and requires a coordinated international response.

The coronavirus have been known belong to a virus’s family that may cause various symptoms such as fever, lung infection, breathing difficulty, and pneumonia. Recently, SARS-CoV-2 become a serious epidemiologic worldwide due to highly contagious disease. Previously, at the beginning the coronavirus family was detected in Saudi Arabia in June 2012, then attributed to Middle East Respiratory Syndrome Coronavirus (MERS-CoV).

SARS-CoV belongs to the family Coronaviridae with an enveloped, positive-stranded RNA virus with ~30,000 nucleotides. Coronavirus (CoV) is a single strand RNA virus with a diameter of 80-120nm. It is divided into four types; α-Coronavirus (α-CoV), β-Coronavirus (β-CoV), δ-Coronavirus (δ-CoV), γ-Coronavirus (γ-CoV). Based on BLASTP using NCBI, it is known that SARS-CoV-2 like SARS-CoV and MERS-CoV belongs to β-coronavirus, a large class of viruses prevalent in nature. If we compared with SARS and MERS, this virus has highly transmissibility and infectivity despite a low mortality rate.

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. 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 share 96% whole genome identity with a bat CoV, BatCoV, RaTG12, from Rhinolophus affinis from Province of Yunnan. However, SARS-CoV and MERS-CoV usually pass into intermediate host, such as civets or camels, before leaping to human. 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. It has been analyze 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. The S1 protein of Pangolin-CoV is much more closely related to SARS-CoV-2 than to RaTG13. Spike protein can interaction with human ACE2 receptor via five key amino acid residues, which is completely consistent between SARS-CoV-2 and Panglion-CoV, but there is four amino acid mutation in RaTG13. Both Panglion-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, researcher suggest that Panglion species are high probably as natural reservoir of SARS-CoV-2 like other Coronavirus.
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.13

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 writing. 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 domain (RBD) region of SARS-CoV-2 which is have enhanced its transmission ability.11,12 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.13,14

Pathogenity 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 transmembrane 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.13,14 Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines.15

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 articles 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 articles from various primary sources, mainly from the journal website, such 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. 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.14 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-UEL systems, and several other tools.17
3. RESULTS AND DISCUSSION

**Virion genetic structure**

Coronavirus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cryo-electron tomography and cyro-electron microscopy. Coronavirus has 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 signal to gain access to the ER and is heavily N-linked glycosylated. Homotrimers of the virus encoded S protein make up the distinctive spike structure on the surface of the virus.

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. 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. Like SARS-CoV and MERS-CoV, the SARS-CoV-2 also requires angiotensin-converting enzyme 2 (ACE2) as a receptor to enter the cell.

The original replicate complex (orf) ab is the most significant gene in the coronavirus family, which encodes the pp 1ab protein and 15 non-structural protein (nsp). The orf1a gene encodes for pp1a protein which also contains 10 nsp. All of these nsps are known as viral RNA-dependent RNA-polymerase, via N-terminal extension domain (NTE), together with possessing high polymerase activity.
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SARS-CoV-2 interaction with receptor binding domain

Coronavirus has Spike protein that significantly determinant of virus entry into host cells. 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. 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 devided 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.

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 strafied epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells. The epidemic of novel coronavirus 2019 is their ability to associate with respiratory disease and few extrapulmonary sign. That data was confirm, that those organs with high ACE-expressing cells should be considered as potential high risk for COVID-19 infection.

Figure 4. The SARS-CoV life cycle in host cells and its spike (S) protein structure

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.

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.27,29

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. 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-α (TNF-α) 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 (GCSF), 10 kD interferon gamma-induced protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), inflammatory protein macrophage 1-α (MIP- 1α), and TNF-α.30

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.31,32

**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).28,33

In innate immune response occurs since SARS-CoV-2 viral particles and viral genome have been detected in monocytes 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.33,34,35 In addition, SARS-CoV-2 infection may also cause pyroptosis in macrophages and lymphocytes.33,34 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-1b in bone marrow-derived macrophages, suggesting the induction of cell pyroptosis, which can cause the release of large amounts of pro-inflammatory factors.36

Innate immune responses that play a role in SARS-CoV-19 infection in the lungs 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).35 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.37 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-κB 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 itself 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 other pro-inflammatory cytokines with very high amounts in periperal blood namely GM-CSF, IL-1β, IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1 and IL-4, which can potentially cause cytokine storms. 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-α while still the cytokines were known and developed as treatment targets.

The complement system is 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 serum. 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 and can trigger inflammatory cell recruitment and neutrophil activation. 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.

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 researchers came from various sources, both natural and synthetic. The researcher also 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 α-ketoamide can form a complex with SARS-CoV-2 that might effective for antiviral candidates by blocking viral replication. Meanwhile, ribavirin, the nucleoside analog was used as antiviral to be shown to have SARS inhibitory effect in vitro. Interferon and cyclosporine able to reduce the virus replication by increase the immune-suppressive effect of CsA, immunosuppressant agents, while IFN-α is immunostimulating protein favoring cell conversion into antiviral agent.

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 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 alkalinization by chloroquine of the phagolysosome, seems effective against coronavirus among which is the severe acute respiratory syndrome (SARS)-associate coronavirus. Colson finding shows that this drug is
also useful as 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 like favipiravir (T-750) by inhibition of virus replication, remdesivir also known has good anti-viral activity as an alternative of treatment SARS-CoV-2 in vitro effective for controlling infections due to the SARS-CoV-2 (Xiao) virus, although further clinical testing is needed. The mechanism by remdesivir is that it inhibits the synthesis of nucleic acid, but has not yet obtained permission for marketing in any country, like Oseltamivir and Chloroquine.

Some of the natural product has been reported might potential as a drug candidate, as a compound Glycyrrhizina, was an extract from liquorice effects in vitro assays on clinical isolates of coronavirus from patients with SARS. Quercetin and TSL-1 from Toona sinensis Roem by Inhibit the cellular entry of SARS-CoV. Emodin derived from genus Rheum and Polygonum it can inhibit interaction of SARS-CoV spike protein and ACE2. 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. Tetrandrine, fangchinoline, and cepharnanthine with mode of action Inhibit the expression of HCoV-OC43 spike and nucleocapsid protein Immunomodulation nitazoxamide has been demonstrated by in vitro assay for anti-MERS-CoV activity, that could be reached with two daily oral does. Alisporivir uses as a drug additive anti-MERS-CoV activity when used in combination with ribavirin. 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, mycophenolate mofetil (MMF) sems synergistic effect with IFN-β1b/MMF was administered to MERS-CoV patients, even had lower APACHE II score, corticosteroids by delayed virus clearance (this may be an extra treatment for reducing viral distribution). Robson 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. 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. 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 changing 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 able to produce other pro-inflammatory cytokines with very high amounts in such as GM-CSF, IL-1β, IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1 and IL-4, which can potentially cause cytokine storms. Several anti-viral drugs candidates have been developed from synthetic drugs and natural products, drug compounds from plants. Albeit, there have to verify by several scientific studies, to re-analyzed using in vitro and in vivo studies, even by modelling using bioinformatics tools.

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SHORT BIOGRAPHY

Indra Lasmana Tarigan, S.Pd., M.Sc. Completed his Bachelor’s degree in Chemistry Education Study Program, Department of Chemistry, Faculty of Mathematics and Natural Sciences, Medan State University in 2014. He completed his Master’s Degree in 2018 at National Central University, Taiwan with a Life Sciences Department with a concentration in Biochemistry and Molecular Biology. In 2018, he became a lecturer at Putra Bangsa STIKes, and since 2019 has worked as a lecturer in the Chemistry Study Program, Faculty of Science and Technology, Jambi University. Subjects taught Biochemistry, Biotechnology, Food Chemistry, Fermentation Engineering, Biochemical Engineering, and Organet Chemistry. Actively researching in the fields of Biochemistry, Natural Product as Antibacterial, Antifungal and Anti-Inflammatory agents.

Kartika Arum Wardani, S.ST., M.Imun. Completed her D-IV in the Medical Laboratory Technology Expert Study Program at the Bhakti Wiyata Kediri Institute of Health Sciences in 2014. Masters education was completed in 2020 at Airlangga University in Surabaya with a concentration in Immunology. Subjects are taught Microbiology, Parasitology, Clinical Chemistry, Immunoserology, Immunology, Laboratory Management, Professional Ethics and Health Promotion. Actively researching in the fields of immune system, Inflammation, and Cytokine Mechanism.