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Original Research Article

The Study of Potential Antiviral Compounds from Indonesian Medicinal Plants as Anti-COVID-19 with Molecular Docking Approach

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Abstract

Corona Virus Disease 2019 (COVID-19) is a new strain of coronavirus called SARS-CoV-2, which was identified in Wuhan, China, in December 2019. The rapid transmission of COVID-19 from human to human forced researchers to find a potent drug by setting aside the time-consuming traditional method in drug development. The molecular docking approach is one a reliable method to screening compound from chemical drug or by finding a compound from Indonesian herbal plants. The present study aimed to assess the potency of compounds from five medicinal plants as potential inhibitors of PL^{pro} and $3CL^{pro}$ from SARS-CoV-2 using molecular study. The molecular docking was performed using Protein-Ligand Ant System (PLANTS) to analyze the potential compounds by the docking score. Remdesivir triphosphate was used as a standard for the comparison of the test compounds. The docking score obtained from the docking of PL^{pro} with native ligand, remdesivir triphosphate, curcumin, demethoxycurcumin, bisdemethoxycurcumin, luteolin, apigenin, quercetin, kaempferol, formononetin-7-O-glucuronide, andrographolide, and neoandrographolide were -111.441, -103.827, -103.609, -102.363, -100.27, -79.6655, -78.6901, -80.9337, -79.4686, -82.1124, -79.1789, and -97.2452, respectively. Meanwhile, docking score with $3CL^{pro}$ for the same ligand were -64.0074, -86.1811, -81.428, -87.1625, -78.2899, -73.4345, -70.3368, -71.5539, -68.4321, -72.0154, -75.9777, and -93.7746. The docking score data suggest that curcumin was the most potential as a PL^{pro} inhibitor, while neoandrographolide was the best as a $3CL^{pro}$ inhibitor.

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INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is a disease caused by the outbreak of SARS-CoV-2 infection, a new coronavirus strain[1]. Food and Drug Administration of America (US FDA) stated that there is still no specific drug to inhibit the virus until this paper was written. Only broad-spectrum antiviral such as remdesivir are used to treat the infection[2]. Remdesivir is a prodrug and nucleoside analog, as a prodrug remdesivir has two active metabolites such as remdesivir nucleoside (GS-441524) and remdesivir triphosphate (GS-443902)[3,4].

The rapid transmission of COVID-19 from human to human forces researchers to find a potent drug, including using natural sources as an alternative[5]. However, natural drug development has its limitation, including it is time-consuming. This limitation could be addressed by using the molecular docking approach[6,7]. Molecular docking is one of the *in silico* approaches used to design or select compounds that can be used as an inhibitor or an activator of a target protein, and it also assesses the mechanism of action in the molecular state[8].

As mentioned by the Indonesian Food and Drug Administration (BPOM Indonesia), several medicinal plants from Indonesia with antiviral activity can be used to treat COVID-19 patients, such as turmeric (*Curcuma longa*), curcuma (*Curcuma xanthorrhiza*), gale of the wind/meniran (*Phyllanthus niruri*), green chiretta/sambiloto (*Andrographis paniculata*), and guava (*Psidium guajava*)[9]. Some research has been done to prove the plants have potential secondary metabolite as an antiviral to support this statement. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin in *C. longa* or *C. xanthorrhiza* have been shown to have an activity to inhibit 3C-like protease ($3CL^{pro}$) and spike protein of SARS-CoV-2 in the *in silico* study. At the same time, another study also reported that curcumin affect $3CL^{pro}$ of SARS-CoV-2 in the *in vitro* research[10,11]. Based on *in vitro* study, quercetin in P. guajava was shown to inhibit SARS-CoV-2 papain-like protease (PL^{pro}) with an IC_{50} of 8.6 µM[12]. Luteolin, apigenin, quercetin, and kaempferol in *P. guajava* also shown potency to inhibit $3CL^{pro}$ of SARS-CoV-2 based on *in silico* study[13]. Based on another *in silico* study with AutoDock Vina, quercitrin in *P. niruri*, as well as andrographolide and neoandrographolide from *A. paniculata*, show the best potential as a $3CL^{pro}$ SARS-CoV-2 inhibitor based on free energy acquisition[14].

In the life cycle of SARS-Cov-2, two non-structural proteins have a crucial role. First, $3CL^{pro}$ plays a role in replicating polypeptides into functional proteins to multiply viruses[15]. The $3CL^{pro}$ plays a role in synthesizing replicas through proteolysis mechanisms, and viruses will use these replicas to construct structural proteins to multiply themself[16]. Meanwhile, PL^{pro} serves as an essential virulence factor for the virus. The PL^{pro} works by untying ISG15 from IRF3, thus inhibiting Interferon (I and III) formation, which serves to signal the immune system[17]. This protein has the potential to be used as a target for treatment; in addition to genetic similarities between SARS-CoV (96%) and SARS-CoV-2, $3CL^{pro}$ and PL^{pro} also has not undergone mutations such as D614G in viral spike proteins[18]. Based on this background, this study aims to assess the potency of compounds from five medicinal plants from Indonesia, as mentioned before, as a potential inhibitor of PL^{pro} and $3CL^{pro}$ from SARS-CoV-2, using a molecular docking approach.

METHOD

Hardware and Software

The hardware used was Asus notebook with Intel® Core™ RAM 4.00 GB, Operation System Windows 10, 64-bit operating system. The software used was YASARA View 19.12.14 from YASARA Bioscience (http://www.yasara.org/), MarvinSketch 5.2.6 from ChemAxon (https://chemaxon.com/products/marvin), and PLANTS (Protein-Ligand Ant System) 64-bit from Universität Tübingen (https://uni-tuebingen.de/fakultaeten/mathematisch-naturwissenschaftliche-fakultaet/fachbereiche/pharmazie-und-biochemie/teilbereich-pharmazie-pharmazeutisches-institut/pharmazeutische-chemie/pd-dr-t-exner/research/plants/).

Ligands

Ligands in this research were divided into two groups: test and standard ligand. The test ligands were curcumin (PubChem ID 969516), bisdemethoxycurcumin (5315472), demethoxycurcumin (5469424), apigenin (5280443), luteolin (5280445), kaempferol (5280863), quercetin (5280343), formononetin-7-O-glucuronide (71316927), andrographolide (5318517), and neoandrographolide (9848024). The standard ligands were remdesivir triphosphate (56832906). The two-dimension structure of each ligand was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), then it was optimized into three-dimension using MarvinSketch to obtain the best conformation with the lowest energy.

Receptors

The receptors used in this study were SARS-CoV-2 PL^{pro} (PDB ID 3E9S) and $3CL^{pro}$ (5R7Y)[19], which downloaded from Protein Data Bank (https://www.rcsb.org).

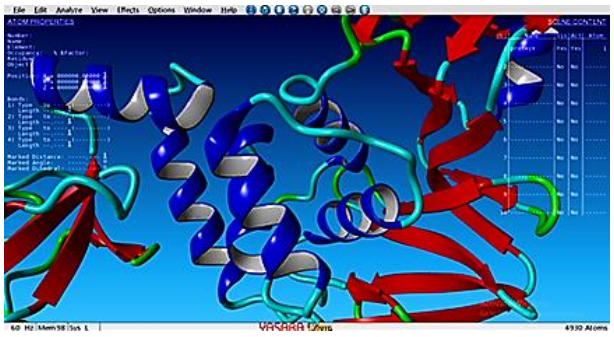
Docking protocol

Overall, the docking protocol used in this study was based on the docking protocol used by Purnomo *et al*[20].

Preparation of target protein and native ligand

The target protein and native ligand preparation were carried out using YASARA View. The protein was obtained by deleting its native ligand in the PDB file (**Figure 1**). In contrast, the native ligand was obtained by deleting the protein from the PDB file (**Figure 2**). In

this step, the protein and native ligand file were obtained in format protein.mol2 and ref_ligand.mol2.



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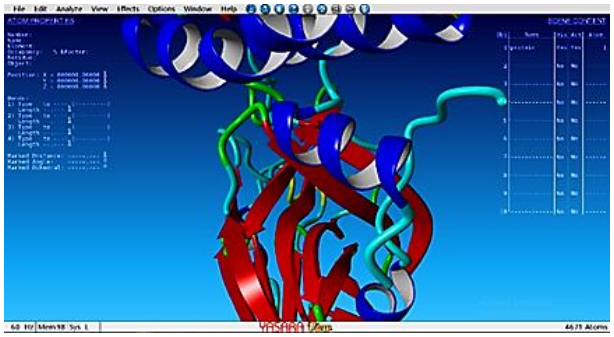
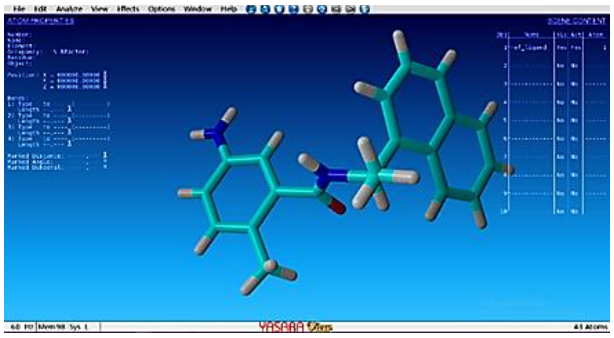


B

Figure 1. Three-dimension structure of (**A**) PL^{pro} and (**B**) $3CL^{pro}$.



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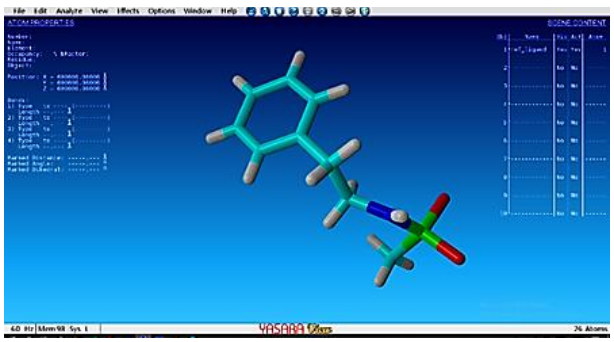

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Figure 2. Three-dimension structure of (**A**) PL^{pro} and (**B**) $3CL^{pro}$ native ligand.

Docking protocol validation

Docking protocol validation aims to obtain a root median square deviation (RMSD) value. The RMSD value was asses using YASARA View by re-docking the native ligand to its protein. Docking protocols stated as a valid protocol if the RMSD value <2 Å[21].

Test ligand docking

Docking was done using PLANTS by typing the commands in cmd.exe. The optimized test ligand was docked to the active site of both PL^{pro} and $3CL^{pro}$. PLANTS will read the command that has been set before to obtain the best docking score of each test ligand. The final result of the docking score would be compared with the best score of the native ligand.

Assessment

The assessment was performed using a descriptive approach. The results from the docking process were the docking score of each interaction between the test ligand and target protein. The docking score indicates affinity between the ligand and target protein. The docking score was described as a negative value, meaning the test ligand had a good affinity and potential as the inhibitor of the target protein[22]. The test ligand was stated to had potential as the target protein inhibitor if the docking score was more negative than the docking score of remdesivir triphosphate.

RESULTS AND DISCUSSION

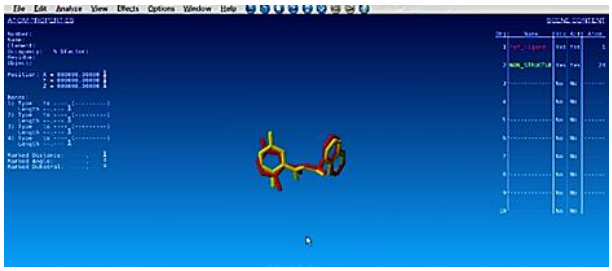
Docking protocol validation

The RMSD value of PL^{pro} and its native ligand 5-amino-2-methyl-N-[(1R)-1-naphthalen-1-ylethyl]benzamide was 0.5707 Å, and the RMSD value of $3CL^{pro}$ with N-(2-phenylethyl)methanesulfonamide was 1.5525 Å (**Figure 3**). Based on the RMSD value, the docking protocol was valid because the value was less than 2 Å.

Curcuma longa and Curcuma xanthorrhiza

The docking score between curcumin, demethoxycurcumin, and bisdemethoxycurcumin with both PL^{pro} and $3CL^{pro}$ was shown in **Figure 4**. The interaction shows that curcumin had the best potency as a PL^{pro} inhibitor because the docking score (-103.609) was almost the same as remdesivir triphosphate (-103.827). Another *in silico* research using AutoDock Vina claimed curcumin acted best as PL^{pro} inhibitor among four other targets like angiotensin-converting enzyme 2 (ACE2),

transmembrane serine protease 2 (TMPRSS2), RNA-dependent RNA polymerase (RdRp), and 3CL^{pro}, with the free binding energy (ΔG) of -8.45 kcal/mol, which was less than those ACE2 (-7.99 kcal/mol), TMPRSS2 (-7.19 kcal/mol), RdRp (-5.3 kcal/mol), and 3CL^{pro} (-7.24 kcal/mol)[23].



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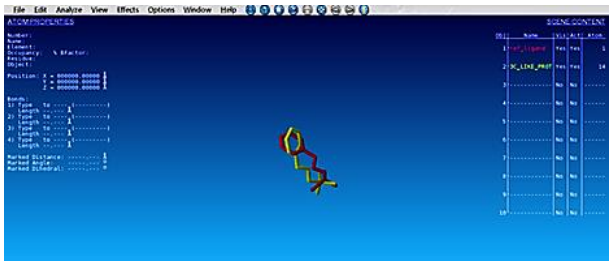


B

Figure 3. RMSD value of (**A**) PL^{pro} (0.5707 Å) and (**B**) 3CL^{pro} (1.5525 Å).

Interaction with 3CL^{pro} shows demethoxycurcumin was the most potent inhibitor of 3CL^{pro}. The docking score of demethoxycurcumin (-87.1625) was less than remdesivir triphosphates (-86.1811). Sharma *et al.*[24] reported that demethoxycurcumin was one of the best inhibitors of 3CL^{pro} with ΔG of -7.02 kcal/mol. This result was based on *in silico* study using AutoDock 4 to assess some medicinal plants metabolites as 3CL^{pro} inhibitor.

Curcuminoids in both plants have been shown to have antiviral activity, in which curcumin shows antiviral activity in HIV as a protease inhibitor in HIV-1 and HIV-2 based on *in vitro* and *in vivo* studies[25]. Other studies suggest that curcumin shows the activity as a SARS-CoV-2 3CL^{pro} and spike protein inhibitor based on molecular docking study[10,11]. Curcumin also reported inhibiting 3CL^{pro} in SARS-CoV with an IC_{50} of 3.3 to 10 μM[26].

Psidium guajava

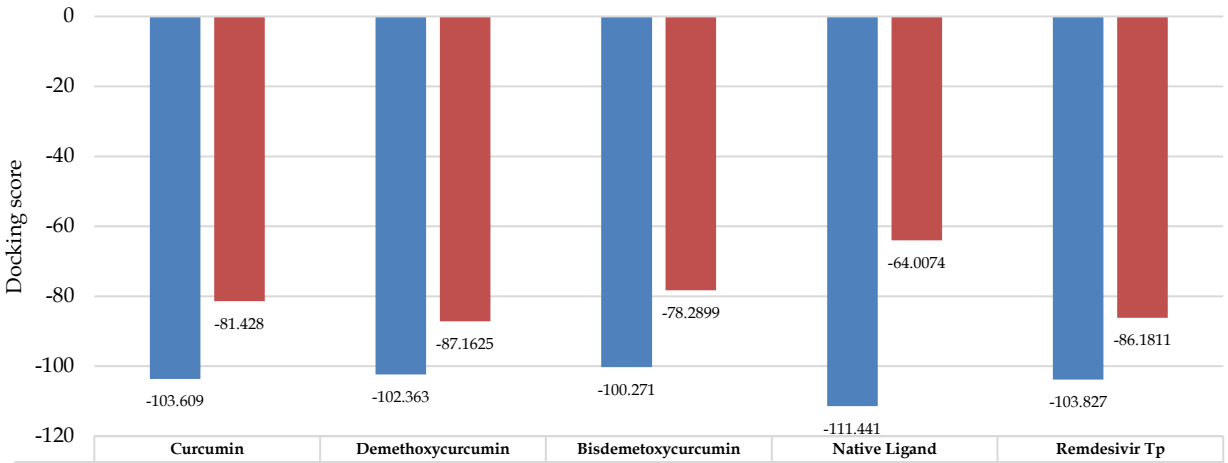
The docking score between luteolin, apigenin, quercetin, and kaempferol with both PL^{pro} and 3CL^{pro} was shown in **Figure 5**. It turns out that the ligands were not potent enough as a PL^{pro} inhibitor. However, among the four ligands, quercetin had the lowest docking score of -80.286. Interaction with 3CL^{pro} shows that luteolin (-73.4345), apigenin (-70.3368), quercetin (-71.5539), and kaempferol (-68.4321) had potency as 3CL^{pro} inhibitor, although the docking score was still higher than remdesivir triphosphate (-86.1811). Previous *in silico* research has shown that based on the free binding energy data, apigenin, luteolin, and quercetin had more potential as 3CL^{pro} inhibitors (-7.4; -7.12; and -6.83 kcal/mol, respectively) than as PL^{pro} inhibitor (-6.6; -6.9; and -6.6 kcal/mol)[23].

Phyllanthus niruri

The docking score of formononetin-7-O-glucuronide with PL^{pro} and 3CL^{pro} was presented in **Figure 6**. The docking score data shows that formononetin-7-O-glucuronide might not have potency as a PL^{pro} inhibitor but had potency as an inhibitor of 3CL^{pro} because the docking score (-72.0154) was less than native ligand (-64.0074) but higher than remdesivir triphosphate (-86.1811). Docking between formononetin-7-O-glucuronide and the receptor for SARS-CoV-2 has not been previously reported, whereas another similar study using a metabolite of *P. niruri* chose nirurin as the test ligand[27].

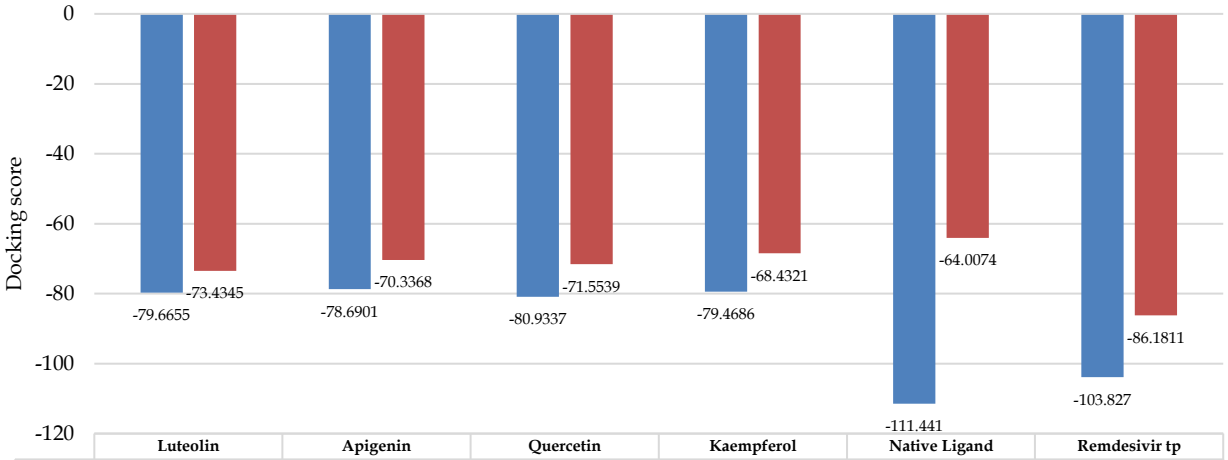
Andrographis paniculata

Andrographis paniculata was an Indonesian plant with the main metabolite in lactone terpenoids such as andrographolide and neoandrographolide[28]. The docking score of andrographolide and neoandrographolide with PL^{pro} and 3CL^{pro} was shown in **Figure 7**. Based on the results, both andrographolide (-79.1989) and neoandrographolide (-97.2452) had no potency as PL^{pro} inhibitors. On the contrary, the interaction between neoandrographolide with 3CL^{pro} shows the docking score (-93.7746) less than remdesivir triphosphate (-86.1811) and could act as the most potent ligand for 3CL^{pro} inhibitor. Murugan *et al.*[14] reported that in the *in silico* research using AutoDock Vina, neoandrographolide had ΔG as 3CL^{pro} (-31.4 kcal/mol), PL^{pro} (-28.5 kcal/mol), RdRp (-17.1 kcal/mol), and spike protein (-23.9 kcal/mol) inhibitors, in which they were best for 3CL^{pro} inhibitor. In addition, andrographolide was the main antiviral compound that was often found in *A. paniculata*[29]. This compound could inhibit the dengue virus in HeLa (EC_{50} 22.739 μM) and HepG2 (EC_{50} 21.304 μM) cells[30].



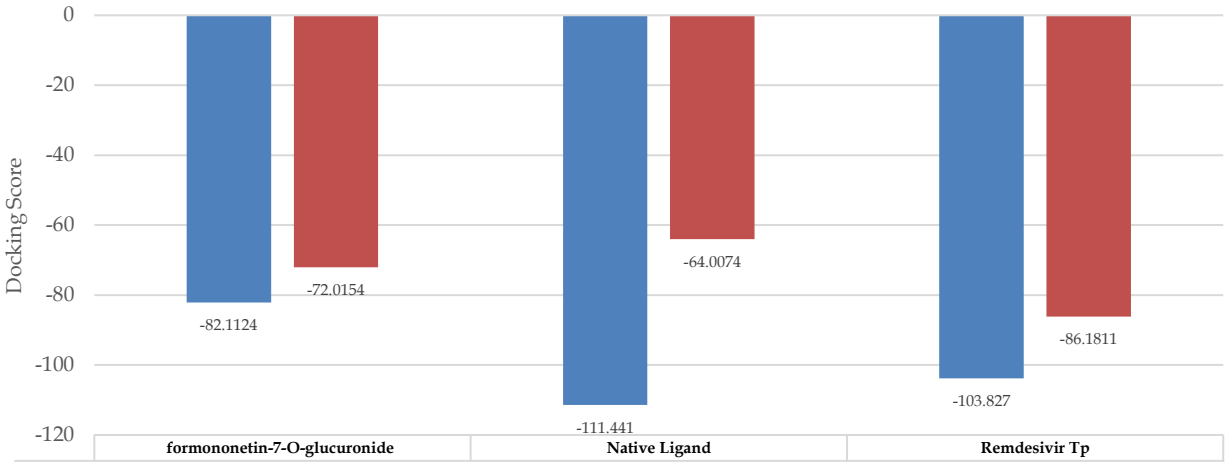
	Curcumin	Demethoxycurcumin	Bisdemetoxycurcumin	Native Ligand	Remdesivir Tp
Plpro	-103.609	-102.363	-100.271	-111.441	-103.827
3CLpro	-81.428	-87.1625	-78.2899	-64.0074	-86.1811

Figure 4. Docking score of curcumin, demethoxycurcumin, and bisdemethoxycurcumin.



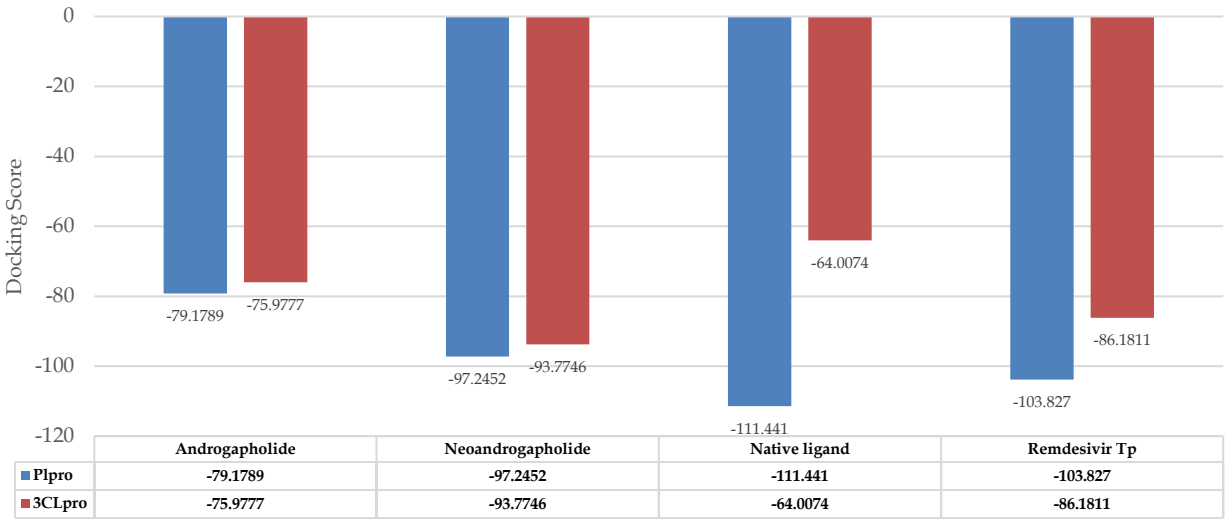
	Luteolin	Apigenin	Quercetin	Kaempferol	Native Ligand	Remdesivir tp
Plpro	-79.6655	-78.6901	-80.9337	-79.4686	-111.441	-103.827
3CLpro	-73.4345	-70.3368	-71.5539	-68.4321	-64.0074	-86.1811

Figure 5. Docking score of luteolin, apigenin, quercetin and kaempferol.



	formononetin-7-O-glucuronide	Native Ligand	Remdesivir Tp
Plpro	-82.1124	-111.441	-103.827
3CLpro	-72.0154	-64.0074	-86.1811

Figure 6. Docking score of formononetin-7-O-glucuronide.



	Andrographolide	Neoandrogapholide	Native ligand	Remdesivir Tp
Plpro	-79.1789	-97.2452	-111.441	-103.827
3CLpro	-75.9777	-93.7746	-64.0074	-86.1811

Figure 7. Docking score of andrographolide and neoandrographolide.

Based on the docking score of test ligands with PL^{pro}, curcumin was the most potent inhibitor of PL^{pro} with the lowest docking score of -103.609, while apigenin was the ligand with the highest docking score, as shown in **Table I**. This result indicates that curcumin had a good affinity when the interaction occurred between the ligand and PL^{pro}. Based on the docking score, neoandrographolide was the ligand with the lowest docking score of -93.7746, while kaempferol was the highest with -68.4321. The docking score of neoandrographolide indicated a good affinity with 3CL^{pro} and potency to acted as the most potent ligand to inhibit 3CL^{pro}. Curcumin and neoandrographolide were stated as the most potent candidate for PL^{pro} and 3CL^{pro} inhibitors, respectively.

Table I. Docking score of test ligands with PL^{pro} and 3CL^{pro}

Ligands	Docking score	
	PL^{pro}	3CL^{pro}
Native ligand	-111.441	-64.0074
Remdesivir triphosphate	-103.827	-86.1811
Apigenin	-78.6901	-70.3368
Andrographolide	-79.1789	-75.9777
Kaempferol	-79.4686	-68.4321
Luteolin	-79.6655	-73.4345
Quercetin	-80.9337	-71.5539
Formononetin-7-O-glucuronide	-82.1124	-72.0154
Neoandrographolide	-97.2452	-93.7746
Bisdemethoxycurcumin	-100.271	-78.2899
Demethoxycurcumin	-102.363	-87.1625
Curcumin	-103.609	-81.428

The prediction from this research could be used to develop an anti-COVID-19 drug from herbal compounds such as combination with extract or isolate that contains curcumin and neoandrographolide as the main compounds. Moreover, combining these two compounds could enhance the inhibitor effect in PL^{pro} or 3CL^{pro} of SARS-CoV-2. However, further *in vitro* and *in vivo* research was required to confirm this finding.

CONCLUSION

Based on the docking score, it can be concluded that curcumin has the most potential as a PL^{pro} inhibitor, while neoandrogapholide has the most potential as a 3CL^{pro} inhibitor.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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None.

DATA AVAILABILITY

All data are available from the authors.

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None.

AUTHORS' CONTRIBUTIONS

Baiq Ressa Puspita Rizma: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, software, supervision, validation, visualization, writing – original draft, writing – review & editing. **Agus Dwi Ananto**:

software, supervision, writing – original draft, writing – review & editing. **Anggit Listyacahyani Sunarwidhi**: supervision, writing – original draft, writing – review & editing.

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