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In Silico Analysis and ADMET Prediction of Flavonoid Compounds from *Syzigium cumini* var. album on α-Glucosidase Receptor for Searching Anti-Diabetic Drug Candidates

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ABSTRACT

Background: One of the causes of death is diabetes. Anti-diabetic drugs currently available do not work optimally because some have been reported to have side effect and resistance. **Objective:** This study aimed to flavonoid compounds from *Syzygium cumini* var. album with the greatest anti-diabetic activity and lower toxicity than acarbose. **Materials and Methods:** This research is an *in silico* study of nine flavonoid compounds from *Syzygium cumini* var. album, starting with PASS online was used to predict the activity spectrum of substances, drug-likeness prediction using DruLiTo, ADMET prediction (absorption, distribution, metabolism, excretion, and toxicity) using pkCSM online. Molecular docking was carried out by the AutoDock 4.2.6 program on α-glucosidase targeting. Visualization is done with the Discovery Studio Visualizer software. **Results:** From the data obtained, D-(+)-Catechin has a high affinity for α-glucosidase with a free energy of binding (ΔG) -5.94 kcal/mol and an inhibition constant (Ki) of 44270 nm. **Conclusion:** Based on the results of the study, it can be concluded that the flavonoid compounds from *Syzygium cumini* var. album has the potential as a promising anti-diabetic drug candidate, where the best candidate is D- (+)-Catechin. However, further studies of flavonoid compounds from *Syzygium cumini* var. album are needed.

Key words: α-glucosidase, Molecular docking, PASS, Pharmacokinetics, Flavonoid.

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INTRODUCTION

Pharmacotherapy of type 2 diabetes mellitus, there are six classes of oral antidiabetic drugs (OAD) with different mechanisms of action, one of which is α-glucosidase inhibitor (AGI). AGI drugs work by reducing the level of carbohydrate absorption in the body. The excess use of the AGI class of drugs is relatively safe because it does not produce insulin secretion so it does not cause hypoglycemic shock and does not cause weight gain, so it is certain, especially in obese and geriatric patients.[1,2] However, currently available AGI class of drugs cause unwanted side effects such as abdominal pain, diarrhea, flatulence, and distension.[3,4] Therefore, it is necessary to develop new natural AGI drugs with lower side effects than synthetic drugs.

One of the plants that empirically reduces blood glucose levels is jamblang (*Syzygium cumini* (L.) Skeels.) from the Myrtaceae family. In general, there are three different varieties of jamblang, namely purple jamblang, white jamblang and marbled jamblang.[5] The white jamblang (*Syzygium cumini* var. album) is a rare type of jamblang and has the smallest distribution compared to other types of jamblang.[6] Based on research reported that the total phenolic and flavonoid levels from the jamlang leaf part were higher than the fruit and stem bark but have not been widely used by the community so that it can be developed pharmacologically.[7]

This jamblang plant is reported to contain chemical compounds including flavonoids, alkaloids, tannins and essential oils.[8] One of the compounds responsible for being antidiabetic is the flavonoid group. Quercetin and myricetin are one of the typical compounds of the flavonoid group found in jamblang plants. The activity of quercetin and myricetin as antidiabetic has been widely reported in recent years. Myricetin is possible to control hyperglycemia in diabetes mellitus through inhibition of alpha glucosidase activity.[9] In addition, the compounds quercetin and myricetin have a low IC_{50} value, so they may be future antidiabetic agents.[10] This study discusses the potential analysis of flavonoid compounds as antidiabetic from *Syzygium cumini* var. album which was obtained from UPLC-QToF-MS/MS through the mechanism of α-glucosidase inhibition using molecular docking.

MATERIALS AND METHODS

Hardware

The specification of the computer that is used: Intel® Core™ i7 8565U@ 1.80 GHz processor (CPU), Nvidia® GeForce MX230 graphics processing unit (GPU), and 8 GB Random Access Memory (RAM) with Windows 10.

Compound test preparation

Flavonoid compounds from *Syzygium cumini* var. album were the results obtained using the UPLC-QToF-MS/MS instrument. The flavonoid compounds from *Syzygium cumini* var. album are as shown in figure 1 and table 1. The test compounds were made in 2D and 3D models, then optimized using the MMFF94 method on Chem3D 20.0. Then, the structure is translated into SMILES format using the Online SMILES Translator (https://cactus.nci.nih.gov/translate/).

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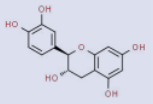
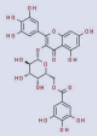
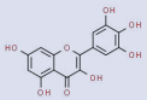
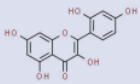
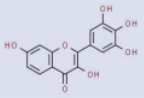
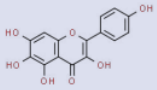
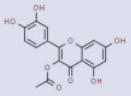
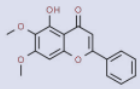
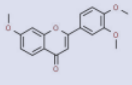
Table 1: The flavonoid compounds from *Syzygium cumini* var. album using the UPLC-QToF-MS/MS instrument.

No	Rt (Min)	Mass M/Z	Calculated M/Z	Formula	IUPAC	2D Models
1	4,42	291.0872	291. 0609	$C_{15}H_{14}O_6$	D-(+)-Catechin	
2	4.80	633.1070	633.1092	$C_{28}H_{24}O_{17}$	5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside	
3	5,37	319.0464	319.0454	$C_{15}H_{10}O_8$	Myricetin	
4	6,13	353.0501	353.0505	$C_{15}H_{10}O_7$	Morin	
5	6,23	302.0426	302.2360	$C_{15}H_{10}O_7$	Robinetin	
6	6,13	302.236	302.0426	$C_{15}H_{10}O_7$	6-hydroxykaempferol	
7	7,02	345.0509	345.0610	$C_{17}H_{12}O_8$	Quercetin acetate	
8	11,56	299.0927	299.0911	$C_{17}H_{14}O_5$	Mosloflavone	
9	11,91	313.1093	313.1076	$C_{18}H_{16}O_5$	Fasciculiferin	

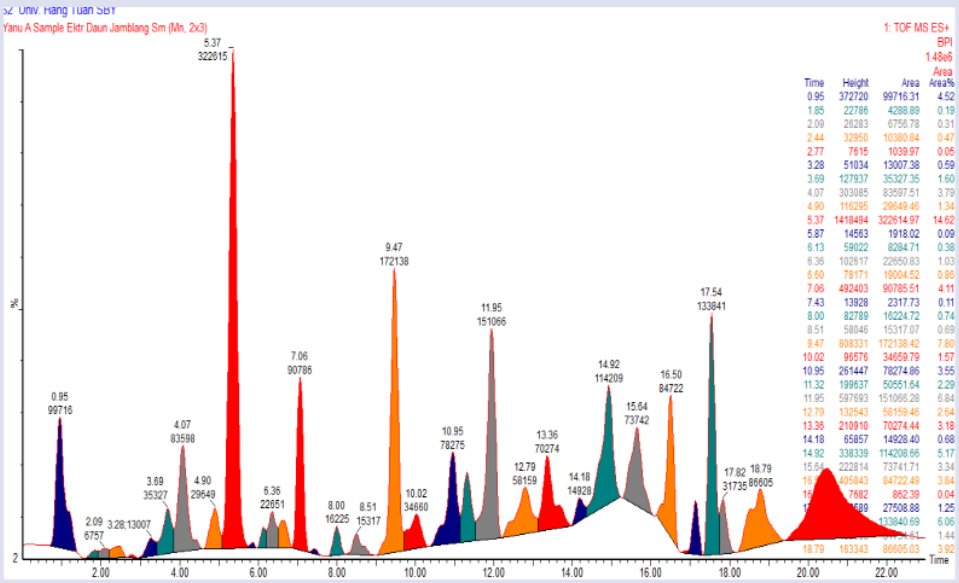


Figure 1: UPLC-QToF-MS/MS chromatogram.

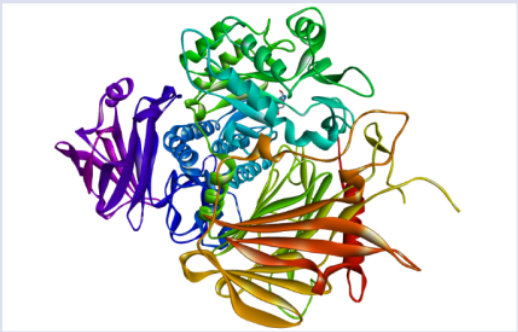


Figure 2: Structure of α-glucosidase (PDB ID: 5DKY).

PASS prediction

To validate compounds as suitable drug candidates, prediction of activity spectra for substances (PASS) (http://www.pharmaexpert.ru/passonline/) is used to predict the possible pharmacological effects of a compound based on structural information by looking at the Pa score (probability " to be active") and Pi (probability "to be inactive") by entering the SMILES format.[11]

Drug-likeness prediction

Three filters of the DruLiTo program (Lipinski's rule, Veber rule, and Ghose filter) were used to predict the drug-likeness of the test compound by entering *sdf file format.[12-14]

ADMET prediction

Prediction of pharmacokinetics (ADME) and toxicity of the flavonoid compounds from *Syzygium cumini* var. album was done by the pkCSM website (http://biosig.unimelb.edu.au/pkcsm/prediction) with the SMILES format.[15]

Molecular docking

The structure of the α-glucosidase target receptor (PDB ID: 5DKY) obtained from the Protein Data Bank (https://www.rcsb.org/) and containing the native ligand (1-deoxynojirimycin) that is shown in figure 2. As for a comparison ligand, Acarbose is also used.

Molecular docking is done using AutoDockTools 4.2.6 program. Starting with the validation process, the redocking method uses the extracted cocrystal ligand from the receptor as the test ligand and the location of the cocrystal ligand as the binding site.[16] The validation results are indicated by the Root Mean Square Deviation (RMSD) value.[17] Center the grid box using a grid box (40 × 40 × 40). The binding site coordinates are x = 16,353; y = 49,298; z = 22,353 with spacing per unit 0.375 angstrom. AutoDockTools 4.2.6 program run with the specified parameters: number generation algorithm 27,000, calculate 2,500,000 times (Medium), population 150, and the implementation of running GA as much as 10 times. Visualization analysis of protein-ligand interactions was performed with Discovery Studio Visualizer v.19.1.0.18287 from BIOVIA.

RESULTS

Flavonoid compound from *Syzygium cumini* var. album (Figure 1).

PASS prediction

The prediction results of the Pa and Pi scores of flavonoid compounds from *Syzygium cumini* var. album are shown in table 2.

Drug-likeness prediction

Prediction results of drug-likeness of flavonoid compounds from *Syzygium cumini* var. album are shown in table 3.

ADMET prediction

The prediction results of the ADMET of flavonoid compounds from *Syzygium cumini* var. album are shown in table 4.

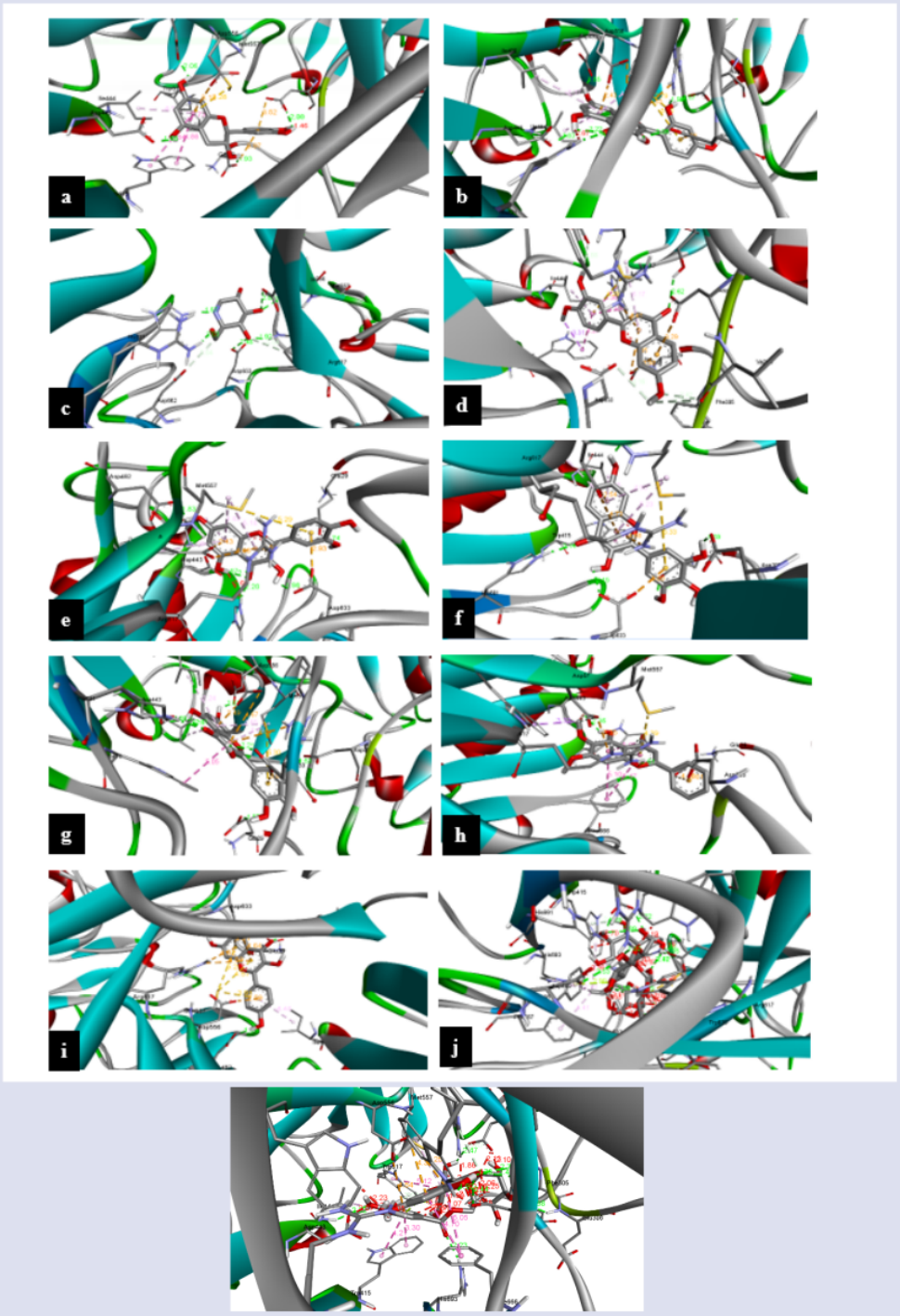


Figure 3: Visualization of D-(+)-Catechin (a) morin, (b) native ligand, (c) fasciculiferin, (d) quercetin acetate, (e) robinetin, (f) myricetin, (g) mosloflavone, (h) 6-hydroxykaempferol, (i) acarbose, (j) 5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside, (k) bound to the active sites of α-glucosidase.

Table 2: **The PASS result.**

Code	Compound Name	Alpha glucosidase inhibitor	
		Pa	Pi
S1	D-(+)-Catechin	0.300	0.003
S2	5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside	0.811	0.001
S3	Myricetin	0.321	0.003
S4	Morin	0.245	0.004
S5	Robinetin	0.245	0.004
S6	6-hydroxykaempferol	0.281	0.004
S7	Quercetin acetate	0.273	0.004
S8	Mosloflavone	0.165	0.008
S9	Fasciculiferin	0.139	0.013

Table 3: **Prediction of Druglikeness with DruLiTo program.**

Kode	MW	logP	HBA	HBD	TPSA	AMR	nRB	nAtom	Lipinski's Rule	Ghose Filter	Veber Rule
S1	290.08	0.852	6	5	110.38	81.07	1	35	1	1	1
S2	632.1	1.802	17	11	293.59	156.02	7	69	0	0	0
S3	318.04	2.182	8	6	147.68	85.04	1	33	0	1	0
S4	302.04	1.405	7	5	127.45	83.44	1	32	1	1	1
S5	312.1	2.101	5	0	53.99	95.27	4	39	1	1	1
S6	302.04	2.263	7	5	127.45	83.44	1	32	1	1	1
S7	302.04	1.834	7	5	127.45	83.44	1	32	1	1	1
S8	298.08	2.413	5	1	64.99	90.23	3	36	1	1	1
S9	312.1	2.101	5	0	53.99	95.27	4	39	1	1	1

MW: Molecular weight, LogP: Partition coefficient, HBA: H-Bond Acceptor, HBD: H-Bond Donor, TPSA: Total polar surface area, AMR: Atom molar refractivity, nRB: Number of rotatable bond, nAtom: Number of atoms. 1 compound follows the rule; 0 compound does not follow the rule.

Table 4: **Prediction of ADMET.**

Code	Intestinal absorption (human)	Skin Permeability	VDss (human)	BBB permeability	CYP2D6 substrate	CYP2D6 inhibitior	Total Clearance	Renal OCT2 substrate	Ames toxicity	Hepatotoxicity
S1	72.06	-2.739	0.141	-1.159	No	No	0.234	No	No	No
S2	31.11	-2.735	-0.131	-3.199	No	No	0.561	No	Yes	No
S3	67.06	-2.735	-0.201	-1.825	No	No	0.521	No	Yes	No
S4	74.62	-2.735	-0.239	-1.478	No	No	0.561	No	Yes	No
S5	77.01	-2.735	-0.282	-1.559	No	No	0.483	No	No	No
S6	66.78	-2.735	-0.112	-1.608	No	No	0.489	No	Yes	No
S7	74.08	-2.735	-0.124	-1.490	No	No	0.523	No	Yes	No
S8	94.93	-2.807	-0.236	-0.364	No	No	0.381	No	No	No
S9	100	-2.660	0.265	-0.024	No	No	0.784	Yes	No	No

Table 5: **Molecular docking binding affinity of flavonoid compounds from Syzygium cumini var. album, ranked by the lowest free energy of binding (ΔG) and inhibition constant (Ki).**

Code	Compound name	ΔG (kcal/mol)	Ki (nM)
S1	D-(+)-Catechin	-5.94	44270
S4	Morin	-5.63	75000
NOJ	Native ligand	-4.86	239900
S9	Fasciculiferin	-4.23	273700
S7	Quercetin acetate	-4.04	1100000
S5	Robinetin	-3.87	1450000
S3	Myricetin	-3.26	4100000
S8	Mosloflavone	-3.24	4200000
S6	6-hydroxykaempferol	-3.24	4230000
A	Acarbose (standard drug)	-3.00	4556000
S2	5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside	-2.94	4652000

Molecular docking

The results of docking validation are indicated by the RMSD value of 1.588, so it can be concluded that the docking protocol can be declared valid because the RMSD value is < 2.[17] Based on the docking results, six flavonoid compounds from *Syzygium cumini* var. album obtained more negative ΔG scores than Acarbose (Table 5). The more negative the ΔG score and the smaller the Ki value, it indicates a very strong complex formed between the ligand and standard. While the visualization of ligands and comparisons can be seen in figure 3 and table 5.

DISCUSSION

The Pa value is the possibility of a compound being active in carrying out biological activities in laboratory experiments, while the Pi value is the opposite. If a compound has a value of Pa > Pi, then the compound has the potential to have this activity. In Table 1, 5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside has strong potential on a laboratory scale because the Pa value > 0.7, while its flavonoid compound have under activity because the Pa value is Pa<0.5.[18] Because these compounds have not been studied on a laboratory scale, further research is needed.

The prediction results of physicochemical properties based on several drug-likeness rules (Table 3) showed that one flavonoid compound from *Syzygium cumini* var. album did not comply with Lipinski's rule, Ghose's filter and Veber's rule ((5,7-Dihydroxy-4-oxo-2-(3,4,4)). 5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside). However, there is one compound that does not comply with Lipinski's rule and Veber's rule, Myricetin (HBD 6). It does not mean that Myricetin is unable to penetrate cell membranes because the drug can penetrate cell membranes if it complies with at least 2 of Lipinski's rules.[19]

ADMET prediction can be seen from (Table 4). Where the prediction of absorption is expressed by the value of intestinal absorption, the distribution is expressed by the value of VDss and BBB permeability, metabolism is expressed by CYP2D6 substrate and inhibitor, excretion is expressed by the value of total clearance, and toxicity is expressed by hepatotoxicity and LD50. It can be seen that the intestinal absorption (human) value of the tested compounds is around 31.11% - 100%, so it can be predicted that the nine compounds will be absorbed well in the human intestine. The VDss is a steady-state volume of distribution that predicts the value total dose of the drug would need to be uniformly distributed to give the same concentration as in blood plasma. The test compounds VDss are range from -0.55 to 0.01 (log L/kg)[15], the predicted results showed VDss relatively low. The BBB (Blood Brain Barrier) values of nine compounds above -1,[15] which means that they can penetrate the BBB moderately. In the table, it can be seen that none of the seven compounds act as substrates or inhibitors of CYP2D6, so it can be predicted that all test compounds to be metabolized by the enzyme cytochrome P450. The total Clearance value of the test compounds ranges from 0.205 to 0.784, and from these values it can be predicted the compound's excretion. OCT2 in the kidney plays an important role in the disposition and clearance of endogenous drugs and compounds.[15] There is one compounds (Fasciculiferin) affecting the OCT2 substrate so that adverse effects or contraindications are predicted. From the results Table 4 shows that five compounds (Myricetin, 5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside, Myricetin, Morin, 6-hydroxykaempferol, and quercetin acetate) are predicted to be active to cause mutagenic effects and all flavonoid compounds from *Syzygium cumini* var. album are non-hepatotoxic.

Molecular docking is computational modeling research that aims to detect the interaction of ligands with receptors. Bond energy is influenced by Gibbs free energy (ΔG), a reaction that takes place spontaneously will have a negative Gibbs free energy at temperature and constant temperature. Bond energy is affected by several components which are expressed by the following equation: ΔG⟧ _Hatanic = ΔG⟧ _Gauss + ⟦ΔG⟧ _Repulsion + ΔG⟧ _HBond + ΔG⟧ _Hydrophobic +ΔG⟧ _Torsion. The more energy components contribute, the smaller the "ΔG" value (becomes negative), the bond impact will be stronger and cause high affinity.[20] From the results of the study [Table 5], it is known that D-(+)-Catechin has a stronger inhibitory activity than acarbose, marked by ΔG of -5.94 kcal/mol and acarbose -3.00 kcal/mol. So that ΔG is very negative, it can be ascertained that the reaction will be proceed spontaneously and lead to high affinity. The Ki values of these compounds are 44270 and 4556000 nM. The Ki value is not only used to indicate the affinity of a ligand; it is also used to predict *in vitro* analysis processes. In this study, the presence of the D-(+)-Catechin had a significant effect on the affinity of the flavonoid compounds from *Syzygium cumini* var. album for the α-glucosidase target receptor. Thus, all flavonoid compounds from *Syzygium cumini* var. album have greater activity against target receptors than acarbose, except 5,7-Dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-3-yl 6-O-(3,4,5-trihydroxybenzoyl)-β-D-galactopyranoside.

CONCLUSION

The development of anti-diabetic drugs with greater therapeutic activity and fewer side effects is an urgent need. This study evaluates the anti-diabetic activity of flavonoid compounds from *Syzygium cumini* var. album targeting α-glucosidase. Therefore, it can be concluded that the flavonoid compounds from *Syzygium cumini* var. album has the potential as a promising anti-diabetic drug candidate, where the best candidate is D- (+)-Catechin. However, further studies of flavonoid compounds from *Syzygium cumini* var. album are needed.

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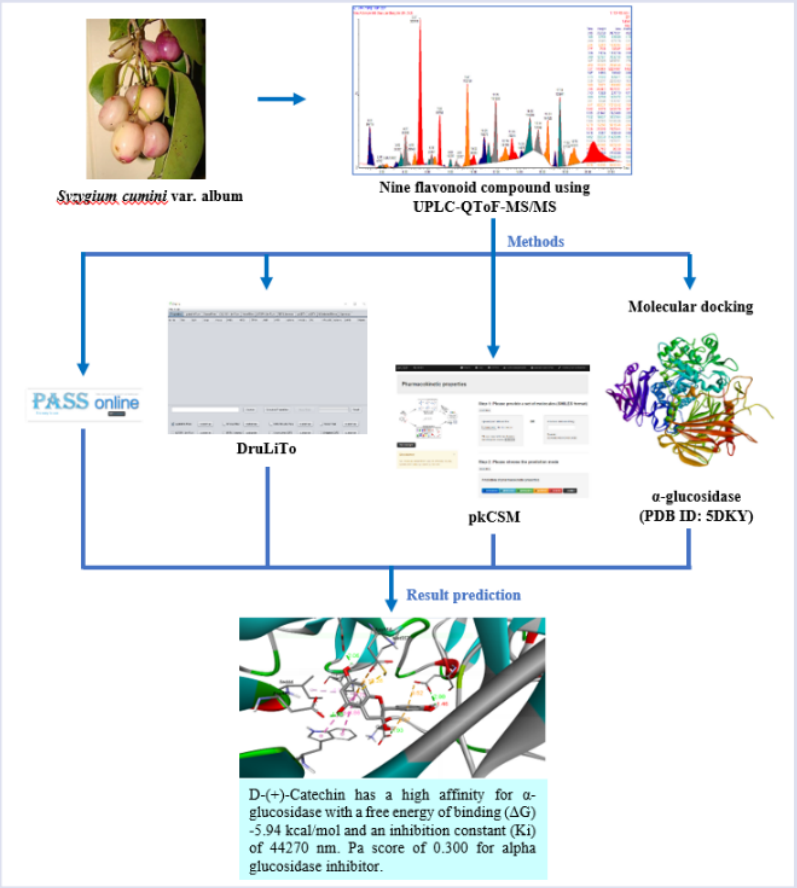

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