Jurnal Sains dan Kesehatan (J. Sains Kes.)

Journal homepage: https://jsk.farmasi.unmul.ac.id

In Silico Study of Bajakah Compounds (*Spatholobus suberectus*) to Protease SARS-CoV-2 Inhibitor

Norhayati, Andika*, Aris Purwanto

University of Muhammadiyah Banjarmasin
*Email Korespondensi: andika@umbjm.ac.id

Abstract

Coronavirus Disease 2019 or COVID-19 is caused by a virus called Severe Acute Respiratory Syndrome Coronavirus 2. Until now, there is no specific treatment guide in dealing with COVID-19 in Indonesia. The curative pharmacological therapy for COVID-19 used is antiviral such as lopinavir, ritonavir, and oseltamivir, currently based on trial and error. This study carried out a Molecular Docking Analysis of 16 compounds owned by the Bajakah plant (Spatholobus suberectus). Oseltamivir was used as a control, and validation was carried out on a natural ligand, namely boceprevir against the main protease CoV or M^{pro}, 7C6S and the result was 1.47 Å using Toshiba hardware and AutoDock Tools, ChemSketch, Discovery Studio, Avogadro, UCSF Chimera software. Lipinski Rules of Five (RO5) analysis and ADMET analysis using SWISSADME and admetSAR. Licochalcone A compound had the best binding energy and inhibition constant values of -7.98 kcal/mol and 1.42 µM. In contrast, the 6-Methoxyeriodictyol compound had fewer binding energy and inhibition constants, namely -5.24 kcal/mol and 143.04 µM, respectively. In addition to the licochalcone A compound, the afrormosin compound, 3'4'7'-trihydroxyflavone, formononetin, cajanin, and dihydrokaempferol showed good binding energy values and inhibition constants compared to oseltamivir (control), so that these compounds have the potential to inhibit Mpro SARS-COV-2 or the virus that causes COVID-19. Analysis of Lipinski Rules of Five and ADMET is used to determine the properties of a molecule on the pharmacokinetics of drugs in the human body, and the results obtained to meet the requirements so that it is potentially effective for oral consumption.

Keywords: SARS-CoV-2, bajakah, molecular docking, licochalcone A

Received: 01 October 2021 **Accepted**: 18 March 2023

DOI: https://doi.org/10.25026/jsk.v5i2.950

How to Cite:

Norhayati, N., Andika, A., Purwanto, A. 2023. In Silico Study of Bajakah Compounds (*Spatholobus suberectus*) to Protease SARS-CoV-2 Inhibitor. *J. Sains Kes.*, **5**(2). 78-89. **DOI**: https://doi.org/10.25026/jsk.v5i2.950

1 Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 or SARS-CoV-2 is a group of the coronavirus family. Coronavirus is an encapsulated, single-positive, segmentless RNA strain. The main structure of the Coronavirus protein, namely: nucleocapsid (protein N), membrane (glycoprotein M), spike (spike S), and sheath (protein E). Coronavirus from the order Nidovirales belongs to the Coronaviridae family can cause various diseases in humans and animals. WHO China Country Office on December 31, 2019, notified that there was a new pneumonia case (the cause of which was unknown) in Wuhan City, China. Furthermore, on January 7, 2020, the Chinese state identified the disease as a new type of coronavirus called the coronavirus disease. On January 30, 2020, WHO designated COVID-19 as a Public Health Emergency of International Concern [1].

In the management of COVID-19 to date, there is no specific treatment. Treatment is only intended as supportive, symptomatic therapy, and there are several research candidates for certain drugs and vaccines that are being studied with clinical trials. A common symptom that someone infected with COVID-19 has is acute respiratory problems [1]. In overcoming the pathogenetic mechanism of SARS-CoV-2, it must focus on the main protease in CoV, namely M^{pro} which functions as proteolytic maturation of the virus and target protein in infection prevention by inhibiting the cleavage of viral polyproteins [2]. One of the M^{pro} of SARS-CoV-2 is 7C6S, so that the presence of this protease structure provides a great opportunity to identify potential treatments that can inhibit M^{pro} of SARS-CoV-2.

Bajakah is included in the Leguminosae family, and phytochemical studies show several types of compounds in Table 2.1, namely alkaloids, non-protein amino acids, amines, flavonoids, isoflavonoids, coumarins, phenylpropanoids, anthraquinones, disesqui and triterpenes, cyanogenic glycosides, and lectins [3]. Besides, the Chinese use bajakah as blood circulation, eliminate digestive tract disorders, menstrual disorders, rheumatism [4], anti-inflammatory activity [5], and antivirus [6]. There are several bioactive compounds possessed by Bajakah (*Spatholobus suberectus*), namely dihydroquercetin, epicatechin, afrormosin, cajanin, 3',4',7'-trihydroxyflavone, and licochalcone A [7]. The findings of post study will provide other researchers with opportunities to identify the rigt drug to combat COVID-19.

2 Materials and Method

2.1 Materials

This research used computer software and hardware. The device was a personal Toshiba computer with specification: Intel® Core™ i3 CPU M380 @ 2.53GHz, 6 gigabyte RAM, Satelite L635, Microsoft Windows® 7 Ultimate, and software such as BIOVIA Discovery Studio 2017 R2 Client, Protein Data Bank, KnapSacck, ChemSketch, UCSF Chimera, Avogadro, and AutoDock Tools.

2.2 Methods

2.2.1 Receptor preparation

In this study, the receptors used are macromolecules from PDB ID: 7C6S downloaded at http://www.rcsb.org/pdb/ stored in .pdb format and the identity of protein macromolecules is U5G (Boceprevir) as native ligand found in chain A.

2.2.2 Ligand preparation

The preparation of the structure of the test compounds was carried out using the SMILES code for each compound found on the KnapSack site and then entered into the ChemSketch. Besides that, the comparators used were oseltamivir and boceprevir, which are co-crystal ligands of 7C6S.

2.2.3 Energy Minimize

Energy minimization is carried out at receptors and ligands using Avogadro with the MMFF94 parameter, aiming to obtain the most stable conformation or molecular shape and more flexible ligand and receptor interactions.

2.2.4 Receptor docking validation

Validation was performed by re-docking the receptors and natural ligands of the 7C6S using AutoDock software. The parameters used are seeing the RMSD value and visually the poses that occur. The criteria for the success of the docking method are if the resulting RMSD value is <2.0 Å [8,9].

2.2.5 Docking simulation

Docking simulations were carried out using AutoDock Tools-1.5.6 to observe interactions between SARS-CoV-2 main protease (ID:7C6S) from Protein Data Bank with Bajakah plant compounds. Molecular docking of protein and target ligands using active site coordinates on the Autogrid [10].

2.2.6 ADMET study

ADMET evaluation is needed to determine the pharmacokinetic profile of a drug compound. The evaluation includes identifying adsorption, distribution, metabolism, excretion, and toxicity using admetSAR and SwissADME.

2.2.7 Data Analysis

After obtaining the results of the binding energy and inhibition constants of each test and control compound, an analysis of the results will be carried out. Molecules that have a high binding energy score show better affinity stability and observe the results obtained from SwissADME and admetSAR with the requirements of RO5 and ADMET.

3 Results and Discussions

This research conducted an in silico study using a molecular docking method. This method is carried out on compounds owned by the Bajakah plant (*Spatholobus suberectus*) which can be seen in Table 1 and Table 2 on the SARS-CoV-2 protease, namely 7C6S, whose structure can be seen in Figure 1. which aims to determine the bonds of the compounds that act as ligands, and target proteins or receptors.

The program used in this research is AutoDock with MGL Tools 1.5.6 from AutoDock Tools. The 7C6S protein is the main protease crystal (M^{pro} or $3CL^{pro}$) from SARS-CoV-2, complex with a natural ligand, namely boceprevir, present in the A chain U5G characteristics and is used as a control and validation process. The selection of the target virus M^{pro} or $3CL^{pro}$ plays a role in the virus replication process [11]. Apart from boceprevir, controls also use oseltamivir, which is one of the drugs used by the Indonesian government in the management of COVID-19 patients [12].

Validation is the basic process of docking simulations carried out with 7C6S protein, which is downloaded at http://www.rcsb.org/, and the water molecules are removed first so that only natural ligands and proteins interact [13]. The validation process is carried out to determine the suitability of the method we are working on and the RMSD (Root Mean Square Deviation), which describes the stability of the distance between the docking results and the target ligand [14]. The RMSD in the validation process must be <2 Å so that it can be interpreted that the method we are using is appropriate and correct (8,9). In the docking validation of the 7C6S, the result was 1.47 Å by adjusting the grid box, namely the dimensions x, y, z were 40.40.40. The grid box center coordinates were x = -16.792, y = -25.915, z = -0.885, which aims to determine the binding site for the interaction between the ligand and the target protein [15]. By obtaining the RMSD results, the method and results of the center grid box coordinates can be continued to test the test compound.

Table 1. Molecular docking result of control to SARS-CoV-2 protease (7C6S)

No	Control	Binding Energy (kcal/mol)	Inhibition Constant (uM)	Torsional Free Energy (kcal/mol)	Final Intermoleculer Energy (kcal/mol)
1	Boceprevir	-8.66	1.77	+2.68	-11.35
2	Oseltamivir	-6.16	185.25	+2.68	-7.78

Table 2. Molecular docking result of bajakah plant (*Spatholobus suberectus*) to protease 7C6S

No	Ligand	Binding Energy (kcal/mol)	Inhibition Constant (μM)	Torsional Free Energy (kcal/mol)	Final Intermoleculer Energy (kcal/mol)
1	Licochalcone A	-7.98	1.42	+2.39	-8.81
2	Afrormosin	-6.75	11.26	+1.19	-7.13
3	3',4',7- Trihydroxyflavone	-6.72	11.80	+1.19	-6.60
4	Formononetin	- 6.61	14.29	+0.89	-7.11
5	Cajanin	-6.23	27.32	+1.49	-7.25
6	Dihhydrokaempferol	-6.21	28.15	+1.49	-6.77
7	Butin	-6.11	33.48	+1.19	-7.29
8	Liquiritigenin	-6.06	36.31	+0.89	-6.76
9	Neoisoliquiritigenin	-6.03	37.96	+3.58	-6.11
10	Eriodictyol	-5.81	55.27	+1.49	-6.46
11	Prunasin	-5.79	56.92	+2.39	-5.98
12	Plathymenin	-5.57	82.50	+1.49	-6.73
13	3,7-Dihydroxy-6-methoxyflavone	-5.52	90.49	+1.19	-5.97
14	Dihydroquercetin	-5.47	97.91	+1.79	-6.98
15	Epicatechin	-5.28	134.40	+1.79	-6.29
16	6-Methoxyeriodictyol	-5.24	143.04	+1.79	-5.56

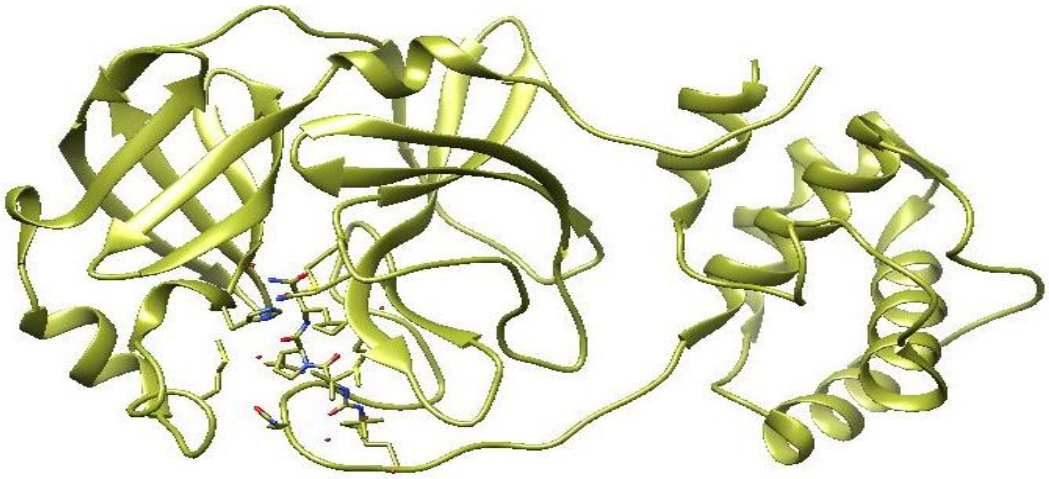


Figure 1. Crystal Structure M^{pro} SARS-CoV-2 with Boceprevir (7C6S)

The test compounds used were 16 plant compounds of bajakah (*Spatholobus suberectus*) obtained from the https://www.knapsackfamily.com site as a substitute for natural ligands in the docking process. Furthermore, the docking process is carried out with 7C6S macromolecules that have been separated from the natural ligand and set the grid box coordinates according to those obtained during the validation process. The resulting output is in the form of *.dlg* which contains data on molecular docking results, namely binding energy, inhibition constant, torsional energy, intermol energy, internal total energy, and unbound energy.

In this study, the results of the binding energy value from the control can be seen in Table 1, namely the native ligand (boceprevir) is -8.66 kcal/mol and oseltamivir -6.16 kcal/mol. Furthermore, the binding energy results of the steel compounds can be seen in Table 2, namely, the highest value obtained by licochalcone A -7.98 kcal/mol and the lowest by the compound 6-Methoxyeriodictyol -5.25 kcal/mol. The

results of the binding energy molecules are arranged according to the ranking of the highest binding energy values. The higher the minus binding energy value, the more stable the conformation of the ligand and protein target[16].

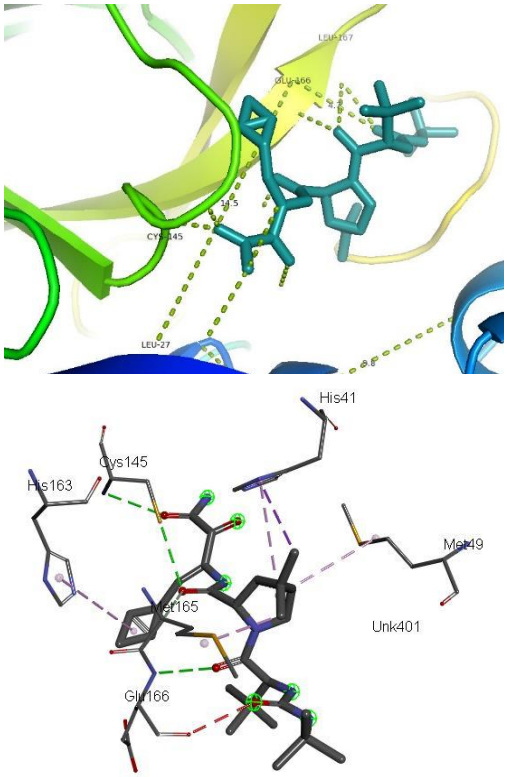


Figure 2. Overlay of docked pose of receptor and natural ligand

Apart from the good binding energy value, there are many licochalcone A compounds in the genus Glycyrrhiza, one of which is in liquorice (*Glycyrrhiza glabra*), which has antioxidant, antimicrobial activity [17,18] and affects antivirus [19]. Afrormosin compounds are often found in legumes such as from the Baptisia species and in teak (*Afrormosia elata*), which a antioxidant [20,21] and anti-inflammatory [22]. The compound 3'4'7'-trihydroxyflavone is found in Trigonella species, the kelabat plant (*Trigonella foenum-graecum*), which has antioxidant activity [23]. Formononetin compounds are found in many clove species, especially red cloves (*Trifolium pratense*), have proliferation blocking activity, showing cytotoxicity against nasopharyngeal carcinoma cells [24] and antivirals [25].

Cajanin compounds are often found in Bali nuts or kayo beans (Cajanus cajan) which have anti-HSV activity [26], antihyperlipidemia [27,28], anti-osteoporotic [29] and antioxidants [30], and antivirals [31]. Moreover, dihdyrokaempferol compounds are found in many Eucalyptus species such as lemon eucalyptus and Prunus species such as almonds (*Prunus amygdalus*) which have antioxidant, anti-tyrosine, cytotoxic activities [32].

The inhibition constant value (Ki) can be seen in Table 1. and Table 2. shows the resistance strength of a compound with the receptor. The smaller the Ki value, the stronger the resistance that occurs [33]. The inhibition constant results from natural ligand control (boceprevir) were 1.77 µM and oseltamivir 185.25 µM. At the same time, for the test compound, the smallest value was obtained by licochalcone A compound 1.42 µM, and the highest was the compound 6-Methoxyeriodictyol 143.04 µM. These results indicate that the licochalcone A compound has good resistance to the receptor compared to all test and control compounds.

The torsional value of free energy, also known as entropy, is a measure of the average heat energy distributed throughout the thermodynamic system. The second law of thermodynamics dictates that heat always flows spontaneously from regions of higher temperature to regions of lower temperature. This reduces the degree of order of the initial system, and therefore, entropy can also be viewed as a measure of disorder in the molecules of a system. Positive values indicate an increase in the degree of freedom of the system, while negative values indicate a decrease [34,35]. In ligand and receptor interactions, negative or positive values can indicate a good value and the occurrence of a bond [36]. The results obtained in Table 1 and Table 2, namely the natural ligand (boceprevir) is +2.68 kcal/mol and oseltamivir +2.68 kcal/mol. In the test compound, the best torsional value was obtained by licochalcone A +2.39 kcal/mol and the least good was 6-Methoxyeriodictyol +1.79 kcal/mol. The entropy result is related to the enthalpy, where the entropy value must be lower than the

enthalpy, the better the interaction between ligands and receptors.

The final intermolecular energy value or enthalpy is the total energy of the thermodynamic system, namely the amount of internal energy of solutes and solvents and the amount of energy needed to make room for the system [37]. In the binding process, ΔH or enthalpy reflects the energy change when the ligands bind to the receptors resulting from the formation of noncovalent interactions (van der waals, hydrogen bonds, ion pairs, etc.). The results obtained in Table 1 and Table 2 show that the enthalpy value in the natural ligand control (boceprevir) is -11.35 kcal/mol and oseltamivir -7.78 kcal/mol, while the highest value of the test compound is licochalcone A -8.81 kcal/mol and the lowest is 6-Methoxyeriodictyol -5.56 kcal/mol. The greater the minus value, the better the space formed between the ligand and the receptor, licochalcone A compound has the best enthalpy value compared to other compounds and also oseltamivir control.

In addition to the results of molecular docking, in finding the potential for new drug compounds, rules can be used to determine the effectiveness of a compound with its pharmacology making the drug administered orally to humans Lipinski Rule of Five. The results of this analysis can be seen in Table 3.

Table 3. Analysis result Lipinski Rule's of Five bajakah compounds

No	Ligand	Molecule Weight (<500) g/mol	Log P (<5)	H-bond Donor (<5)	H-acceptor (<10)	Molar Refractivity (40-130)
1	Licochalcone A	338.40	2.58	2	4	100.39
2	Afrormosin	298.29	3.18	1	5	82.93
3	3',4',7- Trihydroxyflavone	270.24	4.47	3	5	73.99
4	Formononetin	268.26	3.17	1	4	80.48
5	Cajanin	300.26	2.59	3	6	76.44
6	Dihydrokaempferol	288.25	1.48	4	6	72.73
7	Butin	272.25	2.51	3	5	71.57
8	Liquiritigenin	256.25	2.80	2	4	69.55
9	Neoisoliquiritigenin	418.39	0.17	6	9	104.44
10	Eriodictyol	288.25	2.22	4	6	73.59
11	Prunasin	295.29	-0.93	4	7	69.51
12	Plathymenin	288.25	2.22	4	6	73.59
13	3,7-Dihydroxy-6-methoxyflavonone	286.28	2.08	2	5	75.18
14	Dihydroquercetin	304.25	1.19	5	7	74.76
15	Epicatechin	290.27	1.55	5	6	74.33
16	6-Methoxyeriodictyol	318.28	2.22	4	7	80.09

Lipinski Rules' of Five (RO5) analysis was performed using SwissADME and admetSAR and the results can be seen in Table 3. This analysis aims to see the properties of a molecule on drug pharmacokinetics which includes distribution, metabolism and excretion in the human body [38,39] and predicted the similarity of the properties of a molecule with an existing drug (Drug Likeness) from two or more RO5 criteria. The results obtained were that the molecular weight of 16 compounds from the bajakah plant (Spatholobus suberectus) was less than 500 Da, meaning that the compound could diffuse and penetrate the cell membrane, the logP value was related to the ability of the compound to dissolve in a non-polar solvent, lipid, fat, and oil. All compounds showed a logP value <5, meaning that the compound was hydrophobic and could penetrate the lipid bilayer. Hydrophobicity plays a role in determining the distribution in the body after the absorption process and the speed for metabolism and excretion [40].

The number of donor hydrogen bonds has a requirement of <5, only the Neoisoliquiritigenin compound does not meet the criteria because there are 6 donor hydrogen bonds, while the number of acceptor hydrogen bonds, all compounds meet the criteria, which must be <10. The number of donor and acceptor hydrogen bonds shows that the greater the number of bonds, the more energy is required in the absorption process [41]. Molar refractivity indicates the polarity of a compound and has the requirement to be in the range 40-130 and all compounds of steel fall within that range.

The Lipinski Rules of Five rules, all compounds meet the rules for molecular weight, logP value, acceptor hydrogen bonds, molar refractivity, whereas there is one compound that does not meet the criteria for donor hydrogen bonds. All compounds from the Bajakah plant (*Spatholobus suberectus*) that were tested met the requirements of RO5, which means that these compounds have good absorption and are potentially effective for consumption orally by humans.

Table 4. ADMET prediction result of bajakah compounds

No	Ligand	Log S	GIA	BBB	Carcinogens	Caco-2	Hepatoxicity	Acute Oral Toxicity (Kg/mol)
1	Epicatechin	-3.10	High	-	-	-	-	1.972
2	Prunasin	-1.14	High	-	-	-	-	3.204
3	Licochalcone A	-3.87	High	+	-	+	+	2.376
4	Afrormosin	-3.56	High	-	-	+	+	1.667
5	3',4',7-Trihydroxyflavone	-3.08	High	-	-	+	+	2.298
6	Formononetin	-3.46	High	-	-	+	+	1.606
7	Cajanin	-3.19	High	-	-	+	+	2.252
8	Neoisoliquiritigenin	-1.53	Low	-	-	-	+	2.141
9	Plathymenin	-3.37	High	-	-	-	+	1.954
10	3,7-Dihydroxy-6 methoxyflavanone	-3.42	High	-	-	-	+	2.062
11	Dihydroquercetin	-3.00	High	-	-	-	+	2.906
12	6-Methoxyeriodictyol	-3.33	High	-	-	+	+	2.205
13	Butin	-3.37	High	-	-	-	+	1.999
14	Liquiritigenin	-3.24	High	-	-	-	+	1.129
15	Eriodictyol	-3.45	High	-	-	-	+	2.264
16	Dihydrokaempferol	-3.14	High	-	-	-	+	2.13

In addition to RO5 analysis, ADMET analysis must also be carried out to determine the properties of the various compounds present in this study. This analysis was performed using admetSAR and SwissADME and the results can be seen in Table 4. In order to facilitate the process of drug absorption, compounds must be soluble in water so that they can enter the cell membrane [42]. The log S results in Table 4 show a value of less than 1, meaning that all the test compounds present in the steel (*Spatholobus suberectus*) are very soluble in water. All compounds except neoisoliquiritigenin have high gastrointestinal absorption (GIA), so that if they are consumed orally, they can be properly absorbed by the gastrointestinal tract.

On the penetration of the Blood-Brain Barrier (BBB), if it is negatively charged, it shows that the compound is effective in penetrating the blood-brain barrier. The results obtained are that all compounds of steel are negatively charged and only licochalcone A compounds are positive. Furthermore, the prediction of carcinogenic shows a negative value, meaning that all compounds of the steel are non-carcinogenic. In addition, the prediction of the permeability value of caco-2 was used to see the process of drug absorption through intestinal epithelial cell barriers in humans [43]. The results showed that the afrormosin, cajanin, formononetin, licochalcone A, and 3',4',7'-trihydroxyflavone compounds showed good permeability compared to other compounds.

Acute oral toxicity analysis plays an important role in showing that the minimum concentration exerts a toxic effect on oral administration. According to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) there are 5 categories, namely category 1: dose <5 mg/kg, category 2:> 5 mg/kg <59 mg/kg, category 3:> 50 mg/kg < 300 mg/kg, category 4:> 300 mg/kg <2000 mg/kg, category 5:> 2000 mg/kg <5000 mg/kg and > 5000 mg/kg. Category 1 indicates super toxic, category 2 is very toxic, category 3 is very toxic, category 4 is moderate toxic, category 5 is mild/non-toxic. The prediction results obtained were dihydroquercetin, butine, eriodictyol, liquiritigenin, dihydrokaempferol, plathymenin including category 2 (very, very toxic). Then the compounds licochalcone A, afrormosin, 3'4'7-trihydroxyflavone, formononetin, cajanin, dihydrokaempferol, neoisoliquiritigenin,

prunacin, 3,7-Dihydroxy-6-methoxyflavonone, plathymenin, and 6-Methoxyeriodictyol are included in category 3 (very toxic), and epicatechin compounds including category 4 (moderate toxic).

Furthermore, hepatotoxic predictions were also carried out to determine whether the compound could damage the liver. The results can be seen in Table 4, namely licochalcone A, afformosin, 3'4'7-trihydroxyflavone, formononetin, cajanin, dihydrokaempferol, butin, liquiritigenin, neoisoliquiritigenin, eriodictyol, 3, 7-Dihydroxy-6-methoxyflavonone, dihydroquercetin, plathymenin, and 6-Methoxyeriodictyol showed positive hepatotoxic results. In contrast, prunacin and epicatechin compounds were hepatotoxic negatives.

In molecular docking studies, the visualization process plays an important role in determining the amino acid interactions between ligands and target proteins (receptors). Researchers visualized the structure of the test compounds, controls, receptors to describe the bonding process shown in Figure 3.

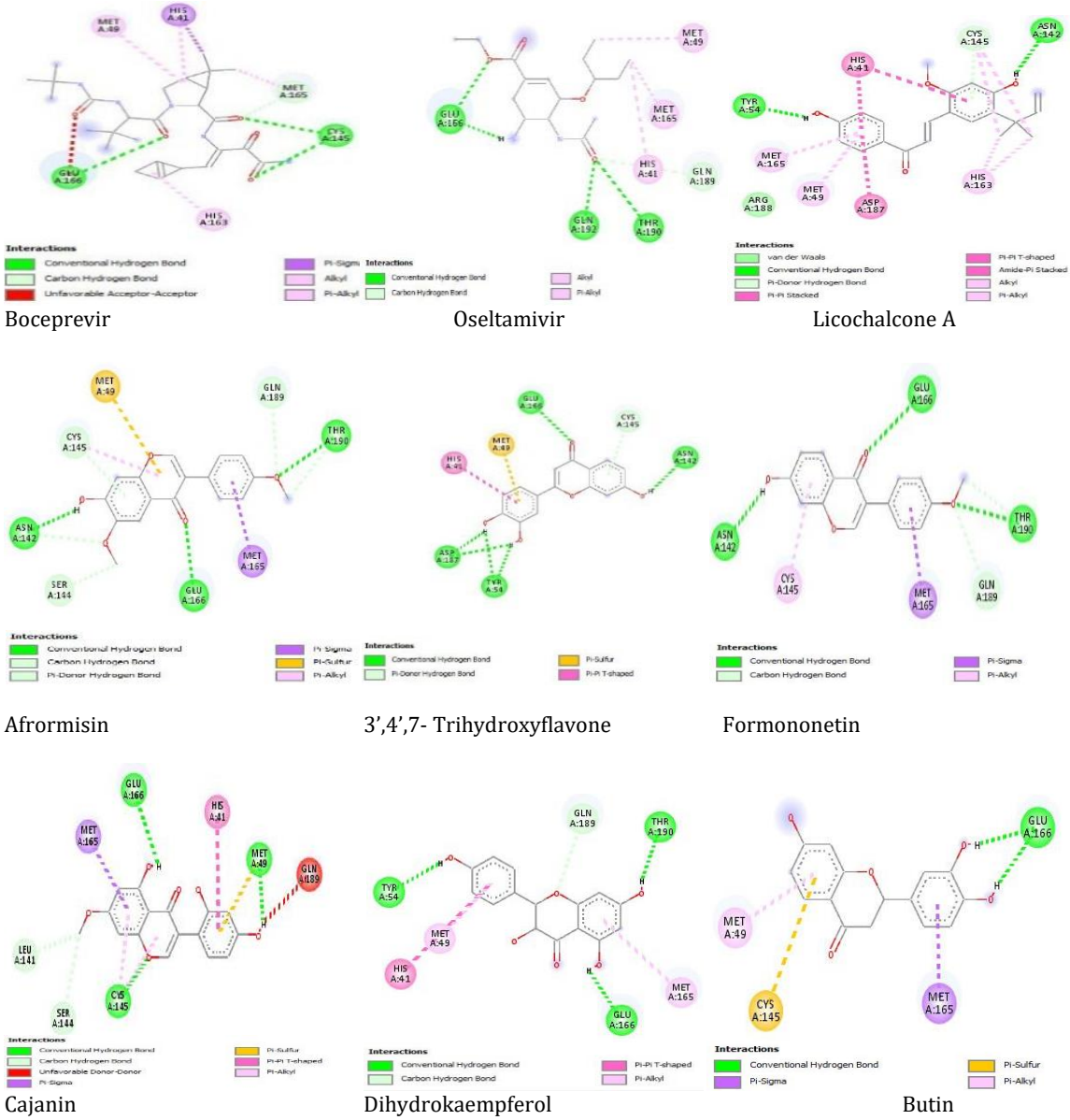
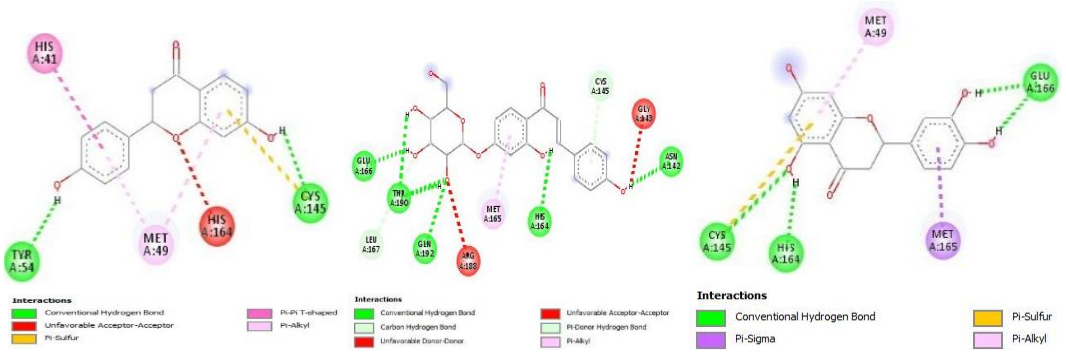
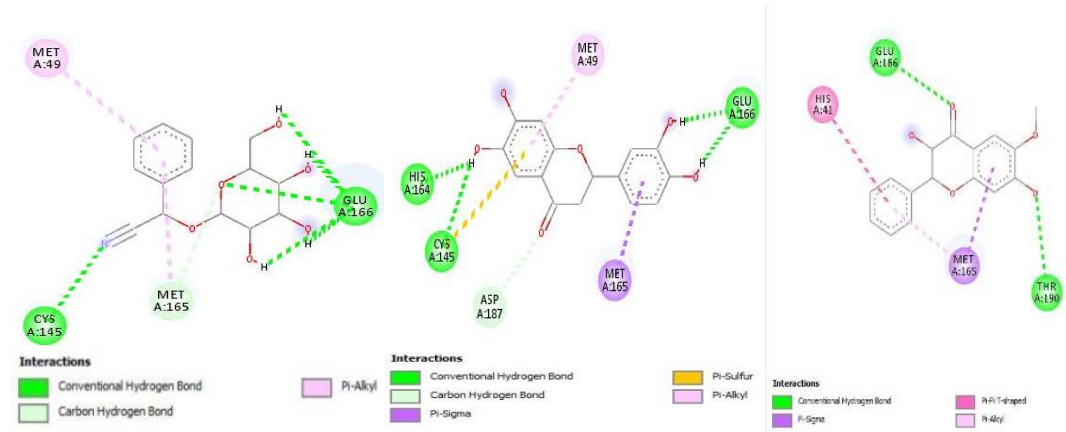


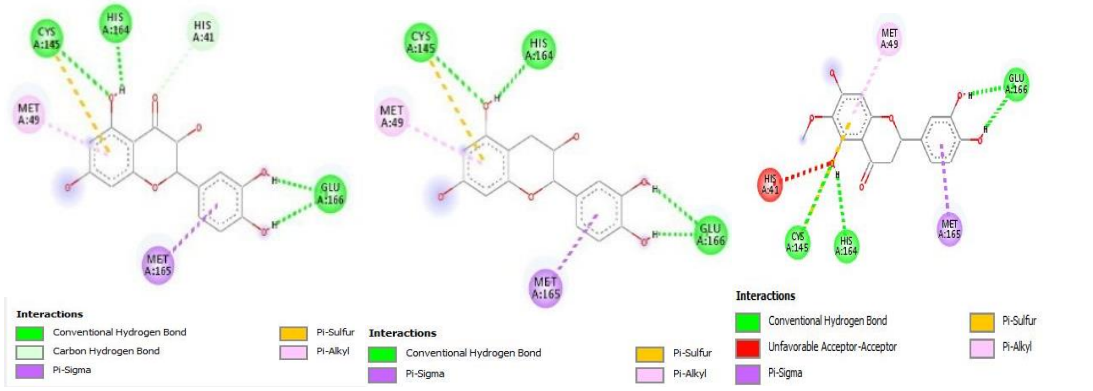
Figure 3. Visualization of Amino Acid Interaction using *Discovery Studio*



Liquiritigenin Neoisoliquiritigenin Eriodictyol



Prunasin Plathymenin 3,7-Dihydroxy-6-methoxyflavonone



Dihydroquercetin Epicatechin 6-Methoxyeriodictyol

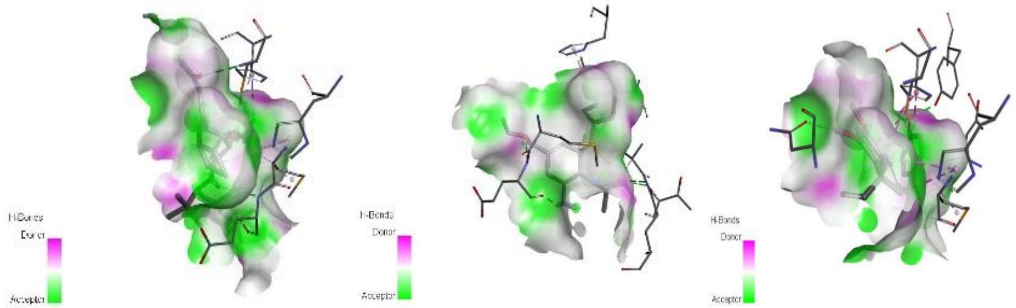
Figure 3. Visualization of Amino Acid Interaction using *Discovery Studio*

The observation results from the 2-dimensional visualization of docking results are shown in Figure 3, and the 3-dimensional visualization can be seen in Figure 4. Observations were made to see the interactions between ligands and receptors after the molecular docking process using Discovery Studio. It can be seen in Figure 4 that the docking result dimension column shows a dotted line showing the interaction between ligands and receptors.

Visualization of amino acid residue interactions aims to see interactions, namely in the form of van der walls interactions, electrostatic interactions, hydrogen bonds, hydrophobic interactions (pi-alkyl, alkyl-alkyl,

pi-sigma pi-pi interactions), and halogens [44]. In the compound with the highest binding energy, namely licochalcone A, two conventional hydrogen bonds, one van der waals bond, and seven hydrophobic interactions. The compound with the lowest binding energy, namely 6-methoxyeriodictyol, has four conventional hydrogen bonds and three hydrophobic interactions.

Conventional hydrogen bonds are stronger than carbon-hydrogen bonds. The more hydrophobic interactions, the more hydrophilic the compound will be, thereby increasing the stability of ligand and receptor interactions [45]. According to the results of the visualization obtained, the licochalcone A compound has the highest binding energy value because it has the most bonds and interactions compared to other compounds. Licochalcone A has amino acid interactions that are similar to natural ligands (boceprevir), namely CYS:145, HIS:41, MET:49, MET:165, and HIS:163. This shows that the compound licochalcone A has the potential as an antiviral by inhibiting M^{pro} of Sars-CoV-2.



Boceprevir Oseltamivir Licochalcone

Figure 4. Visualization of Three-Dimension Donor & Acceptor of Boceprevir, Oseltamivir, and *Licochalcone A*

4 Conclusion

In molecular docking studies, the results of the data that play an important role in showing the strength of the interaction between the ligand and the receptor are the values of the binding energy and the inhibition constant. Based on the results obtained, boceprevir (control) had a binding energy value of -8.66 kcal/mol, an inhibition constant of 1.77 µM and oseltamivir (control) had a binding energy of -6.16 kcal/mol and an inhibition constant of 185 .25µM . Licochalcone A had the best binding energy and inhibition constant values of -7.98 kcal/mol and 1.42 µM. On the other hand, 6-Methoxyeriodidictyol has poor binding energy and inhibition constants, namely -5.24 kcal/mol and 143.04 µM. it can be concluded that the compound licochalcone A has the potential to be a better antiviral agent than conventional drugs (oseltamivir), so that this compound can be further developed and tested as an antivirus.

5 Declarations

5.1 Author Contributions

The names of the authors listed in this journal contributed to this research.

5.2 Funding Statement

This research was not supported by any funding sources.

5.3 Conflicts of Interest

The authors declare no conflict of interest.

6 References

[1] World Health Organization. COVID-19 Public Health Emergency of International Concern (PHEIC) Global research and innovation forum. 2020. Available from: https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-

and-innovation-forum [visited on May 09th 2021]
[2] Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S., Soejipto S. Potential Inhibitor of COVID-19 Main Protease (Mpro) from Several Medicinal Plant Compounds by Moleculer Docking Study. Preprints. 2020.
[3] Wink, M., & Mohamed G. Evolution of chemical defense traits in the Leguminosae: mapping of distribution patterns of secondary metabolites on a molecular phylogeny inferred from nucleotide sequences of the rbcL gene [J]. Biochem Syst Ecol. 2003;31(8):897–917.
[4] Huang KC. The pharmacology of Chinese herbs. Boca Rat CRC Press. 1993;261.
[5] Li, RW., Lin, GD., Myers, SP., Leach D. Anti-inflammatory activity of Chinese medicinal vine plants. J Ethnopharmacol. 2003;5:61–7.
[6] Y Goda, M Shibaya, U Sankawa GY. Inhibitors of prostaglandin biosynthesis from Mucuna birdwoodiana. Chem Pharm Bull. 1987;35:2675–7.
[7] Jiang, S.Y., Huang, K., Liu, W., Fu, F.M., Xu J. Combined AutoDock and comparative molecular field analysis study on predicting 5-lipoxygenase inhibitory activity of flavonoids isolated from Spatholobus suberectus Dunn. Zeitschrift Fur Naturforsch C J Biosci. 2015;70(3–4):103–13.
[8] Jain, A.N., Nicolls A. Recommendations for Evaluations of Computational Methods. J Comput Aided Mol. 2008;(22):133–9.
[9] Moitessier, N., Englebienne, P., Lee, D., Lawandi, J., Corbeil C. Towards the Development of Universal, Fast and Highly Accurate Docking Scoring Methods: a Long Way to Go. Br J Pharmacol. 2008;153(1):7–26.
[10] Morris GM, et al. AutoDock Version 4.2: Automated Docking of Flexible Ligands to Flexible Receptors. La Jolla, California, USA Scripps Res Institute. 2009;
[11] Eris Septiana. Prospek Senyawa Bahan Alam Sebagai Antivirus Dalam Menghambat SARS-CoV-2. BioTrends. 2020;11(1):30–8.
[12] Badan Pengawasan Obat dan Makanan Republik Indonesia. Informatorium Obat COVID-19 di Indonesia. BPOM [Internet]. 2020;24. Available from: ISBN 978-602-415-009-9
[13] Kitchen D., Decornez H, Furr J, Bajorath J. Docking and Scoring in Virtual Screening for Drug Discovery. Nat Rev Drug Discov. 2004;48:507–16.
[14] Hawskins P, Warren G, Skillman A, Nicholls A. How to do an Evaluation: Pitfalls and Traps. J Comput Mol Des. 2008;22:179–90.
[15] Rachmania R., Supandi, Cristina F. Analisis Penambatan Molekul Senyawa Flavonoid Buah Mahkota Dewa (Phaleria macrocarpa (Scheff.) Boerl.) pada Reseptor a-Glukosidase sebagai Antidiabetes. Pharmacy. 2016;13:239–51.
[16] Idrees S, Ashfaq U. Discovery and design of cyclic peptides as dengue virus inhibitors through structure- based molecular docking. Asian Pac J Trop Med. 2014;7(7):513–6.
[17] Chen, M., Zhai, L., Christensen, S., Theander, T., and Kinoshita T. Inhibition of fumarate reductase in Leishmenia major and L. Donovani by chalcones. Antimicrob Agents Chemother. 45:2023–9.
[18] Rafi, M., Rosen, R., Vassil, A., Ho, C., Zhang, H., Ghai G et al. Modulation of bel-2 and cytotoxicity by licochalcone-A, a novel estrogenic flavonoid. Anticancer Res. 20:2653–8.
[19] Adianti, M. et al. Anti-hepatitis C virus compounds obtained from Glycyrrhiza uralensis and other Glycyrrhiza species. Microbiol Immunol. 2014;58:180–7.
[20] Toda, S., Shirataki Y. Inhibitory effects of isoflavones on lipid peroxidation by reactive oxygen species. Phytother Res. 1999;13:163–5.
[21] Ding, B., Yuan, L., Yu, H., Li, L., Ma, W., Bi, Y. et al. Genistein and Folic Acid prevent oxidative injury induced by b-amyloid peptide. Basic Clin Pharmacol Toxicol. 2011;108::333–4.
[22] Huang, W.H., Lee, A.R., Yang C. Antioxidative and anti-inflammatory activities of polyhydroxy flavonoids of Scutellaria baicalensis. Biosci Biotechnol Biochem. 2006;(2371):80.
[23] Jung, M. et al. Antioxidant Activity from the Stem Bark of Albizzia julibrissin. Arch Pharm Res. 2003;26(6):458–62.
[24] Tay K-C, Tan LT-H, Chan CK, Hong SL, Chan K-G, Yap WH, et al. Formononetin: A Review of Its Anticancer Potentials and Mechanisms. Front Pharmacol. 2019;10(July):1–19.
[25] Dai, W. et al. Antiviral Efficacy of Flavonoids against Enterovirus 71 Infection in Vitro and in Newborn Mice. Mdpi Journal, Viruses. 2019;625.
[26] Fu, Y.J., Zhu, Y.G.,Wu, N., Kong, Y., Liu, W., Hua X. Application of Cajanus cajan stilbene acid and pinostrobin in Cajanus cajan leaf in preparing anti-herpes virus medicament. 2009;(CN101485649):7–22.
[27] Sun, L., Luo, Q.F., Yang, J., Chen, D.H., Si, J.Y., Pan, R.L. et al. Application of Cajanus cajan L. extracts in preparing hyperlipemia medicine. 2008;CN10120441(18):6–25.
[28] Luo, Q.F., Sun, L., Si, J.Y., Chen D. Hypocholesterolemic effect of stilbenes containing extract-fractionfrom Cajanus cajan L. ondiet- induced hyper cholesterolemia in mice. Phytomedicine. 2008;15:932–9.
[29] Zheng, Y.Y., Yang, J.,Chen, D.H., Sun L. Effects of the stilbene extracts from Cajanus cajan L. On

ovariectomy-inducedboneloss in rats. Acta PharmSin. 2007;42:562–5.
[30] Luo, Q.F., Sun, L., Si, J.Y., Chen, D.H., Du G. Hypocholesterolemic effect of stilbene extract from Cajanus cajan L. On serum and hepatic lipid in diet-induced hyperlipidemic mice. Acta Pharm Sin. 2008;43:145–9.
[31] Nwodo, U. et al. In vivo evaluation of the antiviral activity of Cajanus cajan on measles virus. Arch Virol. 2011;156:1551–7.
[32] Chunhakant, S., Chaicharoenpong C. Antityrosinase, Antioxidant, and Cytotoxic Activities of Phytochemical Constituents from Manilkara zapota L. Bark. Molecules. 2019;24:2798.
[33] Umamaheswari, M., Madeswaran, A., and Asokkumar K. Virtual Screening Analysis and In-vitro Xanthine Oxidase Inhibitory Activity of Some Commercially Available Flavonoids. Iran J Pharm Res IJPR. 2013;12(3):317–23.
[34] MacRaild C.A., Daranas A.H., Bronowska A. HS. Global changes in local protein dynamics reduce the entropic cost of carbohydrate binding in the arabinose-binding protein. J Mol Biol. 2007;368:822–32.
[35] Bronowska A.K. Thermodynamics of ligand-protein interactions: Implications for molecular design. In: Moreno-Piraján J.C., editor. Thermodynamics—Interaction Studies—Solids, Liquids and Gases. InTech; Rijeka, Croat. 2011;1–48.
[36] Liu S.Q. et al. Protein folding, binding and energy landscape: A synthesis. In: Kaumaya P.T.P., editor. Protein Engineering. InTech; Rijeka, Croat. 2012;207–252.
[37] Li H., Xie Y., Liu C. LS. Physicochemical bases for protein folding, dynamics, and protein-ligand binding. Sci China Life Sci. 2014;57:287–302.
[38] Lipinski C., Lombardo F, Dominy B., Feeney P. Experimental and computational approaches to estimare solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46:3–26.
[39] Lipinski C., Lombardo F, Dominy B., Feeney P. Drug Discovery Today. Technologie. 2004;1(4):337–41.
[40] Wulandari EK. Karya Pascasarjana Kimia : Analisis Interaksi Histone Deacetylase (HDAC) Kelas II Homo Sapiens Dengan Suberoyllanilide Hydroxamic Acids (SAHA) dan Trichostantin A (TSA). 2010.
[41] Weni M, et al. Studi In Vitro dan Penambatan Molekuler Senyawa Bioaktif Ekstrak dan Fraksi Daun Sirih Merah (Piper crocatum) sebagai Inhibitor α-Glukosidase. Bogor (ID); 2018.
[42] Stegemann, S. et al. When poor solubility becomes an issue: From early stage to proof of concept. Pharm Sci. 2007;31:249–61.
[43] O'Hagan, S.and Kell D. The Apparent Permeabilities of Caco-2 Cells to Marketed Drugs: Magnitude, and Independence from Both Biophysical Properties and Endogenite Similarities. Peer J3. 2015;1405.
[44] Rollando. Pengantar Kimia Medisinal. In: Wicaksono SR, editor. Malang, Jawa Timur: CV. Seribu Bintang; 2017.
[45] Arwansyah, Laksmi A. TI. Simulasi Docking Senyawa Kurkumin dan Analognya Sebagai Inhibitor Reseptor Androgen pada Kanker Prostat. Curr Biochem J. 2014;1(1):11–9.