PHARMACEUTICAL JOURNAL OF INDONESIA 2024. 9(2): 79-86

PHARMACEUTICAL JOURNAL OF INDONESIA

Available online at http://pji.ub.ac.id

The Potency of Ficus deltoidei Jack Bioactive as An Antidiabetic Treament: In Silico Study

Wahyurini, D.[1]*, Putri, R. C.[1,2], Hakim, R.W.[2,3], Wibowo, H.[4]

[1] Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, St. Salemba Raya No. 6, Jakarta, Indonesia.*

[1,2] Departement of Pharmacy, Faculty of Medicine, Universitas Indonesia, St. Salemba Raya No. 6, Jakarta, Indonesia.

[2,3] Drug Development Research Cluster IMERI, Faculty of Medicine, Universitas Indonesia, St. Salemba Raya No. 6, Jakarta, Indonesia.

[4] Department of Parasitology, Faculty of Medicine, University Indonesia, Jakarta, Indonesia

***Corresponding author:** dyahati96@gmail.com*

https://doi.org/10.21776/ub.pji.2024.009.02.2

INFO ARTIKEL

Sejarah artikel:

Submission: 3rd June 2024
Revision: 10th June 2024
Acceptance: 24th June 2024

Keywords:
Antidiabetic; *Ficus deltoidea Jack*; PPAR-γ; Type 2 Diabetes Mellitus 2

A B S T R A C T

Introduction: Type 2 Diabetes Mellitus (T2DM) is a metabolic disease with an increasing prevalence. T2DM is related to chronic low-grade inflammation or meta-inflammation conditions. Nowadays, treatment begins to target the molecules or proteins involved in T2DM. Peroxisome Proliferator Activator Receptor gamma (PPAR-γ) is one of the proteins involved in T2DM. The herb, Ficus deltoidea Jack (Tabat Barito), is a potential solution to finding molecular medicine with bioactive compounds. Extract from Tabat Barito (*Ficus deltoidea Jack*) has proven to be an antidiabetic.

Objective: This research aims to analyze the biological and pharmacological bioactive compounds of Ficus deltoidea Jack as an antidiabetic through molecular docking study.

Methods: The bioactive compounds of *Ficus deltoidea Jack* were determined from the literature. PASS (Prediction of Activity Spectra for Substances) was used to analyze the bioactive compounds. SwissADME was used to know the pharmacology properties. Molecular docking was used to find the interaction between bioactive compounds and PPAR-γ.

Results: *Ficus deltoidea Jack* has many bioactive compounds. Lupeol, Vitexin, and Isovitexin were chosen to advance analysis using PASS and SwissADME. All of them had antidiabetic activity. SwissADME was used to identify the pharmacology properties. The result showed that Vitexin has the strong ΔGibbs (- 6.59kcal/ and mol) and Inhibition constant (Ki) (14.77 μM) compare to other compounds.

Conclusion: Ficus deltoidea Jack has the potency to be developed as an antidiabetic herbal through the activity of the Vitexin compound.

Keywords: Antidiabetic; *Ficus deltoidea Jack*; PPAR-γ; Type 2 Diabetes Mellitus

* *Corresponding* author: *Dyahati Wahyurini*, *Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, St. Salemba Raya No. 6, Jakarta, Indonesia*

1. Introduction

Type 2 diabetes mellitus is a metabolic disease caused by multiple factors. The prevalence of type 2 DM increases every year; The International Diabetes Federation (IDF) states that there were around 43 million people (20-79 years old) who had diabetes in the world in 2019, and it is still increasing.(1) Indonesia was ranked 7th in the number of people with diabetes in 2019, with 10.7 million sufferers.(2),(3) Type 2 DM is a comorbid of various diseases, so increasing the prevalence of type 2 DM will affect the prevalence of other diseases. Type 2 DM begins with hyperglycemia, then becomes insulin resistance and leads to metabolic changes, including changes in the immune system. Type 2 DM is followed by the formation of AGEs (advanced *glycation end products*), which activate NF-κB (*nuclear factor kappa-light chain-enhancer of activated B cells*).(4) Conditions of hyperglycemia, activation of NF-κB, and increased ROS result in increased production of inflammatory cytokines and trigger a chronic inflammatory process.(5) Hyperglycemia and increased inflammation increase microvascular and macrovascular complications.(6) Chronic metabolic and immune system changes cause low-grade chronic inflammation or metaflammation.(7)(5) Inflammation plays a pivotal role in metabolic abnormalities in type 2 DM.(8)

The development of diabetes management continues to be developed to obtain appropriate and fast treatment.(9) Metformin and thiazolidinediones are antidiabetics with a mechanism to increase insulin sensitivity.(1) Nowadays, proteins involved in T2DM, such as Peroxisome Proliferator Activator Receptor gamma (PPAR-γ), have developed as target treatments for antidiabetics. PPAR-γ is involved in insulin sensitivity, inflammation, fatty acid storage, and glucose metabolism. (10) Thiazolidinediones (Rosiglitazone and pioglitazone) are antidiabetics with a mechanism as PPAR agonists.(9) PPAR-gamma is a receptor in adipose, liver, and muscle cells. It can increase peripheral glucose uptake and insulin sensitivity.(9) Studies have shown that PPAR-γ agonists as antidiabetics are beneficial for insulin resistance(11)(12) and lipid profile.(11)

The herbal plants are the source of potential solution to finding molecular medicine with bioactive compounds focused on the potential pharmacological targets of PPAR-γ.(10) Extract from *Ficus deltoidea Jack* (Tabat Barito) has proven as antidiabetic. *Ficus deltoidea Jack* has proven to inhibit intestinal α-glycosidase activity, block hepatic glucose production, and down-regulate hepatic PTP1B gene expression.(1) It has many bioactive compounds and can be analyzed using software and molecular docking. *Ficus deltoidea Jack* has Lupeol, vitexin, isovitexin, gallic acid, (24E)-stigmasta-5,8-dien-3β-ol, chryseriol-7O-α-rhamnoside, and others as its bioactive compounds.(1) In silico docking studies can identify novel lead compounds for type 2 Diabetes Mellitus treatment targeting PPAR-γ. (9) This research aims to analyze the biological and pharmacological bioactive compounds of *Ficus deltoidea Jack* as an antidiabetic using computational analysis.

2. Material and Methods

This research was an in-silico study and consisted of several steps. The first step was determining the bioactive compounds that analyzed their biological activity. Next, we determined the pharmacological activity and bioavailability scores. Molecular docking was used to analyze the interaction between the bioactive compounds and the PPAR-γ protein. Ficus deltoidea Jack had many biological compounds, such as Lupeol, vitexin, isovitexin, gallic acid, (24E)-stigmasta-5,8-dien-3β-ol, chryseriol-7O-α-rhamnoside, and others.(1) Three compounds from Ficus deltoidea Jack (lupeol, vitexin, and isovitexin) were analyzed using The Prediction of Activity Spectra for Substances (PASS) and could be accessed at

http://www.pharmaexpert.ru/passonline. Each compound's canonical SMILES notation was inputted on the website, resulting in a comprehensive list of their biological activities based on the pre-existing PASS database. All databases had two important scores: a (probably active) and Pi (probably inactive). A higher Pa score, closer to 1, indicated a better likelihood of activity, while a lower Pi score, closer to 0, suggests a greater likelihood of inactivity.

Table 1. SMILES of *Ficus deltoidea Jack*'s Biological Compound

Biological Compounds	SMILES
Lupeol	CC(=C)C4CCC5(C)CCC2(C)C(CCC3C1(C)CCC(O)C(C)(C)C1CCC23C)C45
Vitexin	OCC1OC(C(O)C(O)C1O)c2c(O)cc(O)c3c(=O)cc(oc23)c4ccc(O)cc4
Isovitexin	OCC2OC(C(OC1OCC(O)C(O)C1O)C(O)C2O)c4c(O)cc3oc(cc(=O)c3c4O)c5ccc(O)cc5

The next step was to analyze the pharmacological activity (ADME) of each biological compound using Swiss ADME. Swiss ADME was a tool that helps researchers in drug discovery and development. The function was to check a potential compound as a drug candidate due to Lipinski's rule. Lipinski's rule was a set of rules that assessed whether a compound was likely to become a good drug. Swiss ADME can be accessed at http://www.swissadme.ch/. Checking Lipinski's rule was a crucial and fundamental step in identifying promising drug candidates. If a compound does not pass this rule, that compound is less likely to be successful as a drug. The Swiss ADME gave researchers an excellent database to determine if their compound has a good chance of becoming a successful medicine. We input the canonical SMILES notation of the compounds into Swiss ADME, and the tool provided researchers with predictions for the compound's pharmacological activity.

Molecular docking was used to find the interaction between bioactive compounds and PPAR-γ. The protein used was PPAR-γ (PDB ID: 5two) from the RCSB Protein Data Bank (https://www.rcsb.org/). Prepared proteins by removing unnecessary water molecules, ligands, and extra components. This study used software Autodock Vina 1.5.7 grid box with dimensions of x= 50, y=50, and z = 50 and center x= 14,974 Å, y= 30,713 Å, z= 187,813 Å for PD-1 and x= 40, y=40, and z = 40 and center x= -23,939 Å, y= -20,434 Å, z= 9,727 Å. Last, the results were presented using Discovery Studio.

3. Result and Discussion

Prediction of the Biological Activity of Compounds.

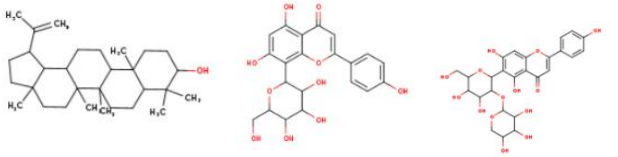
The software Prediction of Activity Spectrum of Substances (PASS) predicted the bioactivity patterns based on chemical structures. This computational analysis was employed to predict the potential bioactivity of lupenol, vitexin, and isovitexin. The PASS generated a list of biological activities and their probabilities of activity (Pa) and probabilities of inactivity (Pi) in antidiabetic activities **(Table 2).**

Table 2. Biological activity related to cancer prediction results analyzed using PASS

Antidiabetic Activities	Lupeol		Vitexin		Isovitexin	
	Pa	Pi	Pa	Pi	Pa	Pi
Antidiabetic	-	-	0.783	0.005	0.808	0.005
Antidiabetic Symptomatic	-	-	0.508	0.007	0.476	0.008
Antiinflammatory	0.708	0.015	0.606	0.030	0.543	0.045
Transcription factor NF kappa B inhibitor	0.511	0.004	0.368	0.008	0.323	0.010
Antioxidant	0.280	0.027	0.780	0,004	0,827	0,003
Diabetic Neuropathy treatment	0.309	0.196	-	-	-	-
Diabetic retinopathy treatment	-	-	0.179	0.025	-	-

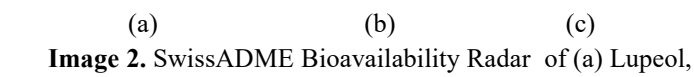
Prediction of Pharmacological Activity (ADME) of Compounds

The Swiss ADME displayed substantial information on biological compounds. The structure of biological compounds illustrated hydrogen bonds **(Image 1).** Swiss ADME showed a bioavailability Radar with six physicochemical properties: size, polarity, solubility, saturation, flexibility, and lipophilicity **(Image 2).**



(a) (b) (c)

Image 1. Compounds Three Dimension Structures (a) Lupeol (b) Vitexin (c) Isovitexin



(a) (b) (c)

Image 2. SwissADME Bioavailability Radar of (a) Lupeol, (b) Vitexin, (c) Isovitexin

A pink area represented a physicochemical range on each axis. The radar plot from the biological compound must be in the pink area to be considered similar to a drug. The three biological compounds analyzed were not in the pink area, but the best radar was vitexin. Then, this study continued with Lipinski's rules analysis. Lipinski's rule consisted of 5 points: molecular weight less than 500 Da, lipophilicity (LogP) < 5, hydrogen bond donors < 5, hydrogen bond acceptors < 10, and the molar refractivity should be between 40–130. (13) Lupeol, vitexin, and isovitexin have different scores **(Table 3)**.

Table 3. Pharmacological Activity (ADME) of Compounds

No	Compounds Name	MW (g/mol)	TPSA* (A^2)	Log S (ESOL)	Log P	Fraction	RB	HBD	HBA	BS
1	Lupeol	426.72	20.23	-8.64	4.68	0.93	1	1	1	0.55
2	Vitexin	432.38	181.05	-2.84	1.38	0.29	1	7	10	0.55
3	Isovitexin	564.49	239.97	-2.47	1.66	0.42	5	9	14	0.17

Notes: *MW: Molecular Weight. TPSA: Topological Polar Surface Area. RB: Rotatable Bonds. HBD: H-Bond Donors. HBA: H-Bond Acceptors. BS: Bioavailability Score.*

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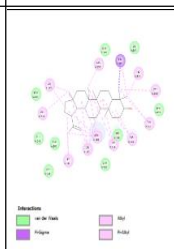
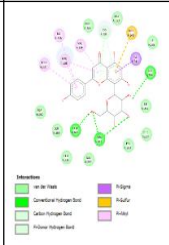
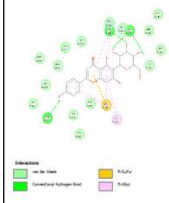
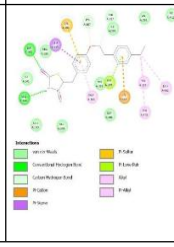
Molecular Docking

Molecular docking was used to determine the potential for biological compounds to interact with the PPAR-γ protein. The results from molecular docking were the values of binding energy, ligand efficiency, inhibition constant, intermol energy, and others **(Table 4)**. The images explained interactions between biological compounds and proteins based on the bonds formed (Vanderwalls or hydrogen bonds). Based on hydrogen bonds, every compound had different results. Lupeol did not form hydrogen bonds. Vitexin binded to proteins through three hydrogen bonds at the amino acid residue: LEU A:340, SER A:342, GLY A:284. Isovitexin had three hydrogen bonds at the amino acid residue: TYR A:473, ARG A:288, and LEU A:340. The ΔGibbs value of Vitexin is -6.59, which is lower than lupeol (ΔGibbs -5.54) and isovitexin (ΔGibbs -3.62).

Table 4. Molecular Docking Results of Lupeol, Vitexin, and Isovitexin on PPAR-γ protein

Compounds Name	2D Docking Visualization	Energy (Kcal/Mol) ΔGibbs	Inhibition Constanta	Hydrogen Bond
Lupeol		-5.54	87.14 uM	-
Vitexin		-6.59	14.47 uM	LEU A:340, SER A:342, GLY A:284,
Isovitexin		-3.62	2.21 mM	TYR A:473, ARG A:288, LEU A:340
Pioglitazone		-8.87	314.14 nM	SER A:342, LEU A:340

4. DISCUSSIONS

Ficus deltoidea Jack is a potential herbal from Kalimantan. The role of three biological compounds (vitexin, isovitexin, and lupeol) as antidiabetics were analyzed in this study. In the first step, we use a PASS analysis. From the PASS analysis, we focused on specific activities related to Type 2 DM like antidiabetic, antidiabetic symptomatic, anti-inflammatory, transcription factor NF kappa B inhibitor, and antioxidant. Diabetic neuropathy and retinopathy are microvascular complications that often occur in type 2 DM, so biological activity assessment can be used as an illustration in preventing complications. PASS results show the Pa and Pi values of each component. Vitexin and isovitexin have

high Pa values for antidiabetics and antioxidant activity; however, lupeol does not have antidiabetic activity but has the highest anti-inflammatory activity **(Table 2)**. Based on PASS analysis, vitexin and isovitexin are biological compounds of *Ficus deltoidea Jack* that have the potential to be further developed because they have antidiabetic, anti-inflammatory, and antioxidant activity.

Vitexin and isovitexin are mono-C glycosylflavones found in various plants.(14) The role of vitexin and isovitexin as antihyperglycemias that correlate with diabetes has been investigated. Vitexin has been shown to reduce postprandial blood glucose drastically in a dose-dependent manner in animals.(14) Nurdiana et al. proved that the group of rats given Ficus deltoidea had lower fasting blood sugar than the other group.(15) Vitexin significantly lowers fasting blood glucose, enhances glutathione reductase (GR) and superoxide dismutase (SOD) activity, increases islet cell regeneration, and decreases islet apoptosis in vivo and in vitro studies.(16)(15) Sarkar studied the effects of vitexin derived from P. cineraria in chronic myeloid leukemia cell lines, and his results indicated that vitexin had antiproliferative action. This result was ascribed to the induction of apoptosis, which was accomplished by elevating ROS, NO, and MDA levels while decreasing SOD activity.(17) Wang et al. showed that vitexin therapy prevented the initiation of P38 MAPK signaling pathways in LPS-mediated INS-1cells. Vitexin prevents LPS-induced cell death in INS-1 cells. Vitexin reduces islet damage and apoptosis by reducing the release of HMGB1 (high mobility group box) and via P38 MAPK.(16) Vitexin also inhibits apoptosis and protects pancreatic β-cell injury.(14)

One of the risk factors for diabetes is obesity. Vitexin was assessed for its potential as a biological compound to prevent obesity. By activating the ERK1/2 MAPK signaling pathway, vitexin has shown significant efficacy in reducing adipose tissue accumulation and storage, sugar consumption, and regulated glycolysis.(18) Sayedan et al., used C. cauliflora and vitexin to control body weight. There was a significant decrease in adipose tissue and body weight. It also reduced serum levels of resistin, IL-6, hyperglycemia, and hyperinsulinemia.(18) Inflammation has a relationship with diabetes and insulin resistance. Vitexin has anti-inflammatory activity to fix it. Vitexin suppressed the secretion of TNF, IL-6, and IL-1β proteins.(19)(20) Vitexin showed significant efficacy in inhibiting TNF-α and the consequent activation of neutrophils.(21) Nikfarjam *et al.* discovered that vitexin and quercetin significantly reduce the production of TNF-α, NO, and MPO in human neutrophils. This research confirmed that vitexin had significant anti-inflammatory effects by suppressing the transcription factor NF-Kb activation and the consequent production of TNF-α. (22)

Diabetes mellitus is a chronic metabolic disorder. Chronic oxidative stress occurs in T2DM and speeds up age-related disorders. It has been suggested that vitexin is a potential antioxidant. Vitexin can prevent insulin resistance caused by reactive oxygen species.(23) Vitexin is an apigenin flavone glycoside with various pharmacological effects, including antioxidant, anti-inflammatory, anticancer, antinociceptive, and neuroprotective effects. Compared to apigenin, it has higher antioxidant action.(24) Vitexin works by activating the AMPK/GSK3β signaling pathway, which protects against oxidative damage and inflammation caused by isoflurane.(25) The enzyme AMPK is essential for maintaining the energy balance of cells because it promotes the uptake and oxidation of fatty acids and glucose.(23)

The second step is Swiss ADME analysis, which displays much information on biological compounds. The Swiss ADME Bioavailability Radar displays six physicochemical properties: size, polarity, solubility, saturation, flexibility, and lipophilicity.(26) The optimal range is represented by the pink area, where size (MW: between 150 and 500 g/mol), polarity (TPSA: between 20 and 130 Å²), solubility (log S not exceeding 6), saturation (fraction of carbons in sp3 hybridization) should be at least 0.25, flexibility, and lipophilicity (XLOGP3: between -0.7 and +5.0).(27) The topological polar surface area (TPSA) technique is used to calculate the polar surface area (PSA), taking phosphorus and sulfur into account as polar atoms. In numerous models and guidelines, TPSA has been shown to be an adequate descriptor for rapidly assessing specific ADME properties, particularly for forecasting biological barrier crossing, like absorption.(26) Vitexin and isovitexin are polar molecules with a PSA value greater than 140. Therefore, for further development, the vitexin structure can be modified to become less polar.The log S values are also converted into mol/l and mg/ml solubility using Swiss ADME. The Log S scale is used to provide qualitative estimations of solubility with a score of insoluble < − 10 < poorly < −6 < −4 < −2 < v highly.(26) Isovitexin (-2.47) and vitexin (-2.84) exhibit log S values that are nearly identical and superior to the log S value of lupeol (-8.64). To further evaluate these compounds, the bioavailability score indicates the availability of biological compounds. Isovitexin has the lowest score among the others. Lupeol and Vitexin have the same score (0.55). It means both of them are in the medium of medicine. To improve the results, it is necessary to carry out further research with the Drug Likeness Score (DLS). DLS assesses a compound's physicochemical properties

compared to existing drugs based on Lipinski's rules. DLS scores are usually between 0 and 1, with 1 indicating a compound's potential as a drug candidate and 0 suggesting that a compound is less likely to be a suitable drug.(26)

The analysis continues with molecular docking. Biological compounds can create complexes with proteins through either covalent or non-covalent means, involving hydrogen bonding, van der Waals forces, electrostatic, and hydrophobic interactions. The primary interactions between phenolic compounds and proteins predominantly involve hydrophobic interactions and hydrogen bonding.(27) Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists are considered to be effective drugs to improve the condition of insulin resistance. The protein PPAR-γ plays a crucial role in regulating adiposity, lipids, glucose homeostasis, and insulin sensitization processes. (28) Consequently, PPARs are targeted for therapeutic interventions in type 2 diabetes mellitus. Thiazolidinedione antidiabetics operate by binding to PPAR-γ, thereby enhancing insulin stimulation through the glucose transporter 4 (GLUT4) receptor and promoting glycogen synthesis. This, in turn, results in heightened insulin signaling and increased insulin sensitivity. Pioglitazone, a thiazolidinedione drug, serves as a standard reference in this study for the comparative analysis of biological compounds.(28)

Molecular docking was conducted to investigate the potential interactions between chemical compounds from *Ficus deltoidea Jack* and the PPAR-γ. The three biological compounds are docked with PPAR-γ. Based on the ΔGibbs value, Vitexin had the lowest. The ΔGibbs value of Vitexin is -6.59, which is lower than lupeol (ΔGibbs -5.54) and isovitexin (ΔGibbs -3.62). Vitexin also has the lowest value in Inhibition Constanta (Ki). The vitexin inhibition constant value is 14.47 uM lower than the inhibition constanta (Ki) of lupeol (87.14 uM) and isovitexin (2.21 mM). The results showed that vitexin had the lowest binding energy. This shows that vitexin does not require too much energy to interact with PPAR gamma compared to other biological compounds. The inhibition constant is also important because it determines the resistance during interaction. The lowest Ki is in isovitexin, but isovitexin requires a large amount of energy to bind. The hydrogen bond shows the position of interaction between biological compounds and proteins. Vitexin and isovitexin have three hydrogen bonds at different locations. Vitexin is a biological compound from *Ficus deltoidea jack* that can be developed as an antidiabetic.

The molecular docking of biological compounds was compared with the standard drug, pioglitazone. Pioglitazone has ΔGibbs:-8.87, Ki value of 314.14 nM, and forms two hydrogen bonds (SER and LEU). Vitexin closely resembles the standard drug, pioglitazone. Vitexin's ΔGibbs closely approximate those of pioglitazone. Vitexin has two identical hydrogen bonds (SER and LEU) with Pioglitazone, whereas isovitexin establishes only one similar bond with Pioglitazone. In molecular docking findings, vitexin stands out as the optimal ligand for PPAR-γ, characterized by the lowest ΔGibbs and Ki values. This superiority is attributed to its remarkably intricate, spontaneous, and stable interactions compared to isovitexin and lupeol. Besides that, Gire et al. stated that vitexin is correlated with the expression of PPAR-γ, leading to a reduction in adiponectin and GLUT-4 levels. (29) Research by Gayatri et al. resulted in consistent findings, demonstrating that vitexin successfully raised PPAR-γ activation.(30)

5. Conclusion

In summary, Lupeol, vitexin, and isovitexin from *Ficus deltoidea Jack* could interact with PPAR-γ. Based on the computational analysis, the strongest interaction is Vitexin. Further research in clinical settings is necessary to enhance and investigate the range of bioactivities of vitexin and the potential of *Ficus deltoidea Jack*.

6. ACKNOWLEDGMENT

The authors express gratitude to the Master's Programme in Biomedical Sciences Faculty of Medicine for supporting us.

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