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ANTIVIRAL ACTIVITY OF FABACEAE AND ASTERACEAE FLAVONOID COMPOUNDS AGAINST SARS-CoV-2 ON SPIKE PROTEIN, MAIN PROTEASE (Mpro) AND RNA DEPENDENT RNA POLYMERASE (RdRp) RECEPTORS WITH IN SILICO METHOD

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A B S T R A K

This study was conducted to analyze the antiviral activity of flavonoid compounds of Fabaceae (Clitoria ternatea, Caesalpinia sappan, Leucaena leucocephala, Indigofera tinctoria) and Asteraceae (Eclipta prostrata, Artemisia vulgaris, Blumea balsamifera, Chromolaena odorata) against SARS-CoV-2 on spike protein, Mpro and RdRp receptors by molecular docking method in silico. The results of molecular docking with AutoDock Vina showed that the flavonoid compounds semiglabrin (-7,5 kcal/mol) and pseudosemiglabrin (-7,0 kcal/mol) has binding energy better than native ligand NAG (-4,9 kcal/mol) and ceftriaxone (-6,8 kcal/mol) as a standard drug against the spike protein receptor. Flavonoid compounds juglanin (-8,5 kcal/mol) and glabratephrin (-8,5 kcal/mol) has binding energy close to the native ligand 4WI/nirmatrelvir (-8,7 kcal/mol) against Mpro receptor. Flavonoid juglanin (-9,5 kcal/mol) has binding energy better than native ligan 1RP/favipiravir (-8,3 kcal/mol) and remdesivir (-8,7 kcal/mol) as a standard drug, while flavonoid apigetrin (-8,7 kcal/mol) has binding energy better than native ligand and has the same binding energy with remdesivir as a standard drug against RdRp receptor.

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1. Introduction

SARS-CoV-2 was first discovered in Wuhan, Hubei Province, China, in December 2019 and then spread worldwide quickly. On 12 March 2020, WHO designated COVID-19 as a pandemic (WHO, 2020; Susilo et al., 2020). Globally 659,567,564 million confirmed cases and 6,687,189 million confirmed deaths. The number of confirmed cases in Indonesia is 6,718,775 million cases and 160,583 deaths (https://coronavirus.jhu.edu/map.html).

SARS-CoV-2 initiates invasion in host cells by the interaction between spike glycoprotein and angiotensin converting enzyme 2 (ACE-2) receptors assisted by the transmembrane protease serine 2 (TMPRSS2) enzyme (Risma, 2021). After an alliance with the receptor, the spike protein undergoes conformational changes that facilitate the fusion of the viral envelope with the cell membrane via the endosomal pathway. SARS-CoV-2 then releases RNA into the host cell. The RNA Genome is translated into two polyproteins (pp1a and pp1ab) by the host ribosome. These polyproteins then undergo cleavage by proteolytic producing 15-16 nonstructural proteins including two cysteine proteases PLpro and CLpro. These proteases are key to the division process of viral multiplication and the infection cycle. The set of non-structural proteins (NSPs) produced come together to facilitate viral replication and transcription and constitute a multi-subunit transcription. Nsp12 also known as RdRp catalyzes the synthesis of complementary RNA strands using viral RNA templates with the help of nsp7 and nsp8 as co-factors. Polymerase produces a series of subgenomic mRNA with discontinuous transcription and is finally translated into relevant viral proteins. Viral proteins and RNA genomes are then assembled into virions in the ER and Golgi, after which they are transported through vesicles to exit the host cell then infect other cells and repeat the above replication cycle (Mouffouk et al., 2020; Shereen et al., 2020).

Since SARS-CoV-2 was first discovered recently, researchers have continued to conduct research to find potential drug candidates to overcome SARS-CoV-2. Currently, there is only one antiviral drug that has received FDA approval, remdesivir. While in Indonesia based on BPOM guidelines referring to the FDA and WHO, drugs used for SARS-CoV-2 therapy consist of remdesivir, favipiravir, molnupiravir, proksalutamid, oseltamivir, regdanvimab, sotrovimab, bamlanivimab + etesevimab, casirivimab + imdevimab (BPOM, 2021).

In addition to drugs derived from synthetic materials, drugs from plant materials are also widely developed because they have bioactive compounds that have been used therapeutically since ancient times and it is known that about 80% of the world's population depends on medicinal plants or herbs to meet their medicinal needs. Many are using the plant as a drug because of its abundant availability and relatively lower cost, and have secondary metabolites such as alkaloids, polyphenols and terpenoids that are claimed to be efficacious in relieving pathogenic infections because of its ability to prevent penetration and replication of viruses in host cells (Alam, 2021).

Bioactive compounds from plants include polyphenols composed of phenolic acids and flavonoids. Flavonoids are polyphenol biomolecules that are abundant in plants and there are more than 6,000 identified flavonoid molecules. Flavonoids are synthesized in plants in response to stressful conditions and play an important role in defending plant cells against pathogens and insects. Flavonoids are distributed throughout the plant kingdom including angiosperms, gymnosperms and pteridophytes. Flavonoids are found in the Fabaceae (2760) and Asteraceae (1064), where the Fabaceae and Asteraceae are part of the three largest tribes in angiosperms (Russo et al., 2020; Tohge et al., 2018; Christenhusz et al., 2016). Flavonoids have several pharmacological properties such as antiviral, antimicrobial, anti-inflammatory and anticancer. As antivirals, flavonoids have been widely evaluated against various DNA and RNA viruses and have various mechanisms in inhibiting the life cycle of viruses such as blocking the attachment and entry of viruses into the host cell, interfering with various stages of the process of viral replication or translation and polyprotein processing to prevent the release of viruses that can infect other cells (Lalani and Poh, 2020).

Fabaceae is the third largest tribe after Orchidaceae and Asteraceae. Fabaceae has about 700 genera and 20,000 species of trees, shrubs, vines and herbs distributed throughout the world (Britannica T, 2019). In addition, most of the medicinal plants (8.84%) are included in the Fabaceae tribe of a total of 5,490 medicinal plants identified in Indonesia (Cahyaningsih et al., 2021). Asteraceae is the second largest member of the tribe after Orchidaceae. The Asteraceae tribe also dominates plant vegetation on earth with a total of 24,700 species and 1,623 genera spread almost all over the world (Christenhusz and James, 2016). The percentage of medicinal plants from the Astereaceae spread in Indonesia is 3.27% of the total 5,490 medicinal plants. Asteraceae has bioactive compound components, such as sesquiterpenes, lactones, pentacyclic triterpenes, alcohols, alkaloids, tannins, polyphenols, saponins and sterols that can be used for medicinal materials (Weigiera et al., 2012).

Fabaceae flavonoid compounds used in this study consisted of kaempferol, quercetin, myricetin 3-neohesperidosides, myricetin 3-rutinosides, myricetin 3-glucosides from Clitoria ternatea. Brazilin, brazilein, sappanol, episappanol, sappanone A, deoxysappanone B, neosappanone a, neoprotosappanin, sappanone B, hematoxylin from Caesalpinia sappan. Farnisin, naringenin, geraldone, taxifolin, myricitrin, myricetin, apigenin, chysoeriol, luteolin, juglanin from leucocephala Leucaena. Glabratephrin, semiglabrin, pseudo semiglabrin, rutin, naringin from Indigofera tinctoria (Lee Rui et al., 2021; Xu Y et al., 2018; Hasan et al., 2021; Gerometta et al., 2020; Syamsunarno et al., 2021).

Flavonoid compounds from Asteraceae used in this study consisted of apigetrin, pratensein, cynaroside,

oroboside from Eclipta prostrata. Eupafolin, homoeriodictyol, hyperoside, jaceosidin, tricine, vitexin from Artemisia vulgaris. Ayanin, blumeatin, chrysosplenol C, eriodictyol, davidigenin from Blumea balsamifera. Rhamnetin, tamarixetin, ombuin, isosakuranetin, odoratin, kaempferid, rhamnocitrin, laciniatin, acacetin, sinensetin, sakuranetin, padmatin, marionol, eupatilin, kaempferol 7,4-dimethyl ether of Chromolaena odorata (Pang Y et al., 2014; Omokhua et al., 2016; Ekeirt et al., 2020; Timalsina and Devkota, 2021).

Molecular docking in silico method used in this study, is a computer-based method that makes the process of drug discovery and development more efficient, building a database of chemical and biological information about ligands and targets/proteins that can be used to identify and optimize new drugs, designing filters in silico to calculate drug similarity or pharmacokinetic properties of chemical compounds before the screening, to detect early compounds that may fail in the clinical stage and later stages (Le et al., 2015).

In this study, the antiviral activity of flavonoid compounds from Fabaceae and Asteraceae will be tested against SARS-CoV-2 on spike protein receptor (PDB ID: 7T9L), Mpro (PDB ID: 7TLL) and RdRp (PDB ID: 7DFG) with cetriaxone, nirmatrelvir, remdesivir and favipiravir comparator using AutoDock Vina program. Drug-likelihood prediction using the Rule of Five (RO5) rule developed by Lipinski (Jia et al., 2020; Tian et al., 2015). Prediction of physicochemical properties with lipophilic parameters using Log P, electronic parameters using Hydrogen Bond Donors, Hydrogen Bond Acceptor, and steric parameters using molecular weight, Topological Polar Surface Area, and Rotatable Bond using PKCSM online web server. Bioavailability and toxicity prediction using pKCSM online webserver and ToxiM program. (Ravi and Kannanbiran, 2016; Siswandono, 2016; Pires et al., 2015; Drwal et al., 2014).

2. Method

Flavonoid Compounds of Fabaceae and Asteraceae

In this study flavonoid compounds used from the Fabaceae and Asteraceae derived from four plants from each tribe. The plants are taken from the database of Indonesian medicinal plants through the website http://herbaldb.farmasi.ui.ac.id/v3/. Fabaceae flavonoid compounds used in this study consisted of kaempferol, quercetin, myricetin 3-neohesperidosides, myricetin 3-rutinosides, myricetin 3-glucosides from Clitoria ternatea. Brazilin, brazilein, sappanol, episappanol, sappanone A, deoxysappanone B, neosappanone a, neoprotosappanin, sappanone B, hematoxylin from Caesalpinia sappan. Farnisin, naringenin, geraldone, taxifolin, myricitrin, myricetin, apigenin, chysoeriol, luteolin, juglanin from Leucocephala Leucaena. Glabratephrin, semiglabrin, pseudo semiglabrin, rutin, naringin from Indigofera tinctoria (Lee Rui et al., 2021; Xu Y et al., 2018; Hasan et al., 2021; Gerometta et al., 2020; Syamsunarno et al., 2021).

Flavonoid compounds from Asteraceae used in this study consisted of apigetrin, pratensein, cynaroside, oroboside from Eclipta prostrata. Eupafolin, homoeriodictyol, hyperoside, jaceosidin, tricine, vitexin from Artemisia vulgaris. Ayanin, blumeatin, chrysosplenol C, eriodictyol, davidigenin from Blumea balsamifera. Rhamnetin, tamarixetin, ombuin, isosakuranetin, odoratin, kaempferid, rhamnocitrin, laciniatin, acacetin, sinensetin, sakuranetin, padmatin, marionol, eupatilin, kaempferol 7,4-dimethyl ether of Chromolaena odorata (Pang Y et al., 2014; Omokhua et al., 2016; Ekeirt et al., 2020; Timalsina and Devkota, 2021).

Receptor and Docking Validation Preparation

The SARS-CoV-2 receptors used in this study were spike protein (7T9L), Mpro (7TLL) and RdRp (PDB: 7DFG) obtained through the website https://www.rcsb.org/. the receptor that has been obtained is then prepared using AutoDock Vina program, where in this preparation process, the receptor is separated from the original ligand by unselecting the original ligand, then removing the water molecule, added Kollman and gasteiger charge and hydrogen charge (only polar only) and then stored in pdbqt format.

The preparation stage of the original ligand is also the same as the receptor, where the original ligand is separated from the receptor by unselecting the receptor, then water molecules are removed, Kollman and gasteiger charges are added and hydrogen charges (polar only) are then stored in pdbqt format.

Validation of receptor Docking and Native ligands

Molecular docking program validation is done by re-docking the receptor with the original ligand using AutoDock Vina program. Furthermore, the re-docking results are visualized using the BIOVIA Discovery Studio Visualizer 2021. Molecular docking program is valid if the validation parameter observed is the value of RMSD (Root Mean Square Deviation) between the original ligand and ligand re-docking ≤ 2Å.

Preparation of Flavonoid compounds of the Fabaceae and Asteraceae

Flavonoid compounds of Fabaceae and Asteraceae with Spatial Data File (SDF) format obtained through the website https://pubchem.ncbi.nlm.nih.gov/. SDF Format is optimized with energy minimization using molecular-mechanics force fields 94 (MMFF94) through MarvinSketch 21.9 program. Energy minimization results obtained consist of four conformation structures, the lowest energy of the four conformation structures is then selected to be converted into mol2 format and stored. The 3D structure of flavonoid compounds of Fabaceae and Asteraceae was then converted into PDB format for the docking process using AutoDock Vina program.

Evaluation of Drug-Likeness dan Toxicity

Physicochemical properties database of flavonoid compounds of Fabaceae and Asteraceae were used for drug-likeness analysis based on Rule of Five from Lipinski et al. Physicochemical parameters used include MLogP, MW, HBA and HBD. Pubchem database

https://pubchem.ncbi.nlm.nih.gov / used to download SMILES flavonoid compounds Fabaceae and Asteraceae to be able to see the characteristics of ADMET using ADMETlab and pKCSM https://niosig.unimelb.edu.au/pkcsm / and the toxicity class uses ProTox-II.

Analysis of Molecular Docking

Molecular docking analysis of 49 flavonoid compounds of Fabaceae and Asteraceae that meet the requirements of drug-likeness to spike protein receptor with grid box size (20x20x20), center grid box at active site x: 233.099, y: 170.088, z: 249.747; Mpro with grid box size (20x20x20), center grid box at active site x: -1.764, y: -0.325, z: 13.954 and RdRp with grid box size (20x18x22), Center grid box on active site X: 129.163, y: 131.751, Z: 141.888 performed using AutoDock Vina program. Fabaceae and Asteraceae flavonoid compounds with the lowest binding energy are potential antiviral candidates that can inhibit SARS-CoV-2. The obtained docking results can be visualized using the BIOVIA Discovery Studio Visualizer 2021 program.

3. Result and Discussion

Validation Docking Receptor dan Native Ligands

The results of molecular docking Program Validation on spike protein receptor (7T9L), Mpro (7TLL), RdRp (7DFG) using AutoDock Vina v.1.5.7 and validation parameters in the form of Root Mean Square Docking (RMSD) obtained using the BIOVIA Discovery Studio Visualizer 2021 program.

Validation of Spike Protein Receptor (PDB: 7T9L)

Validation of docking method on spike protein receptor with native ligand NAG is presented in table 1.

Table 1. Validation Docking Spike Protein with Native Ligand NAG

Grid Box	Grid Center	RMSD (Å)	Binding Energy (kcal/mol)
20x20x20	x: 233.099 y: 170.088 z: 249.747	1.8604	-4,9

Validation of Mpro Receptor (PDB: 7TLL)

Validation of docking method on Mpro receptor with native ligand 4WI/nirmatrelvir is presented in table 2.

Table 2. Validation Docking Mpro Receptor with Native Ligand 4WI/Nirmatrelvir

Grid Box	Grid Center	RMSD (Å)	Binding Energy (kcal/mol)
20x20x20	x: -1.764 y: -0.325 z: 13.954	1.8854	-8,7

Validation RdRp Receptor (PDB: 7DFG)

Validation of docking method on RdRp receptor with native ligand 1RP/favipiravir is presented in table 3

Table 3. Validation Docking RdRp Receptor with Native Ligand 1RP/Favipiravir

Grid Box	Grid Center	RMSD (Å)	Binding Energy (kcal/mol)
20x18x22	x: 129.163 y: 131.750 z: 142.808	2.39014	-8,3

Evaluation of Drug-Likeness

The results of drug-likeness analysis of flavonoid compounds of Fabaceae and Asteraceae according to Lipinski using SwissADME (www.swissadme.ch/) with the requirements of drug-likeness is the "Rule of Five" (RO5) developed by Lipinski include molecular weight (MW) <500, Moriguchi Octanol-Water Partition coefficient (MLogP) <5, Hydrogen Bond Donors (HBD) <5, Hydrogen Bond Acceptor <10 (Tian et al., 2015). Flavonoid compounds that meet the requirements are presented in table 4.

Table 4. Drug Likeness Lipinski Flavonoid of Fabaceae and Asteraceae

Fabaceae						
No	**Flavonoid**	**Parameter Steric MW < 500**	**Paremeter Lipophilic MLogP < 5**	**Parameter Electronic**		**RO5**
				HBA ≤ 10	**HBD ≤ 5**	
Clitoria ternateae						
1	Kaempferol	286.24	-0.03	6	4	Pass
2	Quercetin	302.23	-0.56	7	5	Pass
3	Myricetin 3-neohesperidosides	626.5	-4.35	17	11	No
4	Myricetin 3-rutinosides	626.5	-4.35	17	11	No
5	Myricetin 3-glucosides	480.4	-3.07	13	9	No
Leucaena leucocephala						
6	Farnisin	284.26	0.77	5	2	Pass
7	Naringenin	272.25	0.71	5	3	Pass
8	Geraldone	284.26	0.77	5	2	Pass
9	Taxifolin	304.25	-0.64	7	5	Pass
10	Myricitrin	464.4	-2.32	12	8	No
11	Myricetin	318.23	-1.08	8	6	Pass
12	Apigenin	270.24	0.52	5	3	Pass
13	Chrysoeriol	300.26	0.22	6	3	Pass
14	Luteolin	286.24	-0.03	6	4	Pass
15	Juglanin	418.3	-1.57	10	6	Pass
Caesalpinia sappan						
16	Brazilin	286.28	1.04	5	4	Pass
17	Brazilein	284.26	0.42	5	3	Pass
18	Sappanol	304.29	0.23	6	5	Pass
19	Episappanol	304.29	0.23	6	5	Pass
20	Sappanone A	284.26	0.88	5	3	Pass
21	Deoxysappanone B	286.28	0.96	5	3	Pass
22	Neosappanone A	600.6	-0.55	11	6	No
23	Neoprotosappanin	570.5	1.1	10	8	No

24	Sappanone B	302.28	0.15	6	4	Pass
25	Hematoxylin	302.28	0.49	6	5	Pass
Indigofera tinctoria						
26	Glabratephrin	420.4	1.91	7	0	Pass
27	Semiglabrin	392.4	2.16	6	0	Pass
28	Pseudo semiglabrin	392.4	2.16	6	0	Pass
29	Rutin	610.5	-3.89	16	10	No
30	Naringin	580.5	-2.77	14	8	No
Asteraceae						
No	**Flavonoid**	**Parameter Steric MW < 500**	**Paremeter Lipophilic MLogP < 5**	**Parameter Electronic**		**RO5**
				HBA ≤ 10	**HBD ≤ 5**	
Eclipta prostrata						
31	Apigetrin	432.4	-1.61	10	6	Pass
32	Pratensein	300.26	0.22	6	3	Pass
33	Cynaroside	448.4	-2.1	11	7	No
34	Oroboside	448.4	-2.1	11	7	No
35	Eupafolin	316.26	-0.31	7	4	Pass
Artemisia vulgaris						
36	Homoeriodictyol	302.28	0.41	6	3	Pass
37	Hyperoside	464.4	-2.59	12	8	No
38	Jaceosidin	330.29	-0,07	7	3	Pass
39	Tricine	179.17	-4.32	6	5	Pass
40	Vitexin	432.4	-2.02	10	7	Pass
Blumea balsamifera						
41	Ayanin	344.3	0.17	7	2	Pass
42	Blumeatin	302.28	0.41	6	3	Pass
43	Chrysosplenol C	360.3	-0.35	8	3	Pass
44	Eriodictyol	288.25	0.16	6	4	Pass
45	Davidigenin	258.27	1.66	4	3	Pass
Chromolaena odorata						
46	Rhamnetin	316.26	-0.31	7	4	Pass
47	Tamarixetin	316.26	-0.31	7	4	Pass
48	Ombuin	330.29	-0.07	7	3	Pass
49	Isosakuranetin	286.28	0.96	5	2	Pass
50	Odoratin	314.29	0.47	6	2	Pass
51	Kaempferid	300.26	0.22	6	3	Pass
52	Rhamnocitrin	300.26	0.22	6	3	Pass
53	Laciniatin	346.3	-0.59	8	4	Pass
54	Acacetin	284.26	0.77	5	2	Pass
55	Sinensetin	372.4	0.63	7	0	Pass
56	Sakuranetin	286.28	0.96	5	2	Pass
57	Padmatin	318.28	-0.39	7	4	Pass
58	Marionol	388.4	0.11	8	1	Pass
59	Eupatilin	344.3	0.17	7	2	Pass
60	Scutellarein-tetramethyl ether	342.3	0.94	6	0	Pass

Evaluation of Bioavailability

Bioavailability analysis of flavonoid compounds of Fabaceae and Asteraceae tribes to measure the number of active ingredients that are absorbed into the systemic circulation and reach the site of drug action (Marlene Kim, 2014). Bioavailability analysis (Human Intestinal Absorption) on each flavonoid compounds Fabaceae and Asteraceae tribes 2 databases, among others, ADMETlab and pkCSM. In the use of pkCSM database, HIA is expressed in percentage (%). Compounds with optimal bioavailability if the value of HIA > 30% and bioavailability is not optimal if the value of HIA < 30%. Meanwhile, in the ADMETlab database, HIA is expressed in 2 categories, among others, (+) for compounds with optimal bioavailability if the HIA value is 30%, and (-) for compounds with non-optimal bioavailability where the HIA value is <30% (Pires, Blundell & Ascher., 2015; Dong., et al., 2018: Yang et al., 2019). The results of HIA prediction of flavonoid compounds of Fabaceae and Asteraceae showed a range of values from 14,071% to 100%. A total of 83.33% of secondary metabolites have good absorption, except Myricetin-3-rutinosides, myiricetin-3-neohesperidosides, rutin and naringin with a percentage that can be absorbed <30%. Compounds in conjugated form with sugar groups are mostly deglycosylated by enterocyte-specific enzymes in the small intestine. The enzyme plays an important role in the absorption and metabolism of glycosides, due to compounds in the form of aglycones that can enter enterocytes by passive diffusion (Shi et al, 2016). Evaluation of the Bioavailability of flavonoid Fabaceae and Asteraceae are presented in table 5.

Table 5. Evaluation of Bioavailability and Toxicity Flavonoid Fabaceae and Asteraceae

Fabaceae						
No.	**Flavonoid**	**Bioavailability**			**Toxicity**	
		ADMETlab		**pkCSM**	**Protox II**	
		Probability	**HIA**	**HIA (%)**	**LD_{50} (mg/kg)**	**Class**
Clitoria ternateae						
1	Kaempferol	0.47	+	74.29	3919	5
2	Quercetin	0.438	+	77.207	159	3
3	Myricetin 3-neohesperidosides	0.184	-	15.121	5000	5
4	Myricetin 3-rutinosides	0.21	-	14.071	5000	5
5	Myricetin 3-glucosides	0.155	-	33.394	5000	5
Leucaena leucocephala						
6	Farnisin	0.606	+	94.789	4000	5
7	Naringenin	0.52	+	91.31	2000	4
8	Geraldone	0.606	+	94.865	4000	5
9	Taxifolin	0.438	+	64.709	2000	4
10	Myricitrin	0.394	+	43.334	5000	5
11	Myricetin	0.438	+	65.93	159	3
12	Apigenin	0.531	+	93.25	2500	5
13	Chrysoeriol	0.498	+	82.844	4000	5
14	Luteolin	0.438	+	81.13	3919	5
15	Juglanin	0.177	-	57.279	5000	5
Caesalpinia sappan						
16	Brazilin	0.517	+	94.651	800	4
17	Brazilein	0.579	+	59.621	2000	4
18	Sappanol	0.453	+	64.921	2500	5
19	Episappanol	0.453	+	64.921	2500	5
20	Sappanone A	0.514	+	93.627	3800	5
21	Deoxysappanone B	0.443	+	94.099	2000	4
22	Neosappanone A	0.424	+	87.255	290	3
23	Neoprotosappani	0.454	+	100	800	4

	n					
24	Sappanone B	0.467	+	71.471	2000	4
25	Hematoxylin	0.517	+	80.45	500	4
Indigofera tinctoria						
26	Glabratephrin	0.594	+	100	1213	4
27	Semiglabrin	0.645	+	99.712	5000	5
28	Pseudo semiglabrin	0.645	+	99.712	5000	5
29	Rutin	0.21	-	23.446	5000	5
30	Naringin	0.184	-	25.796	2300	5
Asteraceae						
No.	**Flavonoid**	**Bioavailability**			**Toxicity**	
		ADMETlab		**pkCSM**	**Protox II**	
		Probability	**HIA**	**HIA (%)**	**LD_{50} (mg/kg)**	**Class**
Eclipta prostrata						
31	Apigetrin	0.142	-	37.609	5000	5
32	Pratensein	0.498	+	84.995	2500	5
33	Cynaroside	0.155	-	37.556	5000	5
34	Oroboside	0.155	-	37.52	5000	5
Artemisia vulgaris						
35	Eupafolin	0.455	+	77.294	3919	5
36	Homoeriodictyol	0.462	+	73.251	2000	4
37	Hyperoside	0.155	-	47.999	5000	5
38	Jaceosidin	0.501	+	74.755	3919	5
39	Tricine	0.301	+	21.589	4860	5
40	Vitexin	0.263	-	46.695	832	4
Blumea balsamifera						
41	Ayanin	0.608	+	91.735	5000	5
42	Blumeatin	0.54	+	81.928	2000	4
43	Chrysosplenol C	0.563	+	85.154	5000	5
44	Eriodictyol	0.407	+	74.687	2000	4
45	Davidigenin	0.427	+	91.284	500	4
Chromolaena odorata						
46	Rhamnetin	0.562	+	80.214	5000	5
47	Tamarixetin	0.498	+	73.005	5000	5
48	Ombuin	0.61	+	87.47	5000	5
49	Isosakuranetin	0.54	+	92.374	2000	4
50	Odoratin	0.61	+	93.339	2500	5
51	Kaempferid	0.498	+	79.898	3919	5
52	Rhamnocitrin	0.606	+	87.511	4000	5
53	Laciniatin	0.501	+	67.803	5000	5
54	Acacetin	0.554	+	94.318	4000	5
55	Sinensetin	0.699	+	98.578	5000	5
56	Sakuranetin	0.652	+	92.601	2000	4
57	Padmatin	0.562	+	72.403	2000	4
58	Marionol	0.68	+	100	5000	5
59	Eupatilin	0.509	+	78.996	5000	5
60	Scutellarein-tetramethyl ether	0.699	+	98.35	4000	5

Description:
LD50 : Lethal dose of 50% tested animal (mg/kg)
Class 1 : Fatal if swallowed (LD50 ≤ 5 mg/kg)
Class 2 : Fatal if swallowed (5 < LD50 ≤ 50 mg/kg)
Class 3 : Toxic if swallowed (50 < LD50 ≤ 300 mg/kg)
Class 4 : Harmful if swallowed (300 < LD50 ≤ 2000 mg/kg)
Class 5 : Possibly harmful if swallowed (2000 < LD50 ≤ 5000 mg/kg)
Class 6 : No toxic (LD50 > 5000 mg/kg)

Evaluation of Toxicity

Toxicity analysis of flavonoid compounds of Fabaceae and Asteraceae tribes to ensure safety was performed with LD50 parameter prediction representing acute toxicity. LD50 is a sufficient dose to cause death in 50% of test animals (Siswandono, 2016). LD50 prediction results based on PROTOX-II showed that there were 3 flavonoid compounds of Fabaceae that were toxic if ingested (50 < LD50 ≤ 300 mg/kg), 9 compounds that were harmful if ingested (300 < LD50 ≤ 2000 mg/kg) and 18 compounds that were potentially harmful if ingested. The results of LD50 prediction for flavonoid compounds Asteraceae found that there are 8 compounds that are harmful if ingested (300 < LD50 ≤ 2000) and 22 (2000 < LD50 ≤ 5000 mg/kg) compounds that may be harmful if ingested. Analysis of the toxicity of flavonoid compounds Fabaceae and Asteraceae through the online web program ProTox-II (http://tox-new.charite.de/protox_II/) obtained that all flavonoid compounds Fabaceae and Asteraceae meet the requirements with LD50 more than 150 mg/kg. Evaluation of toxicity flavonoid Fabaceae and Asteraceae are presented in table 5.

Analysis Molecular Docking

Molecular docking analysis between Fabaceae and Asteraceae flavonoid compounds to spike protein, Mpro and RdRp receptors was performed using AutoDock Vina 1.5.7. The results of molecular docking obtained that flavonoid compounds Fabaceae of Indigo tinctoria plants are semiglabrin and pseudo semiglabrin has the potential to inhibit spike protein with binding energy respectively -7.5 kcal/mol and -7.0 kcal/mol higher than the original ligand NAG -4.9 kcal/mol and ceftriaxone as a standard drug with binding energy -6.8 kcal/mol. Flavonoid compounds of Fabaceae, juglanin from Leucaena leucocephala plant and glabratephrin from Indigo tinctoria plant have the potential to inhibit Mpro with the same bond energy of -8.5 kcal/mol which is close to the original ligand bond energy value which is comparable to nirmatrelvir -8.7 kcal/mol. Flavonoid compounds Fabaceae juglanin of Lecaena leucocephala plants have the potential to inhibit RdRp with bond energy -9.5 kcal/mol higher than the comparator favipiravir -8.3 kcal/mol and remdesivir -8.7 kcal/mol. Flavonoid compounds of Asteraceae apigetrin from Eclipta prostrata plants have the potential to inhibit RdRp with bond energy -8.7 kcal/mol which is the same and higher than the standard drug favipiravir -8.3 kcal/mol and remdesivir -8.7 kcal/mol.

Binding Interaction Analysis of Flavonoid Compound Fabaceae and Asteraceae, Native Ligand and Drug References with Spike Protein, Mpro and RdRp Receptor.

Predictive analysis of the activity of subsequent secondary metabolites using binding interaction parameters. The observed bond interactions are hydrogen bonds, hydrophobic bonds, and in addition to these two bonds are grouped in other bonds. A hydrogen bond is a bond between an H atom that has a partial positive charge and another atom that is electronegative and has a pair of free electrons with a complete octet, such as O, N, and F. Hydrophobic bonds are one of the important forces in the process of combining non-polar regions of drug molecules

with non-polar regions of biological receptors (Siswandono, 2016). Interaction between ligand and receptor is important to be analyzed because there are amino acids that are the key to the inhibition and induction of biological target macromolecule activity. Bonding interactions are visualized using the BIOVIA Discovery Studio Visualizer 2021 program. Assessment of activity in terms of bonding interactions that occur in flavonoid compounds of the Fabaceae and Asteraceae includes interactions with important amino acids in the target protein. Bonding interactions between flavonoid compounds of the Fabaceae and Asteraceae were compared with native ligands and reference drugs.

The spike protein receptor complex (PDB code 7T9L) and native ligand (NAG) result in bonding interactions at 7 amino acid residues namely Ser494, Ser496, Tyr501, His505, Arg403, Tyr495 and Tyr453. Hydrogen bonds occur in the amino acids Ser494, Ser496, Tyr501, His505, Arg403, Tyr495 and Tyr453. Ceftriaxone comparison drugs have the same amino acid bond interactions with the original ligands, namely Ser496, Arg403 and Tyr495 and 4 other amino acids, namely Arg493, Arg498, Glu406 and Tyr449. Hydrogen bonds occur in the amino acids Ser496, Arg403, Tyr495, Arg493, Arg498 and Glu406. another pi-sulfur bond occurs in the amino acid Tyr449.

Based on the latest research conducted by Manar D et al, obtained the results that the critical residues of the spike receptor protein that increase the binding affinity with ACE-2 consist of Arg493 forms a new salt bridge with ACE-2, Arg498 forms a new salt bridge with ACE-2, Ser496 that forms a hydrogen bond with ACE-2 and Tyr501 that forms a pi-stacking bond whereas His505 decreases the binding affinity of spike protein because it does not form a hydrogen bond with ACE-2 (Manar D et al, 2022). Flavonoid compounds of the Fabaceae semiglabrin produce bonding interactions on 4 amino acid residues, namely Arg498, Ser496, Tyr501, and His505. Hydrogen bonds occur in Ser496, Arg498 and His505, hydrophobic bonds occur in the amino acid Tyr501. Flavonoid compounds of Fabaceae pseudosemiglabrin produce bonding interactions on 3 amino acid residues namely Tyr501, Tyr449 and His505. Hydrogen bonding occurs in Tyr449, hydrophobic bonding occurs in the amino acids Tyr501 and His505.

The Mpro receptor complex (PDB code 7TLL) and the native ligand nirmatrelvir (4WI) produce bonding interactions at 9 amino acid residues namely Asn142, Cys145, Met49, His163, His172, His41, Gly143, Glu166 and Thr26. Hydrogen bonds occur in amino acids His41, Gly143, Glu166 and Asn142, hydrophobic bonds occur in Cys145, Met49, His163, His172, and other bonds in the form of halogen bonds occur in Thr26. Mpro is known to have an active site located at the junction of domains I and II with the amino acid residues His41 and Cys145 located within S' and forming the CysHis catalytic dyad. Mpro is one of the most interesting drug targets because mpro homologs are not found in humans. (Yan W et al, 2022).

Flavonoid compounds of the Fabaceae juglanin produce bonding interactions on 8 amino acid residues, namely Gln192, Leu141, His163, Glu166, Cys145, His41, Met49 and Met165. Hydrogen bonds occur in Gln192, Leu141, His163 and Glu166, hydrophobic bonds occur in the amino acid His41, other bonds such as pi-cation (electrostatic bonding) occur in the amino acid His41 and pi-sulphur occurs in the amino acids Cys145, Met49 and Met165. Flavonoid compounds of the Fabaceae glabratephrin produce bonding interactions on 6 amino acid residues, namely Asn142, His163, Cys145, His41, Met49 and Met165. Hydrogen bonds occur in Asn142, His163, Cys145 and Met165, hydrophobic bonds occur in the amino acids His41 and Met49.

The RdRp receptor complex (PDB code 7DFG) and favipiravir native ligand (1RP) produce binding interactions at 6 amino acid residues namely Asp623, Cys622, Thr680, Asn691, Thr687 and Ser682. Hydrogen bonding occurs in all amino acids. Remdesivir comparison drug interactions are the same with the original ligand being the amino acids Ser682, Thr680, Asp623, while not the same is the amino acids Arg555, Lys545 and Ala547. Hydrogen bonds occur in the amino acids Ser682, Thr680, Arg555 and Lys545, hydrophobic bonds occur in the amino acid Ala547.

Active site RdRp is located on the palm subdomain and is formed by the A-E motif. The C Motif binds to the 3 ' end of RNA and contains Asp760 and Asp761 residues, which are necessary for RNA synthesis. The F and G motifs reside on the finger subdomain and position the RNA template. Residues Asn691, Ser682, Asp623 can recognize the 2'-OH group of NTP, thus making RdRp specific for RNA synthesis rather than DNA. Important amino acids included in the main binding residues are Arg555, Val557 and Asp618 (Zhang and Zou, 2020; Hillen HS et al., 2020).

Flavonoid compounds of the Fabaceae juglanin produce bonding interactions on 6 amino acid residues, namely Arg555, Arg553, Asp760, Asn691 and Asp623. Hydrogen bonds occur in Arg555, Arg553, Asp760 and Asn691, hydrophobic bonds occur in Arg555 amino acids, and other bonds such as pi-cation occur in Asp623. Flavonoid compounds of Asteraceae apigetrin produce bonding interactions on 2 amino acid residues, namely Arg555 and Lys545. Hydrogen bonds occur in Lys545, hydrophobic bonds occur in the amino acid Arg555, and other bonds such as pi-cation occur in Arg555.

4. Conclusion

Based on the results obtained that the flavonoid compounds apigenin, glabratephrin, semiglabrin, pseudo semiglabrin from Fabaceae and flavonoid compounds apigetrin, acacetin from Asteraceae potentially inhibit spike protein by binding to residues Ser496, Tyr501 and His505. Flavonoid compounds juglanin, glabratephrin from Fabaceae and apigetrin from Asteraceae potentially inhibit the Mpro receptor by binding to His41 and Cys145 residues that are on the active site of the Mpro receptor.

The flavonoid compounds Juglanin of the Fabaceae (binds to the important residues Arg555 and Val557) and apigetrin of the Asteraceae (binds to the important residue Arg555) have the potential to inhibit the RdRp receptor. Further experimental studies such as in vitro assays and molecular dynamics are needed to support the results of this study. The results of this study can be a reference material for researchers who want to research more about plants from the Fabaceae and Asteraceae. In addition, this study can be a database of plants that have the potential to be anti-SARS-CoV-2.

5. Acknowledgement

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6. Conflict Of Interest

The author has no conflict of interest to declare.

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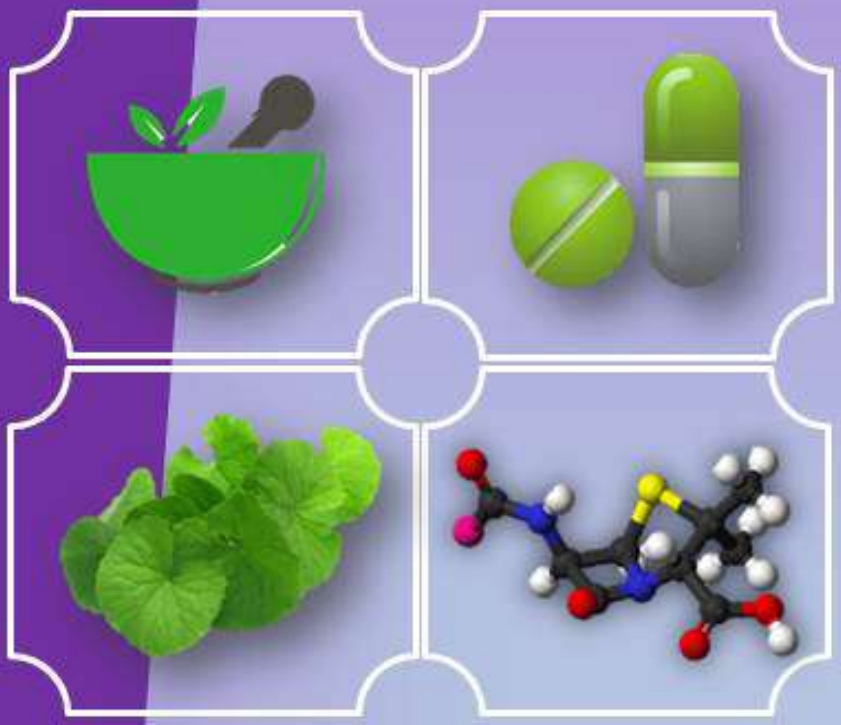

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