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Research Article

Potential of Quercetin Compound from Guava Leaves (*Psidium guajava* L.) as a Inhibitor COVID-19

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Abstract

This research is a computer-based experimental study using the molecular docking method of quercetin compounds in the leaves of the guava plant (*Psidium guajava* L.) against the target protein (receptor), namely Mpro SARS-CoV-2 (PDB ID: 6M2N) using various softwares. consists of Chem Draw Ultra version 7.0, Marvin Sketch, PLANTS, Yasara, Discovery Studio Visualizer 2021, and pkCSM online tool and, protox online tool. This study aims to find out how the potential of the quercetin compound from the leaves of the guava plant (*Psidium guajava* L.) has on its ability to inhibit the spread of Covid-19 by molecular docking. Data analysis in this study was carried out based on data obtained from the analysis of pharmacokinetic profiles, physicochemical properties, molecular docking, and predictions of toxicity to compounds that have potential as drug ingredients. Based on the results of molecular docking, it was shown that the quercetin compound has the potential to act as an inhibitor of the Mpro receptor (PDB ID: 6M2N) as evidenced by the docking score obtained which is smaller than the docking score obtained by the original ligand of the target receptor.

Keywords: Covid-19, Guava Leaves (*Psidium guajava* L.), Quercetin Compounds

Potensi Senyawa Quercetin dari Daun Jambu (*Psidium guajava* L.) sebagai Inhibitor COVID-19

Abstrak

Penelitian ini merupakan penelitian eksperimental berbasis komputer dengan menggunakan metode molekuler docking senyawa quercetin dari daun tanaman jambu biji (*Psidium guajava* L.) terhadap protein target (reseptor) yaitu Mpro SARS-CoV-2 (PDB ID: 6M2N) dengan menggunakan berbagai *software*. terdiri dari *Chem Draw Ultra* versi 7.0, Marvin *Sketch*, PLANTS, Yasara, *Discovery Studio Visualizer* 2021, dan situs pkCSM *online tool* dan *Protox online tool*. Penelitian ini bertujuan untuk mengetahui bagaimana potensi senyawa quercetin dari daun tanaman jambu biji (*Psidium guajava* L.) terhadap kemampuannya dalam menghambat penyebaran Covid-19 dengan metode molekuler docking. Analisis data pada penelitian ini dilakukan berdasarkan data diperoleh dari analisis profil farmakokinetik, sifat fisikokimia, molekuler docking, dan prediksi toksisitas terhadap senyawa yang berpotensi sebagai bahan obat. Berdasarkan hasil molekuler docking menunjukkan bahwa senyawa quercetin berpotensi sebagai inhibitor reseptor Mpro (PDB ID: 6M2N) yang dibuktikan dengan score docking yang diperoleh lebih kecil dibandingkan dengan score docking yang diperoleh oleh ligand asli dari reseptor target.

Kata Kunci: Covid-19, Daun Jambu Biji (*Psidium guajava* L.), Senyawa quercetin

1. Introduction

The effects of the global pandemic caused by the corona virus or also known as Corona Virus Disease 2019 (Covid-19) were felt in almost all countries in 2020. Covid-19 is a disease that spreads through droplets, especially fluids released when breathing, sneezing, coughing and talking. As a result, the virus spreads rapidly and quickly through interpersonal contact. According to WHO (2020), the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Corona Virus-2) is the cause of this outbreak.[1] SARS-CoV-2 is a virus from the genus Betacoronavirus. Previously, it was known that this genus has four strains which include: MERS-CoV, HKU1, OC43, HKU1, and SARS-CoV. However, for SARS-CoV-2 it has been confirmed that the virus is the fifth strain that causes pneumonia of this genus.[2]

Based on data from WHO on July 12 2022, globally there are 561.3 million people who have been infected with the corona virus, and around 6.3 million people have died. The United States (3.4 million inhabitants), France (2.1 million inhabitants), and Italy (1.64 million inhabitants) are some of the countries with the most confirmed cases of Covid-19. Meanwhile, Indonesia is ranked 62th in the world.[3]

Meanwhile, for Covid-19 therapy, favipiravir and remdesivir are used as forms of treatment. It's just that both types of synthetic drugs have side effects that are quite detrimental to humans. Favipiravir has a number of potentially dangerous side effects, including increased uric acid levels, digestive problems, diarrhea, liver changes, and results in animal studies that were teratogenic and embryotoxic.[1] Meanwhile, Remdesivir has side effects such as nausea, acute respiratory disorders, and increased enzymes in the liver.[1] The weakness of these synthetic drugs can support to encourage local/indigenous resources, in order to promote our biodiversity. One of the medical plants that has the potential to inhibit the spread of Covid-19 is the leaves of the guava plant (*Psidium guajava* L.).

Several research results have proven that guava leaves have various pharmacological activities, including anti-inflammatory, analgesic, antimicrobial, antiviral, anticancer, and antioxidant. Studies conducted by Joseph & Priya (2020) It was found that guava leaves can inhibit the activity of various viruses such as OMV (oncorhyncus masou virus), YHV (yellow head virus), and IHNV (infectious haematopoietic necrosis virus).[4] In research conducted by Chollom et al (2012) also proves that guava leaves have the potential as an antiviral against NDV (Newcastle disease virus),[5] as for research from Srwilaijaroen et al (2012) proves that tea made from the leaves of guava plant can protect the body from infection with the influenza virus (H5N1 virus).[6] This is because guava leaves contain compounds that can inhibit viruses, one of which is quercetin.

Quercetin is a phytochemical compound found in many plants that can inhibit the replication process of various viruses such as the highly pathogenic influenza virus, type-2 dengue virus, rhinovirus, poliovirus, HSV-1, respiratory syncytium virus, and adenovirus.[7]

Judging from the leaves of the guava plant and the quercetin compound it contains has the potential as a candidate for a corona antiviral drug, therefore this research was conducted to determine the potential of the quercetin compound from the leaves of the guava plant (*Psidium guajava* L.) for its ability to inhibit the spread of Covid-19 molecularly docking.

2. Metode

This research was conducted from January until May 2023. The type of this research was computer-based experimental research using the molecular docking method of the compound quercetin in the leaves of the guava plant (*Psidium guajava* L.) against the receptor (protein) Mpro (PDB ID: 6M2N).

2.1. Tools

Software used in this study includes the Windows 10 Pro operating system, Chem Draw Ultra version 7.0, Marvin Sketch, PLANTS, Yasara, Discovery Studio Visualizer 2021, pkCSM online tool, and Protox online tool.[8,9,10]

2.2. Bahan

The structure of quercetin from the leaves of the guava plant (*Psidium guajava* L.) and the structure of the Mpro SARS-CoV-2 protein (PDB ID: 6M2N).

2.3. Procedures

2.3.1. Mpro Target Protein Preparation (PDB ID: 6M2N)

Protein and reference ligand (3WL_401) preparation is done by downloading the PDB (Protein Data Bank) code with Id 6M2N via (https://www.rscb.org/pdb), then saving it in *pdb format. Next, the downloaded results were opened in the YASARA application, removing the original ligand and leaving only the target protein. The results are then stored in *mol2 format. The final step is protein and reference ligand preparation by creating a *mol2 file containing only the original ligand.

2.3.2. Preparation of Ligand/Test Compound (Quercetin)

Before preparing the test compound, analysis was carried out first using QSAR analysis to check the suitability of the test compound for the bioactivity determined using the Way2Drug site. After that, the namely the quercetin compound from the leaves of the guava plant (*Psidium guajava* L.) is drawn in a two-dimensional (2D) structure using the Chem Draw Ultra version 7.0 software which will then be transferred to the Marvin Sketch software. Next, protonate it at pH 7.4 and save it in the docking folder with *mrv format. After that, perform geometry optimization by searching 10 conformations. The conformation search's findings are saved in *mol2 format.

2.3.3. Running Molecular Docking and Ligand-Receptor Laying

At this stage, running the best ranking ligand was carried out using the PLANTS and cmd.exe software in which the software would process the running docking for the ten conformations of the ligand that had been prepared previously. After the running docking process has finished up to the result stage, then select the ligand with the smallest (most negative) docking score contained in the results folder and then save it in the docking folder.

The ligand and receptor docking process has the same steps as the running molecular docking process.

2.3.4. Docking Validation

Docking validation is carried out on the Yasara application by loading reference_ligand.mol2 with the docking results that have been previously copied to the docking folder. Then calculate the RMSD value.[11]

2.3.5. Docking Visualization

At this stage, load the ligand with the best docking score through the Yasara application. Then remove the hydrogen atoms then merge the two objects and save them in the docking folder with *pdb format. Then visualize the ligand-protein interactions in 2D and 3D using the Discovery Studio Visualizer 2021.[12]

2.3.6. Data Analysis

Data from analyses of pharmacokinetic profiles, physicochemical characteristics, molecular docking, and prediction of toxicity to compounds that show promise as drug candidates were used to carry out the data analysis in this study.

3. Result and Discussion

3.1. Screening of Physicochemical Properties of Quercetin Compounds

Prediction results of the parameter values for the physicochemical properties of the quercetin compound using the pkCSM online tool. Lipinski's law of five parameters consist of molecular weight is less than 500 g/mol, Log P is less than 5, H-bond donors is less than 5, and H-bond acceptors is less than 10. According to Lipinski et al. (1997) if a compound has one or more of the following characteristics, known collectively as the five Lipinski laws namely: molecular weight greater than 500, log P value greater than 5, H-bond donors (HBD) which is expressed by the number of O-H and N-H groups greater

than 5, and H-bond acceptors (HBA) which is expressed by the number of O and N atoms greater than 10, and the number of O and N atoms larger than 10 is used to express the H-bond acceptors (HBA) property, then the substances will have low permeability and be difficult to absorb in the body.[13] The Table 1 shows the findings of the screening of the physicochemical characteristics of quercetin compounds.

In Table 1 it can be analyzed that the quercetin compound from the leaves of guava plant (*Psidium guajava* L.) studied complies with the requirements of Lipinski's five laws where the compound has a molecular weight of less than 500, log P less than 5, number of H-bond donors less than 5, H-bond acceptors less than 10, torsion value less than 10 and TPSA value less than 140Å. Considering these outcomes, it is predicted that the quercetin compound can be easily absorbed in the body, has good oral bioavailability, and has good permeability.

3.2. Molecular Docking Results

The results of the molecular docking process for both quercetin and reference ligand compounds against the main protein Covid-19 protease (PDB ID: 6M2N) is shown in the Table 2.

Based on the docking score values in Table 2, it shows that both the quercetin compound and the reference ligand (comparison compound) have the same docking score value, which is negative or less than 0 for the target protein Mpro (PDB id: 6M2N). If the tested ligand has a docking score value of less than 0, it indicates that the tested ligand has an affinity for the binding site of the target protein.[14] Considering the outcomes in Table 2, the quercetin compound has a smaller docking score value compared to reference ligand. According to Gogoi et al (2021) It is that the tested chemical exhibits greater selectivity for the target protein if its docking score is lower than that of the reference compound.[15] The lower the docking score, the stronger the bond between the ligand and the target protein.

Due to the stability and the potency of the non-covalent contacts between the drug and the target protein, the bond between the molecule and the protein will be stronger the lower the docking score. As a result, it can be claimed that the test chemical interacts more readily than the reference ligand in the binding site area.[16] These result illustrate that the quercetin compound has the potential to become an inhibitor of the Mpro SARS-CoV-2 receptor (PDB ID: 6M2N) as evidenced by the result of the docking score which has the smallest compared to the original ligand of the receptor.

3.3. Visualization of Ligand-Receptor Interaction Results

Visualization results of the quercetin and reference ligand compounds in both 2D and 3D form through the Discovery Studio Visualizer 2021 application, there are 3 types of bond interactions namely hydrogen bonds, hydrophobic interactions, and electrostatic interactions. To see the ligand-receptor interaction clearly is evident in the Table 3.

Based on Table 3 , the outcomes of the ligand-target protein interaction demonstrate that the quercetin compound has hydrogen bonds with different spacings. Hydrogens bonds serve as the primary bond in molecular docking that keeps proteins. According to Vijayakumar et al., (2020) the strenght of a complex interaction between the protein and the ligand is indicated by a high number of hydrogen bonds and a low binding affinity value indicate a strong interaction.[18] The spacing of hydrogen bonds is a factor that influences the hydrogen bond interactions between the ligand and the receptor. Generally,

Table 1. Predictions of the Physicochemical Properties of Quercetin Compounds

Lipinski's Five Law Parameters						Application of Lipinski's Law 5
WM (g/mol)	Log P	HBD	HBA	T	TPS A (Å 2)	
302.24	1.23	5	7	1	131.36	Yes, 0 error

Table 2. Ligand-Receptor Binding Result with PLANTS

No	Name of Ligand/Compound	Score Docking
1	reference ligand (3 WL_401)	-81.7953
2	Quercetin	-85.3356

a good hydrogen bond distance is between 2.5-3.5 Å. Based on this, the hydrogen bond distance in both the reference ligand and the quercetin compound is fulfilled. Since large interaction distance makes the interaction weak, distance has a significant impact on the strength of the connection.[16] Hydrophobic interactions also play a role in determining the stability of a ligand towards target protein.[19] The findings of the analysis of hydrophobic interaction between the reference ligand and the quercetin compound show that the reference ligand has hydrophobic interactions with Lys5 and Phe291, while the quercetin compound does not. Electrostatic interactions are also responsible for regulating the stability of the ligand to the target protein (receptor). The findings of the research, it is known that both the reference ligand and the quercetin compound have almost the same electrostatic interactions. This demonstrated by the fact the amino acid residues from the reference ligand and the quercetin molecule are identical. Analysis of the same electrostatic interaction between the reference ligand and the quercetin compound strengthens the statement that the quercetin compound occupies the same active site as the reference ligand in the main protease target protein (Mpro) of SARS-CoV-2 (PDBid: 6M2N).

3.4. Pharmacotinetic Profiles of Quercetin Compounds

Pharmacokinetics of quercetin compound using the pkCSM Online Tool site. The pharmacokinetic profile of the quercetin compound can be seen in Table 4 (Absorption Profile, Distribution, Metabolism, and Excretion).

The parameters for analyzing the absorption profile of a compound consist of water solubility, $CaCO_2$ permeability, intestinal absorption, skin permeability, P-gp substrate, and P-gp inhibitor. Compounds that have a water solubility value of less than -6 show low solubility.[20] According to the Table 4, the quercetin compound has a water solubility value of > -6 which is -2.925 so that the quercetin compound shows high solubility.

To estimating the absorption process of drugs administered orally in the body, $CaCO^{-2}$ cells are used as an in vitro modeling parameter of the human intestinal mucosa. If the compound has a permeability coefficient of more than 8x10 cm/s, then the compound has a high level of $CaCO_2$ permeability. Based on Table 4, the $CaCO_2$ permeability prediction value for quercetin compounds is -0.229, indicating that quercetin compounds have a low level of drug absorption.

According to Wijayanti et al (2010) if a substance's absorpstion value is greater than 80% it is deemed to have good absorption, while it is said to have poor absorption if its value is less than 30%.[17] The intestine is the

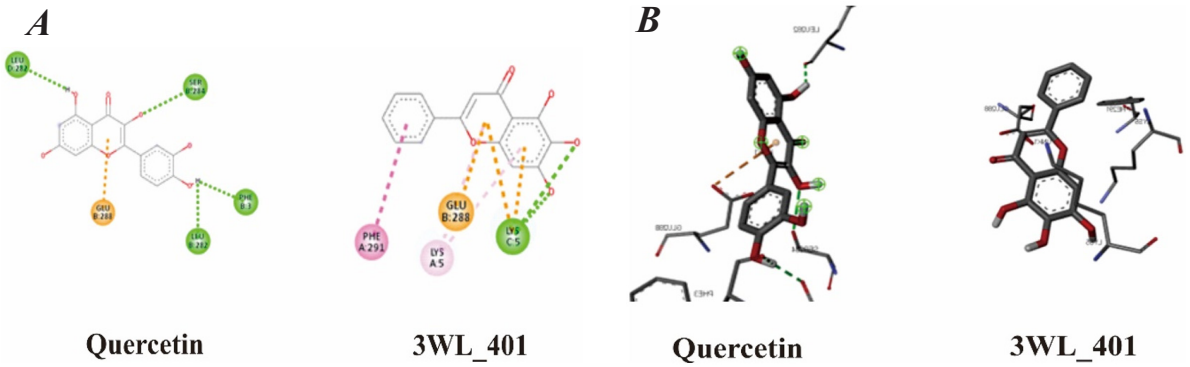

Figure 1. (A) 2D Visualization of Ligand-Receptor Interaction Results, (B) Visualization of Ligand-Receptor Interaction Results in 3D

Table 3. Results of Interaction Between Ligand-Receptors

Compound	Acid Residue Amino	Distance (Å)	Amino-Ligand Acids	Interaction Type
reference ligand (3 WL_401)	Lys5 (C)	2.95	N-H	Hydrogen bond
		3.16	N-H	Hydrogen bond
		4.41		Electrostatic
		4.79		Electrostatic
		4.27		Hydrophobic
	Glu288 (B)	4.45		Electrostatic
	Phe291 (A)	5.00		Hydrophobic
	Lys5 (A)	5.10		Hydrophobic
		4.99		Hydrophobic
Quercetin	Leu282 (B)	2.52	O-H	Hydrogen bond
	Leu282 (D)	2.73	O-H	Hydrogen bond
	Phe3 (B)	2.41	O-H	Hydrogen bond
	Ser28 (B)	3.06	N-H	Hydrogen bond
	Glu288 (B)	4.47		Electrostatic

primary location for medication absorption when taken orally. Table 4 shows that the quercetin compound is predicted to be absorbed quite well in the intestine because this compound has an intestinal absorption (human) value of 77.207%.

According to Abdullah et al (2021) if a compound has a log Kp value of less than -2,5, then the compounds has a relatively low skin permeability1. Table 4 shows that the quercetin compound has a Skin Permeability (log Kp) value of -2.735, which means it is lower than -2.5, so that the compound can be predicted to have good skin permeability.

The ATP binding transporter (ABC) is a P-glycoprotein. P-glycoprotein acts as a

Table 4. Analysis of Quercetin Compound Absorption Profile Results and Results of Quercetin Compound Distribution Profile Analysis

Category	Parameter	Prediction Value	Unit
Absorption	Water Solubility	-2.985	Log mol/L
	$CaCO_2$ Permeability	-0.229	Log Papp ini 10-6 cm/s
	Intestinal Absorption (Human)	77.207	%
	Skin Permeability	-2.735	Log Kp
	P-glycoprotein substrate	Yes	Yes/No
	P-glycoprotein Inhibitor	No	Yes/No
Distribution	VDss (Human)	1.559	Log L/Kg
	Fraction Unbound (human)	0.206	Fu
	BB Permeability	-1.098	Log BB
	CNS Permeability	-3.065	Log PS
Metabolism	CYP2D6 Substrate	No	Yes/No
	CYP3A4 Substrate	No	Yes/No
	CYP1A2 Inhibitor	Yes	Yes/No
	CYP2C19 Inhibitor	No	Yes/No
	CYP2C9 Inhibitor	No	Yes/No
	CYP2D6 Inhibitor	No	Yes/No
	CYP3A4 Inhibitor	No	Yes/No
Excretion	Total Clearance	0.407	Log ml/min/kg
	Renal OCT2 Substrat	No	Yes/No

biological barrier by ridding cells of toxins and xenobiotics. Table 4 shows that the quercetin compound acts as a P-glycoprotein transporter substrate but does not act as a P-glycoprotein transporter inhibitor.

Parameter distribution profile analysis consists of VDss (log L/kg), Fraction unbound, BB permeability (log BB), CNS permeability (log PS). According to Abdullah et al (2021), if the Log VDss values is less than -0.15 then the compound has a low Distribution Volume, while it is said to be high if the Log VDss value is more than 0.45. Based on Table 4 it shows that the quercetin compound has a VDss value of 1.559 which means greater than 0.45, it can be estimated that the compound is capable to be distributed thoroughly and evenly so that it can provide concentrations similar to blood plasma.

Most of the drug in plasma is evenly distributed between the unbound and protein bound states. The quercetin compound has a relatively low unbound fraction value, according to research findings, meaning that it is more bound to serum proteins.

According to Abdullah et al (2021), if a compound's Log BB value is greater than 0.3, it is projected to be able to cross the blood-brain barrier with easea, and if it is less than -1. Based on Table 4, it shows that the quercetin compound has a log weight value of -1.098, which means less or below -1. Therefore, it can be claimed that compound does not properly cross the blood-brain barrier.

The PS log is used as an indicator to measure the level of permeability of the blood-brain barrier. It can be claimed that a compound can enter the Central Nervous System (CNS) if its log PS values is greater than -2, whereas if a compound has a log PS value of less than -3 then it can be said that the compound is unable to penetrate the CNS. Table 4 shows that the CNS cannot be entered by quercetin compound because the log PS value is less than -3, namely -3.065.

Cytochromes consist of various isoform models, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. Based on Table 4 which shows that the quercetin molecule does not interfere with or inhibitor CYP2D6 enzyme, its likely that the P450 enzyme will metabolize the compound produced.

By measuring the Total Clearance Constant (CLOT) and Renal Organic Cation Transporter 2 (OCT2) substrates are a method used to estimate the excretion process of compounds that occur in the body. Table 4 shows that the quercetin compound has a CLTOT value of around 0.407, and this value can be used to estimate the level of excretion of the compound. From Table 4 it also shows that the quercetin compound has no impact on the OCT2 substrate, and as shown in Table 4, shows that the quercetin compound is not an OCT2 substrate.

3.5. Quercetin Toxicity Prediction Results

Toxicity prediction analysis can be carried out by accessing the Protox Online Tool and pkCSM online tool website based on the LD50 parameter. Classification of compound toxicity classes is divisible into 6 classes based on the Globally Harmonized System (GHS).

Based on Table 6, the results obtained show that the quercetin compound belongs to group 3, which means that the compound is slightly toxic when ingested with an LD50 value of around 159 mg/kg. A compound's level of toxicity is influenced by the value of the LD50, if the value of the LD50 is higher, a compound's level of toxicity will also be lower.[23] A compound's level of toxicity is influenced by the value of the LD50, if the value of the LD50 is higher, the level of toxicity of a compound will also be lower. In addition, based on Table 6 it shows that the

Table 5. Toxicity Predictions of Quercetin Compound

Compound	Toxicity				
	LD50 (mg/kg)	Toxicicy Class	Ames Toxicity	Hepatotoxicity	Skin Sensitization
Quercetin	159mg/kg	3	No	No	No

quercetin compound derived from the leaves of the guava plant (*Psidium guajava* L.) tested was not toxic to the liver. Meanwhile, the results of the estimated toxicity level for skin sensitization tests show that the quercetin compound from the leaves of the guava plant (*Psidium guajava* L.) has no potential to irritate the skin.

4. Conclusion

The quercetin compound has been shown to have the ability to inhibitor againts target protein namely main protease (Mpro) with PDB id: 6M2N as evidenced by the docking score value being lower than the original ligand of the receptor. In addition, the quercetin compound has a similar electrostatic interaction. Analysis of similar electrostatic interactions between reference ligand and the quercetin compound strengthens the statement that the test compound and reference ligand occupy the same active site on the Mpro SARS-CoV-2 target protein (PDBid: 6M2N). The outcomes of the prediction of the physicochemical properties of the quercetin compound from the leaves of the guava plant (Psidium guajava L.) comply with the requirements of 5 lipinski law, where the quercetin compound has a molecular weight of less than 500, log P less than 5, number of donor H-bonds less than 5, bond-H aceptor less than 10, torsion value less than 10 and TPSA value less than 140 Å. These findings indicate that the quercetin molecule can be readily good absorbed, has good oral bioavailability, and has good permeability. The prediction of the toxicity of the quercetin compound from the leaves of the guava plant (Psidium guajava L.) shows that the quercetin compound belongs to the class III, indicating that ingesting it could be slightly harmful with an LD50 value of around 159 mg/kg.

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