he coronavirus disease 2019 main protease inhibitor from Andrographis paniculata (Burm.f) Ness

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ORIGINAL ARTICLE

The coronavirus disease 2019 main protease inhibitor from *Andrographis paniculata* (Burm.f) Ness

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has attracted worldwide attention. *Andrographis paniculata* (Burm. f) Ness (AP) is naturally used to treat various diseases, including infectious diseases. Its Andrographolide has been clinically observed for anti-HIV and has also *in silico* tested for COVID-19 main protease inhibitors. Meanwhile, the AP phytochemicals content also provides insight into the molecular structures diversity for the bioactive discovery. This study aims to find COVID-19 main protease inhibitor from AP by the molecular docking method and determine the toxicity profile of the compounds. The results obtained two compounds consisting of flavonoid glycosides 5,4'-dihydroxy-7-*O*-*β*-*D*-pyran-glycuronate butyl ester and andrographolide glycoside 3-*O*-*β*-*D*-glucopyranosyl-andrographolide have lower free binding energy and highest similarity in types of interaction with amino acid residues compared to its co-crystal ligands (6LU7) and Indinavir or Remdesivir. The toxicity prediction of the compounds also reveals their safety. These results confirm the probability of using AP phytochemical compounds as COVID-19 main protease inhibitors, although further research must be carried out.

Key words: 6 LU7, *Andrographis paniculata*, coronavirus disease 2019, main protease inhibitor, molecular docking

INTRODUCTION

The coronavirus (CoV) has attracted attention, especially since its virulence features changed to human infection. Overall, six CoV varieties four of them induce common colds symptoms, while two varieties of SARS and middle-east respiratory syndrome produce more severe to deadly infections.[1] The SARS-CoV-2 caused severe acute respiratory diseases (coronavirus disease 2019 [COVID-19]); which is responsible for the global pandemic and caused 5.67% deaths in confirmed cases. To date, the exponential rates in confirmed cases were observed, in addition, the occurrence of second wave erase.[2]

The development of COVID-19 therapies, show promising results, but is still far from convincing. Vaccine development began, and some claimed have good results.[3] Furthermore, repurposing drugs such as Remdesivir (REM) or Chloroquine is considered to have a good influence on the COVID-19 patients' recovery.[4] Moreover, the researchers also looked at the medicinal plant metabolites. Natural products provide extraordinary in structure and complexity for drug discovery by

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providing a drift for synthetic or semi-synthetic antiviral compounds. As summarized some phytochemicals worked on the virulence proteins key. In particular, *in silico* study of several promising Chinese and Indian medicinal plants for COVID-19 treatment were reported.[5,6] These studies showed that plant metabolites are promising in the discovery of COVID-19 compounds.

Among receptor targets, previous research has developed therapies for COVID-19, the 3C-like protease/3CL^{pro} (SARS-CoV-2 M^{pro}).[7] is an interesting and quite developed one for the COVID-19 therapeutic target. Not only for drug repurposing but it is also a potential point for tracing inhibitors derived from phytochemicals. Screening of medicinal plants library[8] showed potential phytochemical compounds such as Isoflavone and Myricitrin compared to antiviral nelfinavir.

Among the various phytochemicals that have been studied, *Andrographis paniculata* (AP) is one very interesting to be further investigated is. It is commonly used in several countries for common cold treatment and many more diseases[9-11] This Acanthaceae family plant has been reported as SARS-CoV-2 M^{pro} inhibitors.[6] A separate study[1,12] explained that AP suppressed the increase in NOD-like receptor protein 3, caspase-1, and interleukin-1β, which are extensively involved in the pathogenesis of SARS-CoV and possibly SARS-CoV-2 as well. Enmozhi *et al*.[13] even specifically examined the Andrographolide, as SARS-CoV-2 M^{pro} inhibitor with molecular docking method. However, the study only tested andrographolide without considering other contents, and the docking protocol is also not fully listed, making it difficult to reproduce the results.

Moreover, the AP consists of diterpene lactone and flavonoids as well as their aglycone or glycoside derivatives form. Some were including andrographanin, neoandrographolide, 14-deoxyandrographolide, 3-*O*-*β*-*D*-glucopyranosyl-14, 19-dideoxyandrographolide, 5,4-dihydroxy-7-*O*-*β*-*D*-pyran -glycuronate-butyl-ester,[14] apigenin, 7-*O*-methylwogonin, and onysilin.[9,11] These compounds have become an object for synthetic or semisynthetic modification for various diseases that have experienced resistance, for example, as anti-HIV drugs.[15]

From the background and previous research, this study aims to reveal the potency of AP phytoconstituents as SARS-CoV-2 M^{pro} inhibitors. The method used is molecular docking and *in silico* toxicity to compare safety profiles of AP phytoconstituents. The results of this study are expected not only to contribute to the development of new drugs or potential derivatives from AP phytoconstituents but also to provide a scientific basis for the traditional use of AP in COVID-19 therapy.

MATERIALS AND METHODS

Preparation of ligands and receptor

The 45 AP's secondary metabolites ligands are listed in Table 1 base on reference information.[9,11,15,16] The ligands were prepared with hardware, and software as describe Hatama and Gusdinar.[17] The programs were included HyperChem 7.5., OpenBabel 2.4.1 and AutoDockTools 1.5.6.[18] The molecular information in the SMILES format is used in the prediction of toxicity properties.

The structure of 3-chymotrypsin-like protease (3CL-protease, protein data bank [PDB] ID: 6LU7) COVID-19 retrieved from PDB (https://www.rcsb.org/)[19] in.pdb format.[20]

Validation of the docking process

The validation prior docking process was done by extracted the co-crystal ligands from its receptors, and re-docking as well as their point of binding on its protein active sites. The compound co-crystal ligand was prepared.[17] The RMSD redocking obtained with PyMOL 2.3.1.

Molecular docking

Autodock Vina 1.1.2 and Chimera 1.13.1 programs were used for the docking process, while Discovery Studio Visualizer 19.1.0 was used for interaction obtaining. The fixed parameters were the size and position of a grid box as resulted in the validation process.[11,21]

The toxicity prediction of the most potent substances

The toxicity study of the three most potential substances was processed.[22] The results obtained then compared and analyzed further.

RESULTS

The receptor 6LU7 contains a monomer protein (chain A)-N3 (CL) with a resolution of 2.16 Å, while the 6LU7-AP's complex ligands structure resulted in 1.9 Å, *r*-value free and work of 0.262 and 0.229, respectively. These values were good parameter for molecular docking experimental studies, which serves the overlapping/accuracy of the redocking atom's positions to its original ligand.

Table 1 is listed the energy binding (ΔG) of 45 AP's compounds and 7 reference ligands docking with the 6 LU7. The ΔG presents relative binding ligand-receptor affinities. The AP's ligands of 5,4-dihydroxy-7-*O*-*β*-D-pyra n-glycuronate-butyl-ester (DGE) and 3-*O*-*β*-D-glucopyran osyl-andrographolide (GAD) have the lowest ΔG compare to Indinavir and REM. These ligands and 7,8-dimethoxy-2 -hydroxy-5-*O*-*β*-D-glucopyranosyloxyflavone (DGF) have a better affinity compare to its original N3. Furthermore, the Hydroxychloroquine, Chloroquine, and Favipiravir were on the bottom list compare to AP's and others. The three of AP's most potent and two of reference ligands were

Table 1: Energy binding of *Andrographis paniculata*'s and reference ligands

Number	Ligand	ΔG (kcal/mol)	
		Average	SD
1	5,4'-Dihydroxy-7-*O*-*β*-*D*-pyran-glycuronate-butyl-ester	−8.37	0.06
2	3-*O*-*β*-*D*-glucopyranosyl-andrographolide	−8.30	0.00
R1	Indinavir	−8.23	0.12
R2	Remdesivir	−8.23	0.15
3	5,8-Dimethoxy-2'-hydroxy-5-*O*-*β*-*D*-glucopyranosyloxyflavone	−8.20	0.00
N3	N-[(5-methylisoxazol-3-yl)-carbonyl]-alanyl-l-valyl-n~1~-((1r, 2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3-yl]-methyl}-but-2-enyl)-l-leucinamide (CL)	−8.10	0.10
4	3,4-Dicaffeoylquinic acid	−7.90	0.17
5	3-*O*-*β*-*D*-glucopyranosyl-14,19-dideoxyandrographolide	−7.80	0.00
R3	Nelfinavir	−7.77	0.06
6	19-*O*-*β*-Apiofuranosyl-*β*-*D*-glucopyranoyl-3,14-dideoxyandrographolide	−7.73	0.12
7	Apigenin	−7.70	0.00
8	Bisandrographolide A	−7.67	0.06
9	3-O-*β*-*D*-glucosyl-14-deoxyandrographolide	−7.60	0.00
10	Neoandrographolide	−7.53	0.06
11	6-Acetylneoandrographolide	−7.53	0.06
12	Isoandrographolide	−7.50	0.00
13	Andrographiside	−7.43	0.06
14	5,4-Dihydroxy-7-methoxy-8-O-*β*-*D*-glucopyranosyloxyflavone	−7.40	0.10
15	Luteolin	−7.40	0.00
16	Andrographidine C	−7.33	0.06
17	1,2-Dihydroxy-6,8-dimethoxyxanthone	−7.30	0.00
18	5,4-Dihydroxy-7-*O*-*β*-*D*-glucopyranosyloxyflavone	−7.30	0.00
19	7,8,2,5-Tetramethoxy-5-*O*-*β*-*D*-glucopyranosyloxyflavone	−7.30	0.00
R4	Lopinavir	−7.27	0.06
20	7-*O*-methylwogonin	−7.20	0.00
21	Andrographidine A	−7.20	0.00
22	Echiodinin	−7.20	0.00
23	1,8-Dihydroxy-3-7-dimethoxyxanthone	−7.00	0.00
24	3-Oxo-14-deoxyandrographolide	−7.00	0.00
25	14-Deoxy-17-b-hydroxyandrographolide	−6.97	0.15
26	5-methyl-dihydrowogonin	−6.93	0.06
27	14-Deoxy-11,12-didehydroandrographolide	−6.90	0.00
28	14-deoxyandrographolide	−6.90	0.00
29	7-Hydroxy-14-deoxyandrographolide	−6.87	0.15
30	Skullcapavone-1,2-methoxylether	−6.83	0.06
31	5,7,8-Trimethoxydihydroflavone	−6.80	0.00
32	12-Hydroxyandrographolide	−6.80	0.00
33	Andrographolactone	−6.80	0.17
34	Andrographolide	−6.80	0.00
35	1,2-Dihydroxy-2-7-dimethoxyxanthone	−6.77	0.06
36	14-Deoxy-12-hydroxyandrographolide	−6.77	0.06
37	14-Deoxy-11-oxoandrographolide	−6.70	0.10
38	Andrograpanin	−6.70	0.00
39	3-Oxo-14-deoxy-11,12-didehydroandrographolide	−6.77	0.06
40	14-Deoxy-11-hydroxyandrographolide	−6.60	0.00
41	Onysilin	−6.60	0.00
42	8,17-Epoxy-14-deoxyandrographolide	−6.53	0.06
43	3,7,8-Trimethoxy-1-hydroxyxanthone	−6.50	0.00
44	15-Methoxy-3,19-dihydroxy-8,17,13-entlabda-trien-16,15-olide	−6.37	0.15

Contd...

Table 1: Contd...

Number	Ligand	ΔG (kcal/mol)	
		Average	SD
R5	Hydroxychloroquine	−6.27	0.06
45	8,17,13-Ent-λ-labdha-15,16,19-triol	−5.83	0.12
R6	Chloroquine	−5.73	0.06
R7	Favipiravir	−5.10	0.00

R: Reference, CL: Co-crystal ligands, SD: Standard deviation

proceeded for further examination. Figure 1a shows the redocking co-crystal ligand position that almost overlaps with the crystallographic ligand position, while Figure 1b-f presents their visualization, respectively. Figure 2 presents the three most active AP's chemical structures.

The toxicity parameter of DGE, GAD, DGF, two reference compounds INDI and REM were obtained with ProTox II describe in Figure 3.

DISCUSSION

The molecular docking of 45 AP's ligands and 7 reference synthetic drugs, which were consist of 4 anti-HIV Food and Drug Administration approved and 3 most suggested drugs were presented in this study to reveal their potency as COVID-19 main protease inhibitor. The use of reference synthetic drugs in this study was as internal validation process intended, so the results can be compared to others finding. The binding site to the 6LU7 M^{pro} receptor was performed using the X-ray crystal structure of CL as a co-crystal ligand, as can be seen in Figure 1a. This shows that the docking process is validated by producing ligand binding that approaches crystallographic ligands positions. The 6LU7 docking results in the RdRp binding pocket suggests that REM as the anti-HIV drug is *in vitro* highly effective in fighting COVID-19 infection. The REM was used for Ebola and Marburg virus outbreaks (proposed for COVID-19 clinical trials by the Gilead company).

The ΔG of the reference ligand is −8.10 ± 0.10 kcal/mol, with the RMSD value is 1.981 Å. Based on the data presented in Table 1, the two AP ligands (DGE, and GAD) have lower ΔG compare to anti-HIV Indinavir and REM. All of them and DGF, have lower ΔG than its original CL. Interestingly observed similarities among the active ligands, that all of them were glycoside form, while DGE and DGF were share flavone structure with the difference in glycosyl side chain [Figure 2]. The AP's flavone glycoside was reported[14] as HL-60 antiproliferative, while the Andrographolide was known as a broad-spectrum antiviral. Anti COVID-19 of Andrographolide was presented *in silico* study,[13,23] while this research counted its ΔG was −6.80 kcal/mol, which was on least order among the AP's compounds.

Research obtained ΔG phytochemicals to 6LU7 compare to Lopinavir; which were in range of-11.82 to 13.51 compare to −11.62 kcal/mol.[10] While in this research, the Lopinavir (−7.27 ± 0.06 kcal/mol) was listed on the 26th rank among AP's. It showed as good reference, by yielding in range ratio to DGE and Hesperidin (1.151 to 1.620) 1.151 to 1.62. The difference of ΔG values was supposed of varieties on the analysis parameters, which is common in the molecular docking study. Although, these results highlighted the potency of AP's ligands to bind the 6LU7, so as their potency to inhibit COVID-19 replication.

Another finding of this study also obtained the GAD (Andrographolide glycoside form) possessed lower ΔG than its aglycone. The physicochemical of the glycoside influenced the solubility of the ligands. Kren[23] wrote the glycoside influence the polarity of the compounds. This result provides insight of glycoside may induce active site of the 6LU7 receptors. Although Andrographolide has an advantage as main phytoconstituents and easier to absorb due to its small molecule compare to its glycoside form. Furthermore, this research finding was the three most suggested drugs of hydrochloroquine, chloroquine, and favipiravir have the least ΔG compare to most AP's ligands and anti-HIV drugs.

There was 25 total interaction between the N3-6LU7 receptor, with 36% consisted of hydrogen and Van der Walls bonds [Figure 1a]. Figure 1b, presents the interaction of DGE which has 19 bonding. DGE has the highest similarity (76% of amino acid and 36% of bonding type) to the N3 interaction among all ligands.

Figure 1c describes 17% of hydrogen bonds of GAD. This glycoside ligand represented the least interaction compare to others. Figure 1d illustrates DGF interactions. Although it only possessed 2 hydrogen bonds on 143-Gly, 163-His (18%), it has a similarity higher (72% and 32%) than GAD.

The reference antiviral ligands of INDI and REM are defined in Figure 1e and f, respectively. These ligands have 20–21 of bonding interaction out of 25 compares to N3, and have 80% similarities of amino acids residues. REM has a similar type of interaction higher than INDI (48% to 20%). These docking studies suggest that DGE and REM have the most overlapping binding pose with N3.

LD_{50} is an important quantitative parameters for toxicity. All ligands have LD_{50} not <5000 mg/kg/day, except for

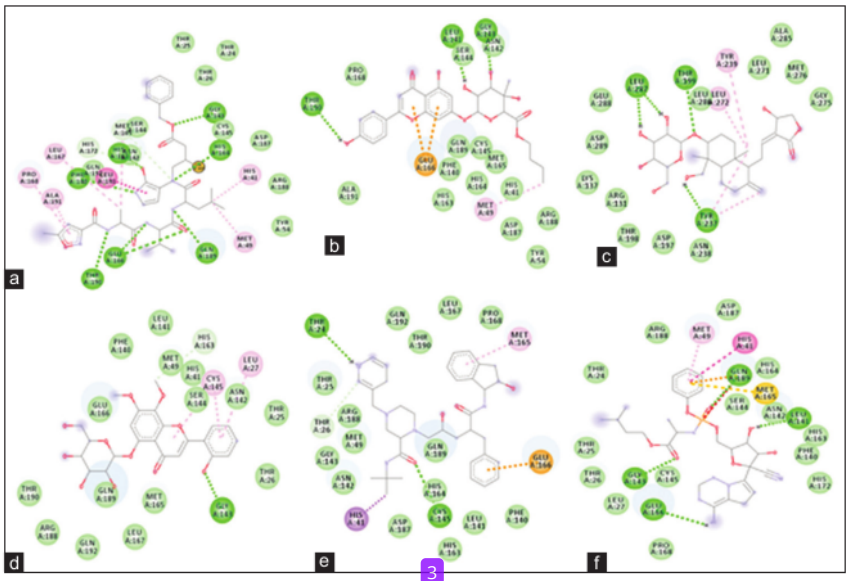

Figure 1: Two-dimension interaction of (a) co-crystal ligand (N3). (b) 5,4'-Dihydroxy-7-O-β-D-pyran-glycuronate-butyl-ester. (c) 3-O-β-D-glucopyranosyl-andrographolide. (d) 7,8-Dimethoxy-2'-hydroxy-5-O-β-D-glucopyranosyloxyflavone. (e) Indinavir. (f) Remdesivir with binding site of 6LU7 receptor (24-Thr) Threonine amino acid number 24, (Ala) Alanine, (Arg) Arginine, (Asn) Asparagine, (Asp) Aspartic acid, (Cys) Cysteine, (Gln) Glutamine, (Glu) glutamic acid, (Gly) Glycine, (His) Histidine, (Leu) Leucine, (Met) Methionine, (Phe) Phenylalanine, (Pro) Proline, (Thr) Threonine, (Tyr) Tyrosine, (Ser) Serine

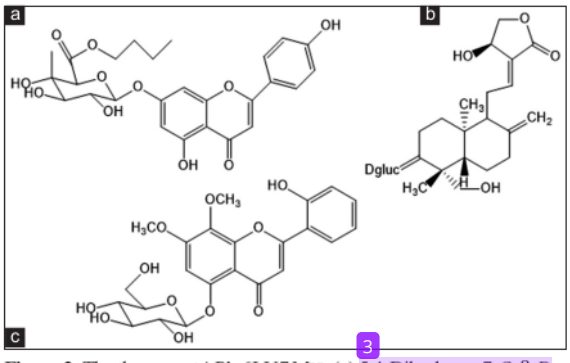

Figure 2: The three most AP's 6LU7 M^{pro}. (a) 5,4-Dihydroxy-7-*O*-β-*D*-pyran-glucuronate butyl ester. (b) 3-*O*-β-*D*-glucopyranosyl-andrographolide. (c) 7,8-Dimethoxy-2'-hydroxy-5-*O*-β-*D*-glucopyranosyloxyflavone

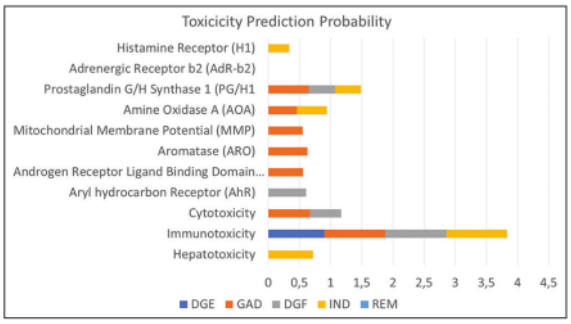

Figure 3: Toxicity prediction probability of AP's ligands and reference, 5,4'-Dihydroxy-7-*O*-β-*D*-pyran-glucuronate-butyl-ester, 3-*O*-β-*D*-glucopyranosyl-andrographolide, 7,8-Dimethoxy-2'-hydroxy-5-*O*-β-*D*-glucopyranosyloxyflavone, Indinavir, Remdesivir

GAD (590 mg/kg) and REM (1000 mg/kg). Therefore, the toxicity class was as may be harmful and slightly toxic if orally taken.[22] The further potential toxicity was including the immunotoxicity, carcinogen-and mutagenicity. The probability of the potential toxicity is relatively low, except for INDI hepatotoxicity. Furthermore, in the 15 model receptors toxicity resulted, most ligands have potential toxicity to PG/H1, except for DGE and REM. Interestingly the GAD was active to many receptors, including AhR, AND-LBD, ARO, and MMP, while DGF was active only to AhR. The GAD and INDI have the toxicity of AOA, while DGF was on AdR-β2 [Figure 3]. These results suggested AP's glycoside flavone of DGE was relatively safer than others. Moreover, these results determine the side effects which may arise.[24] These indicate the association between these docking results and the effectiveness of treating COVID-19 still needs further examination.

CONCLUSIONS

The *A. paniculata* (Burm. f) Ness. have potential as 6LU7 COVID-19 main protease inhibitors. The DGE, GAD, DGF; possess low energy and overlap binding interactions on docking sites to the 6LU7 pockets. The DGE was the safest

AP's compound compare to others. This finding needs further and extended examination of its use for COVID-19 treatment.

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Conflicts of interest

There are no conflicts of interest.

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