



Molecular Docking Study of *Ginkgo biloba* Compounds as Potential Inhibitors of SARS-CoV-2

Putri Mahirah Afladhanti^{1*}, Muhammad Despriansyah Romadhan¹, Haidar Ali Hamzah²,
Safa Nabila Putri¹, Ellen Callista Angelica¹

¹Medical Undergraduate, Faculty of Medicine, Sriwijaya University, Palembang

²Medical Profession, Faculty of Medicine, Sriwijaya University, Palembang

*Correspondence: mahirah.afladhanti@gmail.com

ABSTRACT

Background: COVID-19 pandemic caused by SARS-CoV-2 is a challenge for researchers to find effective drugs for this disease. Previous research had identified the role of Mpro, TMPRSS2, RdRp, and ACE2 which were useful as promising drug targets to inhibit SARS-CoV-2. **Objectives:** This study aims to identify the potential compounds derived from *Ginkgo biloba* as potential SARS-CoV-2 inhibitors using a molecular docking study. **Methods:** A total of twenty-one compounds of *Ginkgo biloba* and comparative drugs were used in this study. The materials were downloaded from RCSB for protein targets and Pubchem for comparative drugs and compounds. In this study, Lipinski rule of five using Swiss ADME web tool was used. Moreover, toxicity analysis using admetSAR 2.0 online test also used to predict toxicological profile of compounds. Dockings were carried out on Mpro, TMPRSS2, RdRp, and ACE2 protein targets by AutodockTools 1.5.6 and Autodock Vina. The visualization of molecular interaction was carried out by Discovery Studio v16. **Results:** Nine compounds met the criteria as drug-like components and were safe. Docking results showed that ginkgolide-C and bilobetin showed strong molecular interactions to all protein targets compared to the comparative drugs and other compounds. In RdRp, ginkgolide-C showed the highest binding energy with -12.7 kcal/mol. Moreover, in TMPRSS2, ACE2 and Mpro, bilobetin also showed the highest binding energy with -12.7, -9.7 and -10 kcal/mol, respectively. **Conclusion:** Ginkgolide-C and bilobetin have the potential to be developed as SARS-CoV-2 inhibitors. Therefore, in vitro and in vivo investigations are needed to bring these compounds to the clinical setting.

Keywords: Bilobetin, *Ginkgo Biloba*, ginkgolide-C, SARS-CoV-2

ABSTRAK

Latar Belakang: Pandemi COVID-19 yang disebabkan oleh SARS-CoV-2 menjadi tantangan bagi para peneliti untuk menemukan obat yang efektif untuk penyakit ini. Penelitian sebelumnya telah mengidentifikasi peran Mpro, TMPRSS2, RdRp, dan ACE2 yang berguna sebagai target obat yang menjanjikan untuk menghambat SARS-CoV-2. **Tujuan:** Penelitian ini bertujuan untuk mengidentifikasi senyawa potensial yang berasal dari *Ginkgo biloba* sebagai inhibitor potensial SARS-CoV-2 menggunakan studi penambatan molekular. **Metode:** Sebanyak dua puluh satu senyawa *Ginkgo biloba* dan obat pembanding digunakan dalam penelitian ini. Materi diunduh dari RCSB untuk target protein dan Pubchem untuk obat dan senyawa pembanding. Lima aturan Lipinski dengan menggunakan Swiss ADME web tool digunakan dalam penelitian ini. Selain itu, analisis toksisitas menggunakan admetSAR 2.0 juga digunakan untuk memprediksi profil toksikologi senyawa. Penambatan dilakukan pada target protein Mpro, TMPRSS2, RdRp, dan ACE2 oleh AutodockTools 1.5.6 dan Autodock Vina. Visualisasi interaksi molekuler dilakukan menggunakan Discovery Studio v16. **Hasil:** Sembilan senyawa memenuhi kriteria sebagai komponen mirip obat dan aman. Hasil penambatan menunjukkan bahwa ginkgolide-C dan bilobetin menunjukkan interaksi molekuler yang kuat terhadap semua protein target dibandingkan dengan obat pembanding dan senyawa lainnya. Pada RdRp, ginkgolide-C menunjukkan energi ikat tertinggi dengan -12,7 kkal/mol. Selain itu, pada TMPRSS2, ACE2 dan Mpro, bilobetin juga menunjukkan energi ikat tertinggi masing-masing dengan

-12,7, -9,7 dan -10 kkal/mol. **Kesimpulan:** Ginkgolide-C dan bilobetin berpotensi untuk dikembangkan sebagai inhibitor SARS-CoV-2. Oleh karena itu, penelitian *in vitro* dan *in vivo* diperlukan untuk membawa senyawa ini ke penelitian klinis.

Kata Kunci: Bilobetin, *Ginkgo Biloba*, ginkgolide-C, SARS-CoV-2

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) has emerged globally as a serious infectious disease at the end of 2019. SARS-CoV-2 has been identified as an enveloped non-segmented positive sense RNA virus in β -coronavirus group. This virus can be spread by human-to-human transmission via droplet or aerosol from infected people.^[1] It attacks human body systems such as respiratory, digestive, and nervous systems with a rapid transmission and a fairly high mortality rate.^[2] The latest report from World Health Organization (WHO) cited until the 20th of February 2022 there have been 418,650,474 confirmed cases with 5,856,224 deaths and Indonesia with 5,197,505 confirmed cases and 146,365 deaths.^[3,4]

The life cycle of SARS-CoV-2 begins with the attachment of S protein to Angiotensin Converting Enzyme 2 (ACE2) as a host cell receptor. Virus that enters the cell will release mRNA in the cytoplasm that is facilitated by Transmembrane Serine Protease 2 (TMPRSS2) and is translated into structural and non-structural proteins. In addition, several proteins such as the main protease (Mpro) and RNA-dependent RNA polymerase (RdRp) also play an important role in the assembly of new virus.^[5] Based on the role of these proteins in the virus life cycle, studies have shown that these proteins were potential as protein targets for COVID-19 treatment

development.^[6] However, until now there is no specific antiviral therapy for COVID-19 patients and primary care is only symptomatic treatment.^[7] Hence, further research related to the discovery of compounds for antiviral drug in inhibit SARS-CoV-2 is required.

In the last few decades, research on the use of herbs as an alternative treatment with minimal side effects has been developed. One of the herbal plants that have the potential for therapy, *Ginkgo biloba*, has a long history in traditional Chinese medicine and its leaf extract has been sold as a phytochemical in Europe and a dietary supplement in the US since the 1960's.^[8] Currently, Ginkgo tree is widely cultivated in Southeast Asia.^[9] Previous researches had identified the role of *Ginkgo biloba* as antiviral, antiinflammatory, antioxidant, and anticancer.^[9,10,11] Based on phytochemical screening, biflavonoids and ginkgolides are the major constituents of *Ginkgo biloba* that exhibit pharmacological activities especially to against RNA and DNA virus such as herpes simplex virus (HSV), influenza virus, and respiratory syncytial virus (RSV).^[12,13,14] Research conducted by Cheng et al. reported that bilobetin, one of biflavonoid derivatives in *Ginkgo biloba*, showed potent antiviral activity against influenza virus polymerase acidic (PA) endonuclease.^[14] Moreover, Sochocka et al. also reported that one of ginkgolides from *Ginkgo biloba* which is ginkgolide-C showed anti-HHV-1 and anti-HHV-2 activity.^[11]

This study aims to identify the potential compounds derived from *Ginkgo biloba* as SARS-CoV-2 potential inhibitors. Therefore, it is necessary to conduct research using molecular docking to predict potential *Ginkgo biloba* compounds in several Sars-CoV-2 protein drug target such as ACE2, TMPRSS2, RdRp, and Mpro.

METHODS

This research is an in silico research using the molecular docking method. This research was done using autodock 1.5.6 and discovery studio 2016 64-bit software and was conducted on the 2nd of September - 20th of December 2021 at the pharmacology department of Faculty of Medicine Universitas Sriwijaya.

There were six steps in this research, namely prediction of drug-likeness properties, prediction of toxicity, selection of protein target and ligands, preparation of protein target and ligands, in-silico molecular docking, and visualization analysis

Prediction of Drug-Likeness Properties

In this study, we refer to Lipinski's Rule of Five as a drug-like compound test. Drug-likeness prediction was performed using SwissADME, a free online website tool (<http://www.swissadme.ch/>).^[15]

Prediction of Toxicity

In this research, we used three indicators to predict toxicity of all the compound. We assessed toxicity of the compounds namely admetSAR 2.0, a free online website tool (<http://lmmd.ecust.edu.cn/admetSar2>).^[16]

Selection of Protein Target and Ligands

In this study, we used compounds from *Ginkgo biloba*. A total of 21 *Ginkgo biloba* compounds were selected in this study. We selected the ligands through online screening based on previous

literature namely amentoflavone (Compound CID: 5281600), apigenin (Compound CID: 5280443), bilobalide (Compound CID: 73581), bilobetin (Compound CID: 53154590), ebselen (Compound CID: 3194), genkwanin (Compound CID: 5281617), ginkgetin (Compound CID: 5271805), ginkgolic acids C13:0 (Compound CID: 161306), ginkgolic acids C15:1 (Compound CID: 5281858), ginkgolic acids C15:0 (Compound CID: 167551), ginkgolic acids C17:1 (Compound CID: 5469634), ginkgolide-A (Compound CID: 9909368), ginkgolide-B (Compound CID: 65243), ginkgolide-C (Compound CID: 24721502), isoginkgetin (Compound CID: 5318569), isorhamnetin (Compound CID: 528164), kaempferol (Compound CID: 5280863), luteolin (Compound CID: 5280445), quercetin (Compound CID: 5280343), quercitrin (Compound CID: 5280459), and sciadopitysin (Compound CID: 5281696) were downloaded from <https://pubchem.ncbi.nlm.nih.gov>. Protein targets that we used in this study namely ACE2 (PDB ID: 7C8C), TMPRSS2 (PDB ID: 5AFW), RdRp (PDB ID: 6XQB), and Mpro (PDB ID: 6YVF) were downloaded from <https://www.rcsb.org>. Besides, the drugs that were used in this study as a comparative drug namely N-acetylsistein (NAC) (Compound CID: 12035), nafamostat (Compound CID: 4413), remdesivir (Compound CID: 121304016), and lopinavir (Compound CID: 92727) were also downloaded from <https://pubchem.ncbi.nlm.nih.gov>.

Preparation of protein target and ligands

We used Autodock and Discovery Studio software to perform the preparation. The preparation of protein target was carried out by removing water molecules, adding polar hydrogen atoms, and removing a natural ligand structure.

Table 1. Coordinate value and grid box size

	ACE2	Mpro	TMPRS 2	RdRp
Center (Å)				
x	-16.214	-11.824	25.08	49.945
y	39.599	14.735	-0.086	55.064
z	12.063	74.152	-12.98	58.633
Box dimension (Å)				
x	92	40	74	126
y	68	40	90	126
z	74	40	90	126

After the preparation, we saved the file in pdbqt format. Meanwhile, the preparation of ligands were performed by creating all bonds being all rotatable then saved the file in pdbqt format.^[17]

In-Silico molecular docking

We executed docking using Autodock Vina software. A protein target site was set with the help of a grid box parameters shown in **Table 1**. The best binding affinities (more negative value) was selected from a set of nine conformation

poses after running docking. A compound showing the best hits was selected to be visualized its molecular interaction.

Visualization analysis

We performed visualization analysis to assess the binding sites of the ligand and observed chemical bonds formed between ligands and protein target. The visualization analysis was carried out using Discovery Studio software and depicted in 3D and 2D.

RESULTS

Lipinski's Rule of Five

Based on Lipinski's Rule of Five that showed in **Table 2**, all compounds except amentoflavone and quercitrin have less than two violations, so all the compounds except these two compounds used in this study were considered drug-like compounds.

Toxicity Test

Toxicity assessment in this study used admetSAR 2.0. We used three indicators in assessing toxicity, namely carcinogenicity, ames mutagenesis, and acute oral toxicity showed in **Table 3**. Based on toxicity test, compounds which have negative results on carcinogenicity and ames mutagenesis along with category III and IV in oral toxicity were continued to be researched using molecular docking.

Table 2. Lipinski's Rule of Five

Compounds	MW <500 (g/mol)	H- donor	H- acceptor	LogP	Violation
Amentoflavone	538.46	6	10	0.25	2
Apigenin	270.24	3	5	0.52	0
Bilobalide	326.30	2	8	0.42	0
Bilobetin	552.48	5	10	0.44	1
Ebselen	274.18	0	1	2.87	0
Genkwanin	284.26	2	5	0.77	0
Ginkgetin	566.51	4	10	0.63	1
Ginkgolic acids	320.47	2	3	4.50	1

C13:0 Ginkgolic acids	346.50	2	3	4.85	1
C15:1 Ginkgolic acids	348.52	2	3	4.94	1
C15:0 Ginkgolic acids	374.56	2	3	5.28	1
C17:1 Ginkgolide-A	408.40	2	9	0.83	0
Ginkgolide-B	424.40	3	10	0.06	0
Ginkgolide-C	440.40	4	11	-0.70	1
Isoginkgetin	566.51	4	10	0.63	1

Table 3. Toxicity

No.	Compounds	Carcinogenicity	Ames mutagenesis	Acute oral toxicity
1.	Amentoflavone	-(1.0000)	-(0.6800)	II (0.6295)
2.	Apigenin	-(1.0000)	-(0.8300)	III (0.7012)
3.	Bilobalide	-(0.9000)	+(0.5200)	III (0.3940)
4.	Bilobetin	-(1.0000)	-(0.6900)	III (0.6544)
5.	Ebselen	-(0.9143)	+(0.5900)	III (0.6820)
6.	Genkwanin	-(1.0000)	-(0.5700)	III (0.8799)
7.	Ginkgetin	-(1.0000)	-(0.5300)	III (0.6505)
8.	Ginkgolic acids C13:0	-(0.7459)	-(0.8600)	II (0.7474)
9.	Ginkgolic acids C15:1	-(0.7316)	-(0.8100)	II (0.6447)
10.	Ginkgolic acids C15:0	-(0.7459)	-(0.8600)	II (0.7474)
11.	Ginkgolic acids C17:1	-(0.7316)	-(0.8100)	II (0.6447)
12.	Ginkgolide-A	-(1.0000)	-(0.5200)	III (0.3661)
13.	Ginkgolide-B	-(1.0000)	+(0.5600)	III (0.5020)
14.	Ginkgolide-C	-(1.0000)	-(0.5400)	III (0.5526)
15.	Isoginkgetin	-(1.0000)	-(0.6000)	III (0.6505)
16.	Isorhamnetin	-(1.0000)	-(0.7300)	III (0.7362)
17.	Kaempferol	-(1.0000)	+(0.7300)	II (0.6238)
18.	Luteolin	-(1.0000)	-(0.5100)	II (0.7348)
19.	Quercetin	-(1.0000)	+(0.9000)	II (0.7348)
20.	Quercitrin	-(0.9857)	+(0.7700)	III (0.5184)
21.	Sciadopitysin	-(1.0000)	+(0.5200)	III (0.5810)

In-Silico molecular docking

In this study, nine *Ginkgo biloba* compounds and four comparative drugs were chosen. Crystal structures of Mpro, TMPRSS2, RdRp, and ACE2 were used. The docking results in this study are presented in **Table 4**. Lopinavir, nafamostat, remdesivir, and NAC showed the binding energies of -7,1, -9,1, -7,7, and -4,0 kcal/mol. In TMPRSS2, bilobetin had the highest binding energy compared to nafamostat and other compounds, which a value of -11.4 kcal/mol. In addition, ginkgolide-C showed the highest binding energy in RdRp with -12.7 kcal/mol binding energy. In Mpro and ACE2, bilobetin showed the highest binding energy which were -10 and -9.7 kcal/mol, respectively.

Visualization Analysis

The visualization of molecular docking results is shown in 3D form in **Figure 1** and 2D form in **Figure 2**. The visualization analysis yield that bilobetin on TMPRSS2 had both two hydrophobic and hydrogen interactions. There were 4 amino acid residues such as Leu198, Lys275, and Gln276(2). Moreover, nafamostat showed four hydrophobic and five hydrogen interactions with amino acid

residues such as Lys621, Arg553, Thr556, Tyr455, Ala558, Arg624, Ser682, Asp623(2), Asp760(2), Cys622, and Asn691. On the interaction with RdRp, ginkgolide-C had both five hydrophobic and hydrogen interactions with six amino acid residues which were Ala685(2), Arg569(3), Asn496, Leu576, Lys577(2), and Asn497. Besides, remdesivir had seven hydrophobic and one hydrogen interactions with amino acid residues such as Arg157(2), Tyr153, Pro158, Pro194(2), Phe5, Phe195, and Tyr162. Moreover, on the interaction of ACE2, bilobetin had four hydrophobic and one hydrogen interactions with amino acid residues of Ile159, Gln160, Tyr18, and Leu14(2). Meanwhile, NAC only showed four hydrogen interactions with amino acid residues of His493, Trp478(2), Glu489, and Arg482. Bilobetin also bound in Mpro with amino acid residues of Arg298(2), Pro9(5), Met6(2), and Ser10. The interaction with Mpro had nine hydrophobic and one hydrogen interactions, while lopinavir had seven hydrophobic and one hydrogen interactions with amino acid residues of Arg157(2), Tyr153, Pro158, Pro194(2), Phe5, Phe195, and Tyr162.

Table 4. Molecular Docking Results

Compounds	Mpro	TMPRSS2	RdRp	ACE2
Apigenin	-7.7	-8.4	-8.0	-7.7
Bilobetin	-9.7	-11.4	-10.7	-10.0
Genkwanin	-7.0	-9.0	-8.8	-8.8
Ginkgetin	-9.6	-10.3	-7.8	-9.6
Ginkgolide-A	-6.9	-9.8	-11.9	-8.3
Ginkgolide-C	-7.0	-10.9	-12.7	-8.0
Isoginkgetin	-9.2	-9.2	-11.0	-9.9
Isorhamnetin	-7.3	-9.2	-10.0	-8.0
Luteolin	-7.5	-9.2	-8.2	-8.2
Comparative drugs				
Lopinavir	-7,1			
Nafamostat		-9,1		
Remdesivir			-7,7	
NAC				-4,0

DISCUSSION

Before done the molecular docking and visualization analysis, drug-likeness properties and toxicity assesment were used to eliminate the compounds. Lipinski's Rule of Five describes a relationship between pharmacokinetics and physicochemical parameters.^[18] The Lipinski rule of five can help to distinguish between drug-like compounds and non-drug-like compounds. The rules consist of molecular weight less than 500 Dalton, number of H-bond acceptors less than 10, number of H-bond donors less than 5, and LogP less than 5 with violation no more than two violations.^[19] Based on our study, amentoflavone and quercitrin are eliminated due to have two violations. Meanwhile, toxicity assesment in this study used three indicators such as carcinogenicity, ames mutagenesis, and acute oral toxicity. Carcinogenicity test shows the results of whether a compound

is carcinogenic or not. In this study, all compounds showed negative results so all compounds were non-carcinogenic. Ames toxicity test is helpful to determine whether a compound is mutagenic or not. The positive results showed that compounds are mutagenic. In this study, only fifteen compounds showed negative results, which means non-mutagenic. Acute oral toxicity has four categories to state whether the compound is oral toxic or not. Category I ($LD_{50} \leq 50$ mg/kg) and category II (50 mg/kg $< LD_{50} \leq 500$ mg/kg) considered as toxic while category III (500 mg/kg $< LD_{50} \leq 5000$ mg/kg) and category IV ($LD_{50} > 5000$ mg/kg) considered as non-toxic.^{20,16} Based on toxicity assesment, ten compounds such as bilobalide, ebselen, ginkgolide-b, kaempferol, quercetin, and sciadopitysin along with ginkgloid acids C13:0, C15:1, C15:0, and C17:1 were excluded in this study.

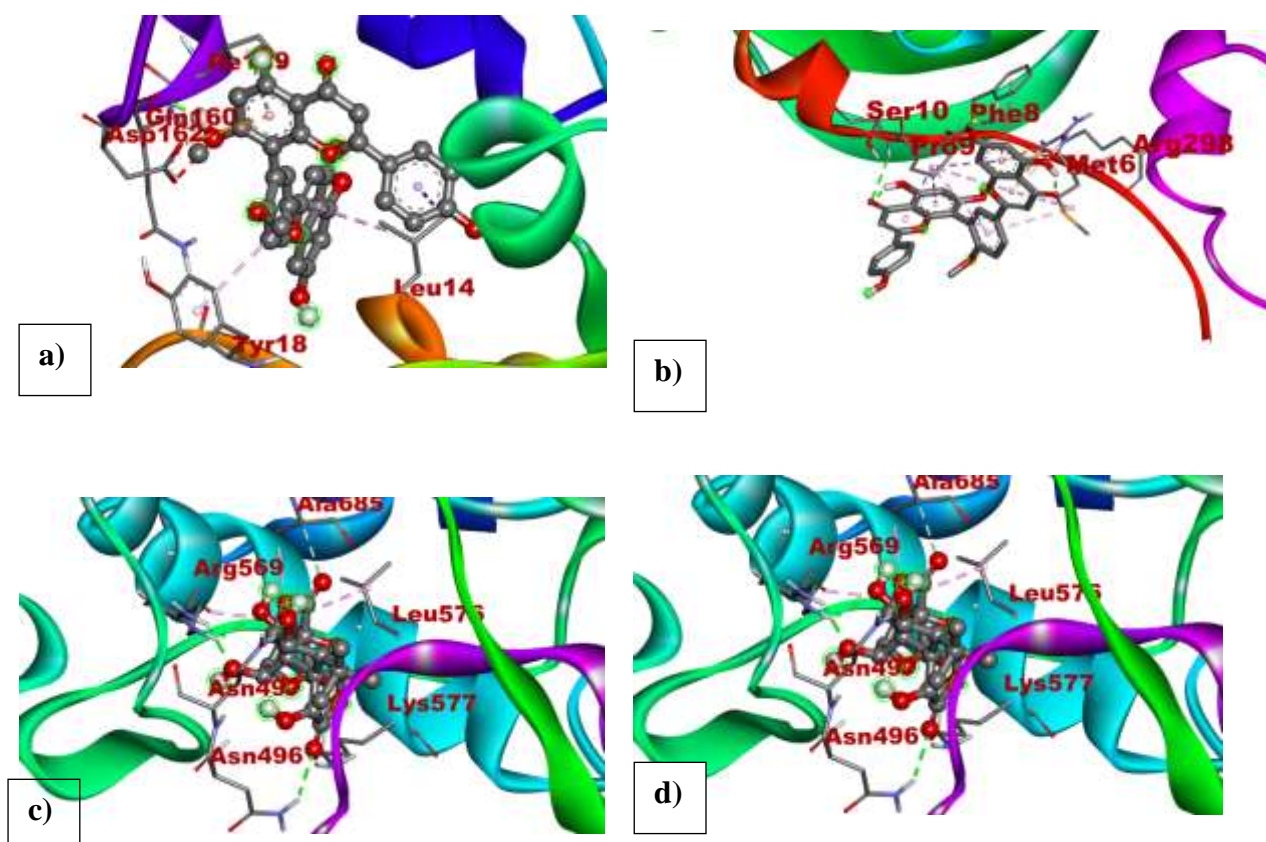


Figure 1. 3D structures of interaction between visualization a) ACE2 and bilobetin; b) Mpro and bilobetin; c) RdRp and Ginkgolide-C; d) TMPRSS2 and Bilobetin.

The remaining nine compounds had higher binding energies compared to comparative drugs. Ginkgolide-C and bilobetin were the best potential compounds among others according to the binding energy result. Binding energy (ΔG) is a parameter of conformational stability between ligands and target proteins. Ligands and proteins that interact with each other will tend to be at the lowest energy state, which causes the molecule to be at stable state. Therefore, the lower ΔG value (the greater the negative value), the higher the binding energy between the ligand and protein target.²¹ In addition, Zafar et al. stated that there is a linear correlation between inhibition constant value (K_i) with binding

energy value. Thus, the value of binding energy can be used to predict the ability of a compound to inhibit proteins.^[22] Jin et al. reported that the threshold of binding energy is ≤ -5.0 kcal/mol, so values less than -5.0 kcal/mol are considered to have strong binding effect with the key proteins.^[23]

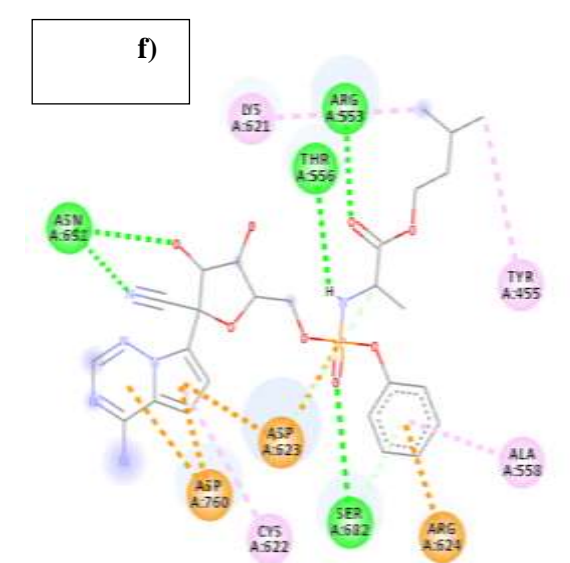
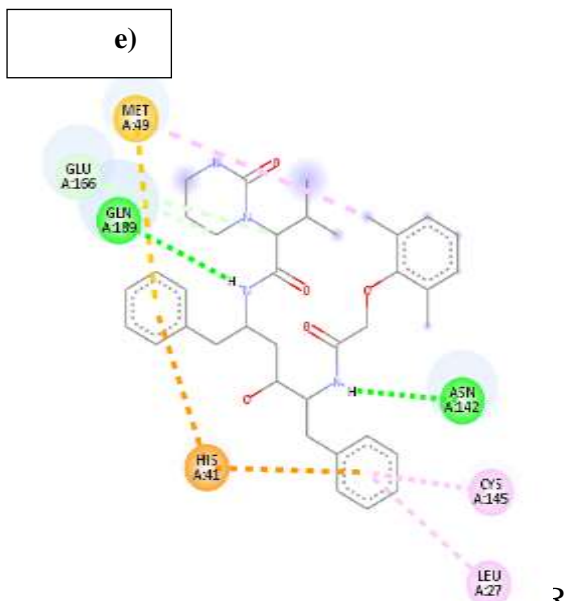
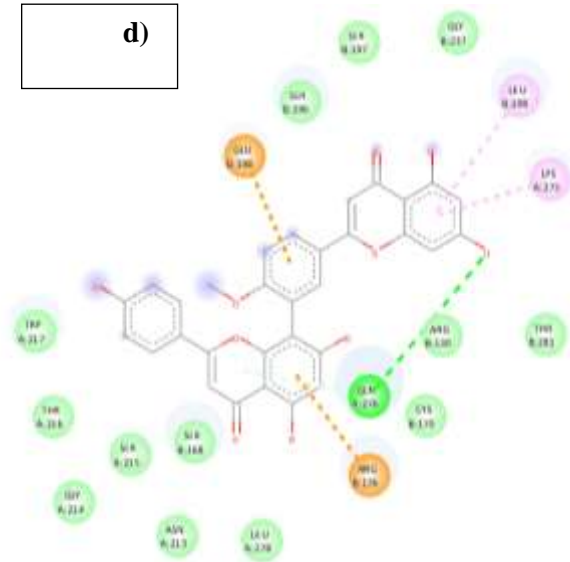
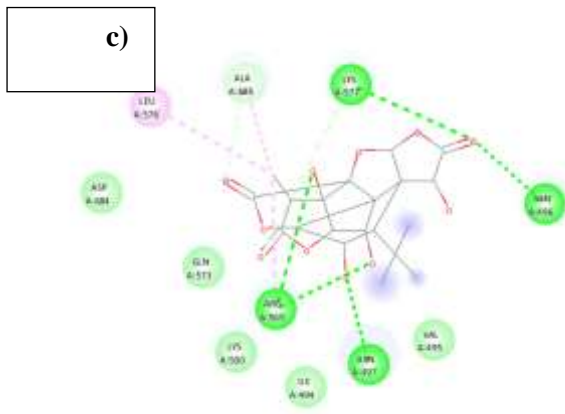
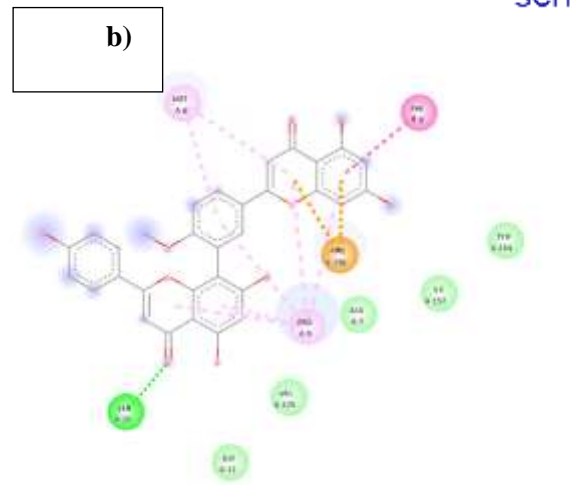
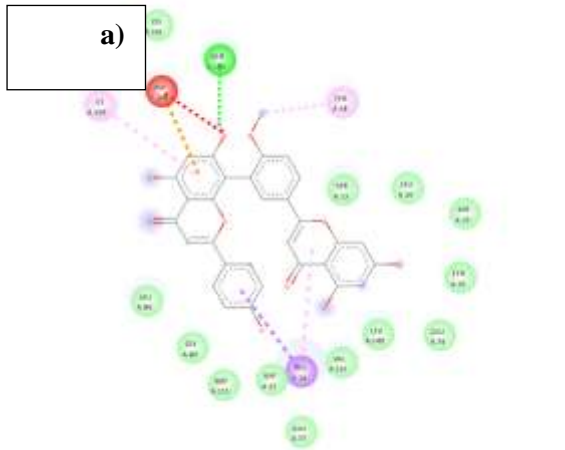
A molecular docking study conducted by Hussain et al. showed that the binding sites of TMPRSS2 were amino acid residues of Gln276, Arg413, Glu299, and Thr387.^[24] Meanwhile, Poustforoosh et al stated that the residues which are included in the active sites of RdRp were Ile494, Asn496, Val410, Lys411, His439, Phe440, Phe441, Phe442, Gln444, Asp452, Tyr455, Tyr456, Ala490, Asn491, Val493,

and Val495.²⁵ These studies are in line with our findings that bilobetin had two Gln276 as amino acid residue and ginkgolide-C showed the same amino acid residues with previous study which was Asn496. Therefore, bilobetin interacted in the active sites of TMPRSS2 and ginkgolide-C in the active sites of RdRp. Meanwhile, In ACE2 and Mpro no residues were same between bilobetin and comparative drugs. Thus, both of them bound in the different binding sites of the receptors. The active site or the binding pocket is the binding area of proteins that are involved in amino acid residues and have a role in the binding. In addition, there is a correlation between binding energy and the active sites of the proteins.^[26] Therefore, the interaction of amino acid residues at the active site with the compound causes the compound to have the ability to inhibit protein target as a competitive inhibitor.

Furthermore, we also analyzed two types of interactions that affect the binding energy value. Those interactions are hydrogen and hydrophobic bond interactions. The hydrogen bond can be defined as the interaction between hydrogen atoms and electronegative atoms such as fluorine (F), nitrogen (N), and oxygen (O).^[27] Meanwhile, the hydrophobic bond is an interaction that occurs between non-polar molecules which those interactions are alkyl-alkyl, pi-alkyl, pi-pi stacked, and pi-pi T-shaped interactions.^[28] Previous research stated that hydrogen and hydrophobic interactions can stabilize the compound at the active site of the protein and change binding energy value as well as enhance the efficacy of the compounds when

interacting with the protein.^[29] Macchiagodena et al. stated that hydrophobic interaction is more optimal to contribute the bond strength of the molecules compared with hydrogen interactions.^[30] However, Glowacki et al. stated that increasing the number of hydrophobic interactions at the active site of the protein can enhance biological activity or effect of the compound.³¹ Other study conducted by Varma et al. emphasized that both hydrogen and hydrophobic interactions have large contributions to the compound stability.³² Based on our results, it can be concluded that all of the top compounds in each protein targets have both hydrophobic and hydrogen interactions. Thus, those interactions have roles to strengthen the molecular bonds or enhance binding energy.

Previous studies reported that *Ginkgo biloba* have been proven as antiviral activities. Research conducted by Zhang et al, reported that bilobetin showed antiviral activity of influenza virus. Bilobetin effectively inhibited the PA endonuclease activity in gel-based endonuclease activity assay with IC50 values of bilobetin in PAN and PAN-I38T were 26.62 ± 8.99 and 38.84 ± 3.52 μ M, respectively.¹⁴ Meanwhile, Sochoka et al also reported that 100 μ g/mL of Ginkgolides A,B, and C had high anti-HHV-1 and anti-HHV-2 activity in non-toxic concentrations and significantly reduces the infectivity of both pathogens.^[11] In addition, Freitas et al also stated that bioflavonoids exhibit antiherpes activity with bilobetin present in this plant seem to be main responsible for this antiviral activity.^[33]



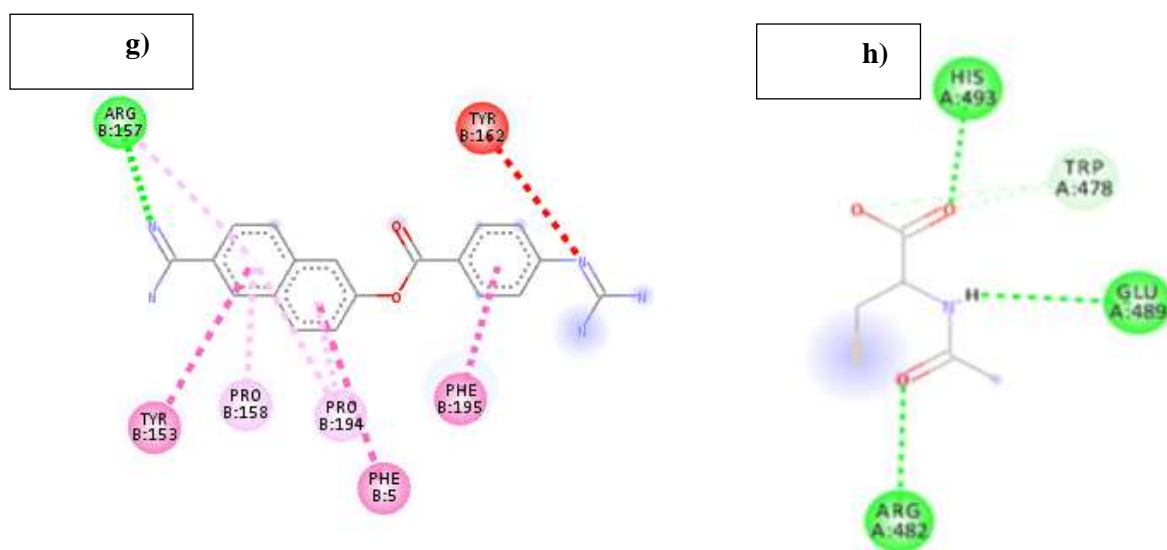


Figure 2. 2D structures of interaction between visualization a) ACE2 and bilobetin; b) Mpro and bilobetin; c) RdRp and Ginkgolide-C; d) TMPRSS2 and Bilobetin; e) Lopinavir and Mpro; f) Nafamostat and TMPRSS2; g) Remdesivir and RdRp; h) NAC and ACE2

CONCLUSION

In conclusion, based on the docking scores and the interactions with four protein targets, all of the selected compounds in this study had strong binding effects to block protein targets. Ginkgolide-C showed the highest binding energy compounds in RdRp. Meanwhile, bilobetin showed the highest binding energy in TMPRSS2, Mpro, and ACE2. Ginkgolide-C and bilobetin are nontoxic and have potential to be developed as SARS-CoV-2 inhibitors.

RECOMMENDATIONS

Further in vitro and in vivo investigations are needed to bring these compounds to the clinical setting.

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