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Research Article

The Potential of Antivirus Compounds in Gletang (*Tridax procumbens* Linn.) in Inhibiting 3CLpro Receptor of SARS-CoV-2 Virus by In Silico

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ABSTRACT
SARS-CoV-2 virus has caused pandemic disease since the end of 2019. Virus transmission occurs through droplet and infects the host's respiratory tract rapidly. Viral propagation occurs through translation process of genome +ssRNA, then it being replicated forming some new body parts of virus and assemblied into virions that ready to infect. During the replication process, the translated viral genome in the form of polyprotein will be cut into smaller components by proteases, which one is 3CLpro. The presence of the 3CLpro receptor is used in drug development through in-silico molecular docking process to minimize failures before laboratory test. The antivirus compounds that used to inhibit the 3CLpro receptor are from gletang plant (*Tridax procumbens* Linn.). This study aim is to determine the value of binding affinity, the interaction between compounds and receptor, and the effect of drug components. The research was conducted by in-silico through the molecular docking process of 3CLpro receptor and antivirus compounds of gletang (*Tridax procumbens* Linn.), including betulinic acid, kaempferol and lignan. The results showed that the binding affinity of betulinic acid was -6.6 kcal/mol, kaempferol was -5.6 kcal/mol and lignan was -5.4 kcal/mol. The interaction form of compounds and receptor was hydrogen bond, electrostatic, hydrophobic, and van der Waals. Compared to baicalein compound as a positive control with the value of binding affinity was -6.7 kcal/mol and its interaction with 3CLpro receptor, showed betulinic acid, kaempferol and lignan have smaller ability but they have the potential to inhibit the 3CLpro receptor.
Key words: 3CLpro receptor, Antivirus, Gletang, *In-silico*, SARS-CoV-2.

INTRODUCTION

On December 31, 2019, there were 41 confirmed cases of pneumonia that have not known happened in Wuhan City, Hubei District, China.[1] On January 7, 2020, the Chinese Centre for Disease Control and Prevention (CCDC) got the causing agent isolated from lung epithelial cells of infected humans by Coronavirus (CoV), called Novel Coronavirus-Infected Pneumonia (NCIP).[2] On January 12, 2020, genetic sequence from a new type of Coronavirus was identified and had similarity to Severe Acute Respiratory Syndrome (SARS) about 85-87% from reservoir of bat, so it was called SARS-CoV-2 or 2019 novel Coronavirus (2019-nCoV) by International Committee on Taxonomy of Viruses.[2-4] On February 12, 2020, World Health Organization (WHO) called the disease with Coronavirus Disease 2019 (COVID-19).[5]

Replication process of SARS-CoV-2 virus is affected by enzyme, which one is 3-chymotrypsin-like protease (3CLpro). The enzyme originated from the translation result of positive single-stranded RNA (+ssRNA) genome with polyprotein form of non-structural protein 5 (nsp5). 3CLpro works as proteolysis to cut polyprotein in 11 sites becomes nsp4-16. 3CLpro will mediate the maturation of non-structural protein for the life cycle of virus. This replication process depends on 3CLpro, thus it could be used as the inhibition target for drug development.[6] Drug development is being progressed to treat the infection of SARS-CoV-2 because antivirus have not been found yet.[7]

Herbal plant become the source of drug development from the environment because it is easy to find, which one is gletang (*Tridax procumbens* Linn.). The use of gletang as the herbal plant had been used in medicine of some diseases in some countries. Gletang had been used as a medicine for anemia, fever, inflammation, and hepatopathy in America. Meanwhile, gletang had used as a medicine for diabetes, bite of insects, diarrhea, and inflammation in India. Also in Africa, gletang used as antimalarial, antibacterial, and wound healing.[8] However, the used of gletang in Indonesia is unknown and it considered as wild plant growing in every environmental condition to interfere the cultivation as weeds.[9] Gletang (*Tridax procumbens* Linn.) has some phytochemical compounds potentially as drug, especially in part of leaf. Some of these phytochemical compounds have pharmacological potential as antivirus, such as kaempferol, betulinic acid, and lignan.[10]

Drug development could be conducted by *in-silico* of bioinformatics study using molecular docking. This method used database and software for theoretical analysis to get the result of binding affinity and protein-ligand interaction. In-silico could decrease the cost and time to predict the level of success from drug development before laboratory test (*in-vitro* and *in-vivo*). However, in-silico study showed a

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prediction or theoretical result that make less of drug affectivity, thus the result of this method should be further tested in the laboratory.[11]

In-silico research for drug development would be useful to get the potential of an appropriate drug, especially for medicine of SARS-CoV-2 infection causing COVID-19. Depend on the research by Zhang *et al.* that in-silico study had been conducted to find the potential compounds from Chinese herbal plants to inhibit SARS-CoV-2.[12] The infection process of virus with the main factor of 3CLpro could be used for docking process by antivirus compounds of an herbal plant of gletang (*Tridax procumbens* Linn.) such as kaempferol, betulinic acid, and lignan. In order, this research would be conducted by molecular docking of antivirus compound from gletang (*Tridax procumbens* Linn.) to inhibit the 3CLpro receptor of SARS-CoV-2 virus.

MATERIALS AND METHODS

Materials

The materials used structure 3D protein of 3CLpro receptor with ID 6M2N and native ligand of baicalein compound from online database of Protein Data Bank (PDB) with link of https://www.rcsb.org (Figure 1a). Ligand of antivirus compounds from gletang (*Tridax procumbens* Linn.) were betulinic acid (CID: 64971), kaempferol (CID: 5280863) and lignan (CID: 261166) from online database of PubChem with link of https://pubchem.ncbi.nlm.nih.gov (Figure 1b, 1c, and 1d).

Tools

a. Hardware

Laptop manufacture ASUSTek Computer Inc. with specifications:

1) Processor AMD A4-9125 Radeon R3
2) RAM (*Random Access Memory*) 4 GB
3) Operation system of Windows 10 *Home Single Language* versi 1809
4) Hardisk 1 T

b. Software

c. PyRx – Python Prescription 0.8

d. Discovery Studio Visualizer v20.1.0.19295

Methods

This research used in-silico method with molecular docking process. First, Structure 3D protein was validated using Ramachandran Plot analysis in Structure Assessment from Swiss-Model site with link of https://swissmodel.expasy.org/assess.[11,29] Then, protein sterilization was conducted by removing the water molecule and ligand native used software of Discovery Studio Visualizer v20.1.0.19295.[13,30] Ligands analysis used Lipinski to predict drug molecule with link of http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp, then the format file was being changed from sdf to pdb with minimization process in PyRx - Python Prescription 0.8 software.[11,27,28]

Molecular docking used software of PyRx - Python Prescription 0.8 with 'Vina Wizard' plugin. The result of molecular docking was the average value of binding affinity from 10 times repetition and the interaction range of ligand-receptor. Visualization of structure 3D and 2D used software of Discovery Studio Visualizer v20.1.0.19295.

RESULTS AND DISCUSSION

Protein structure validation of 3CLpro receptor

3CLpro receptor has an important role as an enzyme in proteolysis process of virus replication to cut polyprotein of SARS-CoV-2 virus to be some small parts of protein. This role makes 3CLpro receptor become a main target of inhibition as drug-making target conducted by in-silico in molecular docking. The protein 3D structure of 3CLpro receptor from Protein Data Bank with ID 6M2N was analyzed by protein structure validation to show the protein stereochemical quality and to predict the success of using the docking method.[11,14,31] Protein structure validation used Ramachandran Plot based on amino acid residue geometric through Ψ (phi) and Φ (psi) rotation. The graphical display of protein structure validation of 3CLpro receptor showed in figure 2.

Graphical display of Ramachandran Plot showed the amino acid residues position marked with blue-red dot. These positions located in areas with deep green gradation. According to the statement of Widodo *et al.* that the position of amino acid residue in dark colour of gradation (*core regions*) gave the best Ψ (phi) and Φ (psi) rotation.[15,32,35] The validity score showed the value of Ramachandran Favoured (best area) 97.20% and Ramachandran Outlier (unwanted area) 0.08%. The best validity score of protein 3D structure quality has Ramachandran Favoured more than 50% and Ramachandran Outlier less than 15%, better if the score of Ramachandran Favoured bigger and Ramachandran Outlier smaller.[16,33,34] Thus, protein 3D structure of 3CLpro receptor had the best quality.

Drug molecule analysis of compounds

Potential compounds of chemical components as drug had been analyzed by Lipinski analysis. This analysis depend on the bioavailability as oral drug from biological materials of ADME (absorption, distribution, metabolism, and excretion). The analysis of antivirus compounds from gletang (*Tridax procumbens* Linn.) showed in table 1.

Drug molecule analysis of compounds used five rules by Lipinski include mass molecule less than 500 Dalton, hydrogen bond donor less than 5, hydrogen bond acceptor less than 10, logP calculation (lipophilicity) less than 5, and molar reactivity about 40-130.[17,36] The result of Lipinski

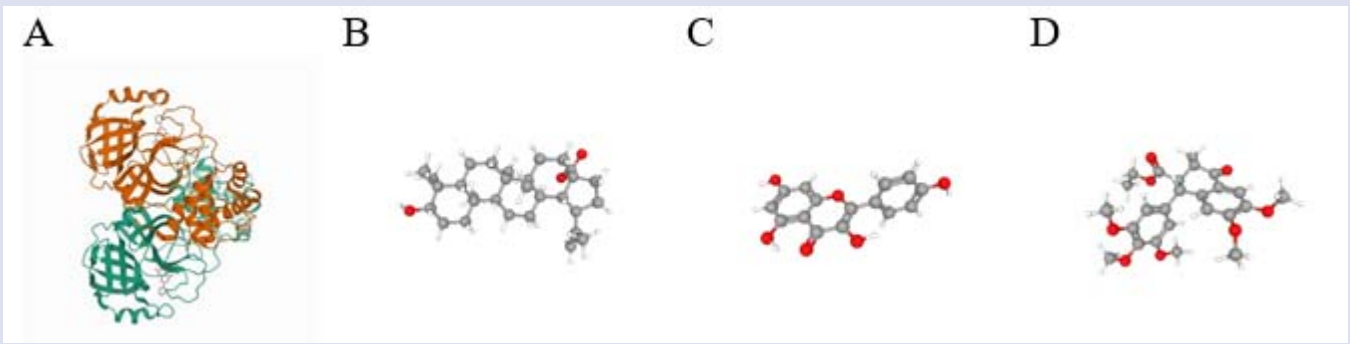

Figure 1: Structure of protein and ligand. A: 3CLpro receptor; B: Betulinic acid; C: Kaempferol; and D: Lignan.

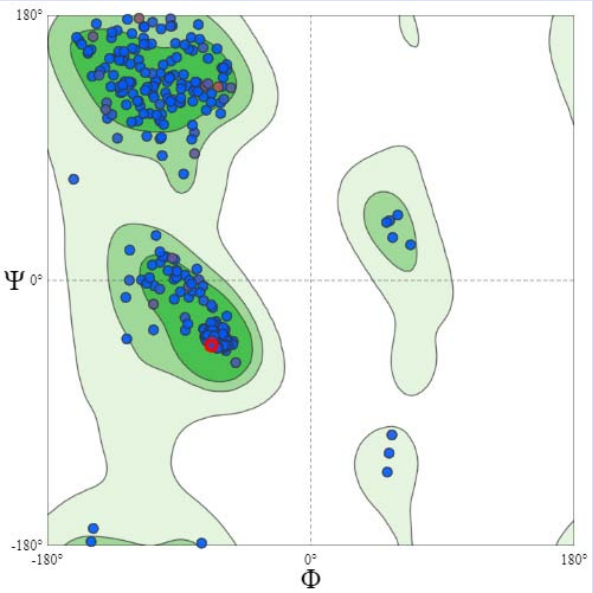

Figure 2: Protein 3CLpro receptor validation.

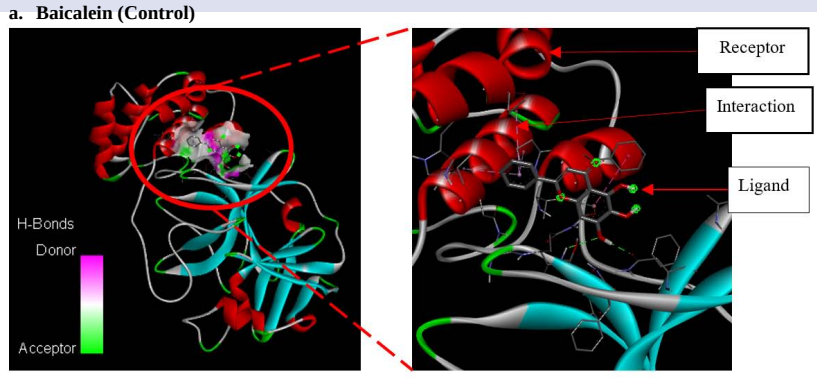

Figure 3: Visualization of 3D structure for Baicalein and 3CLpro receptor.

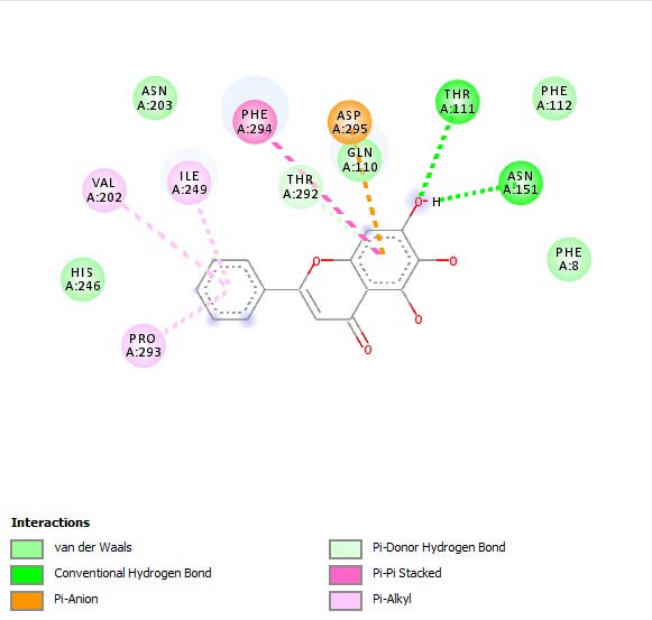

Figure 4: Visualization of 2D structure for Baicalein and 3CLpro receptor.

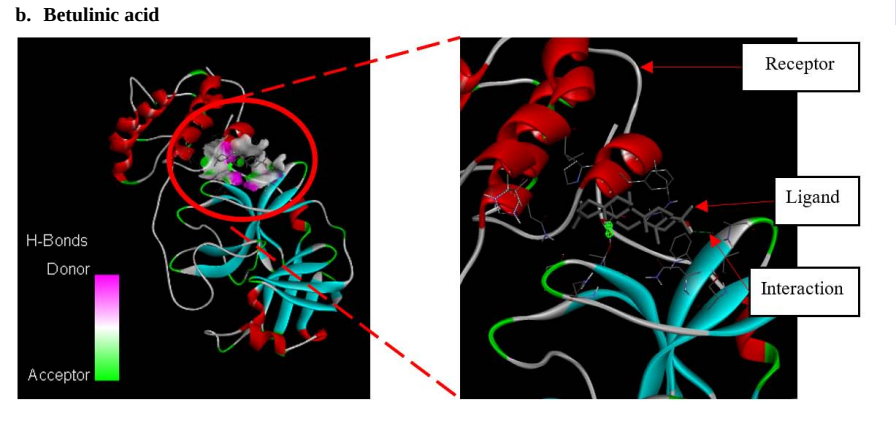

Figure 5: Visualization of 3D structure for Betulinic acid and 3CLpro receptor.

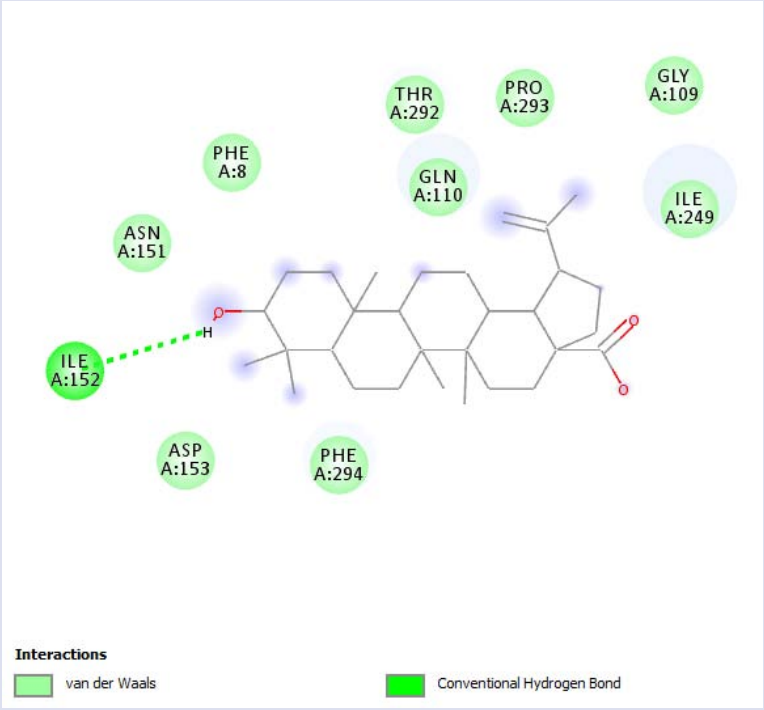

Figure 6: Visualization of 2D structure for Betulinic acid and 3CLpro receptor.

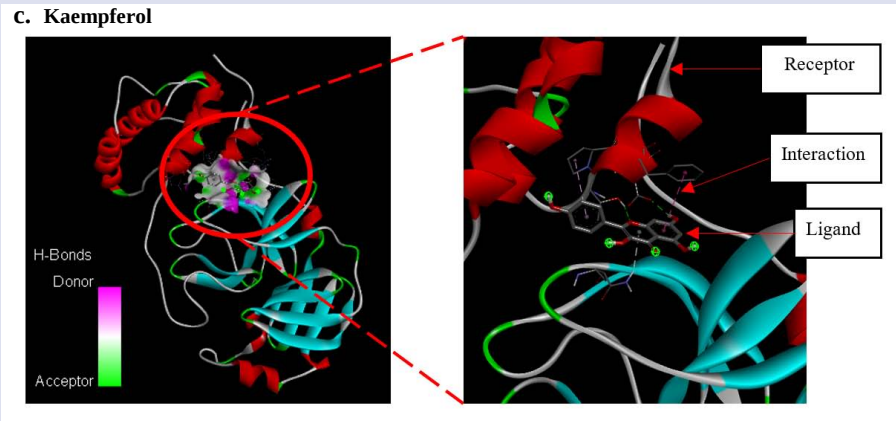

Figure 7: Visualization of 3D structure for Kaempferol and 3CLpro receptor.

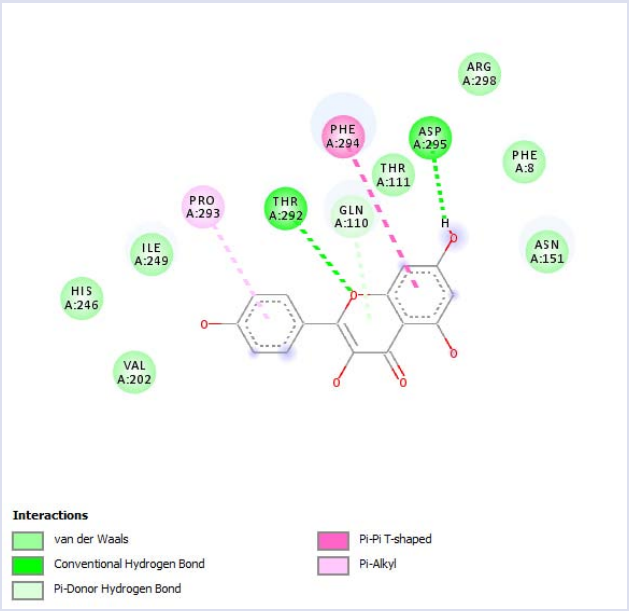

Figure 8: Visualization of 2D structure for Kaempferol and 3CLpro receptor.

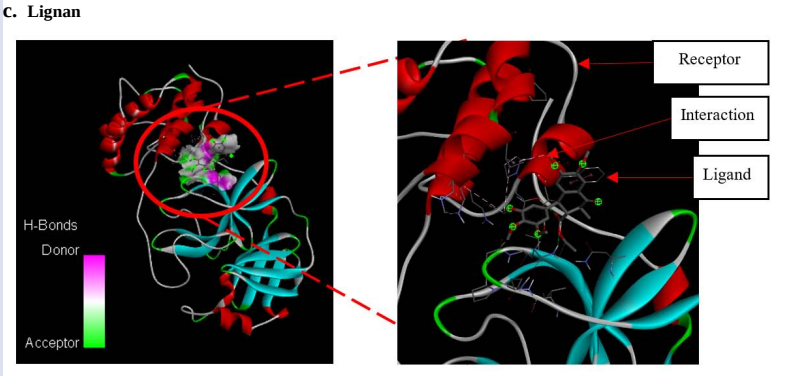

Figure 9: Visualization of 3D structure for Lignan and 3CLpro receptor.

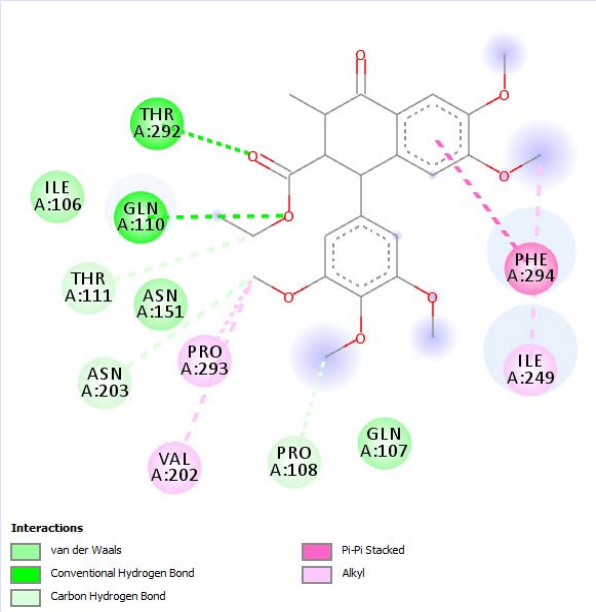

Figure 10: Visualization of 2D structure for Lignan and 3CLpro receptor.

Table 1: **Result of lipinski analysis.**

Compound	Mass Molecule	Hydrogen Bond Donor	Hydrogen Bond Acceptor	LogP	Molar Reactivity
Baicalein (control)	270	3	5	2.419599	70.813881
Betulinic Acid	456	2	3	7.089501*	132.611557*
Kaempferol	286	4	6	2.305299	72.385681
Lignan	458	0	8	3.873199	121.104454

Note: Result marked with (*) not complied with Lipinski rules

Table 2: **Molecular docking result of compounds and 3CLpro receptor.**

Ligand	Binding affinity (kcal/mol)	RMSD (Å)
Baicalein (Kontrol)	-6.7	1.24
Betulinic Acid	-6.6	1.31
Kaempferol	-6.4	1.46
Lignan	-5.9	1.80

Table 3: **Interaction of baicalein (Control) with 3CLpro receptor.**

Residue	Distance(Å)	Interaction	Type
ASN151	2.02891	Hydrogen Bond	Conventional Hydrogen Bond
THR111	2.85532	Hydrogen Bond	Conventional Hydrogen Bond
THR292	3.14513	Hydrogen Bond	Pi-Donor Hydrogen Bond
ASP295	4.69501	Electrostatic	Pi-Anion
PRO293	4.65248	Hydrophobic	Pi-Alkyl
ILE249	4.88161	Hydrophobic	Pi-Alkyl
VAL202	5.16561	Hydrophobic	Pi-Alkyl
PHE294	5.34833	Hydrophobic	Pi-Pi Stacked
PHE8	-	van der Waals	-
PHE112	-	van der Waals	-
ASN203	-	van der Waals	-
GLN110	-	van der Waals	-
HIS246	-	van der Waals	-

Table 4: **Interaction of betulinic acid with 3CLpro receptor.**

Residue	Distance(Å)	Interaction	Type
ILE152	2.78253	Hydrogen Bond	Conventional Hydrogen Bond
ILE249	-	van der Waals	-
GLY109	-	van der Waals	-
PRO293	-	van der Waals	-
GLN110	-	van der Waals	-
THR292	-	van der Waals	-
PHE8	-	van der Waals	-
ASN151	-	van der Waals	-
ASP153	-	van der Waals	-
PHE294	-	van der Waals	-

Table 5: **Interaction of kaempferol with 3CLpro receptor.**

Residue	Distance(Å)	Interaction	Type
ASP295	2.12983	Hydrogen Bond	Conventional Hydrogen Bond
THR292	2.31663	Hydrogen Bond	Conventional Hydrogen Bond
GLN110	3.14109	Hydrogen Bond	Pi-Donor Hydrogen Bond
PRO293	4.66665	Hydrophobic	Pi-Alkyl
PHE294	4.9252	Hydrophobic	Pi-Pi T-shaped
ARG298	-	van der Waals	-
PHE8	-	van der Waals	-
ASN151	-	van der Waals	-
THR111	-	van der Waals	-
ILE249	-	van der Waals	-
HIS246	-	van der Waals	-
VAL202	-	van der Waals	-

Table 6: Interaction of lignan with 3CLpro receptor.

Residue	Distance(Å)	Interaction	Type
THR292	2.18086	Hydrogen Bond	Conventional Hydrogen Bond
GLN110	2.33463	Hydrogen Bond	Conventional Hydrogen Bond
THR111	3.33176	Hydrogen Bond	Carbon Hydrogen Bond
ASN203	3.51411	Hydrogen Bond	Carbon Hydrogen Bond
PRO108	3.70587	Hydrogen Bond	Carbon Hydrogen Bond
ILE249	3.83146	Hydrophobic	Alkyl
VAL202	4.8332	Hydrophobic	Alkyl
PRO293	4.97055	Hydrophobic	Alkyl
PHE294	4.93739	Hydrophobic	Pi-Pi Stacked
GLN107	-	van der Waals	-
ASN151	-	van der Waals	-
ILE106	-	van der Waals	-

analysis showed that kaempferol and lignan compounds complied of five rules, however betulinic acid compound complied of three rules. Based on a statement of Kharisma *et al.* that analysis for drug molecule of compounds prediction followed in minimal two from all Lipinski rules.[11] Thus, all antivirus compounds from gletang (*Tridax procumbens* Linn.) had the component of drug molecules.

Analysis compounds as inhibitor of 3CLpro receptor

Molecular docking used protein target binding site to get the force interaction value of binding energy (binding affinity).[18] The binding site set through positive control grid docking with position on *center* (Å) X:-36.6 Y:-39.6 Z:34.8 and *dimensions* (Å) X:20.0 Y:20.0 Z:27.0. Compounds with ability to inhibit target protein on binding site like control showed similar ability with control.[19] Molecular docking process was conducted with 10 repetitions to find the stability of ligand-protein interaction with result based on the average value of binding energy.

Based on table 2, the result of molecular docking process of antivirus compounds from gletang (*Tridax procumbens* Linn.) with 3CLpro receptor showed the difference value of binding affinity. The binding affinity value of betulinic acid was -6.6 kcal/mol, kaempferol was -6.4 kcal/mol, and lignan was -5.9 kcal/mol. Betulinic acid, kaempferol and lignan compounds had a less negative result than control. Ligand and protein interaction happened spontaneously because the changed of free energy (ΔG) on negative position to reach a stable position with constant pressure and temperature.[19] The binding energy with more negative value had the stronger ligand ability to inhibit the protein activities.[18]

The distance of compounds binding with 3CLpro receptor showed on the result of RMSD (*Root Mean Square Deviation*). RMSD value for baicalein compound as positive control was 1.24Å. Betulinic acid, kaempferol, and lignan compounds had the RMSD value 1.31Å, 1.46Å and 1.80Å, showed a bigger result than control. The closer RMSD value to zero gave the best structure conformation.[20]

Analysis compounds and 3CLpro receptor interaction

Molecular docking visualization was conducted with Discovery Studio Visualizer software to show the 3D and 2D structure interaction of ligand-protein. Interaction of 3D structure showed the binding site position of compound on receptor, marked in the red circle. The white cloud around the ligand showed the existence of hydrogen bond, purple was donor position and green was acceptor position. Interaction of 2D structure marked with dotted line, light blue and green was hydrogen bond, purple was hydrophobic bond, and orange as electrostatic bond. Interaction of van der Waals showed in light green circle of amino acid residue.[21]

The 3CLpro receptor was composed with 1224 amino acid residues that folded and coiled to form a protein with a three-dimensional structure. Amino acids were formed from a carboxyl group and an amino group connected by an asymmetric carbon atom. This asymmetric carbon atom had an amino group, a carboxyl group, a hydrogen atom and a side chain. The side chains of these amino acids determined the physical and chemical properties based on their polarity. Amino acids with nonpolar side chains had hydrophobic properties, namely GLY (glycine), ALA (alanine), VAL (valine), LEU (leucine), ILE (isoleucine), MET (methionine), PHE (phenylalanine), TRP (tryptophan) and PRO (proline). The amino acids with polar side chains had hydrophilic properties, namely SER (serine), THR (threonine), CYS (cysteine), TYR (tyrosine), ASN (asparagine) and GLN (glutamine). The presence of carboxyl groups on amino acids often ionized at cellular pH resulting in charged amino acids and hydrophilic properties. The negatively charged amino acids was acid, namely ASP (aspartic acid) and GLU (glutamic acid). The positively charged amino acids was alkaline, namely LYS (lysine), ARG (arginine) and HIS (histidine).[22]

The interaction of antiviral compounds in gletang (*Tridax procumbens* Linn.) based on visualization showed that all compounds and positive controls could bind to amino acid residues at the binding site position of the 3CLpro receptor. Amino acid residue was used for ligand binding site by its interaction with side chain that give the in-silico value of binding energy (binding affinity).[23] The form of interaction was hydrogen bond, electrostatic, hydrophobic, and van der Waals.[24] Baicalein compound as positive control had 13 interactions, include 3 hydrogen bonds, 1 electrostatic interaction, 4 hydrophobic bonds, and 5 van der Waals interactions. Betulinic acid compound had 10 interactions, include 1 hydrogen bond and 9 van der Waals interactions. Kaempferol compound had 12 interactions, include 3 hydrogen bonds, 2 hydrophobic bonds, and 7 van der Waals interactions. Also lignan compound had 12 interactions, include 5 hydrogen bonds, 4 hydrophobic bonds, and 3 van der Waals interactions. Compared with control that betulinic acid, kaempferol, and lignan had a smaller count of interactions.

Hydrogen bond is the main interaction on the drug molecule, showed with the distance of interaction was smaller than other interaction.[21] According to statement of Friesner *et al.* and Listyani *et al.* that the smaller the interaction distance between the ligand and the receptor, the stronger the interaction that occurs.[20,23] Hydrogen bond interactions occur through the replacement of water molecules in proteins by ligands, which can increase entropy to achieve stability in the sequence of amino acid residues.[21,23] In contrary, hydrophobic bonds occur due to the presence of nonpolar amino acid residues that bind to ligands, in the form of covalent bonds between two carbon atoms (pi-pi stacked) or between carbon and hydrogen atoms (pi-alkyl).[21] Nonpolar molecules will gather to form aggregates in an aqueous environment

which reduces entropy because water cannot form hydrogen bonds with nonpolar molecules.[25] The target of in-silico determination of drug compounds has a combination of hydrophobic interactions with one to three hydrogen bonds to increase the potential for stability in laboratory-scale testing.[23]

The existence of electrostatic and van der Waals interactions can be useful in indicating the position of the binding site. This electrostatic interaction can provide a coordinate direction for the ligand to move towards the protein with greater force if it is positively charged and maintain the stability of the ligand on the receptor.[21,23] While, van der Waals interactions can occur when two atoms are sufficiently close together, in all types of polar and nonpolar molecules. The interaction causes random fluctuations in the electron distribution. If two atoms with noncovalent bonds are close enough, then electrons from one atom will perturbate on the other atom producing a transient dipole that attracts the two atoms to each other.[25] The van der Waals interaction can predict the position of the binding site better with the presence of atoms at a certain distance which gives rise to an energy.[26] This interaction is needed by the body, especially for use as a drug molecule with the ability to bond back to its original state, that is, the compound and the receptor can combine to produce a response and eventually separate.[22]

CONCLUSION

In summary, molecular docking process for antivirus compounds from gletang with 3CLpro receptor had the binding affinity value for betulinic acid was -6.6 kcal/mol, kaempferol was -6.4 kcal/mol, and lignan was -5.9 kcal/mol, also positive control of baicalein was -6.7 kcal/mol. The ligand-protein interactions were hydrogen bond, hydrophobic, and van der Waals. Antivirus compounds from gletang had the ability to inhibit the 3CLpro receptor through in-silico based on the drug components, the value of binding affinity and the interactions for ligand-protein, but not stronger than control.

Antivirus compounds from gletang were betulinic acid, kaempferol, and lignan could be the candidate for SARS-CoV-2 antivirus drug to develop the COVID-19 drug. However, this research was conducted by in-silico study based on molecular docking prediction to show the ability of drug compounds, so further laboratory test should be done to show the biological effect.

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DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

ABBREVIATIONS

2D: Two dimension; 3CLpro: 3-Chymotrypsin-Like protease; 3D: Three dimension; ADME: Absorption, Distribution, Metabolism, and Excretion; ALA: Alanine; ARG: Arginine; ASN: Asparagine; ASP: Aspartic acid; CCDC: Chinese Centre for Disease Control and Prevention; CID: Compound identifier; CoV: Coronavirus; COVID-19: Coronavirus Disease 2019; CYS: Cysteine; GLN: Glutamine; GLU: Glutamic acid; GLY: Glycine; HIS: Histidine; ID: Identification code; ILE: Isoleucine; LEU: Leucine; LYS: Lysine; MET: Methionine; NCIP: Novel Coronavirus-Infected Pneumonia; nsp: non-structural protein; PDB: Protein Data Bank; PHE: Phenylalanine; PRO: Proline; RMSD: Root Mean Square Deviation; SARS: Severe Acute Respiratory Syndrome; SARS-CoV-2: Severe Acute Respiratory Syndrome-novel Coronavirus-2; SER: Serine; ssRNA: single stranded RNA; THR: Threonine; TRP: Tryptophan; TYR: Tyrosine; VAL: Valine; WHO: World Health Organization.

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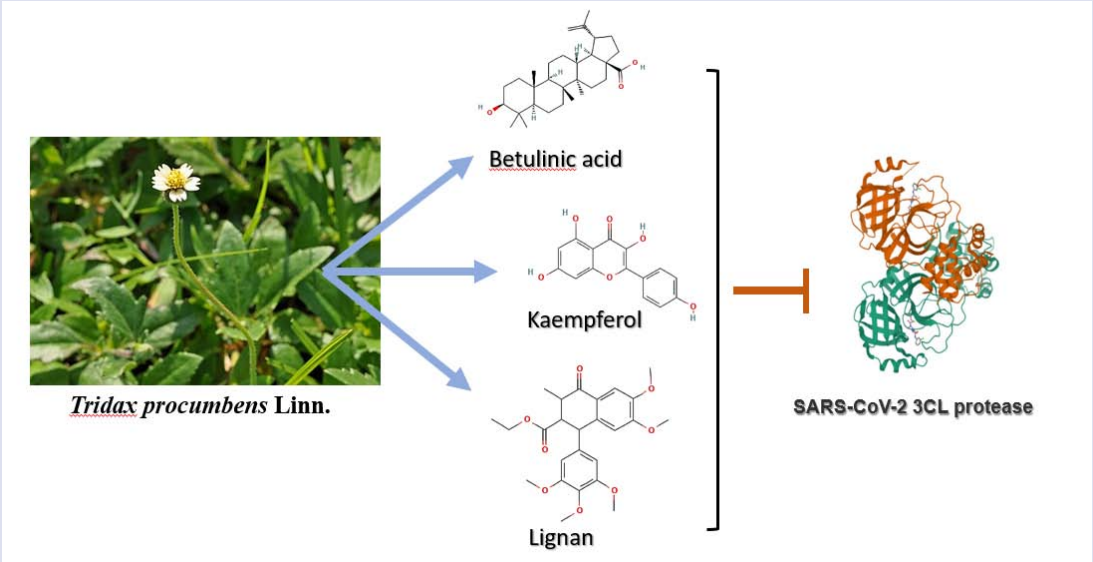
GRAPHICAL ABSTRACT



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