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In Silico Analysis of Bioactive Compounds in The Faloak (*Sterculia quadrifida* R. Br) Stem Bark to Identify Antidiabetic Activity

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Abstract

Sterculia quadrifida R. Br or known as the faloak plant is a typical plant originating from the East Nusa Tenggara region, Indonesia. This plant has long been used by local people in the treatment of diabetes. *In vivo*, bioactive compounds from the extract of stem bark *Sterculia quadrifida* R. Br have been reported to have antidiabetic activity. The present study aims to analyse the potential of bioactive compounds in the faloak stem bark as inhibitors of the enzymes α-glucosidase, PPAR-γ, SGLT2, and DPP-IV. The preparation of bioactive compounds and their comparison was conducted utilising ChemDraw 2D & 3D, while proteins were obtained from the Protein Data Bank (PDB). The docking process used *Molegro Virtual Docker*, and visualisation was performed using BIOVIA Discovery Studio. Pharmacokinetic prediction (ADMET) was also carried out using the pkCSM website. The results of molecular docking with DPP-IV receptors showed that three bioactive compounds of faloak have better affinity than the comparative compounds, namely beta sisterol (-98.8838) to Alogliptin, Linagliptin, and Sitagliptin. While epicatechin (-83.9022) and cathecin (-83.4336) have better affinity than the comparative compounds Vidagliptin, Saxagliptin.

Keywords: Antidiabetic; faloak stem bark; *Molecular Docking*; *in silico*; *Sterculia quadrifida* R. Br.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease whose prevalence continues to increase globally. Based on data from the International Data Federation (IDF), in 2021, there were around 537 people worldwide with diabetes. This number is predicted to increase to 643 million in 2030 and 783 million in 2045. According to the IDF, Indonesia is the fifth country with the highest number of diabetes with 19.5 million sufferers in 2021 and is predicted to be 28.6 million in 2045. The World Health Organization (WHO) states that diabetes is one of the diseases in Indonesia that causes death. Diabetes can trigger other diseases (Asyikin & Ratnasari Dewi Poltekkes Kemenkes Makassar, 2024).

One of the causes of the high prevalence of diabetes is an unhealthy diet and lifestyle. With the increasing number of diabetics in Indonesia every year, two steps can be taken, namely the treatment of patients who have diabetes and prevention of diabetes for those who have not experienced it. Treatment of diabetes can be done with two types of treatments, namely the provision of drug therapy and non-drug therapy. The treatment is not only focused on the control of blood glucose levels, but also involves the management of disease complications and the use of safer and more efficient therapies (Asyikin & Ratnasari Dewi Poltekkes Kemenkes Makassar, 2024).

Nowadays, people tend to choose treatment by utilising natural products as traditional medicine based on experiences passed down from generation to generation. Moreover, Indonesia is a tropical country, with rich biodiversity in each region. One of the potential plants in the treatment of diabetes is the faloak plant (*Sterculia quadrifida* R. Br), which has long been used by local people as a traditional treatment for diabetes on the island of Timor, East Nusa Tenggara (NTT) (Octaviany & Iskandar, 2023).

Faloak has many chemical compounds, including flavonoids, tannins, alkaloids, steroids, and triterpenoids. Local people often utilize faloak as a raw material for herbal medicines, and the part that is often used is the stem bark which has been proven by several studies conducted. However, the bioactive compounds and pharmacological activities of faloak plants are still very limited due to the lack of scientific research and knowledge (Octaviany & Iskandar, 2023). As a first step

in predicting the activity of bioactive compounds in a plant, a molecular docking approach can be used.

According to Fernandez, *et al.* (2017), stated that the stem bark of the faloak plant has antidiabetic activity by showing a decrease in blood glucose in glucose-induced test animals (*in vivo*). Fernandez added that further research is needed to determine the levels of active compounds in faloak bark and further explore its profile and safety (Fernandez & Edel, 2017). Therefore, a molecular docking approach can be carried out and continued with the prediction of its pharmacokinetic profile (ADMET).

The docking process begins by using bioactive compounds of a plant with a protein receptor obtained from the Protein Data Bank (PDB). The stem bark of *S. quadrifida* R. Br has several chemical contents including flavonoids, tannins, alkaloids, steroids, and triterpenoids (Octaviany & Iskandar, 2023). In addition, specific compounds such as β-sitosterol, catechin, epicatechin and scopoletin have been identified in the stem bark of the faloak (Riwu et al., 2024). These specific biocompounds will be used in the docking process with protein receptors obtained from Protein Data Bank with mechanisms as inhibitors of α-glucosidase, PPAR-γ, SGLT2, DPP-IV.

This study aims to strengthen the understanding of the mechanism of action of bioactive compounds in the stem bark of the faloak plant as inhibitors of important enzymes associated with diabetes, such as α-glucosidase, PPAR-γ, DPP-IV, and SGLT2. The pharmacokinetic profile of the bioactive compounds in the stem bark of *S. quadrifida* R. Br was also obtained, which can support the potential of faloak as a source of natural materials in the development of new antidiabetic drugs that are safer and more effective, and is expected to be the basis for the development of plant-based therapies in the future.

MATERIALS AND METHODS

Data Collection and Ligand Preparation

A comprehensive review of the existing literature was conducted to identify bioactive compounds of potential interest from the stem bark of the faloak plant. Shown in Table 01, the identified compounds included β-sitosterol, catechins, epicatechins and scopoletin. Bioactive compounds and ligands were prepared using the ChemDraw 2D application, with the resultant files being saved in the (.cdx) format. Energy optimization was carried out with ChemDraw 3D, by selecting Minimize Energy MM94 and saved in (.mol2) format.

Protein Preparations

Protein complex structures in the (.pdb) format were obtained from the Protein Data Bank, which was downloaded from the website http://www.rscb.org/ . The files were prepared using the Molegro Virtual Docker application, and subsequently saved in the (.mol2) format. Protein receptors were selected based on their central role in diabetes, including as inhibitors of α-glucosidase (3TOP), PPAR-γ (5Y20), SGLT2 (7VSI) and DPP-IV (2RGU) (Table 02).

Internal Validation

Prepared proteins were validated with 12 combinations (4 scoring functions and 3 algorithms) until RMSD ≤ 2Å was obtained. This validation aims to ensure that the docking protocol is appropriate.

Physicochemical Analysis

The drug-likeness of the physicochemical compounds was evaluated using Lipinski's Rule of Five. For a compound to persuade as a drug, it must satisfy a set of parameters that will prove its compatibility, efficiency, and toxicity.

Molecular Docking

The molecular docking process between the ligand of the comparison compound and the bioactive compound was carried out using the Molegro Virtual Docker application. The results obtained docking score of the comparator compound ligand which will be compared with the score of the bioactive compound ligand.

Visualization

Ligand-receptor complexes of bioactive compounds predicted to have antidiabetic activity were generated using BIOVIA Discovery Studio. The visualization results were interpreted to determine each amino acid interaction that binds to the protein's active site.

In Silico Pharmacokinetic Parameter Prediction (ADMET)

The pharmacokinetics/ADMET properties of these compounds were investigated using pkCSM an online web server (https://biosig.lab.uq.edu.au/pkcsm/prediction). pkCSM provides a platform for the analysis and optimization of pharmacokinetic and toxicity properties implemented in a user-friendly manner.

RESULTS AND DISCUSSION

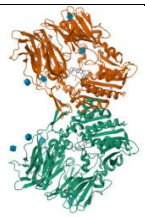
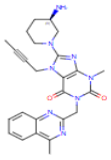
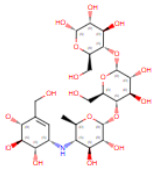
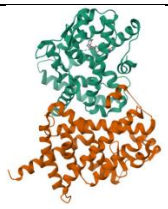
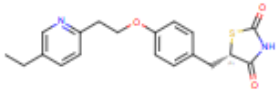
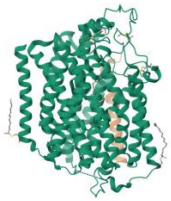
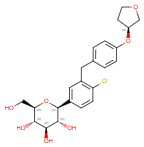
Data Collection and Ligand Preparation

Table 1. Ligand Preparation Results.

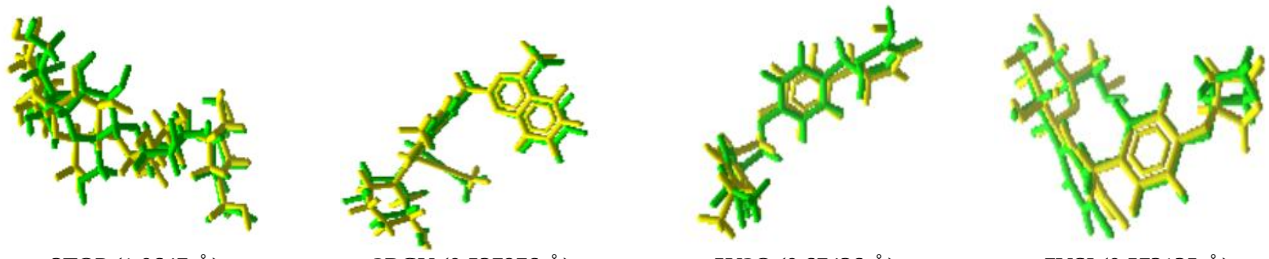
No	CID	Name of Compounds	IUPAC Name	Isomeric SMILES
1	9064	(+)-catechin	(2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	C1[C@@H]([C@H](OC2=CC(=CC(=C21)O)O)O)C3=CC(=C(C=C3)O)O)O
2	72276	epicatechin	(2*R*,3*R*)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2*H*-chromene-3,5,7-triol	C1[C@H]([C@H](OC2=CC(=CC(=C21)O)O)O)C3=CC(=C(C=C3)O)O)O
3	5280460	Scopoletin	7-hydroxy-6-methoxychromen-2-one	COC1=C(C=C2C(=C1)C=CC(=O)O2)O
4	222284	β-sitosterol	(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(2*R*,5*R*)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[a]phenanthren-3-ol	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C

Protein Preparation

Table 2. Protein Preparation Results.

No	3D Structure of Protein	Description	Native Ligand
1	 2RGU	Organism: Homo sapiens Method: X-RAY DIFFRACTION Resolution: 2.60 Å Mutation: No	 356 8-[(3R)-3-Aminopiperidin-1-yl]-7-but-2-yn-1-yl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-d ione
2	 3TOP	Organism: Homo sapiens Method: X-RAY DIFFRACTION Resolution: 2.88 Å Mutation: No	 alfa-acarbose
3	 5Y2O	Organism: Homo sapiens Method: X-RAY DIFFRACTION Resolution: 1.8 Å Mutation: No	 (5S)-5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione
4	 7VSI	Organism: Homo sapiens Method: ELECTRON MICROSCOPI Resolution: 2.95Å Mutation: No	 7R3 (2S,3R,4R,5S,6R)-2-[4-chloranyl-3-[[4-[(3S)-oxolan-3-yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol

Internal Validation



3TOP (1,0647 Å) 2RGU (0,537976 Å) 5Y2O (0,67436 Å) 7VSI (0,573135 Å)

Figure 1. Position of the native ligand superimposed on the redocked native ligand.

Table 3. Root-Mean-Square Deviation of Protein Data Bank of a. 3TOP (α-glucosidase) b. 2RGU (PPAR-γ) c. 5Y2O (SGLT2) and d. 7VSI (DPP-IV).

a.

Algorithm / Scoring Function	Moldock optimizer (Å)	Moldock SE (Å)	Iterated simplex (Å)
Moldock score	2,52913	3,0255	1,2467
Moldock (grid) score	**1,0647**	2,46952	3,74578
Plants score	1,42316	3,87905	2,09881
Plants score (grid)	1,30646	1,48438	2,08955

b.

Algorithm / Scoring Function	Moldock optimizer (Å)	Moldock SE (Å)	Iterated simplex (Å)
Moldock score	0,538373	**0,537976**	1,57811
Moldock (grid) score	1,64074	1,56222	8,43536
Plants score	2,03736	1,54417	2,56408
Plants score (grid)	1,96009	1,37038	1,52665

c.

Algorithm / Scoring Function	Moldock optimizer (Å)	Moldock SE (Å)	Iterated simplex (Å)
Moldock score	1,22248	**0,67436**	0,975562
Moldock (grid) score	1,07309	3,3379	1,47244
Plants score	1,0898	0,992484	1,05486
Plants score (grid)	1,55609	1,6986	1,01191

d.

Algorithm / Scoring Function	Moldock optimizer (Å)	Moldock SE (Å)	Iterated simplex (Å)
Moldock score	0,799375	1,04281	0,966411
Moldock (grid) score	1,11362	1,08267	1,02383
Plants score	0,86853	0,69421	0,800193
Plants score (grid)	0,906024	**0,573135**	0,782356

Physicochemcical Analysis

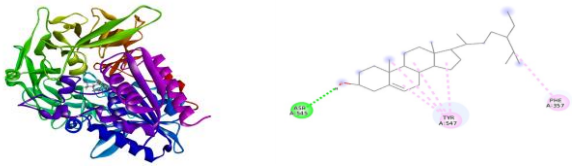
Table 4. The Lipinski's Rule of Five Analysis Results.

Compound	Molecular Weight (g/mol)	Num. H-bond acceptors (<10)	Num. H-bond donors (<5)	Lipophilicity (log p<5)	No. of Lipinski's violation
Beta cytosterol	414.71	1	1	8,024803	1
Catechin	290.27	6	5	1,546099	0
Epicatechin	290.27	6	5	1,546099	0
Scopoletin	192.17	4	1	1,333000	0

Molecular Docking

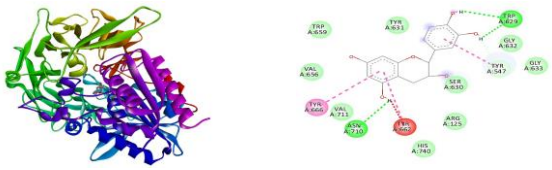
Table 5. Molecular Docking Results.

Compound	CID	Docking *Score*			
		7VSI	3TOP	5Y2O	2RGU
Beta Cytosterol	222284	-119,548	-107,759	-78,7945	**-98,8838**
Catechin	9064	-94,293	-82,5122	-82,733	**-83,4336**
Epicatechin	72276	-99,5256	-65,3541	-81,9963	**-83,9022**
Scopoletin	5280460	-71,3226	-66,4612	-65,0435	-58,7893
Alogliptin	11450633	-	-	-	-94,7326
Linagliptin	10096344	-	-	-	-93,8655
Sitagliptin	4369359	-	-	-	-87,8399
Vildagliptin	6918537	-	-	-	-78,2888
Saxagliptin	11243969	-	-	-	-66,9827
Acarbose	41774	-	**-145,932**	-	-
Troglitazone	5591	-	-	**-131,227**	-
Pioglitazone	4829	-	-	**-114,821**	-
Rosiglitazone	77999	-	-	**-110,379**	-
Dapagliflozin	9887712	**-122,592**	-	-	-
Canagliflozin	24812758	**-136,445**	-	-	-
Empagliflozin	11949646	**-135,666**	-	-	-



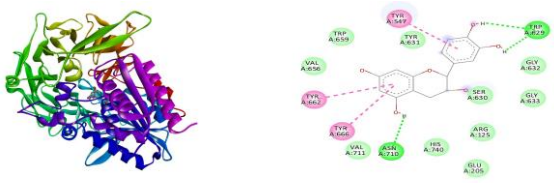
3D **2D**

Figure 2. Beta cytosterol best interacts with receptors.



3D **2D**

Figure 3. Catechin best interacts with receptors.



3D **2D**

Figure 4. Epicatechin best interacts with receptors.

In Silico Pharmacokinetic Parameter Prediction (ADMET)

Table 6. The predicted ADMET properties of the bioactive compounds; 1-Water solubility (log mol/L) 2 -CaCO2 Permeability (Papp) 3-Human Intestinal absorption (%) 4-Volume of distribution at steady-state (log L/kg) 5-Fraction unbound (Fu) 6-Blood brain barrier permeability (log BB) 7-Cytochromes P450 substrates 8-Cytochromes P450 inhibitors 9-Total clearance (log ml/min/kg) 10-Renal Organic cation transporter 2 substrate 11-AMES toxicity 12-Max tolerated dose (human) (log mg/kg/day) 13-Lethal Dose 50 (mol/kg) 14-Hepatotoxicity.

Compound	Absorption			Distribution			Metabolism		Excretion		Toxicity			
	WS_1	CP_2	HIA_3	$Vdss_4$	FU_5	BBB_6	$CYPS_7$	$CYPI_8$	TC_9	ROS_{10}	$AMES_{11}$	MTD_{12}	LD_{13}	HT_{14}
Beta cytosterol	**-6.773**	**1.201**	**94.464**	0.193	0	0.781	3A4	-	0.628	No	No	-0.621	2.552	No
Catechin	-3.117	-0.283	68.829	**1.027**	0.236	**-1.054**	-	-	0.183	No	No	0.438	2.428	No
Epicatechin	-3.117	-0.283	68.829	**1.027**	0.236	**-1.054**	-	-	0.183	No	No	0.438	2.428	No
Scopoletin	-2.504	1.184	95.277	0.034	0.383	-0.299	-	1A2	0.730	No	No	0.614	1.950	No

Discussion

Internal Validation

Validation was performed by tethering a standard ligand as a re-docking protocol with a pre-prepared receptor. The standard ligand was utilized as a tethering protocol to predict the position and ligand-protein interaction. The tethering was performed using Molegro Virtual Docker and the RMSD (*Root Mean Square Deviation*) value was observed (Zubair et al., 2020). The root-mean-square deviation value is utilized to evaluate the similarity of coordinates between two atoms, as illustrated in Figure 01. As shown in Table 3, the re-docking results of the standard ligands in this study have an RMSD of 1.067 Å (3TOP); 0.537976 Å (2RGU); 0.67436 Å (5Y2O); and 0.573135 Å (7VSI). From the validation results carried out it can be seen that the RMSD is qualified as it is < 2 Å.

Physicochemical Analysis

Drug-likeness screening qualitatively assesses the possibility of a molecule becoming an oral drug regarding bioavailability (Santos, G.B; Ganesan, A; Emery, 2016). Lipinski's "rule of five" highlights possible bioavailability problems if two or more properties are violated. Lipinski's "rule of five" is an experimental and computational method to estimate solubility, membrane permeability, and efficacy in the drug development setting. According to Lipinski (Lipinski et al., 2001), a compound can be used as a drug candidate if it has a molecular weight of less than 500 g/mol, a Log P of less than 5, at least one H-bond donor of less than 5, and at least one H-bond acceptor of less than 10. According to Table 4, the four compounds from the stem bark of the faloak plant can be considered as new drug candidates as antidiabetics. However, scopoletin shows results that fulfil all Lipinski's rules, while the other bioactive compounds have some rules that are not fulfilled. However, this rule does not predict whether a compound is pharmacologically active (Kowalska et al., 2018).

Molecular Docking

Before molecular docking, all bioactive compounds from the stem bark of the faloak plant were prepared using the Molegro Virtual Docker application. The results obtained three bioactive compounds with potential as antidiabetics in DPP IV inhibitors. Bioactive compounds of faloak plants that have potential in DPP IV inhibitors on the target protein 2RGU are β-sitosterol with a score value (-98.8838) compared to the comparison compounds alogliptin (-94.7326), linagliptin (-93.8655) and sitagliptin (-87.8399); catechin (-83.4336) and epicatechin (-83.9022) compared to the comparator compounds Vildagliptin (-78.2888) and Saxagliptin (-66.9827). Table 5 shows the full molecular docking results.

Visualization

The visualization of 2D images of the three bioactive compounds from the stem bark of the faloak plant is possible due to their hydrogen bond interactions with amino acid residues. Hydrogen bonds are known to be strong bonds, although not as strong as covalent bonds. The selection of hydrogen bonds as a metric in this study is predicated on their capacity to influence the physical and chemical properties of compounds, including boiling point, solubility in water, the ability to form chelates, and acidity (pH). Moreover, hydrogen bonds have been demonstrated to impact the biological activity of drugs (Noolvi & Patel, 2013). Beta cytosterol hydrogen bonds (figure 02) have been observed to occur specifically at the amino acid residue ASP 545, while catechin hydrogen bonds (figure 03) have been observed to occur at amino acid residues TRP 269 and ASN 710. As for the bioactive compound Epicathecin (figure 04), hydrogen bonding has been observed to occur at amino acid residues TRP 629 and ASN 710.

In Silico Pharmacokinetic Parameter Prediction (ADMET)

The results of ADMET prediction were obtained by entering the isomeric smile data of bioactive compounds from *Sterculia quadrifida* R.BR stem bark on the pkCSM

website. ADMET prediction is carried out to analyze the secondary metabolites of *Sterculia quadrifida* R.BR so that absorption, distribution, metabolism, excretion and toxicity are known. The results of the ADMET prediction are shown in Table 6.

Absorption

a. The aqueous solubility of a compound indicates the solubility of the molecule in water at 25°C. It is widely acknowledged that fat-soluble drugs are less well absorbed than water-soluble drugs, especially when administered enterally (Yeni & Rachmania, 2022). The results show that beta-sitosterol is poorly soluble. The logarithm of the molar concentration (log mol/L) is the accepted measure of the predicted water solubility of a compound.
b. The term 'CaCO2 permeability' is employed to denote the capacity of a compound to facilitate the movement of carbon dioxide, and is denoted by the parameter 'Papp'. The value of 'Papp' must exceed 8 x 10-6 cm/s for a compound to be considered to have high CaCO2 permeability. For predictions on pkCSM, high CaCO2 permeability would result in a value of 0.90 (Yeni & Rachmania, 2022).
c. The gut is typically the main site of drug absorption from orally administered solutions. The present method was developed estimate the proportion of compounds absorbed through the small intestine. The prediction of compounds with favorable intestinal absorption is facilitated by identifying molecules exhibiting more than 30% absorbance, as these are deemed well absorbed. Compounds with less than 30% are considered poorly absorbed (Yeni & Rachmania, 2022). All compounds showed results above 30%. However, beta-sitosterol showed the highest results to be well absorbed.

Distribution

a. The volume of distribution is the theoretical volume required to distribute the total drug dose to produce the same concentration as in blood plasma evenly. The higher the volume of distribution value, the more drug is distributed in the tissues in the plasma. A value of less than 0.71 L/kg indicates a low distribution volume (Prasetiyo et al., 2024). Catechin and epicatechin compounds had the best results compared to other bioactive compounds.
b. The blood-brain barrier (BBB) is a vital component of the central nervous system (CNS) that acts as a protective barrier against exogenous compounds. BBB permeability is defined as the capacity of a pharmaceutical agent to traverse the blood-brain barrier. This parameter is important in reducing adverse effects and toxicity, or enhancing the efficacy of drugs whose pharmacological activity is confined to the brain. It is widely accepted that compounds with a logBB greater than 0.3 are considered to cross the blood-brain barrier with ease, while those with a logBB less than -1 are less likely to be distributed to the brain (Prasetiyo et al., 2024). Similar to the volume of distribution results, the results for catechins and epicatechins showed that these compounds could not cross the blood-brain barrier.

Metabolism

Cytochrome P450 is an important detoxification enzyme in the body, mainly found in the liver. Cytochrome P450 oxidizes xenobiotics to facilitate their excretion. Many drugs are inactivated by cytochrome P450 and some can be activated. Inhibitors of these enzymes may affect drug metabolism and are contraindicated. Therefore, it is important to assess the ability of compounds to inhibit cytochrome P450 (Prasetiyo et al., 2024).

Excretion

Drug clearance is measured by the proportionality constant CLtot, and occurs mainly as a combination of hepatic clearance (metabolism in the liver and biliary clearance) and renal clearance (excretion through the kidneys). This is related to bioavailability, and is important for determining the dose rate to achieve steady-state concentrations. The excretion values of the test compounds from pkCSM-pharmacokinetics ranged from 0.99 to 1.314 log ml/mln/kg. The excretion results indicate that the four test compounds did not meet the range of total clearance values. This suggests that the body slowly excretes the four compounds (Prasetiyo et al., 2024).

Toxicity

The toxicity level of the compound is predicted by pkCSM, with the lethal concentration value (LD50) describing the amount of compound given that can cause death by 50%, which ranges from 2,162 to 2,651 mg/kg/day. The maximum tolerated dose (MTD) is defined as the toxic dose threshold of chemicals in humans. According to the pkCSM, an MTD of less than or equal to 0.477 log (mg/kg/day) is considered low toxicity, while an MTD exceeding 0.477 log (mg/kg/day) is classified as high toxicity (Prasetiyo et al., 2024).

CONCLUSIONS

Molecular docking and pharmacokinetic studies were carried out on four bioactive compounds from the stem bark of the faloak plant. This study confirmed that three bioactive compounds such as beta-sitosterol, catechin and epicatechin have antidiabetic activity as DPP-IV receptor blockers. As a result of their pharmacokinetic profiles, these bioactive compounds may have potential as drugs for the treatment of diabetes.

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