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SOME NATURAL FLAVONOIDS FROM GUAVA (*PSIDIUM GUAJAVA* L.) AGAINST SARS COV-2, INSILICO PREDICTION AND DRUGS EVALUATION

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ABSTRACT
SARS-CoV-2 is a new virus that little is known about it, which has infected many people around the world. As COVID-19 cases continue to rise, it means more people are being infected, and there is still no targeted therapy for COVID-19 patients. Important for an emergency is to find the most potential Hesperidin, Kaempferol-3,4'-di-O-methyl ether (Ermanin); Myricetin-3-glucoside, Peonidine 3-(4'-arabinosylglucoside); Quercetin 3-(2G-rhamnosylrutinoside); and Rhamnetin 3-mannosyl-(1–2)-alloside as a lead compound from guava to develop new drugs from flavonoid analogue. Docking method through iGEMDOCK software was used to design a new lead compound candidate from several flavonoid and study its interaction with of 3CLpro (PDB ID: 7DPU). The docking method were carried out using the iGEMDOCK software version v2.1, also in the chimera-1.13.1 program is used to know the interaction profile. Druglike properties were calculated using Lipinski's rule of five as calculated using SWISSADME prediction. Toxicity prediction herein used ADMETSAR webserver (http://lmmd.ecust.edu.cn:8000/predict/). Less toxic and showing greater affinity with a docking score stronger was found in Quercetin, is apart from good pharmacokinetic profile.

Keywords: Molecular docking; Chemical interaction; Flavonoid on guava; Toxicity

1. INTRODUCTION

SARS-CoV-2 is a new virus that little is known about it, which has infected many people around the world. As COVID-19 cases continue to rise, it means more people are being infected, and there is still no targeted therapy for COVID-19 patients. Ongoing studies look for potential barriers to containing the pandemic. In the current scenario, repositioning of the drugs could be considered the new avenue for the treatment of COVID-19.

Natural compounds belonging to the class of alkaloids and synthetics that have been found as antiviral enteropathogenic coronavirus transmissible gastroenteritis virus (TGEV) are phenanthroindolizidines and phenanthroquinolizidines. They also decreased cytopathic effect in Vero 76 cells infected by SARS CoV. These compounds are known to reduce the cytopathic effect of vero 76 cells in patients with SARS CoV-2. This alkaloid compound called 'tylophorine' can be a potential anti-coronavirus drug candidate for the treatment of TGEV and SARS CoV-2 infection (Yang et al., 2010).

In 1818, in collaboration with Caventou, French pharmacist Pelletier, they both visited the Scientific French Academia, where quinine was found isolated from the bark of the Cinchona tree in 1820 and the extraction method has been shown to the company without intelectual property to defeat the widespread incidence of malaria, and then less decade quinine has been used to handle malaria. Its derivations chloroquine and hydroxychloroquine are now used in the treatment of SARS-2 at the original position of the complaint (Topçu et al., 2020).

The molecular docking approach can be used to model the interaction and has lately been perceived as a capable fantasize for the efficacy of active compounds other than eucalyptus oil as an anti-proteinase such as 1,8-cineole (eucalyptol) (Sharma, 2020). Treatment with an additional 1.8-cineole (3x 200 mg/day) for 6 months changed the asthma cycle significantly, increased lung function, nocturnal asthma and quality of life scores and COPD exacerbation reduction (-38.5%) (during winter) (L. J. Juergens et al., 2020). Blend AB1 was also effective against H1N1 and HSV1 viruses. With this dual activity, against H1N1 and S. aureus and S. pneumoniae notably. AB1 (Cinnamomum zeylanicum, Daucus carota, Eucalyptus globulus) and Rosmarinus officinalis EOs may be interesting to treat influenza and post influenza bacterial pneumonia infections (Brochot et al., 2017).

Data attained showed that-cineole interaction with Mpro can occur so that viral reduplication can be inhibited. The Mpro/eucalyptol complex interacts hydrophobically, forms hydrogen bonds, and is strongly ionically linked, independently (Sharma, 2020). However, to find out the efficacy, it is still needed to be invitro and invivo tested to verify the effectiveness of jensenone/-cineole against SARS-CoV-2 proteinase. The pharmacological capabilities of these two compounds,-cineole are more considerably studied against various respiratory diseases (U. R. Juergens et al., 2003). Data from preclinical and clinical trials both show promising therapeutic possibilities from the potential of the eucalyptus plant with the active element, namely eucalyptol in the prevention and treatment of COVID-19. Natural substances have previously shown highly effective antivirals as a treatment against COVID-19 may seem promising, which suggests the potential of flavonoids to be useful in dealing with the covid pandemic (Lau et al., 2008).

Guava is a well known tropic tree that is abundantly flavonoids compounds i.e myricetin, quercetin, luteolin, kaempferol and isorhamnetin (Hamid Musa et al., 2015), and Hesperidin (Trujillo-Correa et al., 2019). Luteolin has been reported as a furin protein inhibitor (Peng et al., 2017) which is triggered through the S protein cleavage as in MERS into units S1 and S2 (Kleine-Weber et al., 2018). In the S1 unit, bonding occurs because there is ACE2 peptidase in the Receptor Binding Domain (RBD) so that the virus can attach to the host. The potential for entry of SARS-CoV-2 can be inhibited by Hesperidin through the interaction between the SARS-CoV-2 RBD protein S and the ACE2 receptor in human insilico (Wu et al., 2020). Oseltamivir is an antiviral drug used in the CDC protocol to treat and help influenza A and influenza B (flu) as well as Luteolin (Erlina et al., 2020). As similar, one of the most important ways in developing new medicine is to find supereminent emulsion in the extract. Webbing of active composites in guava fruit is the most concern for us where guava is presently one of the most consumed fruits in Indonesia. iGEMDOCK is one of the powerfull analyses that will be used for insilico webbing of anti-coronavirus composites on some flavonoid composites in Guava.

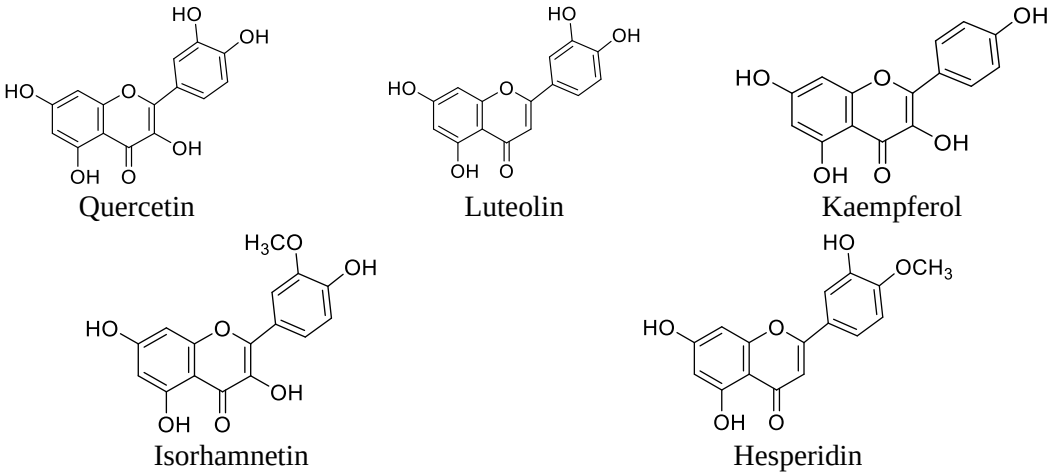

Figure 1. Flavonoid Compound in Guava

Molecular docking analysis from virtual screening on HerbalDB, six flavonoid compounds, i.e Hesperidin, Kaempferol-3,4'-di-O-methyl ether (Ermanin); Myricetin-3-glucoside, Peonidine 3-(4'-arabinosylglucoside); Quercetin 3-(2G-rhamnosylrutinoside); and Rhamnetin 3-mannosyl-(1–2)-alloside, that prognosticated could inhibit the 3CLpro protein of SARS-CoV-2. Thus, further studies are urgently required in this regard.

2. METHODS

2.1. Designed Chemical Structure

Herein, CS ChemDraw was employed to hold the chemical structure of Favipiravir, Hesperidin, Isorhamnetin, Luteolin, Kaempferol and Quercetin, to get the product patch. It was accounted to be an implicit medicine patch targeting 3CLpro as a list point. The Five blocks of flavonoid reported that the compound is grounded on six-member heterocyclic composites and important natural exertion is reported in the former studies. They've shown a promising part as Sars Cov-2 impediments (Kumar et al., 2020).

2.2. Instrumentation

The molecular docking was using a personal computer with Intel Core i5-6200U 2.3 GHz, ram 4GB, window 10 operating system. The main docking analysis was performed using the iGEMDOCK software version v2.1 and assessing residue interactions in the complex using chimera-1.13.1 (Pettersen et al., 2004).

2.3. Ligand Structure Preparation

The five composites and favipiravir for reference motes from molecular docking simulation were erected a model and formed. The conformation decision was exploiting ChemOffice v15.1 software by import configuration, also the minimal energy was computed.

2.4. Molecular Docking

To obtain the crystal structure of 3CLpro of Sars Cov-2 can obtain from the RCSB. protein data bank at judgments of 1.75 Å independently. The junking of redundant tittles like water, and atoms, and adding definite hydrogen in both models (ligand & target protein) was done exploiting UCSF Chimera-1.13.1 soft programe (Kumar et al., 2020). iGEMDOCK calculates the geometry change and ligand interaction relative to the target protein active point based on GA and the optimized results in terms of total complex minimal energy list.

2.5. Drugs Likeness Properties

Further, the webbing of five motes was filtered through Drugs likeness parcels. Druglike parcels were computed applying Lipinski's rule of five, which proposes that motes with poor permeation and oral absorption have molecular weights >500, ClogP >5, further than 5 hydrogen bond donors, and further than 10 acceptor groups Adherence with Lipinski's rule of five as computed applying SWISSADME vaticination (Daina et al., 2017).

2.6. Toxicity Prediction

Herein, the authors using ADMETSAR webserver (http://lmmd.ecust.edu.cn:8000/predict/), to predict carcinogenicity and acute oral toxicity values with types of oral route administration for rats. The acute toxicity of quercetin, luteolin, kaempferol, isorhamnetin, and hesperidin has been calculated (Cheng et al., 2012).

3. RESULTS AND DISCUSSION

iGEMDOCK is used for molecular docking five flavonoid compounds are taken based on the least binding energy of the complex system. 3CL protease (3CLpro) is a very considered cysteine proteinase that is fundamental for polyprotein replication, has been postulated as an attractive target for antiviral therapies. Protein with code ID, PDB: 7DPU was provided by the protein data bank. Contain one molecule was 7-O-metyl-myricetin as the native ligand. The

docking protocols were validated through a redocking experiment to ensure that the receptors were capable of application in the molecular docking course. Grounded on the protein confirmation course, it attained a root mean square deviation (RMSD) of 0,534 Å where its value was less than 2Å, this result has been used as the best docking protocol. In general, the rmsd from the flexible docking protocol will be worse than that from the rigid docking protocol. This is because allowing the protein flexibility will take it away from the starting crystal structure and make it harder to achieve the exact binding pose against this structure **Figure 2**.

Figure 2. Alignment Native Ligand (white) and Docked Ligand (blue) PDB ID:7DPU (Visualization Data by Chimera, 2021)

The details of the binding energy of the designed motes against the CL3pro of Sars Cov-2 are given in **Table 1**. The binding energy of the motes or compounds obtained from the redocking was further studied, five molecules in Guava showed minimum total binding energy as in **Table 1**. The affinity calculation results show a fairly high value because iGEMDOCK uses an empirical base scoring function so that the value obtained does not directly refer to the energy in kcal/mol. Their molecular interactions as in **Table 2** and **Figure 2**.

Table 1. Docking Flavonoid Compound in Guava with 7DPU

Compound	Energy	VDW	HBond
Hesperidin	-89.191	-64.454	-24.737
Isorhamnetin	-98.819	-78.858	-19.961
Kaempferol	-89.588	-62.127	-27.462
Luteolin	-85.582	-66.531	-19.051
Quercetin	-94.453	-64.861	-29.592
Favipiravir	-78.380	-43.390	-34.990

The stylish suit of the supreme number of relations had been anatomized, denoted by binding energy value in the iGEMDOCK The stylish docking disguise of 2 configurations of each emulsion was anatomized for commerce exploration. Docking results meaning the smallest list energy cluster were accounted as average list countries. The minimum binding affinity indicates that the target protein is successfully attached to the ligand motes as an antiviral properties (Yi et al., 2004). Docking outcome disclosed the strongest commerce had the right pose. Protein ligand relations were imaged in 3D.

The results of Hesperidin, Isorhamnetin, Kaempferol, Luteolin, and Quercetin docking using IDB ID receptor: 7DPU with 7-O-metil-myricetin as a native ligand shows the docking scores in **Table 1**. From the five flavonoid ligands was observed that isorhamnetin had the smallest docking score, denoting that isorhamnetin had better antibacterial eventuality to interact with the target protein, but this is a probability. The energy value obtained is an empirical base so it does not refer directly to its value in kcal/mol units. In common, the contrast in the electronegative group substituents in a compound affected the eventuality of the compound.

Favipiravir displayed consequential amino acids that interacted with target proteins such as Gly143, Ser144. In its interactions, favipiravir involved F with Ser144 via hydrogen bonds

(Hacceptor) and O (C=O) from the carbonyl amide group interacting with Gly143 and Ser144 residues via hydrogen bonds (Hacceptor) **Figure 3**.

Table 2. Free Energy, Hydrogen and Van der walls Bonding Residue and Ligand

Compounds	Main Chain Receptor				Side Chain Receptor			
	H-bond-residue	ΔG Kcal/mol	V-bond-residue	ΔG Kcal/mol	H-bond-residue	ΔG Kcal/mol	V-bond-residue	ΔG Kcal/mol
Hesperidin	GLY-143	-3.50	HIS-164	-5.98	HIS-41	-5.41	HIS-163	-6.30
	SER-144	-5.41	MET-165	-7.94	SER-144	-2.50	MET-165	-7.69
	GLU-166	-3.50	GLU-166	-5.74	CYS-145	-2.50		
					GLU-166	-2.50		
					GLN-189			
Isorhamnetin	GLY-143	-2.80	HIS-164	-5.78	CYS-145	-5.00	HIS-41	-4.06
	GLU-166	-3.50	MET-165	-9.02	GLN-189	-2.50	MET-165	-10.01
	ARG-188	-4.65	GLU-166	-8.07			GLU-166	-4.16
			ARG-188	-4.90				
Kaempferol	LEU-141	-2.50	HIS-164	-5.45	HIS-41	-5.37	MET-165	-11.04
	GLY-143	-3.48	MET-165	-9.58	GLN-189	-2.50		
	SER-144	-2.53	GLU-166	-4.00				
	GLU-166	-4.03	ARG-188	-4.56				
Luteolin	CYS-145	-3.50	MET-165	-9.78	SER-144	-2.50	MET-165	-5.78
	ARG-188	-4.27	GLU-166	-9.10	CYS-145	-2.50	GLU-166	-6.80
	GLN-189	-3.50			HIS-163	-2.78	GLN-189	-4.71
Quercetin	GLY-143	-6.97	HIS-164	-5.01	HIS-41	-4.39	HIS-41	-4.71
	HIS-164	-2.50	MET-165	-8.88	SER-144	-2.50	MET-165	-9.61
			GLU-166	-6.16	CYS-145	-4.94		
Control								
Favipiravir	LEU-141	-3.10	LEU-141	-6.04	ASN-142	-7.00	ASN-142	-6.92
	GLY-143	-7.00	ASN-142	-8.91	SER-144	-5.89		
	SER-144	-3.50	GLY-143	-5.19	CYS-145	-5.00		
	CYS-145	-3.50						

GLY = Glycine; SER = Serine, GLN = Glutamine; ARG = Arginine; LEU = Leucine
CYS = Cysteine; HIS = Histidine

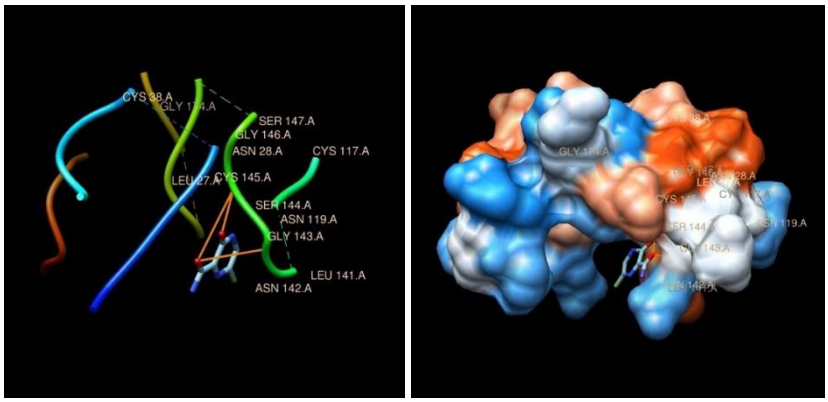

Figure 3. Binding Surface and Ligand Interaction of Favipiravir (Visualization Data by Chimera, 2021)

Hesperidin showed strong interaction with amino acid Leu141, involving closest for the interaction of hydrogen bonds in the benzene ligand group with H atoms of hydroxy. Isorhamnetin with excess hydroxy groups has greater opportunities to interact, the docking score showed greater than other reciprocal reference compound favipiravir. Isorhamnetin interacted with three amino acids Gly143, Glu166, and Gln189 involving the interaction of hydrogen bonds in the benzene ligand group with H atoms of hydroxy and oxygen from eter groups **Figure 4**. That was because the positive charge on the oxygen carbonyl atom gives the phi electron a resonance effect so that the partial positive charge is evenly distributed. Kaempferol showed an interaction involving the amino acid Leu141, Gly143 via H donor, and Glu166 via H acceptor hydrogen bonds. This interaction had no similarities with luteolin even though they have the same number of hydroxy as functional groups **Figure 5**. Hydroxy groups would activate the benzene ring, demonstrating that the electronegative atom was the center of action other than carbonyl since it sounded that some amino acids could interact with it **Figure 6**. The position of hydroxy groups in benzen ring luteolin, the lone pair on -OH can be "donated" into that aromatic ring to the carbonyl

groups namely resonance effect (**Figure 7**). So negative charge spreads in the molecule. Quercetin had the greatest potential as an antiviral since it had the lowest binding energy and high affinity with active residue (**Figure 8**). The number of hydroxy groups of quercetin are most important in binding energy.

Quercetin has a stronger affinity for the main protein 3CLpro and side spike receptor than hesperidin, isorhamnetin, kaempferol, luteolin, and antivirals such as favipiravir. This disported that quercetin and other flavonoid compounds are more stable after forming a ligand-receptor complex so that the effect of antiviral activity becomes stronger. Molecular docking results are displayed in **Table 2**.

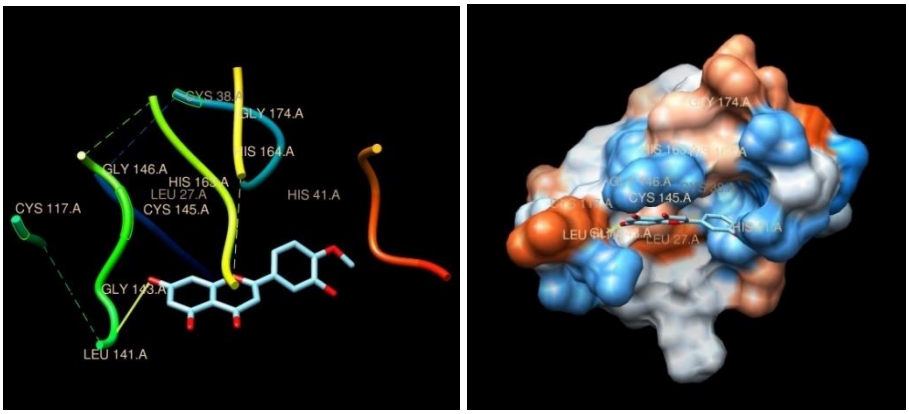

Figure 4. Binding Surface and Ligand Interaction of Hesperidin (Visualization Data by Chimera, 2021)

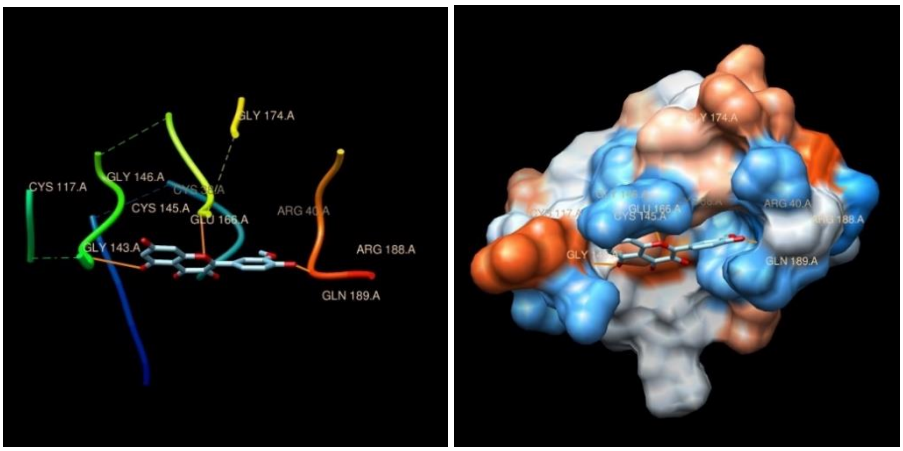

Figure 5. Binding Surface and Ligand Interaction of Isorhamnetin (Visualization Data by Chimera, 2021)

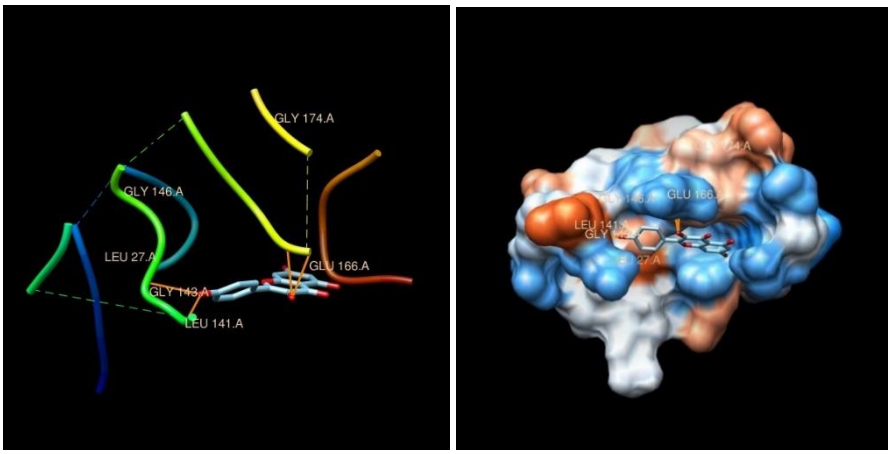

Figure 6. Binding Surface and Ligand Interaction of Kaempferol (Visualization Data by Chimera, 2021)

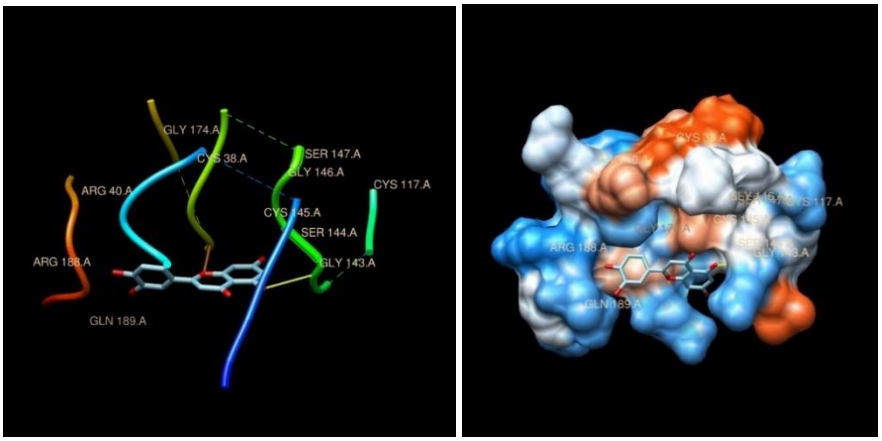

Figure 7. Binding Surface and Ligand Interaction of Luteolin (Visualization Data by Chimera, 2021)

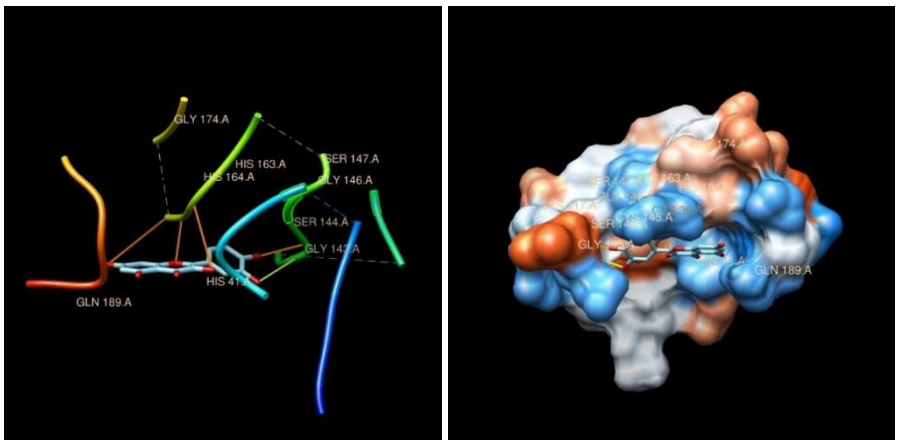

Figure 8. Binding Surface and Ligand Interaction of Quercetin (Visualization Data by Chimera, 2021)

Differences in position of hydroxy group some flavonoid derivatives (**Figure 1**) also cause differences in the strength of affinity for the protein receptors. The strength of successive affinities in the Gly143 3CLpro protein receptor is favipiravir > quercetin > kaempferol > hesperidin > isorhamnetin > luteolin. Meanwhile, glycoprotein spike is favipiravir > quercetin > kaempferol > hesperidin > isorhamnetin > luteolin.

According to (Yi et al., 2004) TGG and luteolin have good opportunities to be further developed for clinical use as anti-SARS drugs which supported relevance of the research data. In addition, this work also increasing all of molecules to give interaction with nucleic acid residue in 7DPU protein. Quercetin has the highest affinity value when H-bonding with Gly143 with the energy of -6.97, van der walls bonding Met165 is -8.88. The same condition occurs in favipiravir where there is hydrogen bonding with the Gly143 residue with a value of -7.00 higher than the other residues. This shows that the hydrogen bonds that occur from these interactions are the strongest compared to other flavonoid molecules in the main chain receptor.

A toxicity test is carried out through analysis of differences in chromophore groups in different structures so that it affects the interactions that occur. The results of the analysis based on this pharmacophore are believed to be more related to the fact.

Hesperidin, isorhamnetin, and kaempferol did not conjugate as substrates with the cytochrome P450 enzymes (CYP2C9, CYP2D6, and CYP3A4), likewise favipiravir. However, suffer metabolism by acting as an asset of these metabolic enzymes. The production of metabolites like prognosticated to be pharmacologically inactive or indeed produce the undesirable hazardous chemicals. This appraisal is proven by the advanced hesperidin toxins value, as well as isorhamnetin and kaempferol. In discrepancy, luteolin, quercetin, and favipiravir showed lower situations of toxins. Five flavonoid molecules from the guava in **Table 1** data are taken from docking for prediction of physicochemical properties, lipophilicity, water-solubility,

pharmacokinetics, drug-likeness, and bioactivity score as in **Table 3**. Data vaticination of pharmacokinetic biographies and toxin of all active composites will be validated by Lipinski's Rules of Five. This test is to ensure the suitability of these components to be used as a drug guide in humans. Characteristics of the synergistic pharmacokinetic profile with low toxicity and agreement with Lipinski's five rules, suggest that quercetin is very potential to be used as an alternative anti sars Cov-2, based on aot data (II) up to the dose level (mg/kg) did not produce any toxic effects. Predictive results of the pharmacokinetics and toxicity profile are shown in **Table 3**.

According to the criteria of biological parameters, the best 5 compounds were obtained. Pharmacokinetic Pattern Each drug compound is influenced by its physicochemical properties. Some factors affect the adsorption process of a compound, such as lipophilicity, hydrogen bonding, molecular size, and pKa charge (Lawson et al., 2013).

Table 3. Pharmacokinetic Profiles and Toxicity Flavonoid on Guava

Compounds	Absorption and bioavaibility					Metabolism						Toxicity		Lipinski's Role of five
	Bbb	Hib	Pgp_S	Log P	Tpsa (Å)	CYP 2C9 _sub	CYP 2D6 _sub	CYP 3A4 _sub	CYP 2C9 _inh	CYP 2D6 _inh	CYP 3A4 _inh	Carc	Aot	
Hesperidin	-	High	S	2.24	96.2	NS	NS	NS	I	I	I	NC	III	+
Isorhamnetin	-	High	NS	2.35	120.3	NS	NS	NS	I	NI	I	NC	III	+
Kaemperol	-	High	S	1.70	111.1	NS	NS	NS	I	NI	I	NC	II	+
Luteolin	-	High	S	1.86	111.1	NS	NS	NS	NI	NI	I	NC	III	+
Quercetin	-	High	S	1.63	131.3	NS	NS	NS	NI	NI	I	NC	II	+
Control														
Favipiravir	+	High	NS	0.39	88.84	NS	NS	NS	NI	NI	NI	NC	III	+

Bbb = Blood brain barrier, Hib = Human Intestinal absorption, S/NS = Subtrate/non subtrate, C/NC = Carcinogenic/non carcinogenic, I/NI = Inhibitor/non inhibitor, Aot = Acute oral toxicity

Log P and Topological Polar Surface Area (TPSA) are parameters used to assess the adsorption power of a compound. The content of compounds with better adsorption ability was Hesperidin, isorhamnetin, kaempferol, luteolin, quercetin, and favipiravir with log P<5 and TPSA<140. However, the absorption of isorhamnetin is thought to be higher than hesperidin, kaempferol, luteolin, quercetin, and favipiravir, because isorhamnetin aren't Pgp protein substrates. The pgp protein in membrane proteins acts as the last drug that functions as drug efflux that enters the cell out of the cell so that the intracellular concentration of these compounds is low. Pgp is known to be present in the digestive complex, especially in the intestine (Siddik, 2003). All test compounds had low intestinal mortal immersion values indicated by TPSA values <140. Nonetheless, the prognosticated pharmacokinetic results of five flavonoid composites in guava quite expose high adsorption power.

4. CONCLUSION

In this work, finding a promising candidate against 3CLpro from Sars Cov-2 was explored through docking calculations and drug stimulation. Molecular docking results on quercetin showed a higher docking score and also a good pharmacokinetic profile with lower toxicity, compared to other flavonoid compounds and antiviral controls. Based on the findings, it can be developed for experimental research at a later stage, related to the clinical use of quercetin as an alternative to COVID-19 antivirals.

5. ACKNOWLEDGMENT

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6. CONFLICT OF INTEREST

The author declares that there no competing conflicts of interest.

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