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In Silico Study of Secondary Metabolites in *Dendrobium* spp. as SARS-CoV-2 Antivirus on Main Protease (Mpro)

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ABSTRACT

Infection and deaths cases by SARS-CoV-2 still increase and have not decreased significantly. Main protease (Mpro) plays an important role in the replication of SARS-CoV-2 life cycle and causes of rapid transmission. Natural compounds are potential to be antiviral candidates with high bioavailability and low cytotoxicity. Orchids of *Dendrobium* genus have high diversity in Indonesia. Dendrobium has been used as traditional Chinese medicine and contains a group of secondary metabolites with antiviral activity. This study aimed to determine the potential of secondary metabolites of *Dendrobium* orchids as antiviral candidates against Mpro SARS-CoV-2 within silico molecular docking. Secondary metabolites obtained from the KNApSAck and PubChem act as ligands. N3 inhibitors as native ligands were obtained from the RCSB. Mpro SARS-CoV-2 (6LU7) as a target macromolecule. Molecular docking was carried out using the online Covid-19 Docking Server using AutoDock Vina device. The most negative binding affinity value for each ligand compared to the native ligand binding affinity. Visualization with Discovery Studio software has been used to observe the protein amino acid residues contact for each ligand. The binding affinity of the native ligand inhibitor N3 is -7.5 kcal/mol. Based on the results of Mpro docking, three phytochemicals from *Dendrobium* spp., i.e., dendrocandin B, denthyrsinone, and denthyrsinol compounds have binding affinities of -7.7 kcal/mol, -7.9 kcal/mol, and -8.1 kcal/mol, respectively. It can be concluded that in Dendrobium orchid, denthyrsinol has the highest chance of binding so it has the potential to inhibit the Mpro SARS-CoV-2 activity.

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INTRODUCTION

The pandemic of COVID-19 caused by positive-sense RNA of β-coronaviridae known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The first case started to spread in Wuhan, China, in December 2019 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020; Holshue et al., 2020). There were 2-3% infection and death cases caused by SARS-CoV-2, and continue to increase without any significant decreasing number (Hamid et al., 2020). World Health Organization (WHO) reported that for now on, effective treatment using antiviral agents against SARS-CoV-2 is still not available (Pandey et al., 2020). Several symptoms of COVID-19 disease are sputum production (28%), headache

(8%), hemoptysis (5%), and diarrhea (3%) (Huang et al. 2020). According to several studies, other symptoms such as anosmia, fever, cough, alveolar destruction, and acute pneumonia were detected after ten days of infection with more severe symptoms in comorbid patients and old patients >70 years old (Chen et al., 2020; Li et al., 2020; Tian et al., 2020; Wang W et al., 2020; Zhu et al., 2020).

Indonesia is known as a country with high biodiversity and has several plants used as traditional medicine. One of them is orchids (Darmawati et al. 2018; Fandani et al. 2018). Orchids include in the Orchidaceae family with high distribution over the world and very abundance in species richness. There are almost 5000 of 30.000 species of orchids can be found in the Indonesia archipelago (Sapto, 2009). The genus of *Dendrobium* become the second largest genus in the Orchidaceae family (Moudi et al., 2013). *Dendrobium* has been used as a natural traditional medicine in China and the studies show that some of the species contain secondary metabolites group with antiviral activity (Fan et al., 2001). Particular of secondary metabolites group as flavonoids, alkaloids, derivatives of bibenzyl have potential in the medication field (Gutierrez, 2010).

Herbal medication is a treatment using complex mixture of plant organic compounds (Ren et al., 2020). A secondary metabolite is an intermediate substance which do not have a role in the main metabolic processes, specifically and has a certain function in each plant family (Semiarti et al., 2020). Plant secondary metabolite useful for inhibitor of specific disease with lower side effect also beneficial as alternative of an antiviral candidate with high bioavailability and low cytotoxic effect (Umadevi et al. 2020). Catechins, zingerols, gingerols, alicins, quercetins, and epitacetin reported have inhibition activity towards SARS-CoV-2 by *in silico* study (Khaerunnisa et al. 2020). The quest of antiviral candidates from the natural substance as anti-SARS-CoV-2 facing challenges due to differences in genome sequence with SARS-CoV-1 or MERS-CoV (Septiana, 2020).

The antiviral candidate analysis in botany sectors should be started with *in silico* study (Trivedi et al. 2020). In silico study expected to optimize research process and prevent loss in *in vitro* and *in vivo* steps, appropriately, accurately, rapidly, and effectively (Sumon et al. 2021). Mostly researches that discusses the effects of the secondary metabolite is still in progress of *in vitro* testing and the *in vivo* testing effectiveness is not yet guaranteed (Septiana, 2020). Experimental research to find drug candidates from natural substance is difficult in the pandemic condition. *In silico* method approach based on molecular docking need to be done due to it is relatively fast and safe. The aim of this study was to determine the potential of secondary metabolite on *Dendrobium* orchid species as an antiviral candidate on main protease (M^{pro}) SARS-CoV-2 using molecular docking by *in silico* method.

MATERIALS AND METHODS

Molecular Docking

Secondary metabolites of *Dendrobium* listed from KNApSAck: Metabolite Ecology. 3-dimension structure of secondary metabolites downloaded from PubChem databases with .sdf format. Molecular docking conducted at online platform small molecule Covid-19 Docking Server parameter https://ncov.schanglab.org.cn/index.php. (Kong, 2020). Structure of secondary metabolites act as ligand in docking. Sars-CoV2 main Protease (M^{pro}) with PDB ID: 6LU7 selected as target (Jin et al. 2020). Centre Coordinate of Grid Box set in x = −10.85 Å; y = 12.58 Å; z = 68.72 Å and the size of grid box 30 Å (r=12) (Vicidomini et al. 2021). Rate of exhaustiveness in 12. The higher rate of exhaustiveness would get a more constant result (Forli, 2016). The result downloaded in .zip format.

Ligand Profiling

Binding affinity score between target and ligand which lower than inhibitor N3 (Table 1) as native ligand would analyze furthermore by ligand profiling. Manifesting ligand profile by Lipinski's rule of five that is hydrogen bond donors (the total number of nitrogens–hydrogen and oxygen–hydrogen bonds), hydrogen bond acceptors (all nitrogen or oxygen atoms), molecular mass less, and lipophilicity (log P) conducted by http://www.swissadme.ch/index.php

Data Visualization

Ligand and target 3-dimension structure conformation visualized in Software Discovery Studio 2020. The three strongest ligand and target interaction were analyzed the amino acid residue contact and interaction in binding pocket.

RESULTS AND DISCUSSION

Dendrobium is generally found growing well in high areas or mountainous areas 1400-1600 m above sea level, in a fairly humid and foggy environment, and with a mild average temperature (Lam et al., 2015). In this study, secondary

metabolites of the genus *Dendrobium* acted as ligand-independent variables. Secondary metabolites composed of *Dendrobium* polysaccharide compounds have antiviral activity (Hwang et al., 2012). Binding of secondary metabolites to viral nucleoprotein regions can inhibit oligomerization and export of viral nucleoproteins (Ti et al., 2021). Medioresinol is capable of causing the accumulation of intracellular ROS and apoptosis of microbial cells (Hwang et al., 2012). Terpenoids in *Dendrobium nobile* play a role in the proliferative activity of murine T and B lymphocytes as antiviral immunomodulators (Singh et al., 2012). Naringenin is believed to have potential as a treatment compound that can inhibit SARS-CoV in Mpro and ACE2 (Tutunchi et al., 2020).

The main protease (M^{pro}) is known to play an important role in the live replication process of SARS-CoV-2 and is one of the causes of rapid transmission (Purwaniati and Asnawi, 2020). The M^{pro} structure of SARS-CoV-2 consists of A and B Chains (Zhang et al. 2020). M^{pro}, also called the 3CL protease, is a 33.8-kDa cysteine protease that mediates functional polypeptide maturation in the assembly of viral replication machinery (Cui et al. 2020). The role of M^{pro} in the life cycle of SARS-CoV-2 uses one of the important targets in the design of COVID-19 antivirals (Purwaniati and Asnawi, 2020). In this study, M^{pro} SARS-CoV-2 (6LU7) was used as a macromolecular target.

N_3 inhibitors or known as Michael Acceptor Inhibitors have been investigated to be able to inhibit the virus and specifically inhibit M^{pro} SARS-CoV (Yang et al. 2005). In this study, N_3 inhibitors were used as native ligands obtained from the RCSB website (Jain and Mujwar, 2020). The N_3 inhibitor covalently binds to SARS-CoV-2 M^{pro} via the Michael reaction and blocks its active site (Griffin, 2020; Xue et al., 2008). N_3 cytotoxicity 50% concentration of 133μM, ebselen and N_3 antiviral activity had the strongest effect at 10 M concentration for Vero cells infected by SARS-CoV-2, N inhibitor compounds were able to penetrate cell membranes to access more targeted targets (Jin et al., 2020).

Table 1. Ligand Profiling secondary metabolite of *Dendrobium*

Secondary metabolites	*Binding affinity* Kcal/Mol	*Bioavailability Score*	Lipinski's rule				
			Log^p	*Violation*	H-*Bond* Donor	H-*Bond* *Acceptor*	MR (g/mol)
Medioresinol	-8	0.55	3.29	0	2	7	388.41
Denthyrsinol	-8.1	0.55	3.98	0	4	6	478.49
Dendroside D	-8.2	0.17	2.21	3	9	14	592.63
Nobilin E	-8	0.55	3.38	1	3	8	544.59
(+)-Lirioresinol B	-7.9	0.55	3.52	0	2	8	418.44
Denthyrsinone	-7.9	0.56	2.41	1	3	8	522.50
Naringenin	-7.8	0.55	1.75	0	3	5	272.25
Dendrocandin B	-7.7	0.55	4.24	0	2	8	482.52
4,4'-Dihydroxy-3,5 dimethoxybibenzyl	-7.6	0.55	2.67	0	2	4	274.31
Acanthoside B	-7.6	0.17	3.5	2	5	13	580.58
Inhibitor N3	-7.5						

Table 2. Binding affinity and Binding Pocket secondary metabolites of *Dendrobium* with M^{pro}

Species	Secondary metabolites	*Binding affinity* (kcal/mol)	*Bio-availability Score*	*Binding Pocket*
Dendrobium thysiflorum	Denthyrsinol	-8.1	0.55	**ASN142**, **CYS145**, **GLU166**, GLY143, LEU27, SER144, THR26
Dendrobium thysiflorum	Denthyrsinone	-7.9	0.56	**CYS145**, **GLU166**, GLY143, **HIS163**, **HIS41**, PHE140
Dendrobium candidum	Dendrocandin B	-7.7	0.55	**CYS145**, **GLU166**, **HIS163**, HIS172, HIS41, MET165, MET49, PHE140, THR190, THR25
Inhibitor N3		-7.5	0.17	**ASN142**, **CYS145**, GLN189, **GLU166**, **HIS163**, **HIS41**, LEU27, MET49

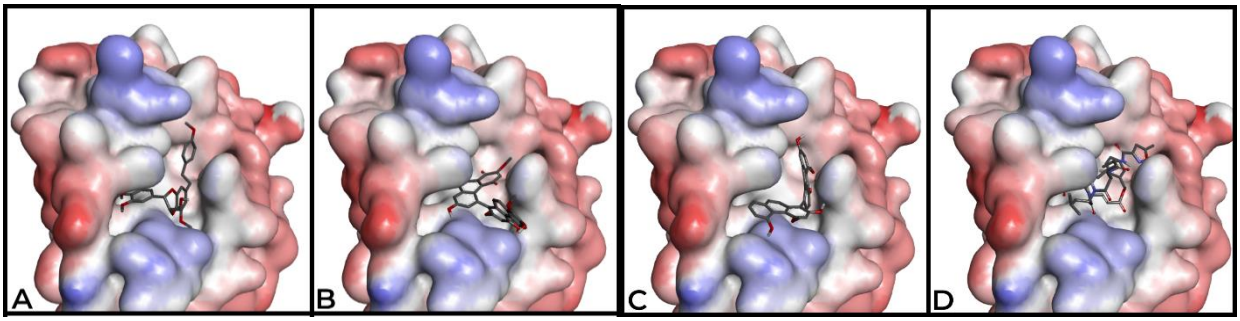

Figure 1. Visualization of strongest conformation secondary metabolites of *Dendrobium* spp., with M^{pro} A. Dendrocandin, B. Denthyrsinone, C. Denthyrsinol, D. Inhibitor N3

In this research, an *insilico* study was conducted with the mechanism of the stages (1) ligand preparation, (2) target preparation, (3) target ligand molecule docking, (4) ligand-protein interaction visualization, and (5) data analysis (Sari et al., 2020). Molecular docking is a popular method in in silico

studies, especially to initiate drug design (de Ruyck et al. 2016). The docking process is divided into two types, namely blind docking and oriented docking (Pradani et al., 2021). Blind docking is a docking process without knowing the exact location of the active site of the receptor, while oriented docking is done after knowing the exact location of the active site of the receptor (Syahputra et al., 2014). Molecular docking can be done with the PyRx software using the Autodock tool.

In this study, molecular docking was carried out with the Online Covid-19 Docking Server using the AutoDock Vina device (Vicidomini et al. 2021). Autodock Vina and CoDock PP were used as docking engines to predict the binding mode between COVID-19 targets and potential ligands. Covid-19 Docking Server is economically and operationally easy to use (Kong et al. 2020). One of the studies using the Online Covid-19 Docking Server is Pendyala and Patras (2020), which examines several bioactive compounds in food ingredients to inhibit M^{pro} COVID-19. Research conducted by Barik et al. (2020) also used the Online Covid-19 Docking Server as a method to analyze the types of bonds in chloroquine, hydroxychloroquine, ramdesivir and arbidol compounds. The web-based docking platform has been validated by its developers with the evaluation of re-docking trials for targets, including M^{pro} with N_3 inhibitors (Vicidomini et al., 2021).

The most negative binding affinity value for each ligand compared to the native ligand binding affinity (Chen et al., 2016; Xue et al., 2008). Based on the results in Table 1., there are 10 secondary metabolites of *Dendrobium* with a lower binding affinity value than the native ligand Inhibitor N3. The metabolites dendroside D, denthyrsinol, medioresinol, and nobilin E respectively had the lowest binding affinity, namely -8.2 kcal/mol, -8.1 kcal/mol, -8 kcal/mol, and -8 kcal/mol. Binding affinity indicates the strength of the drug to bind to the receptor (Arwansyah et al., 2014). The lower the binding affinity value, the higher the affinity between the receptor and the ligand and vice versa (Prabowo and Santoso, 2018). The smaller the binding affinity value, the more stable the interaction between the ligand and the receptor (Arwansyah et al., 2014).

The ligand profile in Table 1 shows that of the 10 secondary metabolites of Dendrobium, only Dendroside D and Acanthoside B are not potential drugs because they have Violation >2 (Wells and McGee, 2008). The profile of ligands according to Lipinski's five rules includes molecular weight, logP (lipophilicity), number of hydrogen bond donors, number of hydrogen bond acceptors, and Violation (Rachmania et al., 2015). Lipinski's rule describes the solubility of certain compounds to penetrate cell membranes by passive diffusion (Syahputra et al., 2014). Compounds are more permeable and active as ligands if they have <5 hydrogen bond donors, <10 hydrogen bond acceptors, molecular mass <500 Da, and logP value <5 (Afriza et al., 2018). The value of Mr (molecular weight), H-Donor and H-acceptor is a measure of the permeability of a drug to be able to pass through the lipid bilayer of a cell (Suhadi et al., 2019). Lipophilicity is defined as the logarithm of the ratio of the hydrophobicity of the drug partitioning into the organic phase to the aqueous phase and is referred to as logP (Ivanovic

et al., 2019; Utomo et al., 2017). Violation is related to the potential for dependence and the amounts of illegal drugs used (Wells and McGee, 2008). Hydrogen bonds generally act as a facilitator to increase the binding affinity of ligands by moving protein-bound water molecules into a large volume of solvent (Chen et al., 2016).

Visualization of ligand-protein interactions of 10 secondary metabolites showed that there were only 3 strongest metabolite modes. Secondary metabolites with the strongest mode against M^{pro} were found in *Dendrobium thysiflorum and Dendrobium candidum* orchids. The strongest metabolite mode in terms of the lowest binding affinity and interactions with the most hydrogen bonds, especially on key amino acids. Based on the results of Table 2, the metabolites that have the highest probability of binding to M^{pro} are dendrocandin B, denthyrsinone, and denthyrsinol. Denthyrsinol has the lowest binding affinity of -8.1 kcal/mol which is predicted to be more stable when bound to M^{pro}. The interactions formed by Denthyrsinol and M^{pro} are hydrogen bonds, electrostatic interactions, and hydrophobicity with the amino acids GLY143, LEU27, SER144, THR26 and ASN142, CYS145, GLU166 as key amino acids. The interaction between the ligand and the protein receptor is expected to inhibit the performance of M^{pro} SARS-CoV-2 (Trott and Olson, 2010).

CONCLUSION

Based on molecular docking using *in silico* method, it can be concluded that Denthyrsinol is a the most potential secondary metabolite in orchid *Dendrobium thyrsiflorum* as an antiviral candidate on main protease (Mpro) SARS-CoV-2.

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