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RESEARCH PAPER

Molecular Study of Antiviral Compound of Indonesian Herbal Medicine as 3CLpro and PLpro Inhibitor in SARS-COV-2

Baiq Ressa Puspita Rizma,[a] Yek Zen Mubarok,[b] Dian Fathita Dwi Lestari,[c] Agus Dwi Ananto*[d]

[a] Pharmacy Departement
Faculty of Medicine, Mataram University, Indonesia
Jl. Majapahit No. 62 Mataram Nusa Tenggara Barat, 83125, Indonesia
E-mail: baiqressapuspitarizma@gmail.com
[b] Pharmacy Departement
Faculty of Medicine, Mataram University, Indonesia
Jl. Majapahit No. 62 Mataram Nusa Tenggara Barat, 83125, Indonesia
E-mail: zenmubarok@gmail.com
[c] Pharmacy Departement
Faculty of Medicine, Mataram University, Indonesia
Jl. Majapahit No. 62 Mataram Nusa Tenggara Barat, 83125, Indonesia
E-mail: dianfathitadwilestari@gmail.com
[d] Lecturer of Chemistry Education
Faculty of Medicine, Mataram University, Indonesia
Jl. Majapahit No. 62 Mataram Nusa Tenggara Barat, 83125, Indonesia
E-mail: agus_da@unram.ac.id

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Abstract: Rapid transmission of COVID-19 disease and the fatal effects of the disease lead researchers to use various way to find potential anti-COVID-19 compounds, including using modern approaches. Molecular docking is one of the methods that can be used to analyse antiviral compounds and its molecular target from Indonesian herbs that are believed to have properties as anti-COVID-19. This study aims to analyse antiviral compounds from 5 herbs that have the potential as inhibitors of PLpro and 3CLpro, which both are a non-structural protein in SARS-CoV-2 by molecular docking approach using PLANTS. Remdesivir triphosphate, the active metabolite of remdesivir, was used as the comparison compound in studies. The results showed docking scores obtained from interactions between natural ligands, remdesivir trifospat, curcumin, demetoksikurkumin, bisdemetoksikurkumin, luteolin, apigenin, kuersetin, kaempferol, formononrtin-7-O-glucoronide, androgafolide, and neoandrogafolide with PLpro are as follows -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.Combination between quercetin, neoandrographolide, bisdemethoxycurcumin, demetoxycurcumin, and curcumin showed a synergy effect by reduce its docking score. Meanwhile its interaction with the protein 3CLpro showed docking score for those compounds as follows 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.Combination between andrographolide, neoandrographolide, bisdemethoxycurcumin, demetoxycurcumin and curcumin, also shows synegy effect in 3CLpro allow them to reduce the docking score.This study concludes that curcumin was known as the most potent compound that act as a PLpro inhibitor based on a docking score of -103,609, while in 3CLpro all the compound have a potential to inhibit 3CLpro with demethosxycurcumin and neoandrogafolide as the most potent compound with a docking score -87,126 and -93.7746.

Keywords: Indonesian herbs, antiviral compounds, anti-COVID-19, molecular docking, Plants

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INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is a respiratory system disease caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). The disease affected the entire world include Indonesia. WHO declared COVID-19 to become a worldwide pandemic in March 2020 [1]. The COVID-19 spreads through droplets, saliva, or release from the nose of an infected individual after sneezing or coughing [2]. According to WHO, from January 2020 to July 2021, there have been 2.950.058 confirmed cases of COVID-19 in Indonesia [3]. The high number of confirmed cases encourages the government to continue suppressing the spread of COVID-19 in Indonesia. Some of the efforts that have been done by the government are the implementation of lockdown, tightening health protocols, etc.

Individuals that confirmed mild symptoms suggested having self-isolation at home. A self-isolation and tracing contact is some effort has been done to reduce the transmission of COVID-19. There are no specific drugs to treat or prevent COVID-19. In their current treatment, medical professionals use a broad-spectrum antiviral named Remdesivir as a treatment for COVID-19. Remdesivir known as GS-5734 is a prodrug of an adenosine analog expanded to respond to the Ebola outbreak in West Africa [4]. There are two non-structural proteins SARS-CoV-2, such as papain-like protease (PLpro) as a virulence factor of SARS-CoV-2, and 3C-like protease (3CLpro) are believed used for replicating new viruses [5]. SARS-CoV-2 replications according to viral RNA-dependent RNA polymerase RdRp is the most credible target of the investigational nucleotide analog Remdesivir (RDV) [6,7].

Indonesian Food and Drug Administration (BPOM) mentioned that several Indonesian medicinal plants contained an antiviral activity compound that can be used to treat infections of COVID-19. The mentioned plants are sambiloto (*Andrographis paniculata*), turmeric (*Curcuma longa),* guava (*Psidium guajava*), Curcuma (*Curcuma xanthorrhiza*), and meniran (*Phyllanthus niruri*) [8]. There are some researches have been done to prove the plants have antiviral activity compounds. These compounds actively inhibit two non-structural proteins in SARS-CoV-2. Based on a scientific study, quercetin in guava can inhibit papain-like protease (PLpro) in SARS-CoV-2 [9], curcumin in *Curcuma longa* can inhibit the 3C-like protease (3CLpro) of SARS-CoV-2 [10].

The plants as mentioned before can be an alternative drug for COVID-19. Based on the context of the researchers aimed to approve the potency of several Indonesian medicinal plants to inhibit PLpro and 3CLpro, two main non-structural proteins of SARS-CoV-2 using a molecular docking method. Molecular docking is routinely used for understanding drug-receptor interaction. Molecular docking gives helpful information about drug-receptor interactions and is often used to predict the binding direction of the ligands of drug candidates to their protein targets to predict the affinity and activity of the ligands [11]. Molecular docking has more advantages in this pandemic era, it is more efficient to use. Molecular docking can be done online so it will lessen the physical contact between the researchers. This study aims is to identify the potent compunds as inhibitor PLpro and 3CLpro.

MATERIALS AND METHODS

Software and Hardware

There are three software used in this research, such as marvinSketch 5.2.6 from ChemAxon, YASARA View 19.12.14 from YASARA Bioscience , and PLANT (Protein-Ligand Ant System) 64 bit from CHemAxon. The hardware used Asus notebook Intel® Core™ RAM 4.00 GB, Operation system Windows 10, 64-bit operating system.

Ligands

The two-dimension structure of each ligand in this research was downloaded from PubChem database and it was reformed into a three-dimension structure using MarvinSketch to get the best conformation. The ligands were divided into two types: standard ligand and test ligand. Remdesivir triphosphate (PubChem ID 56832906) as the standard ligand. The test ligands were andrographolide (5318517), curcumin (965516), kaemferol (5280863), bisdemethoxycurcumin (5469424), neoandrographolide (9848024), quercetin (5280343), and formononetin-7-glucuronide (71316927).

Receptors

The receptors used in this research were two non-structural proteins of SARS-CoV-2, 3CLpro (PDB ID 5R7Y)19 and PLpro (3E9S) It was downloaded from Protein Data Bank [12].

Docking protocol

There are three steps docking protocol used in this research, first preparation of target protein and native ligand, second docking protocol validation, and third test ligand docking.

Preparation of native ligand and target protein

Preparation of native ligand and target protein using YASARA view. This step aims to delete the native ligand of each protein.

Docking protocol validation

Docking protocol validation aims to get an RMSD (Root Median Square Deviation) value using YASARA view by re-docking the native ligand to its protein. Docking protocol validation is accurate if the RMSD value is less than 2 amstrong [13].

Test ligand docking
Test ligand docking was done by typing the commands in cmd.exe using PLANTS. The active site of PLpro and 3CLpro was docked to the test ligand. PLANTS will read the command to get the best docking score. The best docking score would be contrasted to the best score of the naïve ligand.

Docking protocol combination
The docking protocol combination aims to find the synergic relation between the compounds to obtain sufficient stability to bind to each target protein. Docking protocol combination was done by arranged the compounds according to the average docking score. The compounds with the highest docking score and the target protein are saved in a file named protein.mol2 and would be docked to the compounds with a lower docking score.

RESULTS AND DISCUSSION

Validation of Docking Protocol
The validation protocol is a step to ensure the docking protocol used has been validated so it can be used for the next docking process. RMSD (Root Mean Square Deviation) is one of validation parameter that obtained from redocking the native ligand with the protein. A docking protocol was stated as a valid protocol if the RMSD value <2Å [14]. Redocking of *5-amino-2-methyl-N-[(1R)-1-naphthalen-1-ylethyl] benzamide* – the native ligand of PLpro- to protein PLpro shown the RMSD value was 0,5707 Å. Whereas, *5-amino-2-methyl-N-[(1R)-1-naphthalen-1-ylethyl] benzamide* - the native ligand of 3CLpro – to protein 3CLpro shown the RMSD value was 1.5525 Å.

Docking in Plpro
Among 10 test ligands, the docking score of curcumin (-103,609) is almost equal to remdesivir triphosphate (-103,827) (Shown in **Table 1**). This result indicates that curcumin forms a stable interaction and a good affinity as well as remdesivir triphosphate in PLpro. Based on this result we can conclude that, curcumin has a potential as an inhibitor of PLpro.

Curucmin usually found Curucma longa L. and Curcuma xanthorrhiza Roxb. This two plants has a large mount of curcuminoid which are curcumin, demethoxycurcumin dan bisdemethoxycurucumin (Shown in **Figure 1**).

Curcumin, demethoxycurcumin and bisdhemetoksicurucumin has differences in the presence of methoxy group in both aromatic rings of the compounds. Curcumin has pharmacophores that responsible for its biological activities such as hydroxyl groups (OH) and methoxy groups (OCH3) in both of its aromatic rings. While demethoxycurucummin lost one of the methoxy group and bisdemethoxycurucumin lost both methoxy groups.

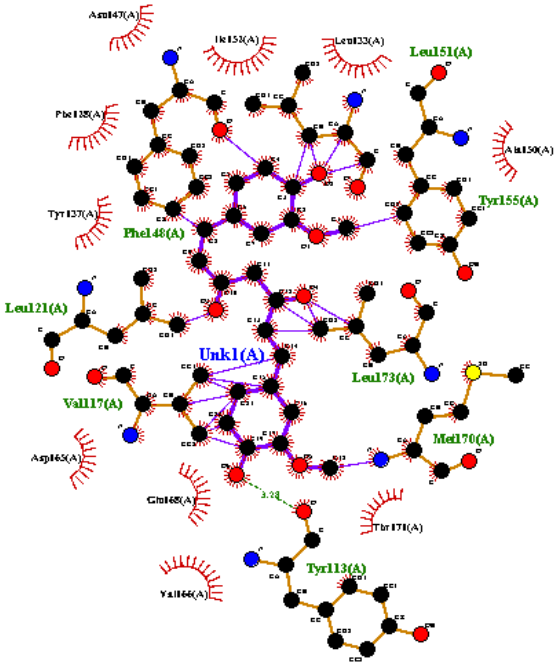
The existence of methoxy group is predicted to have an important role in helping to stabilize the affinity and chemical bond between the compounds on PLpro. The methoxy group in curcumin form an interaction with amino acids such as Met170 and Tyr155. While demethoxycurcumin which has one methoxy group only form an interaction with Met170. In other hand, bisdemethoxycurcumin that does not have any methoxy group cannot form an interaction or form a chemical bond to both of Met170 or Tyr155. Thus, the loss of methoxy group in demethoxycurucumin and bisdemethoxycurcumin lead to decrease in chemical bond stability and affinity of the compound to the target protein, resulting in a greater docking score compare to curucumin (Shown in **Figure 1**).

Table 1. Docking Score of Test Ligand to PLpro

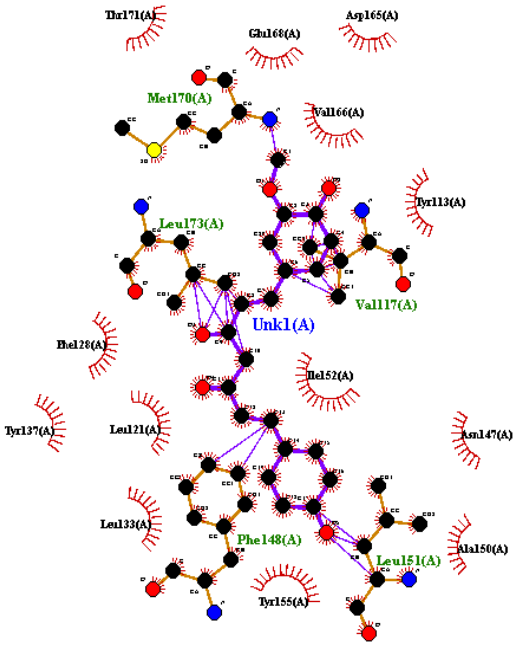
Compounds	Docking Score with PLpro	Remdesivir Tp (-103.827)
Curcumin	-103.609	=
Demethoxycurcumin	-102.363	>
Bisdhemetoxycurcumin	-100.271	>
Luteolin	-79.6655	>
Apigenin	-78.6901	>
Quercetin	-80.9337	>
Kaempferol	-79.4686	>
Formononetin 7-O-Glucoronida	-82.1124	>
Androgapholide	-79.1789	>
Neoandrogapholide	-97.2452	>
Symbol Explanation : Smaller than (<), Bigger than (>), Equal as (=)		

Previous in silico research with AutoDock Tools1.5.6 also shown that curcumin have the smallest free binding energy (kcal/mol) with PLpro (-8,45) compared to other target such as ACE2 (-7,99), TMPRSS2 (-7,19), RdRp(-5,3), and 3CLpro (-7,24) [15].

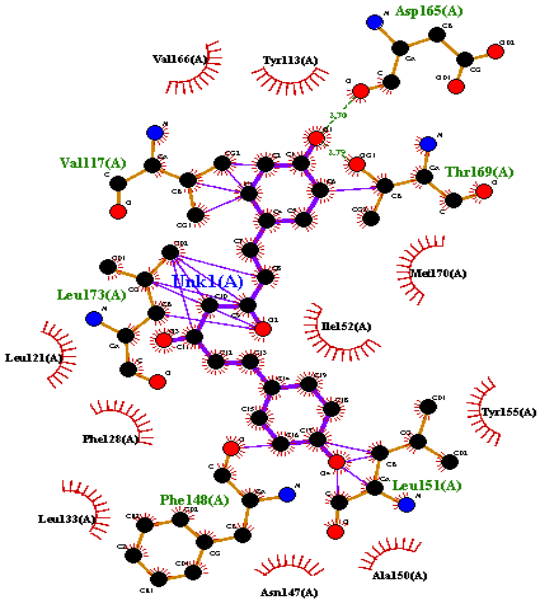
Based on docking score there are 5 compounds with the smallest docking score, the compouds are Quercetin (Q), Neoandrographolide (N), Bisdemethoxycurcumin (B), Demetoxycurcumin (D) and Curcumin (C). We try to combine these compounds to identify is there any difference when between a single compound and the combination as PLpro inhibitor based on its docking score.



Kurkumin_3e9s



Demetoksikurkumin_3e9s



bisdemetoksikurkumin_3e9s

Figure 1. Visualisation of Curcumin, Demethoxycurcumin, and Bismedethoxycurcumin in interaction with PLpro using LigPlot.

Among 22 combination variation there are 12 combination that has a smaller docking score compare to curcumin (-103.609) and remdesivir triphosphate (-103,807). From this results we can conclude that there are synergic effect between the compounds to increase the stability of chemical bond and increase their affinity to PLpro in results of decreasing in docking score (Shown in **Table 2)**

Table 2. Docking Score of Combination in PLpro

	Compunds	Docking Score
Combination	QNBDK	-105.93
	QDK	-105.887
	QNDK	-105.871
	BK	-105.781
	QBDK	-105.754
	QBK	-105.738
	NK	-105.728
	NBDK	-105.713
	QNBK	-105.645
	DK	-105.567
	BDK	-105.436
	QK	-104.518
	QNK	-104.318
	BDK	-103.856
Single	Curcumin	-103.609
	Demethoxycurcumin	-102.363
	Bisdemethoxycurcumin	-100.271
	Neoandrogapholide	-97.2452
	Kuersetin	-80.9337

Docking in 3CLpro

The docking score that was obtain between the 10 test ligands with 3CLpro shown that demethoxycurcumin (-87,1625) and neoandrograplide (-93,7746) are two compounds that has potency as 3CLpro inhibitor because their docking score was smaller than remdesivir thriphosphate (-86,1811) (Shown in **Table 3)**. This docking score indicates that both test ligand form a stable chemical bond and good affinity with the target protein [16].

Even though demethoxycurcumin only have one methoxy group when the curucmin have two methoxy groups, but the docking score of demethoxycurcumin are smaller than curcumin. It can be explained by looking at the hydrophobic contact that form in two compunds. Demethoxycurcumin form 16 hydrophobic contact with amino acids residue in 3Clpro.

Table 3. Docking Score of Test Ligand to 3CLpro

Compounds	Docking score with 3CLpro	Remdesivir Tp (-86,1811)
Curcumin	-81,428	>
Demethoxycurcumin	**-871,625**	<
Bisdemethoxycurcumin	-782,899	>
Luteolin	-734,345	>
Apigenin	-703,368	>
Quercetin	-715,539	>
Kaempferol	-684,321	>
Formononetin 7-O-Glukoronida	-720,154	>
Andrographolide	-759,777	>
Neoandrogapholide	**-937,746**	<
Symbol Explanation : Smaller than (<), Bigger than (>), Equal as (=)		

Meanwhile curucmin only form 11 hydrophpbic contact with amino acids residue in 3Clpro (Shown in **Figure 2)**. The hydrophobic contact help the non polar site of demethoxycurcumin to bound with non polar site of 3CLpro in an watery environment, the movement of the water when the two non polar site try to bound reduce its energy as the result of decreasing its docking score [17].

This research are supported by research conducted by khaerunnisa (2020), showing that based on in silico research with AutoDock Vina, demethoxycurcumin have a smaller free energy binding (-7,99kcal/mol) than curcumin (-7,05 kcal/mol) as 3CLpro inhibitor [18].

The interaction of neoandrogafolide with 3CLpro showed results in contrast to their interactions with PLpro.Neoandrogafolide (-93.7746), categorized as a compound with good bond stability and affinity at 3CLpro because it has a docking score that smaller than the natural ligands (-64.0074) and remdesivir trifospat (-86.1811).The interaction of androgafolide compounds (-75.9777) with the protein 3CLpro showed the compound had no better bond stability and affinity than neoandrografolide, despite having a lower docking score compared to natural ligands (-64.0074), but still larger than remdesivir trifospat (-86.1811).

Andrografolide and Neoandrografolide differ from each other in terms of the addition of glucose groups in neoandrografolide, hydroxyl groups in glucose structure are thought to play an important role in compound activities. Existing glucose groups help neonadrografolide bind to amino acids such as Val114, Phe113,Ser113,Phe150, Leu115, Gly14, and Val148 which in andrografolide are not found . Although similarities with natural ligands and remdesivir trifospat are still quite far away, but in terms of docking scores,

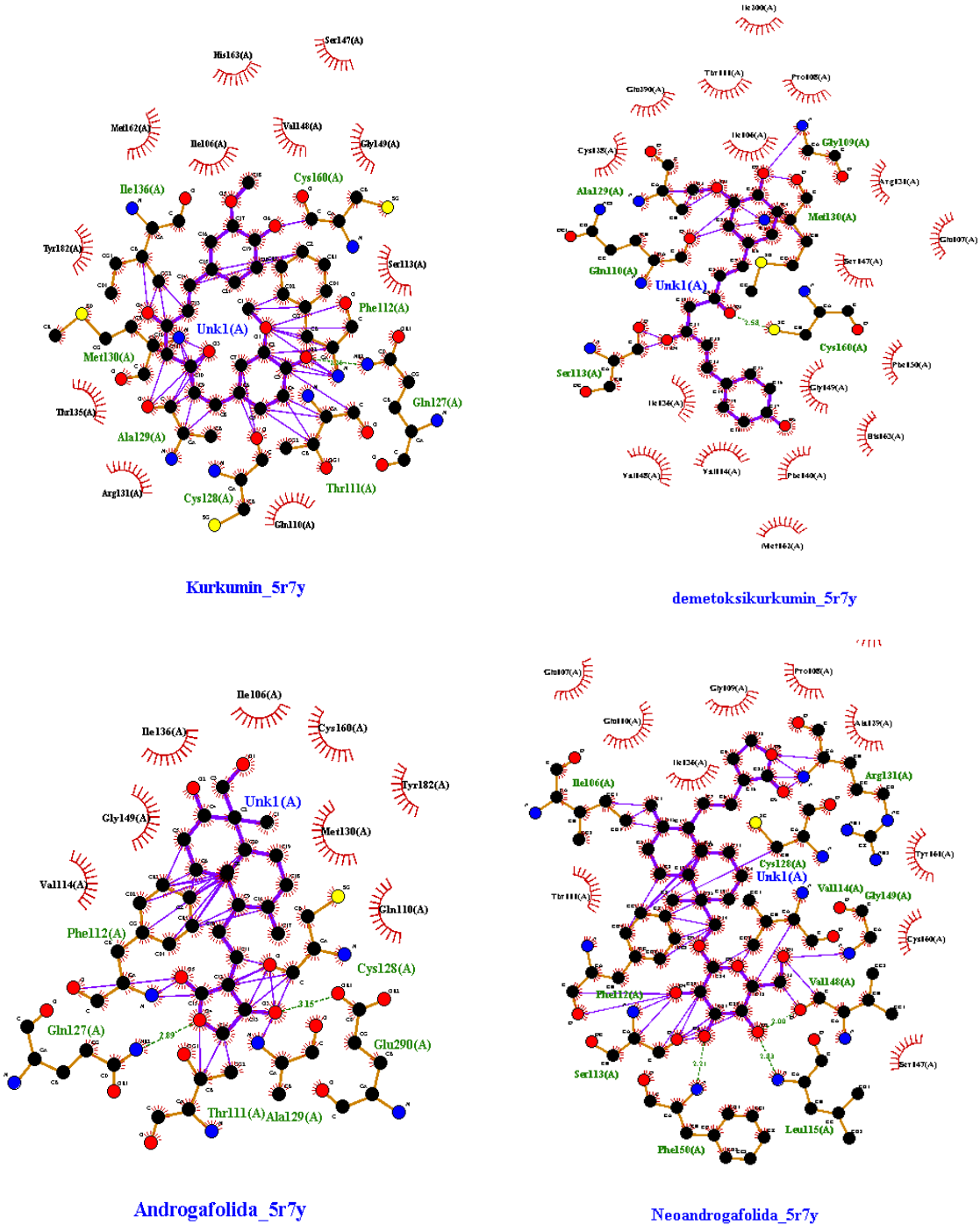


Figure 1. Visualisation of Curcumin, Demethoxycurcumin, Andrografolide and Neoandrografolide in interaction with 3CLpro using LigPlot

neoandrografolide has good bonding stability and affinity on 3Clpro (Shown in **Figure 2).**

This results was supported by previous in silico research using AutoDock that shown among 4 andographis paniculata main compounds such as andrographolide (AGP1), 14-deoxy 11,12-didehydro andrographolide (AGP2), neoandrographolide (AGP3) and 14-deoxy andrographolide (AGP4). AGP3 has the smallest free binding energy (kcal/mol) in interaction with 3CLpro (-31,4) compare to other target such as PLpro (-28,5), RdRp (-17,1) and Spike (-23,9) [19].

Table 4. Docking Score of Combination in 3CLpro

	Compunds	Docking Score
Combination	KDN	-93.7718
	ABDN	-93.771
	DN	-93.7631
	AND	-93.7566
	AKDN	-93.7564
	BKDN	-93.7503
	KN	-93.746
	AKN	-93.7303
	BN	-93.728
	BDN	-93.7276
	AN	-93.7272
	BKN	-93.7221
	ABN	-93.7212
	ABKDN	-93.6937
	ABKN	-93.6872
Single	Neoandrogapholide	-93.7746
	Demetoksikurkumin	-87.1625
	Curcumin	-81.428
	Bisdemetoksikurkumin	-78.2899
	Androgapholide	-75.9777

Based on the docking score of 10 test ligand with 3CLpro there are 5 compunds with the smallest docking score, the compounds are andrographolide (A), Bisdemethoxycurcumin (B), curcumin (C), demethoxycurcumin (D), and Neoandrographolide (N).

Among 22 variation of combination, there are 15 combinations that have a smaller docking score compare to remdesivir triphosphate, but when compare to neoandrographolide there is no significan difference in the docking score. So we can conclude that the synergy effect between these compunds have no big impact to increase its inhibitory effect in 3CLpro.

This research results is just a prediction with computer simulation help, it still need a further research such as in vitro and in vivo to validate this results. This research also have some limitation such as, this research didn't perform quantitative structure-activity relationship so we can't identify steric, hydrophobic and electrolic factor of the compound and we can't predict the pharmacochinetic properties of the compounds like molecular dynamic method. This research also only use one molecular docking application to perform the docking process, docking with different application may lead to different results to because of the different algorithm used.

CONCLUSION

In conclusion, curcumin is an antiviral compounds which is has a potency as PLpro inhibitor. Meanwhile, combination that are show a potency as PLpro inhibitor are QNBDK, QDK, QNDK, BK, QBDK, QBK, NK, NBDK, QNBK, DK, NBK, QK, QNK, and BDK. Demethoxycurcumin and neoandrografolide are an antiviral compounds which are has the potency as 3CLpro inhibitor. Meanwhile, combination that are show a potency as 3CLpro inhibitor are AN, BN, KN, DN, AKN, ADN, BKN, BDN, KDN, ABKN, ABDN, AKDN, BKDN and ABKDN.

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