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In silico analysis: Activity of active compounds in passiflora foetida to diabetes

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ABSTRACT

Plants contain good compounds that are simple to complex including medicinal plants. Herbs are all plant species that are around settlements, cultivated, wild plants that are known to have medicinal properties. An example is the rambusa plant (*Passiflora foetida* L.). Rambusa leaves are efficacious in relieving fever, insomnia, colds, headaches, diabetes, and asthma. The purpose of this study is to find out physicochemical & pharmacokinetic predictions, toxicity levels, and the affinity of active compounds and a comparison of toxicity levels and affinity of rambusa plants or *Passiflora foetida* L. with metformin. The method used in this study is qualitative descriptive. *Molecular docking* with *in silico approach* between active compound *Passiflora foetida* L. with target protein *Alpha-glucosidase* subunit B to inhibit blood sugar levels (diabetes). The compound that has the best pharmacokinetic profile compared to metformin is *Passifloricin A. 5-Hydroxy-7,4'-dimethoxyflavone, Deidaclin, Linamarin, Volkenin, (1S,4S)-Tetraphyllin B (S)-Tetraphyllin A* and *Passifloricin A* compounds are relatively safer, not mutagen and not toxic to the liver, except *Passifloricin A* is toxic to the liver, because the compound has a safer level of toxicity compared to the comparison medicine, metformin.

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INTRODUCTION

Each plant contains good compounds that are simple to complex, including medicinal plants. The richness of this content gives a plant a lot of potential to prevent and treat a disease, especially degenerative diseases. Degenerative diseases are caused due to reduced antioxidant ability to neutralize increased free radical activity in the body that causes cell damage (Mulyani et al., 2022).

Herbs are all plant species that are around settlements, cultivated, or wild growth that are known and believed to have medicinal properties (Lingkubi et al., 2015). Herbs are believed by traditional people to cure diseases, both minor and severe diseases. As well herbs, namely turmeric to cure minor diseases such as ulcers, as for cancer, namely antanan plants. The plant parts used can come from leaves, fruits, seeds, bulbs, stems, roots, and rhizomes.

Figure 1. Morphology of parts of the vine: (a) roots, (b) stems, (c) leaves, (d) flowers, (e) fruits; (f) seeds (Source: Personal Documentation)

Rambusa (*Passiflora foetida* L.) is one type of plant that is found creeping on other plants. This plant is usually found in watery areas such as swamps and rivers (Lim, 2016). Rambusa has anti-inflammatory, antitumor, anticancer, anti-hepatotoxicity, and antimicrobial activity (Nagulapati et al., 2021). According to Yepes et al., (2021), rambusa leaves are efficacious in relieving fever, insomnia, colds, headaches, and asthma.

Passiflora foetida L. is a family *of Passifloraceae* native to South America, which has spread to tropical regions around the world, including Thailand. The leaves of this plant are also used as a folk remedy for the treatment of hysteria, fever, ear infections, emmenagogue, asthma, insomnia, and skin diseases. among them are Pseudomonasputida, Vibriochlerae, Shigellaflexnerian, and Streptococcus pyogenes. Further research conducted by Mohanasun from etal. did not show the active compound content in a crude extract of *Passiflora foetida*. The main phytochemical constituents *Passiflora foetida* have several active constituents such as hydrocyanic acid, flavonoids, harmful alkaloids, passifloricin, polyketides, a-pyron, and vitexin. Vitexin is reported to have antioxidant, anti-inflammatory, anti-thyroid, anti-arteriosclerotic, antihypertensive, and antihepatotoxic properties. Vitex levels in different plant extracts have been determined by various techniques, including spectroscopic and chromatographic methods. High-performance thin-layer chromatography (HPTLC), coupled with densitometry (Shuayprom et al., 2016).

According to Fatimah (2015), Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or the body cannot use the insulin produced effectively. This causes the concentration of glucose in the blood to be high (hyperglycemia). The combination of genetic factors and environmental factors can be the etiology of diabetes. Genetic factors are inherited from parents and inherited, while environmental factors are factors influenced by lifestyle. In addition, factors for the occurrence of diabetes, namely age ($\geq$ 40 years), obesity, heredity (genetic), and smoking habits have a higher risk of diabetes (Arisma et al., 2017). Along with lifestyle changes that tend to be less healthy, the prevalence of diabetes is getting higher. Indonesia

was ranked 7th as the country with the highest number of diabetics in 2019 (Ministry of Health of the Republic of Indonesia, 2020).

Diabetes mellitus affects the quality of human resources and will have an impact on increasing health costs. Therefore, all communities actively participate in efforts to overcome and prevent diabetes mellitus. This diabetes mellitus can also cause diabetic retinopathy (DR) disease is an important microvascular complication that is very specific for diabetes mellitus (DM), from these complications to permanent vision loss or even blindness (Wang et al., 2023).

According to the World Health Organization (WHO) in 2030 there will be an increase in the population affected by Diabetes Mellitus by at least 366 million people. While the results of a survey conducted by WHO, Indonesia is included in the 4 highest countries whose population suffers from DM as well as China, the US, and India (Utomo et al., 2020). While WHO predicts around 21.3 million Indonesians will be at risk of diabetes by 2030 (Arisma et al., 2017). Meanwhile, during this pandemic, diabetes mellitus is in the second position as the most comorbid for COVID-19 patients in Indonesia, reaching 33.6% (Wahyuni et al., 2022).

The use of traditional medicine for keeping health and disease disorders is still needed and developed, especially with the high cost of treatment and the price of medicines. The use of traditional medicine is studied by the community through ethnobotany (Wulansari, 2020). According to Khaerati et al., (2015) the results of their research tested the effectiveness of rambusa leaf extract (*Passiflora foetida* L.) can reduce blood sugar levels in mice with the dose used 750mg / kg body weight which is most effective as an antidiabetic.

Current technological advances cause the initial procedure of testing acetic acid compounds for blood sugar controllers in the body, it is necessary to predict in advance to see the performance of compounds by modeling chemical structures through an in silico approach (Hairunnisa, 2019). The technique used in this in silico approach is reverse docking which is a technique to analyze the potential of a compound against target proteins in the human body (Issa et al., 2019).

For this reason, the purpose of this study is to find out: 1) physicochemical and pharmacokinetic predictions *of Passiflora foetida* L. compounds to inhibit sugar in the blood; 2) the level of toxicity of the active compound *Passiflora foetida* L. in silico; 3) the affinity of the active compound *Passiflora foetida* L. to alpha-glucosidase receptors on blood sugar in silico; 4) comparison of the level of toxicity and affinity of the active compound *Passiflora foetida* L. with metformin comparison medicine in silico; and 5) The novelty of the research conducted is molecular docking using Biovia Studio Discovery 2021 software and Autodock Tools 1.5.7 to analyze compounds found in rambusa plants (*Passiflora foetida* L.).

RESEARCH METHODS

Research Design

This research is research with a qualitative descriptive method, namely the data collected in the form of words or images so that it does not emphasize numbers and emphasizes more processes than products (Sugiyono, 2016). The object of this study is plants that have the potential as antidiabetic candidates. These plants contain several active compounds that can inhibit blood sugar levels. molecular docking with an in silico approach between the active compound *Passiflora foetida* L. with the target protein Alpha-glucosidase subunit B to inhibit blood sugar levels (diabetes).

Instruments

The tools used in this study are hardware in the form of an Asus Vivobook Laptop with model specifications named S14, Intel AMD Ryzen 5 3500U CPU, 8 GB RAM, 512 GB SSD Storage, 14.0" IPS LCD Full HD Display, and 4 Cell Battery. The *software* used is the Windows

11 Home SL operating system, MGLTools 1.5.7 which is equipped with Autodock Tools 1.5.7, the Biovia Discovery Studio Visualizer 2021 application, Protein Data Bank (https://rcsb.org/) to download 7KBJ receptors, PubChem (https://pubchem.ncbi.nlm.nih.gov/) to download the active compound *Passiflora foetida* L. (ligand), KNApSAck (http://www.knapsackfamily.com/knapsack_core/top.php), to see the active compound content in *Passiflora foetida* L., pkCSM (pkCSM (unimelb.edu.au)), for pharmacokinetics and toxicity tests and ProTox online tools (https://tox-new.charite.de/protox_II/) for toxicity tests. The ingredients used are 7 active compounds in *Passiflora foetida* L

Procedures

The research procedure starts from the stage of identifying problems for medicine of diabetes from rambusa plant compounds (*Passiflora foetida* L.), then conducting literature studies related to diabetes and *Passiflora foetida* L. plants, then determining the purpose of the study, then collecting data in the form of names of active compounds found in *Passiflora foetida* plants. from the KNApSack website, then downloading the 3-dimensional conformation of active compounds obtained from the PubChem database, then downloading the *docking* target macromolecules obtained from the protein data bank (GDP) provider site, then processing data through the Discovery Studio Visualizer 2021 software, AutoDock Tools 1.5.7, the pkCSM website to predict pharmacokinetics and physicochemistry, the ProTox website to predict toxicity from Compounds are used, and finally make analyzing results from data processing.

Predict physicochemistry of active compounds in *Passiflora foetida* L. using five parameters (*Lipinski rule of five*) including molecular mass weight, logarithm of partisioctanol/water coefficient (Log P), hydrogen bond donor (HBD), Hydrogen bond Acceptor (HBA), and violation. As for pharmacokinetic prediction using ADME indicators (*Absorbtion, Distribution, Metabolism,* and *Excretion*). How to see the toxicity of the active compound *Passiflora foetida* L. can be seen from the LD50 value, *ames toxicity*, *hepatotoxicity,* and toxicity class using *the protox online tool* website and pkCSM, where each parameter has a maximum value limit.

How to see the affinity value between the active compound and *the Alpha-glucosidase* receptor is by taking data from autodock tools 1.5.7 and biovia discovery studio visualizer 2021 software. The software is used for docking via command prompt, and getting the affinity binding value, rmsd u.b, rmsd lb. From this value, it can be seen that the more negative the value of the affinity binding, the better the ligand is to bind to the receptor.

Comparing toxicity parameters such as LD_{50} the greater the value, the better the compound can be tolerated by the human body, ames toxicity if the positive results show that the compound is mutagenic and can act as a carcinogen, hepatoxicity to find out the potential of medicines that can induce damage to the liver, toxicity class if the higher the value then the compound is not toxic. While affinity is seen from ligands that have the most negative affinity value, if the active compounds contained in research plants and comparison medicines have the most negative affinity value, then the compound can be said to be the best ligand to bind to the receptor.

Data Analysis

Data analysis uses qualitative descriptive analysis techniques. Qualitative descriptive analysis was carried out by predicting physicochemistry using five parameters (Lipinski Rule of Five), namely, consisting of molecular mass weight (BM) < 500, logarithm of partisioctanol/water coefficient (Log P) < 5, hydrogen bond donor (HBD) < 5, hydrogen bond acceptor (HBA) < 10, and violation < 2 (Sharma et al., 2023). This prediction uses the help of an online website, Swiss-ADME prediction. Pharmacokinetic predictions were analyzed using ADME (Absorbtion, Distribution, Metabolism, and Excretion) indicators through the pkCSM online website. The

toxicity prediction by looking at the LD50 value, ames toxicity, hepatotoxicity, and toxicity class using the protox online tool and pkCSM online website. Meanwhile, affinity energy prediction is carried out by molecular docking using Autodock Tools 1.5.7 software and Biovia Discovery Studio Visualizer 2021.

RESULTS

Based on the results of this study, there are several results, namely from prediction of physicochemical properties, prediction of pharmacokinetic properties, prediction of toxicity properties, molecular docking, ligand, and amino acid interactions.

Prediction of physicochemical properties

Prediction of physicochemical properties by looking at the parameters of Lipinski's rule of five with the help of pkCSM online tool. The following are the results of the prediction of the physicochemical properties of the ligands of the test compounds in Table 1.

Table 1. Results of prediction of physicochemical properties of compounds using pkCSM Online Tool.

Compound Name	Parameters of Lipinski's Rule of Five				Application of Lipinski's Rule of Five
	BM (g/mol)	Log P	HBA	HBD	
5-Hydroxy-7,4'-dimethoxyflavone	562,524	-0,5092	13	7	Yes, 3 errors
Deidaclin	271.269	-1.58472	7	4	Yes, 0 error
Linamarin	247.247	-1.89492	7	4	Yes, 0 error
Volkenin	287.268	-2.61392	8	5	Yes, 1 error
(1S,4S)-Tetraphyllin B	287,268	-2,61392	8	5	Yes, 1 error
(S)-Tetraphyllin A	271,269	-1.58472	7	4	Yes, 0 error
Passifloricin A	454.692	5,9825	5	3	Yes, 0 error
Metformin (control)	129.167	-1.24383	1	3	Yes, 0 error

Description of the Maximum Limit of the Law of Five Lipinski:
BM : Molecular Weight < 500;
Log P: Partition coefficient < 5;
HBA : Hydrogen Bond Acceptor < 10; and
HBD : Hydrogen Bond Donor < 5.

After testing, physicochemical predictions showed that some compounds did not meet Lipinski's rule of five, namely 5-Hydroxy-7,4'-dimethoxyflavone, volkenin, and (1S,4S)-Tetraphyllin B. The results of this study also showed that there are five compounds that meet Lipinski's rule of five, and one of these compounds is metformin (control) compound.

Prediction of Pharmacokinetic Properties

Prediction of pharmacokinetic properties of test compounds is carried out by looking at the Absorption, Distribution, Metabolism, and Excretion (ADME) parameters using the help of the pkCSM online tool website. The results of the prediction of pharmacokinetic properties can be seen in Table 2.

Table 2. Prediction of Pharmacokinetic Properties of Test Compounds

Compound Name	Absorpsi		Distribution			Metabolism		excretion	
	Intestinal Absorption (%)	Skin permeability (Log kp)	Distribution Volume (Log L/kg)	BBB Permeability (Log BB)	Fraction Unbound (FU)	CYP2 D6 Inhibitor	CYP3 A4 Inhibitor	Renal OCT1 2	Total Clearance (log ml/min/kg)
5-Hydroxy-7,4'-dimethoxyflavone	34,969	-2,735	-0.254	-1.764	0.248	No	No	No	0.225
Deidaclin	45,894	-3,246	-0.104	-0.865	0.8	No	No	No	1.46
Linamarin	40,86	-3,246	-0.214	-0.888	0.828	No	No	No	1.422
Volkenin	38,743	-2,988	-0.002	-0.956	0.808	No	No	No	1.465
(1S,4S)-Tetraphyllin B	38,743	-2,988	-0,002	-0,956	0,808	No	No	No	1.465
(S)-Tetraphyllin A	45,894	-3,246	-0.104	-0.865	0.8	No	No	No	1,46
Passifloricin A	91,043	-2,754	-0.362	-1.106	0.064	No	No	No	1.874
Metformin (control)	59,401	-2,735	-0,232	-0,946	0,811	No	No	No	0,1

It can be seen in Table 2. Passifloricin A compounds have a good percentage of intestinal absorption with a value of 91.043%, and all compounds have good skin permeability values, Deidaclin, Volkenin, (1S,4S)-Tetraphyllin B and (S)-Tetraphyllin A compounds have VDss log values of -0.104; -0.002; -0.002 and -0.104. The compounds 5-Hydroxy-7,4'-dimethoxyflavone, and Passifloricin A have log BB values of <-1 which are -1.764 and -1.106 so it is said that they cannot be evenly distributed, the six active compounds of *Passiflora foetida* L. have lower unbound fraction values than the control compounds. All active compounds of *Passiflora foetida* L. also have no inhibition on the CYP isoform and do not affect OCT2 substrates.

Prediction of Toxicity Properties

This toxicity prediction uses LD_{50} parameters, toxicity class, ames toxicity, and hepatotoxicity. The predicted toxicity results of the test compound and metformin comparison compound can be seen in Table 3. Where there is only one active compound *Passiflora foetida* L. that is toxic to the liver, namely the compound Passifloricin A. From the results of this study, there are also class 6 with 1 compound, class 5 with 1 compound, and class 4 with 5 active compounds *Passiflora foetida* L.

Table 3. Results of prediction of toxicity properties.

No.	Compound Name	Toxicity			
		LD 50 (m/kg)*	*Ames Toxicity***	*Hepatotoxicity***	Toxicity Class*
1	5-Hydroxy-7,4'-dimethoxyflavone	3.919	Yes	No	5
2	Deidaclin	2.000	No	No	4
3	Linamarin	29.700	No	No	6
4	Volkenin	2.000	No	No	4
5	(1S,4S)-Tetraphyllin B	2.000	No	No	4
6	(S)-Tetraphyllin A	2.000	No	No	4
7	Passifloricin A	1.890	No	Yes	4
8	Metformin (control)	680	Yes	No	4

Note:
(*) Using the ProTox Online Tool (**) Using pkCSM Online Tool

Molecular docking ligand of test compound with protein Alpha-glucosidase Sub-unit B

The results of molecular docking in the form of binding affinity and the values of RMSD L.B and RMSD U.B can be seen in Table 4.

Table 4. Results of *molecular docking* of test compounds and comparison medicines at 7KBJ receptors.

No.	Ligand	Conformation	*Binding Affinity* (kcal/mol)	*dist. from best mode*	
				rmsd Lb.	rmsd u.b.
1	5-Hydroxy-7,4'-dimethoxyflavone	1	-10,4	0,000	0,000
		2	-10,4	10,636	14,995
		3	-10,2	11,390	15,004
		4	-9,8	3,079	8,957
		5	-9,7	24,919	27,861
		6	-9,7	2,090	2,586
		7	-9,6	30,128	33,328
		8	-9,5	14,592	17,983
		9	-9,5	25,651	29,517
2	Deidaclin	1	-7,4	0,000	0,000
		2	-7,4	15,370	17,935
		3	-7,2	2,252	3,763
		4	-7,1	14,951	17,254
		5	-7,1	14,424	16,332
		6	-7,1	13,641	15,209
		7	-7,0	16,541	19,232
		8	-6,8	13,491	14,812
		9	-6,8	17,541	19,529
3	Linamarin	1	-7,7	0,000	0,000
		2	-7,0	1,611	3,981
		3	-6,7	2,213	5,369
		4	-6,4	22,695	24,656
		5	-6,4	35,500	37,413
		6	-6,3	2,489	5,103
		7	-6,3	12,989	14,172
		8	-6,3	21,547	23,434
		9	-6,3	22,099	23,990
4	Volkenin	1	-7,5	0,000	0,000
		2	-7,4	13,020	15,602
		3	-7,3	13,100	16,271
		4	-7,2	14,421	16,294
		5	-7,2	15,246	16,279
		6	-7,2	22,304	23,890
		7	-7,2	2,271	4,162
		8	-7,2	2,568	4,138
		9	-7,1	2,318	5,828
5	(1S,4S)-Tetraphyllin B	1	-8,3	0,000	0,000
		2	-8,2	15,848	19,140
		3	-7,9	27,005	28,287

No.	Ligand	Conformation	*Binding Affinity* (kcal/mol)	*dist. from best mode*	
				rmsd Lb.	rmsd u.b.
5	(1S,4S)-Tetraphyllin B	4	-7,8	2,278	3,526
		5	-7,7	31,342	33,373
		6	-7,7	2,737	3,493
		7	-7,7	2,964	3,871
		8	-7,6	2,628	3,587
		9	-7,6	16,850	20,358
6	(S)-Tetraphyllin A	1	-7,3	0,000	0,000
		2	-7,3	18,149	21,253
		3	-7,3	32,194	34,743
		4	-7,1	17,458	19,573
		5	-7,0	14,359	16,897
		6	-6,9	24,641	25,644
		7	-6,9	5,306	7,328
		8	-6,8	27,527	29,248
		9	-6,8	20,116	22,186
7	Passifloricin A	1	-9,1	0,000	0,000
		2	-8,9	29,198	34,401
		3	-8,8	16,844	22,597
		4	-8,7	14,916	19,449
		5	-8,6	31,452	33,941
		6	-8,6	35,766	38,850
		7	-8,6	23,502	26,350
		8	-8,4	36,947	41,362
		9	-8,4	28,471	33,869
8	Metformin (control)	1	-5,3	0,000	0,000
		2	-4,8	36,756	37,920
		3	-4,7	1,431	2,269
		4	-4,7	19,682	20,816
		5	-4,6	39,837	40,991
		6	-4,4	38,479	39,837
		7	-4,4	38,745	39.386
		8	-4,4	20,221	21,167
		9	-4,3	21,260	22,593

The results are shown in the data in Table 4. All active compounds of *Passiflora foetida* L. have greater values of binding affinity than control compounds and have lower bound rmsd and upper bound rmsd values with valid poses on ligands of -9.7 kcal/mol.

Ligand and Amino Acid Interactions

The results of the amino acid interaction of the test compound with the alpha-glucosidase receptor (7KBJ) are shown in Table 5.

Table 5. Results of amino acid interactions of test compounds on 7KBJ receptors.

No.	Compound Name	Amino Acid Interactions
1	5-Hydroxy-7,4'-dimethoxyflavone	Conventional Hydrogen Bond: TRP C463, PHE C468, GLY C498
		Van der Waals Bond: PRO C471, GLN C470, PRO C469, THR C462, TRP A523, TYR C499, ARG C500, ASP A496, VAL A495, SER A497, PRO A526, SER A528, GLU C553
		Hydrocarbon Bond: ASP C456
		Alkyl Hydrophobic Bond: PRO C465, LEU C472
		Unfavorable donor-donor Bond: LYS A494
2	Deidaclin	Conventional Hydrogen Bond: SO C41023*, ARG A705, ARG A426, ARG C422
		Van der Waals Bond: LEU C701, ARG C426, ASN C424, GLY C704, ASN A424, TYR A425, ASP A430
		Alkyl Hydrophobic Bond: ARG C705
3	Linamarin	Conventional Hydrogen Bond: THR C703
		Van der Waals Bond: ARG C705, LEU C701, TRP C423, SO C41023*, ASN A424, ARG A422, ARG A705, TYR A425
		Alkyl Hydrophobic Bond: LEU A701, ARG C426, ARG A426
		Unfavorable donor-donor Bond: ARG C422*, ASN C424
		Unfavorable acceptor-acceptor Bond: ARG C422, ASN C424
4	Volkenin	Conventional Hydrogen Bond: GLY C498, PHE C461, TRP C463
		Van der Waals Bond: ASP A496, TYR C499, ARG C500, THR C462, PRO C465, ASP C456, ARG C459, ARG A459, LYS A494, ASP A496
		Hydrocarbon Bond: GLU C553
5	(1S,4S)-Tetraphyllin B	Conventional Hydrogen Bond: ASP C456, GLY C498, PRO C469
		Van der Waals Bond: ARG A459, ARG C459, LYS A494, THR C462, PRO C465, TRP C463, TRP A523, PRO C471, GLN C470, GLU C553, MET C546, ARG C500, TYR C499, VAL C501
6	(S)-Tetraphyllin A	Conventional Hydrogen Bond:
		Van der Waals Bond: VAL A576, ASP H305, PHE H307, ARG A624, MET A565, PHE A673, PHE A674, TRP A423, HIS A700, TRP A525
		Hydrophobic bonds of pi-alkyl: PHE A571
		Unfavorable acceptor-acceptor Bond: ASP A640

No.	Compound Name	Amino Acid Interactions
7	Passifloricin A	Conventional Hydrogen Bond: THR A466
		Van der Waals Bond: GLN A436, LYS A481, LEU C701, ARG A467, TRP C423*, HIS C700, PHE C674, TRP C525, PHE C571, VAL C576, ASP J305, SO B41803, GLN A436, LYS A481
		Alkyl Hydrophobic Bond: HIS A477, LEU A432, ALA A429
		Hydrophobic bonds of pi-alkyl: HIS A477, LEUS A432, ALA A429
		Pi-Anion Bond: PHE J307
8	Metformin (control)	Conventional Hydrogen Bond: LEU C701, ASN C424
		Van der Waals Bond: TRP C423, ARG A426, THR C703
		Attractive Charge Bond: SO C41023
		Unfavorable donor-donor Bond: ARG C705, ARG C426, ARG C422
		Unfavorable positive-positive Bond: ARG C705, ARG C426, ARG C422

(*): Same Amino Acid residue as Metformin control.

From Table 5. It can be seen that compounds that have the same bond, namely Linamarin in the ARG C422 protein and Passifloricin A in the TRP C423 protein.

DISCUSSION

The predicted results of physicochemical tests in Table 1. show that 6 active compounds in *Passiflora foetida* L. meet the lipinski's rule of five, namely having a molecular weight of <500 and the number of H bonds of acceptors (HBA) <10, all active compounds of *Passiflora foetida* L. meet the Log P value of <5, and 4 active compounds whose number of donor H bonds (HBD) <5 (Fakih &; Dewi, 2020). This means that it is predicted to be easily absorbed, has good permeability, and has good oral bioavailability. Based on the lipinski's rule of five and the results of analysis, almost all active compounds of *Passiflora foetida* L. have the potential to be medicine.

The compound that has the greatest molecular weight is 5-Hydroxy-7,4'-dimethoxyflavone. That is, the compound is quite difficult to penetrate through biological membranes. The greater the molecular weight, the more difficult it is to penetrate through biological membranes. Medicines with a molecular weight greater than 500 have a large molecular size so it is quite difficult to penetrate through biological membranes (Ruswanto, 2015). Other compounds have a molecular weight smaller than 500 so they are said to be able to be penetrated through biological membranes.

Log P value is related to lipophility or hydrophobicity, namely the ability of chemical composition to be soluble in fats, oils, lipids and nonpolar solvents (Ruswanto, 2015). Compounds that have a Log P value greater than metformin are 5-Hydroxy-7,4'-dimethoxyflavone and Passifloricin A. meaning that the test compound is easier to penetrate biological membranes so that it easily binds to receptors than metformin.

The compound 5-hydroxy-7,4'-dimethoxyflavone has HBA values of 13 and HBD 7, in addition, volkenin and (1S,4S)-Tetraphyllin B has HBD values of 5. The value of hydrogen bond acceptor and hydrogen bond donor has a relationship with the biological activity of a medicine molecule. Changes that can affect the biological activity of compounds caused by hydrogen bonds

are the chemical-physical properties of compounds, namely boiling point, melting point, solubility in water, ability to form chelate, and also similarity (Ruswanto, 2015).

See Table 2. Passifloricin A compound with a percentage of intestinal absorption sequentially, namely, 91.043%. The compound has an intestinal absorption value of more than 80% and not less than 30% which indicates the compound has good absorption. Compounds can be said to have good absorption if the intestinal absorption value is > 80% and is said to be less good if the intestinal absorption value is < 30% (Chander et al., 2017).

A compound is said to have low skin permeability if it has a log Kp value of > -2.5 (Pires et al., 2015). All compounds have a log value of Kp > -2.5. This means that all compounds have good skin permeability. Medicinal materials that have good skin permeability can be used to advance consumer products in developing new medicines by trans-dermal administration (Pires et al., 2015).

The distribution parameters are carried out by looking at the VDss value, blood-brain barrier, and fraction unbound. The higher the VDss value, the more medicine is distributed into tissues rather than plasma. The compound is said to have a low VDss value if the VDss log value is < -0.15 and high if the VDss log value is > 0.45 (Pires et al., 2015). The compounds Deidaclin, Volkenin, (1S,4S)-Tetraphyllin B and (S)-Tetraphyllin A respectively have a VDss log value of -0.104; -0,002; -0.002 and -0.104. This means that the compound has a value greater than -0.15 and less than 0.45 so it is said to be evenly distributed to provide the same concentration as in blood plasma. While other compounds are not able to provide the same concentration in blood plasma because the VDss value is less than -0.15.

The human brain is protected by exogenous compounds by the blood-brain barrier. The ability of a medicine to enter the brain is an important parameter to consider to help reduce side effects and brain toxicity. The compound is said to be able to penetrate the blood-brain barrier well if it has a log BB value of > 0.3 and is said to be unable to be well distributed if it has a log BB value of < -1 (Pires et al., 2015). The compounds 5-hydroxy-7,4'-dimethoxyflavone, and Passifloricin A have log BB values of <-1 which are -1.764 and -1.106 so it is said to be unevenly distributed. While other compounds are predicted to be able to be distributed evenly so that they can provide the same concentration in blood plasma.

Most medicines in plasma will exist in equilibrium between unbound states or bound to serum proteins. The efficacy of the medicine is influenced by the extent to which it binds to proteins in the blood (unbound value). The more that is bound, the less efficient it will be in crossing cell membranes or diffusing (Pires et al., 2015). The results said the six active compounds *Passiflora foetida* L. has a lower unbound value than metformin, because if the greater the unbound value of a compound, the more it will bind to plasma proteins, so that the six active compounds *Passiflora foetida* L. are efficient in crossing cell membranes or diffusing.

Metabolic profiles were analyzed using the presence or absence of inhibition in cytochrome P450, especially in CYP2D6 and CYP3A4 isoforms. Cytochrome P450 is an important detoxification enzyme in the body, mainly found in the liver. This cytochrome is capable of oxidizing xenobiotics to provide its excretion facility. Some medicines are inactivated by cytochrome P450 and some can be activated by P450. This enzyme inhibitor is similar to grape fruit juice which can affect medicine metabolism and is contraindicated (Pires et al., 2015). From the results of the prediction above, all compounds in *Passiflora foetida* L. do not have inhibition in cytochrome P450 isoform CYP2D6 and isoform CYP3A4.

In predicting the excretion process is carried out with constant parameters. Total Clearance (CLtot) and Renal Organic Cation Transporter 2 (OCT2). CLtot is a combination of hepatic clearance (metabolism in the liver and bile) and renal clearance (excretion through the kidneys). CLtot is related to bioavailability and it is very important to determine the dosing rate to achieve

steady-state concentrations (Pires et al., 2015). From this CLtot value can be predicted the speed of a compound to excrete. All compounds have higher total clearance values than metformin. OCT2 is a renal uptake transporter that plays an important role in the disposition and clearance of endogenous medicines and compounds. OCT2 substrates potentially exert adverse interactions when administered together with OCT2 inhibitors (Pires et al., 2015). All compounds do not affect OCT2 substrates so it is predicted that they are not OCT2 substrates.

The results of the study in Table 3 with toxicity parameters, namely Ames Toxicity, is a widely used method to assess the mutagenic potential of a compound using bacteria. Positive results indicate that the compound is mutagenic so that it can act as a carcinogen (Pires et al., 2015). Based on the results of the prediction above, all test compounds are not mutagen in silico. Hepatotoxicity test is a test to determine the presence or absence of potential medicines that can induce damage to the liver (Pires et al., 2015). From the results of the prediction above, it can be seen that six active compounds in *Passiflora foetida* L. and metformin comparison medicines are not toxic to the liver, except Passifloricin A is toxic to the liver.

Compounds in class 4 (Deidaclin, Volkenin, (1S,4S)-Tetraphyllin B, (S)-Tetraphyllin A, and Passifloricin A), class 5 (5-Hydroxy-7,4'-dimethoxyflavone) and class 6 (Linamarin) are relatively safer, not mutagen and not toxic to liver, except for Passifloricin A compounds which are toxic to liver. This means that the compound has a safer level of toxicity compared to the comparison medicine, metformin.

Binding affinity is a measure of a medicine's ability to bind to a specified receptor. The lower the value, the higher the affinity between receptors and ligands, and vice versa, the higher the value, the lower the affinity between receptors (Saputri et al., 2016). The ligands of the test compounds that have better binding affinity values than metformin are 5-Hydroxy-7,4'-dimethoxyflavone, Deidaclin, Linamarin, Volkenin, (1S,4S)-Tetraphyllin B, (S)-Tetraphyllin A and Passifloricin A with sequential binding affinity values of -10.4 kcal/mol, -7.4 kcal/mol, -7.7 kcal/mol, -7.5 kcal/mol, -8.3 kcal/mol, 7.3kcal/mol and 9.1 kcal/mol. Meanwhile, the binding affinity value of metformin is -5.3 kcal/mol. The best ligands are those ligands that have the most negative binding affinity value (Yahmin et al., 2019).

There are two RMSD values, namely, lower bound RMSD (RMSD lb.), and upper bound RMSD (RMSD ub.). The RMSD value for the conformational alignment of the structure that is still acceptable is < 3 but it is optimal if it is < 2, if the closer to 0, the better the alignment value (Listyani &; Herowati, 2018). Based on this theory, it was found that not all ligands with interaction poses between these receptors are said to be valid. Ligands that interact well in valid poses are found in ligands of the test compounds 5-Hydroxy-7,4'-dimethoxyflavone, Deidaclin, Linamarin, and (1S,4S)-Tetraphyllin B by -9.7 kcal/mol, -7.2 kcal/mol, -7.0 kcal/mol, and -7.8 kcal/mol, respectively. While the valid pose on the ligand of the comparison medicine metformin was obtained at -4.7 kcal / mol. From these results, it can be predicted that the test compound 5-Hydroxy-7,4'-dimethoxyflavone has a better ability than metformin to inhibit the enzyme Alpha-glucosidase to the 7KBJ receptor.

The interaction of amino acid residues seen in Table 5 is the same as the comparison compound or native ligand and can be said to have the same biological activity ability as the comparison compound or native ligand (Prasetiawati et al., 2021). Test compounds that have the same bond with comparison medicines, namely metformin on ARG C422 protein is Linamarin, and TRP C423 protein on Passifloricin A so it is predicted that both compounds have the same mechanism of action as metformin. The two compounds together with metformin form interactions with unfavorable donor-donor bonds and van der Waals bonds. Active compounds can be said to have strong bonds with target receptors if they have strong bonds through hydrogen

bonds and can bond on the active side with one of the same amino acid residues (Wibisono &; Martino, 2023).

CONCLUSION

Based on research, almost all active compounds *Passiflora foetida* L. meet Lipinski's rule of five it is said to be a candidate medicine. The compound that has the best pharmacokinetic profile compared to metformin is Passifloricin A. 5-Hydroxy-7,4'-dimethoxyflavone, Deidaclin, Linamarin, Volkenin, (1S,4S)-Tetraphyllin B (S)-Tetraphyllin A and Passifloricin A are relatively safer, not mutagen and not toxic to hepar, unless Passifloricin A is toxic to liver, because the compound has a safer level of toxicity compared to comparison medicines, namely metformin. Test compounds that have better binding affinity values than Metformin are 5-Hydroxy-7,4'-dimethoxyflavone, Deidaclin, Linamarin, Volkenin, (1S,4S)-Tetraphyllin B (S)-Tetraphyllin A and Passifloricin A with consecutive binding affinity values of -10.4 kcal/mol, -7.4 kcal/mol, -7.7 kcal/mol, -7.5 kcal/mol, -8.3 kcal/mol, -7.3 kcal/mol and -9.1 kcal/mol. The most valid test compound compared to metformin in certain poses is 5-Hydroxy-7,4'-dimethoxyflavone with binding affinity -9.7 kcal/mol, RMSD value l.b 2.090 and RMSD u.b 2.586. In contrast to metformin which has a binding affinity of -4.7 with RMSD l.b 1.431 and RMSD u.b 2.269. Further research is needed on the potential of the active compound *Passiflora foetida* L. as an antidiabetic candidate in inhibiting blood sugar levels in vitro or in vivo.

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