Research Article

Secondary Metabolites of Various Indonesian Medicinal Plants as SARS-CoV-2 Inhibitors: In Silico Study

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ABSTRACT: *Corona virus disease 2019 caused by SARS-CoV-2 infection emerged in late 2019 and still become a worldwide pandemic up to this point with the drug remain unavailable. Meanwhile, Indonesia has an abundance variety of medicinal plants that are potential to be developed as inhibitors. By using the key role proteins as drug targets, namely spike glycoprotein and RNA-dependent RNA polymerase (RdRp) of delta variant of SARS-CoV-2 (which is known as strongly transmitted and highly virulent), we can develop inhibitors for the target proteins from potential Indonesian medicinal plants to prevent the protein interactions for viral entry and proliferation that leading to organ disfunction and death. This study aimed to identify the secondary metabolites of various Indonesian medicinal plants as SARS-CoV-2 inhibitors. The 184 ligands from nine plants were collected from IJAH webserver and their SMILES notation were collected from PubChem. Meanwhile 3D structures of spike glycoprotein (PDB ID: 6VXX) and RdRp (PDB ID: 6M71) were obtained from protein data bank (PDB). Molecular docking was conducted between ligands and the two SARS-CoV-2 proteins using Autodock Vina in PyRx with hesperidin and remdesivir as control compounds. Several potential compounds were selected for drug-likeness analysis and toxicity analysis. Results showed that lantanolic acid has the same amino acid interaction with RdRp as the control compound. It formed a hydrogen bond with Ser784 and hydrophobic bonds with Tyr32 and Ser7709. It had lower binding affinity than the control compounds, eligible as oral drug, and had LD_{50} of 2589 mg/kg.*

Keywords: *drug development; molecular docking; viral infection*

1. Introduction

In late 2019, a disease was emerging caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and becoming a global pandemic. As of June 2021, there were four different SARS-CoV-2 Variants of Concern (VOC), namely Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.6717.2). There are also seven Variant of Interest (VOI), namely Epsilon (B.1.427/B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1617.1), and Lambda (C.37) [1]. These viruses can be transmitted from human to human through respiratory droplets and saliva that entered human body. People infected with SARS-CoV-2 may show no symptom at all (asymptomatic); mild symptoms such as fatigue, dry-cough, mild fever, and sore throat; and up to severe symptoms like acute respiratory distress syndrome (ARDS) and pneumonia [2].

The number of COVID-19 cases are still increasing worldwide. In Indonesia, there are more than 2 million cases with the total of more than 55 thousand deaths and more than 20 thousand new cases per day [3]. At present, there is still 4.82% of Indonesian population that fully vaccinated [4]. With the current condition, physical distancing, quarantine, and contact tracing are important to help controlling the spread of the virus [5]. Meanwhile, development of drugs is equally important since COVID-19 is predicted to last for another three years [6]. By inhibiting the viral entry and replication in the host cell, we can prevent the excessive inflammatory response that results in the cytokine storm leading to organ dysfunction and death [7].

SARS-CoV-2 consists of two kinds of protein, structural and non-structural protein. Among structural proteins, spike protein plays a key role to initiate infection in host. It mediates receptor binding and fusion of the viral and cellular membrane [8]. Meanwhile, RdRp is an essential non-structural protein involved in virus replication [9]. Thus, spike and RdRp protein can be held as potential drug targets.

Plants have been used as part of traditional medicines for a long time. They are considered as important sources for drug development because of their active compounds. Indonesia as a country with rich biodiversity has abundant medicinal plants that can be used as sources for COVID-19 drug development. Hesperidin can be used as a promising prophylactic agent against COVID-19 infection [2]. It can prevent the virus from entering the host cell by disrupts SARS-CoV-2 spike interaction with ACE-2 receptor and block its entry into the lung cell [2]. Remdesivir, a nucleotide analog RdRp-inhibitor, successfully inhibited SARS-CoV-2 in vitro [10]. Thus, hesperidin and remdesivir were used as the control compounds.

The activity, drug-likeness and toxicity of traditional medicinal plant active compounds were predicted, molecular docking was used to identify the interaction between the active compounds and the target protein, and ProTox-II webserver was used for toxicity analysis. It contributed in selecting potential compounds to be evaluated in experimental study. The aim of this study was to investigate potential active compounds from traditional medicinal plants as inhibitors of spike and RdRp protein in silico, thus would provide useful data for the subsequent in vitro and in vivo research.

2. Materials and methods

2.1. Compounds and protein preparation

Literature studies were done for eighty-five plants in organic garden of an organic herbal company in East Java, Indonesia [11-19]. Plants were selected based on its properties as antiviral for influenza or SARS-CoV that has been reported in previous in vitro or in vivo findings. Out of the eighty-five, nine plants were found as being potential as inhibitors of spike and RdRp protein and their 184 secondary metabolites were collected using IJAH webserver (ijah.apps.cs.ipb.ac.id). PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was used to obtain the compound's

SMILES and 3D structure in .sdf format, which later converted into PDB format with Openbabel in PyRx software. Hesperidin and remdesivir were chosen as the control compounds [20,21].

The 3D protein structures of SARS-CoV-2 Spike glycoprotein (PDB ID: 6VXX) and RdRp (PDB ID: 6M71) were obtained in Protein Data Bank (PDB) (https://www.rcsb.org/) and were prepared with ChimeraX software to remove the cofactors (nsp 7 and nsp 8) from RdRp and water molecules [22].

2.2. Molecular docking study

AutoDock Vina in PyRx software was used for molecular docking analysis to detect preferred binding sites. The coordinate center for 6VXX is X= 227.7064, Y= 213.8563, Z= 207.3773 and dimensions(Å) X= 105.371267548, Y= 79.742883606, Z= 158.584052582. While 6M71 coordinate center is X= 120.488, Y= 123.026, Z= 129.0006 and dimensions(Å) X= 79.2587, Y= 84.2557, Z= 100.0821. The strength of bonding between protein and ligand is indicated by the negative binding affinity score. The optimal and the strongest binding spot is the one with the lowest binding affinity score [23].

2.3. Drug-likeness analysis

SWISS ADME webserver (http://www.swissadme.ch/index.php) was used for drug-likeness analysis and GI absorption prediction [24]. The potential compounds must meet the Lipinski Rules of Five criteria and have a high GI absorption [25].

2.4. Toxicity analysis

ProTox-II webserver (https://tox-new.charite.de/protox_II/index.php?site= compound_ input) was used for toxicity analysis [26]. It predicts the toxicity class, lethal dose, organ toxicity, and toxicity endpoints.

2.5. Protein-ligand visualization

Complexes of protein and potential ligands were visualized using ChimeraX software and analyzed by LigPlot+ software to identify the interaction taking place [22,27].

3. Results and discussion

Spike glycoprotein is a protein that plays a vital role for SARS-CoV-2 interaction with the surface receptor (ACE-2) and its subsequent entrance into host cell. It consists of S1 and S2 domain with the size of 200 kDa. S2 has a carboxy-terminal domain that manages viral entry and cell fusion [28]. Meanwhile, RdRp, also known as Nsp12, is an essential enzyme for SARS-CoV-2 replication and transcription [29]. Inhibiting both proteins are expected to prevent the viral entry and proliferation that leading excessive inflammatory response, organ disfunction and death. Therefore, both proteins become important and attractive targets for drug development [30, 31].

Results study conducted for eighty-five plants in organic garden of an organic herbal company in East Java, Indonesia showed the binding affinity score between target proteins and the 184 ligands (Supplementary 1 and Supplementary 2). Binding affinity indicates the ability of ligand to bind and inhibit the activity or spike glycoprotein and RdRp. Strong interaction is defined by a lower binding affinity than control compounds. There were twelve ligands interact with spike glycoprotein that have lower binding affinity than the control compounds: fridelin (-8.5 kcal/mol), alpha-amyrin (-8.4 kcal/mol), pseudotaraxasterol (-8.3 kcal/mol), lantadene A (-8.3 kcal/mol), chitranone (-8.2 kcal/mol), lantanolic acid (-8.2 kcal/mol), stigmasterol (-8.2 kcal/mol), ursonic acid (-8.2 kcal/mol), 3,3'-biplumbagin (-8.1 kcal/mol), lantadene B (-8.1 kcal/mol), lantanilic acid (-8.1 kcal/mol), and beta-amyrin (-8.1 kcal/mol). Those ligands showed lower binding affinity than the control compounds, hesperidin (-7.9 kcal/mol) and remdesivir (-5.6 kcal/mol). Meanwhile, there were seven ligands interact with RdRp that have lower binding affinity than the control compounds: rutin (-9.6 kcal/mol), taraxasterol (-9.3

kcal/mol), 3,3'-biplumbagin (-9.2 kcal/mol), beta-amyrin (-9.0 kcal/mol), lantanolic acid (-9.0 kcal/mol), friedelin (-8.9 kcal/mol), and alpha-amyrin (-8.9 kcal/mol). Those seven ligands showed lower binding affinity than the control compounds, hesperidin (-8.8 kcal/mol) and remdesivir (-8.4 kcal/mol). Moreover, hesperidin as a control compound has lower binding affinity than remdesivir. Thus, ligands having lower binding affinity score than hesperidin were taken for further analysis (Table 1 and Table 2).

Drug-likeness and toxicity analysis were further conducted upon potential ligands to see the eligibility of ligands to be developed as oral drug candidate. Ligands should meet the criteria of Lipinski's rule of five and has a high GI absorption (Table 3). Lipinski's Rule of five including (1) molecular weight ≤500 Dalton, (2) hydrogen bond acceptors ≤10, (3) hydrogen bond donors ≤5, (4) high lipophilicity ≤5, and (5) molar refractivity between 40-130 [26]. Because they affected the compound's aqueous solubility and intestinal permeability, these physicochemical properties are crucial to oral absorption of drugs [32]. Table 3 showed that, although majority of ligands are eligible according to Lipinski's Ro5, only 3,3'-biplumbagin, lantanolic acid, and chitranone that have high GI absorption. GI absorption is one of the pharmacokinetic behaviors crucial to estimate during drug discovery process. to minimize failure in later phases of development [33]. Furthermore, toxicity of all ligands that met the drug-likeness criteria were analyzed (Table 4).

Toxicity of ligands can be shown through its toxic dose (LD_{50}), toxicity class, organ toxicity (hepatotoxicity), and toxicity endpoints [26]. Toxic dose is given as LD_{50} values in mg/kg body weight, meaning that the dose at which 50% of test subjects die upon exposure to a compound. Toxic dose is highly related to classification of the six toxicity classes; class 1 ($LD_{50} \leq 5$) and class 2 ($5 < LD_{50} \leq 50$) meaning fatal if swallowed, class 3 ($50 < LD_{50} \leq 300$) is toxic if swallowed, class 4 ($300 < LD_{50} \leq 2000$) is harmful if swallowed, class 5 ($2000 < LD_{50} \leq 5000$) maybe harmful if swallowed, and class 6 ($LD_{50} > 5000$) is non-toxic [34]. Result showed that remdesivir, 3,3'-biplumbagin, and chitranone are belongs to class 4 with LD_{50} 1000 mg/kg, 1190 mg/kg, and 1000 mg/kg, respectively. Lantanolic acid belongs to class 5 with LD_{50} = 2589 mg/kg. Meanwhile, hesperidin classified as non-toxic (class 6) with LD_{50} = 12000 mg/kg. All compounds showed inactive ability towards hepatotoxicity, carcinogenicity,

Table 1. Binding affinity of spike glycoprotein (PDB ID: 6VXX)-ligands

PubChem ID	Ligand	Binding Affinity (kcal/mol)
91472	Friedelin	-8.5
73170	alpha-Amyrin	-8.4
3034659	Pseudotaraxasterol	-8.3
6436598	Lantadene A	-8.3
633072	Chitranone	-8.2
3003153	Lantanolic acid	-8.2
5280794	Stigmasterol	-8.2
9890209	Ursonic acid	-8.2
183757	3,3'-Biplumbagin	-8.1
15560077	Lantadene B	-8.1
101316804	Lantanilic acid	-8.1
73145	beta-Amyrin	-8.1
10621	Hesperidin	-7.9
121304016	Remdesivir	-5.6

Table 2. Binding affinity of RdRp (PDB ID: 6M71)-ligands

PubChem ID	Ligand	Binding Affinity (kcal/mol)
5280805	Rutin	-9.6
441686	Taraxasterol	-9.3
183757	3,3'-Biplumbagin	-9.2
73145	beta-Amyrin	-9.0
3003153	Lantanolic acid	-9.0
91472	Friedelin	-8.9
73170	alpha-Amyrin	-8.9
10621	Hesperidin	-8.8
121304016	Remdesivir	-8.4

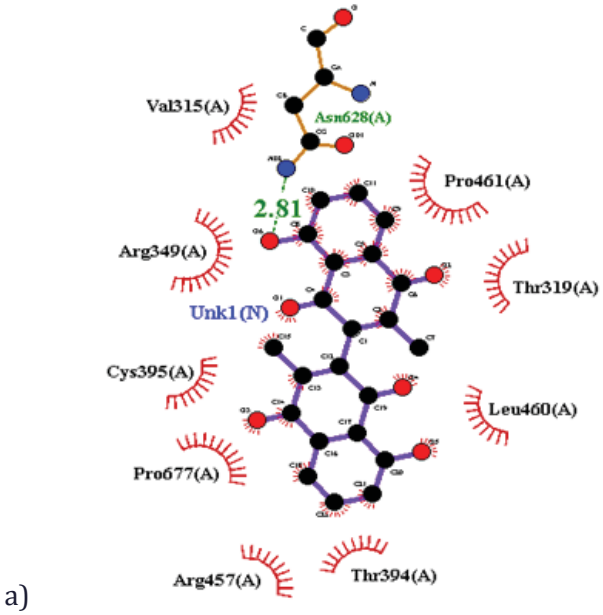
Table 3. Drug-likeness of the potential ligands

PubChem ID	Ligand	Lipinski Rule of Five					Eligibility	GI Absorption	Drug-likeness as Oral Drug
		MW	Ha	Hd	MR	MLogP			
91472	Friedelin	426.72	1	0	134.39	6.92	Yes	Low	NO
5280794	Stigmasterol	412.69	1	1	132.75	6.62	Yes	Low	NO
5280805	Rutin	610.52	16	10	141.38	-3.89	No	Low	NO
183757	3,3'-Biplumbagin	374.34	6	2	100.03	0.62	Yes	High	YES
3003153	Lantanolic acid	470.68	4	2	135.66	5.38	Yes	High	YES
73170	alpha-Amyrin	426.72	1	1	135.14	6.92	Yes	Low	NO
3034659	Pseudotaraxasterol	426.72	1	1	135.14	6.92	Yes	Low	NO
6436598	Lantadene A	552.78	5	1	160.54	5.61	No	Low	NO
633072	Chitranone	374.34	6	2	100.98	0.62	Yes	High	YES
9890209	Ursonic acid	454.68	3	1	135.95	5.73	Yes	Low	NO
15560077	Lantadene B	552.78	5	1	160.54	5.61	No	Low	NO
101316804	Lantanilic acid	568.78	6	2	160.51	5.29	No	Low	NO
73145	beta-Amyrin	426.72	1	1	134.88	6.92	Yes	Low	NO
10621	Hesperidin	610.56	15	8	141.41	-3.04	No	Low	NO
121304016	Remdesivir	602.58	12	4	150.43	0.18	No	Low	NO

Table 4. Toxicity analysis of ligands

PubChem ID	Ligand	LD_{50} (mg/kg)	ToxClass	Accuracy (%)	Probability Toxicity				
					H	Ca	I	M	Cy
10621	Hesperidin	12000	6	72.90	I	I	A	I	BT
121304016	Remdesivir	1000	4	54.26	I	I	I	I	I
183757	3,3'-Biplumbagin	1190	4	100.00	BT	BT	A	I	I
3003153	Lantanolic acid	2589	5	69.26	BT	BT	A	I	I
633072	Chitranone	1000	4	68.07	BT	BT	A	I	BT

Note: H = Hepatotoxicity; Ca = Carcinogenicity; Im = Immunotoxicity; M = Mutagenicity; Cy = Cytotoxicity. Numbers given in probability toxicity are confidence estimate for the prediction, followed by its status: I = Inactive; A = Active; BT = Below Threshold, therefore omitted and considered safe.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Asn628(A)
Pro461(A)
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Arg349(A)
Thr319(A)
Unk1(N)
Cys395(A)
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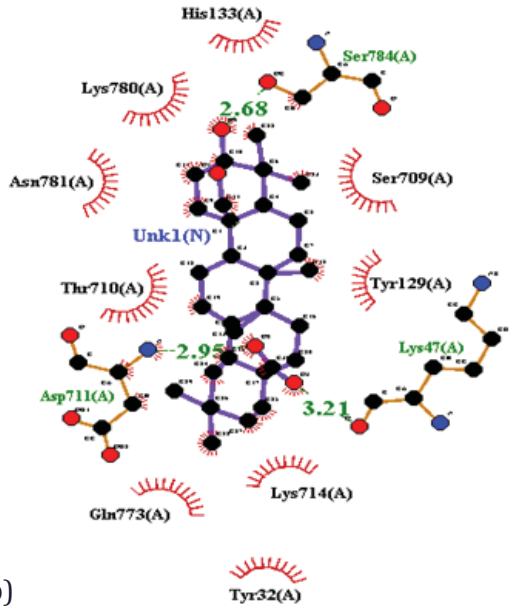
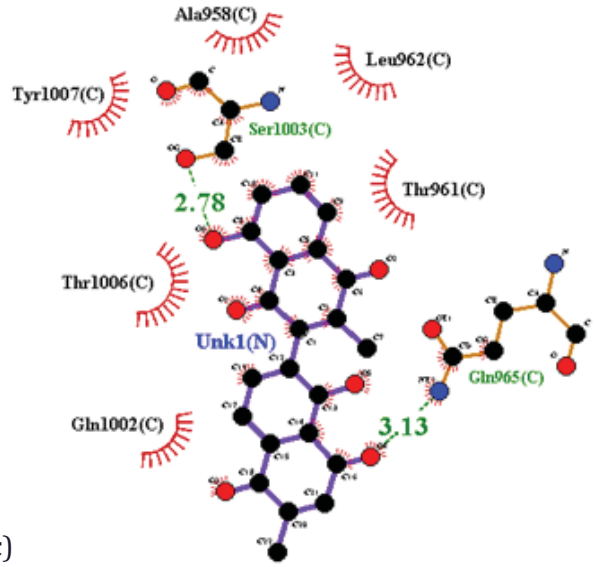
Pro677(A)
Arg457(A)
Thr394(A)

a)


His133(A)
Ser784(A)
Lys780(A)
2.68
Asn781(A)
Ser709(A)
Unk1(N)
Thr710(A)
Tyr129(A)
2.95
Lys47(A)
Asp711(A)
3.21
Lys714(A)
Gln773(A)
Tyr32(A)

b)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Leu962(C)
Tyr1007(C)
Ser1003(C)
Thr961(C)
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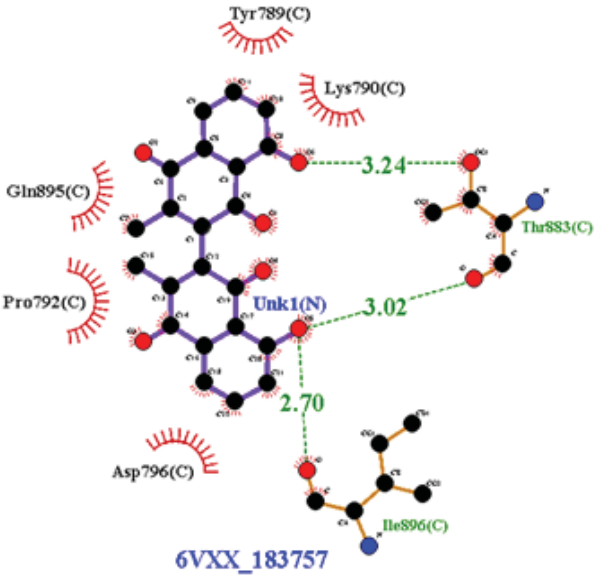
Thr1006(C)
Unk1(N)
Gln965(C)
Gln1002(C)
3.13

c)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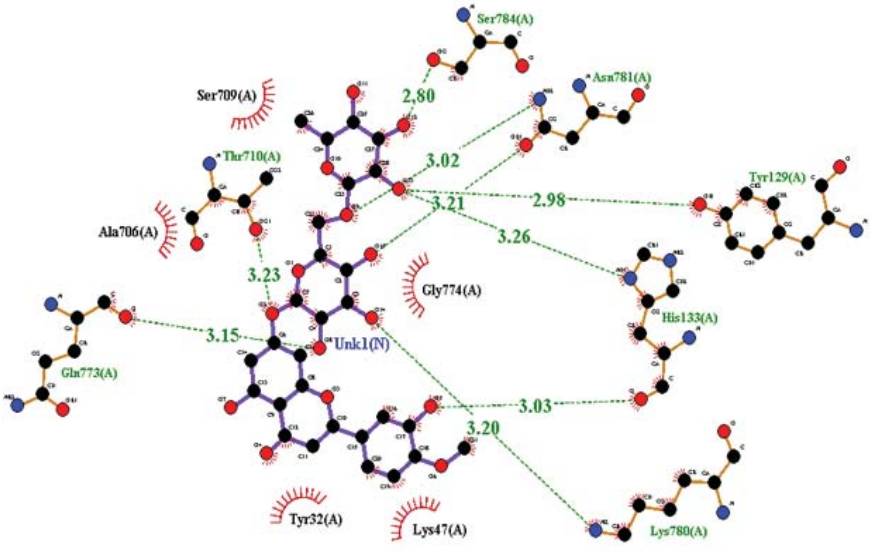
Asp796(C)
Ile896(C)
6VXX_183757


Ser784(A)
Ser709(A)
2.80
Asn781(A)
Thr710(A)
3.02
Tyr129(A)
3.21
2.98
Ala706(A)
3.26
3.23
Gly774(A)
His133(A)
3.15
Unk1(N)
Gln773(A)
3.03
3.20
Tyr32(A)
Lys47(A)
Lys780(A)

d)

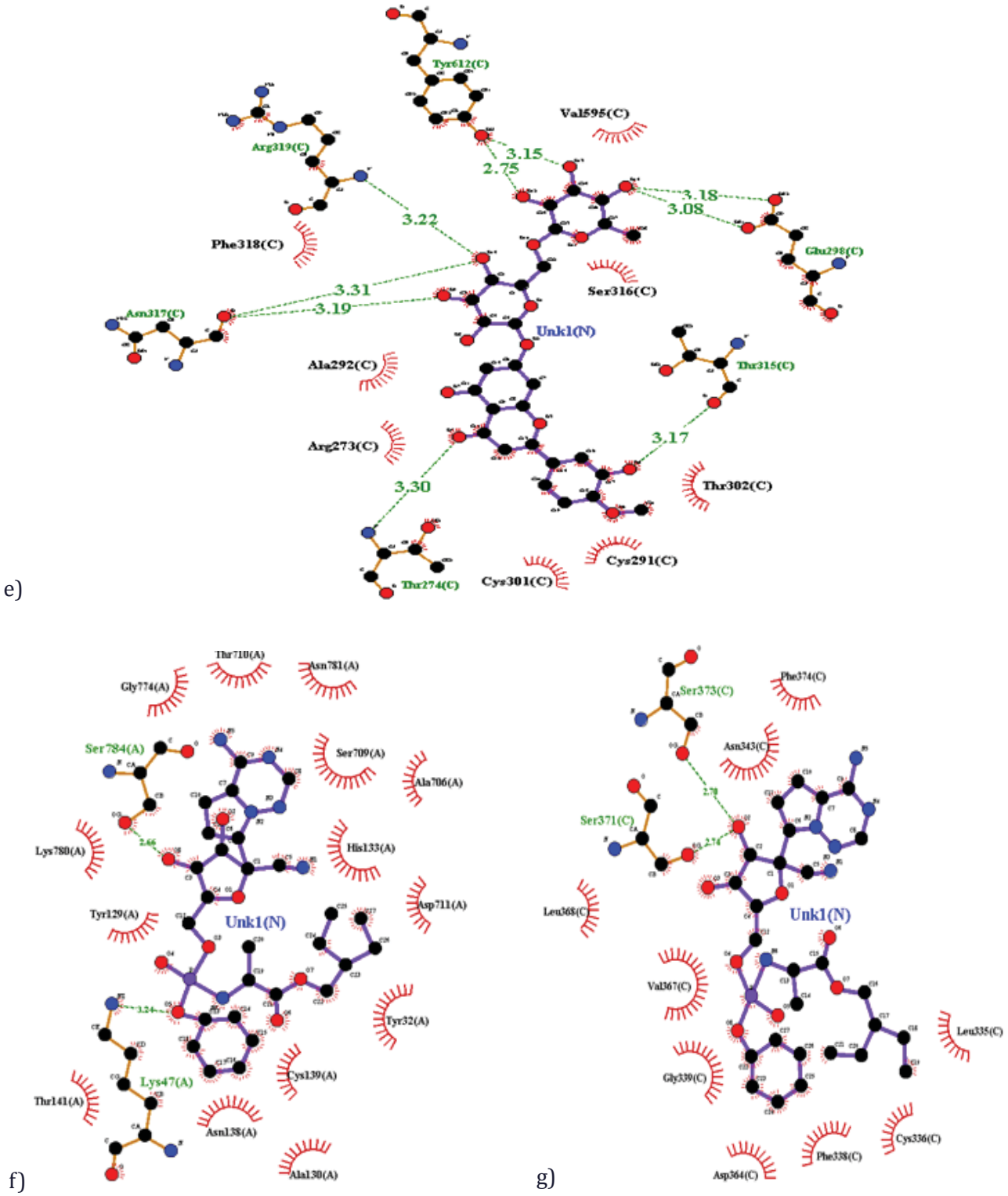


Figure 1. Visualization of interaction between a) RdRp-3,3'-Biplumbagin; b) RdRp-Lantanolic acid; c) Spike glycoprotein-Citranone; d) RdRp-Hesperidin; e) Spike glycoprotein-Hesperidin; f) RdRp-Remdesivir; g) Spike glycoprotein-Remdesivir.

mutagenicity, and cytotoxicity. Furthermore, all compounds showed an active ability of immunotoxicity, except remdesivir. It is possible that the ligands give adverse effects on the functioning of local and systemic immune system upon exposure, although it depends on specific conditions [35]. Allergy, immunosuppression and, in some cases, autoimmunity, are highly affected the po-

Table 5. Spike glycoprotein (PDB ID: 6VXX) amino acid residues-ligands interaction

Ligand	Hydrogen Bond	Hydrophobic Bond
Hesperidin	Tyr612: 3.15, 2.75 Å Arg319: 3.22 Å Asn317: 3.31, 3.19 Å Thr274: 3.30 Å Thr315: 3.17 Å Glu298: 3.08, 3.18 Å	-Val595, Ser316, Thr302, Cys291, Cys301, Arg273, Ala292, Phe318
Remdesivir	Ser371: 2.74 Å Ser373: 2.70 Å	Asn343, Phe374, Leu335, Cys336, Phe338, Asp364, Gly339, Val367, Leu368
Chitranone	Gln965: 3.13 Å Ser1003: 2.78 Å	Ala958, Thr961, Leu962, Gln1002, Thr1006, Tyr1007
Lantanolic acid	Lys300: 2.83 Å Ser297: 3.03 Å	Val289, Asp287, Ala288, Phe220, Thr286, Asp290, Leu293, Phe58, Phe59, Thr33, Gly219
3,3'-Biplumbagin	Thr883: 3.02, 3.24 Å Ile896: 2.70 Å	Lys790, Tyr789, Gln895, Pro792, Asp796

Table 6. RdRp (PDB ID: 6M71) amino acid residues-ligands interaction

Ligand	Hydrogen Bond	Hydrophobic Bond
Hesperidin	Tyr129: 2.98 Å His133: 3.26, 3.03 Å Thr710: 3.23 Å Gln773: 3.15 Å Lys780: 3.20 Å Asn781: 3.02, 3.21 Å **Ser784**: 2.80 Å	**Tyr32**, Lys47, Ala706, **Ser709**, Gly774
Remdesivir	**Lys47**: 3.24 Å **Ser784**: 2.66 Å	**Tyr129, Lys780,** Gly774, **Thr710, Asn781, Ser709**, Ala706, His133, Asp711, Tyr32, Cys139. Ala130, Ala138, Thr141
3,3'-Biplumbagin	Asn628: 2.81 Å	Val315, Thr319, Arg349, Thr394, Cys395, Arg457, Leu460, Pro461, Pro677
Lantanolic acid	**Lys47**: 3.21 Å Asp711: 2.95 Å **Ser784**: 2.68 Å	**Tyr32, Tyr129, His133, Ser709, Thr710,** Lys714, Gln733, **Lys780**, **Asn781**

Note : The bold amino acids indicate the same interactions between the ligands and control compounds (hesperidin and remdesivir).

larization of the immune response by immunotoxicants, rather than independent outcomes of chemical exposure [36]. Complexes of protein and potential ligands having similar amino acid interactions with the control compounds (hesperidin and remdesivir) and meet Lipinski Rules of Five criteria were as follows (Figure 1). Thus, all potential ligands are eligible to be developed as drug compounds. Furthermore, interaction between amino acid residues of target protein and potential ligands were analyzed. Table 5 and Table 6 showed hydrogen and hydrophobic bonds between amino acid residues-ligands.

Among the three potential ligands, there is only one ligand that has similar amino acid inte–ractions as the control compounds, namely lantanolic acid. It has two hydrogen bonds with Lys47 and Ser784. Furthermore, it also has hydrophobic bonds with Tyr32, Tyr129, His133, Ser709, Thr710, Lys780, and Asn781. The formation of three hydrogen bonds between lantanolic acid and Lys47, Asp711, and Ser784 from RdRp would be able to stabilize the ligand-target protein complex and increase the potential inhibition of ligand. Lantanolic acid can be found in *Lantana camara* L. (Kembang Telek).

4. Conclusion

The 184 secondary metabolites from nine Indonesian medicinal plants in organic garden of an organic herbal company in East Java, Indonesia were analyzed to discover suitable inhibitors for SARS-CoV-2 proteins as potential COVID-19 drugs from phytochemicals. The study showed that lantanolic acid has a lower binding affinity score than hesperidin and remdesivir control compounds, eligible as a drug compound according to the Lipinski's Rule of Five. It has high GI absorption, and a LD_{50} of 2589 mg/kg. Lantanolic acid can be found in *Lantana camara* L. (Kembang Telek). Further evaluation for the prospective lantanolic acid could be done using molecular dynamics simulation.

Acknowledgement

The authors have no conflicts of interest regarding this study.

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