PHARMACON
Jurnal Farmasi Indonesia
Pharmaceutical Journal of Indonesia

Pharmacon: Jurnal Farmasi Indonesia
Vol. 22 No. 2, 2025, pp. 292-303
DOI:10.23917/pharmacon.v22i2.13447
p-ISSN: **1411-4283**, e-ISSN: **2685-5062**

In Silico Analysis of *Momordica charantia* L. as Antidiabetic Agents of GSK-3β Receptors and Its Antioxidant Activity

Asri Dwi Endah Dewi Pramesthi [1]*, Khairunnisa [2], Aurelia Nabilla Zuliet [3], Melani Pebriana Putri [4], Paula Mariana Kustiawan[5]

[1-5]Pharmacy Department, Faculty of Pharmacy, Universitas Muhammadiyah Kalimantan Timur, 75124 , Indonesia
**Corresponding author: asridwiendah@umkt.ac.id*

ARTICLE HISTORY:
Submitted : 2025-10-23
Accepted : 2025-12-30
Published : 2025-12-31

KEYWORDS:
GSK-3β Receptors; *Momordica charantia* L.; Metformin

Citation:
Pramesthi, A.D.E.D, Khairunnisa, Zuliet, A.N, Putri, M.P, Kustiawan, P.M. (2025). In Silico Analysis of *Momordica charantia* L. as Antidiabetic Agents of GSK-3β Receptors and Its Antioxidant Activity. Pharmacon: Jurnal Farmasi Indonesia, 22(2), 292-303. https://doi.org/10.23917/pharmacon.v22i2.13447

ABSTRACT

Diabetes mellitus is included in the group of degenerative diseases with the highest incidence rate globally. This study was conducted to evaluate the potential of bioactive compounds contained in bitter melon (*Momordica charantia* L.) as antidiabetic and antioxidant agents using an in silico approach. The methods used include molecular docking simulations, pharmacokinetic and toxicological analyses were carried out using Absorption, Distribution, Metabolism, Excretion, and Toxicology parameters as well as drug suitability tests based on the Lipinski rule of five. The test results showed that bitter melon juice obtained an IC50 of 63.18 µg/ml while vitamin C as a comparison obtained an IC50 of 7.60 µg/ml. The docking results show that the Kaemferol compound has the highest binding affinity (-6.64 Kcal/mol), Quercetin (-6.28 Kcal/mol) and Charantoside I (6.07 Kcal/mol) have stable binding energy, the interaction of charantin, quercetin, kaemferol and charantoside I residues is similar to native ligands such as Valine 135, Cysteine 199, Valine 70 and Lysine 85. Based on the ADMET profile results, the quercetin and kaemferol compounds have high absorption, Caco-2 permeability which supports oral bioavailability, and do not show the ability to penetrate the blood-brain barrier, which indicates safety for the central nervous system, as well as low AMES toxicity and hepatotoxicity. As the conclusion, kaempferol and quercetin compounds have the potential as GSK-3β inhibitors. Antioxidant activity of bitter melon juice and vitamin C are categorized as strong. Further research regarding the mechanism of action of *Momordica charantia* L. as an alternative therapeutic agent in the management of type 2 diabetes is needed.

INTRODUCTION

Diabetes mellitus is the most common degenerative disease suffered by people worldwide with the fourth rank worldwide estimated at more than 346 million people suffering from diabetes mellitus (IDF, 2021). According to the International Diabetes Federation in 2020 in adults aged (20-79 years) it was reported that around 537 million were living with diabetes mellitus. The increase in 2030 to 643 million) and in 2045 to 784 million. Diabetes mellitus in 2021 caused 6.7 million deaths (IDF, 2021).

GSK-3β is related to insulin production and glycogen synthesis control. GSK-3β is the main treatment for type 2 diabetes because it has Reported to significantly improve insulin efficacy, stimulate glycogen production, and boost glucose metabolic activity within the skeletal muscles of patients with diabetes (Rajagopal, 2022). GSK-3β causes insulin secretion failure and insulin resistance in type 2 diabetes mellitus by activating homeostatic regulation of glucose enzymes and inhibiting enzymes from glycogen synthase which are needed in the formation of glycogen and glucose (Afriana & Dewi, 2022). Metformin is an anthropogenic biguanide derivative used as a first-line treatment for type 2 diabetes (T2DM), which can lower blood glucose levels and suppress appetite (Scott et al., 2024). Metformin

is one of the diabetes drugs that can lower blood sugar levels by increasing insulin. Bitter melon (*Momordica charantia* L.) has the same hypoglycemic effect as metformin by increasing the insulin secretion, increasing glucose absorption on adipose tissue and muscle, and inhibiting glucose absorption from the liver (Bakare et al., 2010). It can also increase b-cell protection, by decreasing glucose absorption from the intestine and glucose production from the liver, thus affecting the brain because glucose becomes a source of energy (Richter et al., 2023).

Beside it's hypoglicemic effect, Bitter melon (*Momordica charantia* L.) has the ability to lower blood glucose levels by functioning as an antioxidant that can reduce insulin resistance, reduce liver gluconeogenesis, increase insulin sensitivity, glycogen synthesis, glucose oxidation, and tissue glucose intake (Nirnadia et al., 2020). Its compounds have shown promising effects in restoring pancreatic β-cell function, stimulating insulin release, and ameliorating insulin resistance which can control and prevent several metabolic diseases (Akmal and Sasongko, 2023). In addition, bitter melon also has beneficial effects that can minimize inflammation, acts as a free radical scavenger , In various in vitro and in vivo studies, and influence intracellular signaling mechanisms.

Antioxidants can eliminate potentially damaging oxidative agents that are very important for Promoting optimal health, the inhibition of amylase can slow down starch digestion by preventing substrate access to the enzyme's active site. Carbohydrate absorption can slow down the inhibition of enzymes responsible in the digestive system where bitter melon can help in the control, treatment, and prevention of DMT2 (Mahmoud et al., 2013). Charantin is a treatment for diabetes that has the potential to replace medication completely. Momordicin and momorcharin are control blood sugar levels and have a similar molecular structure to insulin (Richter et al., 2023).

METHODS

Antioxidant Activity Assay Using the DPPH Method

Bitter melon fruit samples were prepared using 600 grams of fresh, cleaned and blended bitter melon pulp without adding water. The resulting sample was filtered and then centrifuged. 0.05 grams of DPPH powder was dissolved in 96% ethanol in a 50 mL volumetric flask to the mark. The DPPH solution was stored and protected from sunlight. To determine the DPPH wavelength, an adequate amount of DPPH solution was taken into a vial and the wavelength was measured at approximately 400-800 nm. 0.005 grams of bitter melon juice was weighed, and a stock solution of 5000 ppm was prepared by dissolving it in 96% ethanol in a 10 mL volumetric flask and shaking until homogeneous. A series of sample solutions were prepared at various concentrations (100 ppm, 150 ppm, 200 ppm, 250 ppm, 300 ppm) of 0.2, 0.3, 0.4, 0.5, and 0.6 mL. The absorbance of the IC50 value was measured using the DPPH and sample methods. Each bitter melon juice sample concentration was taken in a test tube, 4 mL of DPPH, and 1 mL of DPPH. The samples were then shaken until homogeneous and incubated for 30 minutes at room temperature. After incubation, the absorbance of the samples was measured at a wavelength and maximum absorbance of 517 nm, using 96% ethanol as a blank solution.

Preparation of ascorbic acid (Vitamin C) concentration series solution

A 1000 ppm ascorbate solution was made as a comparison solution of 0.005 gr then dissolved with 96% ethanol in a 50 mL measuring flask to the boundary mark, the solution was shaken until homogeneous. Preparation of a vitamin concentration series with concentration variations (10 ppm, 20 ppm, 30 ppm, 40 ppm, 50 ppm, 60 ppm), each concentration of 3 mL, added 1 mL of DPPH then dissolved with 96% ethanol to the boundary mark.

Ligand and Protein Preparation

Several compounds from *Momordica charantia* L. were selected to be evaluated as ligands. On the pubcem website, the three-dimensional structure of each ligand can be downloaded. To prepare the ligand, hydrogens were added along with Gastraiger charges. Protein Data Bank (RSCB PDB) (https://www.rcsb.org/) provides the protein structure of GSK-3β (4PTE) used in this study using Auto Dock Tools 1.5.7, each substrate protein was prepared for docking by removing unnecessary amino acid chains, removing water molecules, adding hydrogens, and adding kollman charges. For PDBID: 4PTE, the grid

center size is 32, 26, 28 (xyz coordination). The grid box size used is -24.542 x 17.919 x -9.680.

ADME and Toxicity properties

Using the Open Babel software, each ligand is converted into smiles format before being sent individually to the Swiss ADME and ADMETLab Web servers. The software offers information on the Absorption, Distribution, Metabolism, Excretion and Toxicity of each ligand based on the Lipi Rule of Five calculations.

Molecular docking

The number of hydrogen atoms, the number of hydrophobic contacts, and the strength of the binding energy are all determined by the research findings. With the help of the Lamarckian Genetic Algorithm, which is included in the AutoDock package, the docking process is configured to generate the top 100 conformations. Based on the lowest binding energy value, the optimal conformation is selected, and the Discovery Studio Visualizer program is used to visualize the 2D interactions. This study uses the overlay method with the pymol application to validate molecular docking. To use the overlay approach, the conformation of the native ligand must be exactly the same as the crystallography. The purpose of this validation is to evaluate the performance of the docking program to prevent errors or deviations. One popular method for calculating the average distance between the ligand from the redocking results and the crystallographic ligand is by using the root mean square deviation (RMSD) value. It is generally agreed that the RMSD evaluation of the docking program capacity.

RESULT AND DISCUSSION

Determination of the antioxidant activity of bitter melon juice was carried out by quantitative analysis, namely the DPPH (1,1-diphenyl-2-picrylhydrazyl) method. Testing with the DPPH method aims to see antioxidant activity, this method is used because it is sensitive, fast, and simple to use. DPPH testing is based on the reduction of purple in the DPPH solution (Abdullah *et al.*, 2022), the higher the concentration of the test material, the lower reading, which indicates the greater the activity of the material in capuin DPPH radicals (Kurniadi, 2024).

Table 1. The Average Results of Sample Absorbance

No	Group	Absorbance Average± SD				
		0.6	0.5	0.4	0.3	0.2
1	Bitter Melon Juice	0.0387±0.0003	0.0376±0.0009	0.0363±0.0001	0.0359±0.0004	0.0358±0.0019
2	Blank	0.889±0.003				
3	Positive control	0.2578±0.0582				

Table 2. The Average Results of Antioxidant Activity Assay

No	Group	Antioxidant Activity Average (%) ± SD				
		0.6	0.5	0.4	0.3	0.2
1	Bitter Melon Juice	56.52	57.75	59.25	59.66	59.78
2	Positive control	71				

The average absorbance results is shown in **Table 1**. Absorbance results then used to calculate the inhibitory concentration (IC50). IC50 is the concentration of samples and standard that provide antiradical activity percentation of 50% compared to a control from the linear regression line equation between a level and radical scavenging percentation (Andriani and Murtisiwi. 2020; Saputri *et al*. 2020). By comparing the antioxidant activity percentation and the concentration of bitter melon juice as written in **Figure 1**. the IC50 result of bitter melon was obtained as 1.412 µg/ml with antioxidant activity results was up to 60%. its IC50 still categorized as very strong. The positive control IC50 was obtained as 0.168 µg/ml and also categorized as very strong. It is known that if the IC50 value is less than 50µg/ml it is said to be very strong. an IC50 of 50-100µg/ml is said to be strong. and an IC50 value

of 151-200 µg/ml is said to be moderate (Andriani and Murtisiwi. 2020). It can be concluded that the antioxidant activity of bitter melon juice and vitamin C produce are both categorized as very strong (**Table 2**).

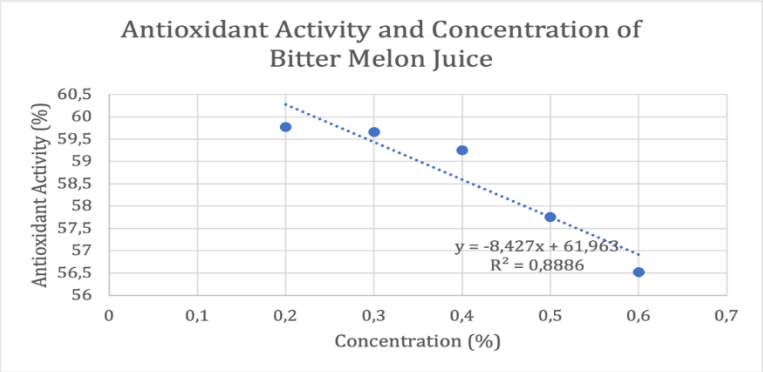


Figure 1. Antioxidant Activity (%) and Concentration of Bitter Melon Juice

Table 3 Lipinski rule of five on Metformin and test compound

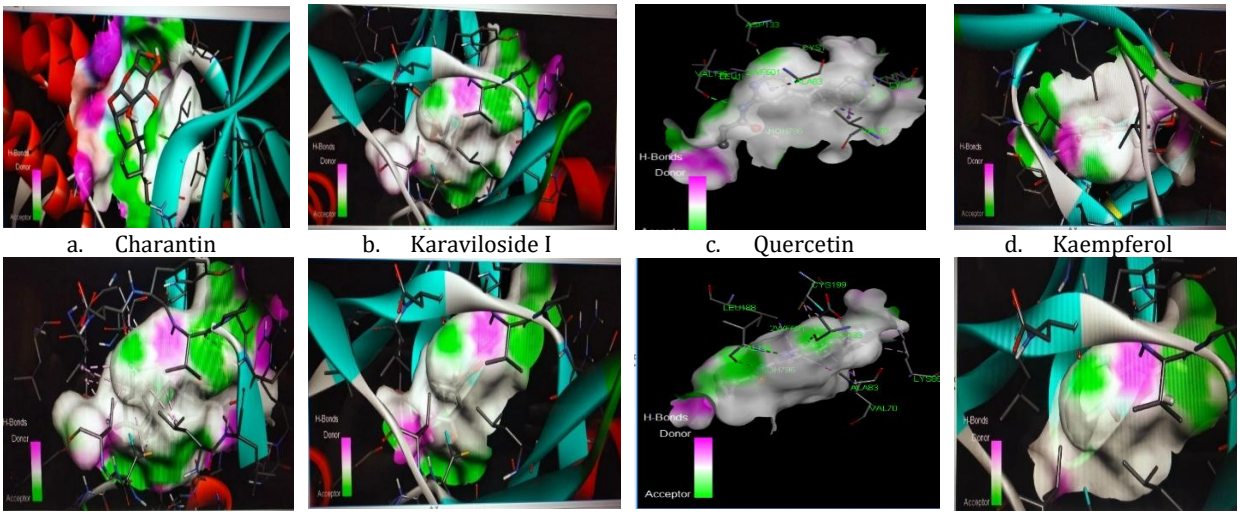
Compounds	Molecular (Mw) <500g/mol	H-Bond Acceptors <10	H-Bond Donors <5	Molar Refactivity 40-130 cm/mol	LogP <5
Metformin	129.1	2	3	36.93	0.34
Charantin	576.44	12	8	330.75	11.61
Karaviloside I	648.46	8	4	181.21	5.76
Quercetin	302.24	7	5	78.03	2.01
Momordicilin	540.45	3	1	165.31	5.45
Charantoside I	630.85	8	4	173.85	4.89
Kaempferol	286.24	6	4	76.01	0.64

Table 4 Interaction of Metformin and test compound

Ligand	Konformasi	*Binding Energy*	Hydrogen Bond	Hydrophobic Bond
Metformin	100	-3.79	Val 135. Asp 133	-
Charantin	100	-2.15	Val 135. Ile 62. Tyr 134. Pro 136	Val 70. Lys 85.Cys 199. Phe 67.Leu 132. Ala 83. Leu 188
Karaviloside I	100	-2.14	Cys 199. Asp 133. Ala 83	Val 70
Quercetin	100	-6.28	Val 135. Cys 199. Ile 62	Val 70. Lys 85
Momordicilin	100	-1.87	Val 135. Asp 200	Lys 85. Phe 67
Kaempferol	100	-6.64	Val 135. Cys 199. Ile 62	Val 70. Lys 85. Leu 188. Ala 83
Charantoside I	100	-6.07	Val 135. Arg 141	Lys 85. Val 70. Cys 199. Tyr 140.Leu 188. Leu 132. Val 110. Ala 83

Lipinski Rule of Five is the maximum value for LogP (5). molecular weight (<500 g/mol). hydrogen bond donors no more than 5. hydrogen bond acceptors no more than 10 and molar refraction between 40-130 cm3/mol which are used as 'drug-likeness' parameters proposed by Lipinski. Kaempferol compound has a molecular weight of 286.24 g/mol. hydrogen bond acceptors are 6. hydrogen bond donors are 4 and molecular refraction is 76.01 and LogP 2.94 according to Lipinski requirements (**Table 3**). If there are one or more criteria that do not meet

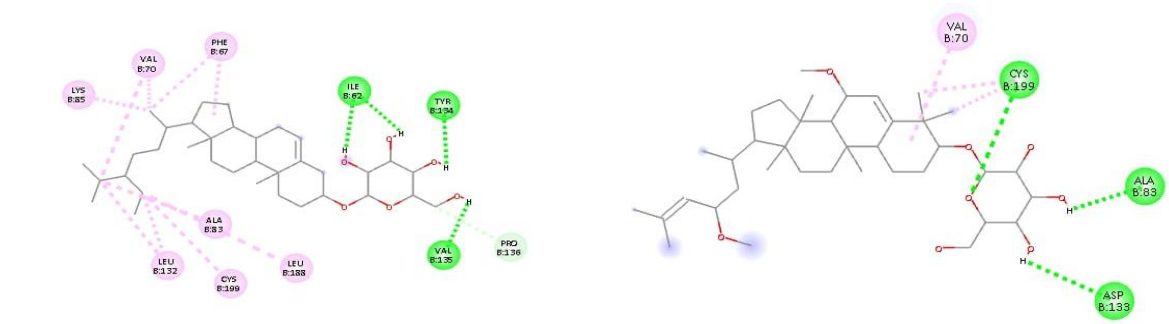
the Lipinski Rule of Five. it is likely that oral absorption will be disrupted. so the potential for success as an oral drug becomes smaller (Ischak *et al*.. 2023). Compounds that do not meet the RO5 criteria still have holds significant potential for further exploration as a prototype in new drug discovery pipelines (Wulandari *et al*.. 2023; Yang *et al*.. 2020).



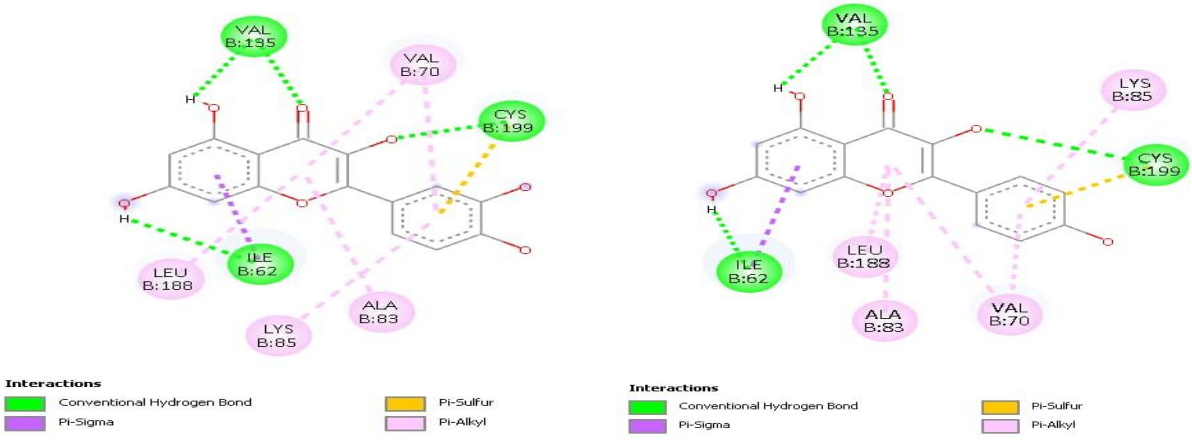
a. Charantin b. Karaviloside I c. Quercetin d. Kaempferol

e. Charantoside f. Momordicilin g. Native ligand h. Metformin

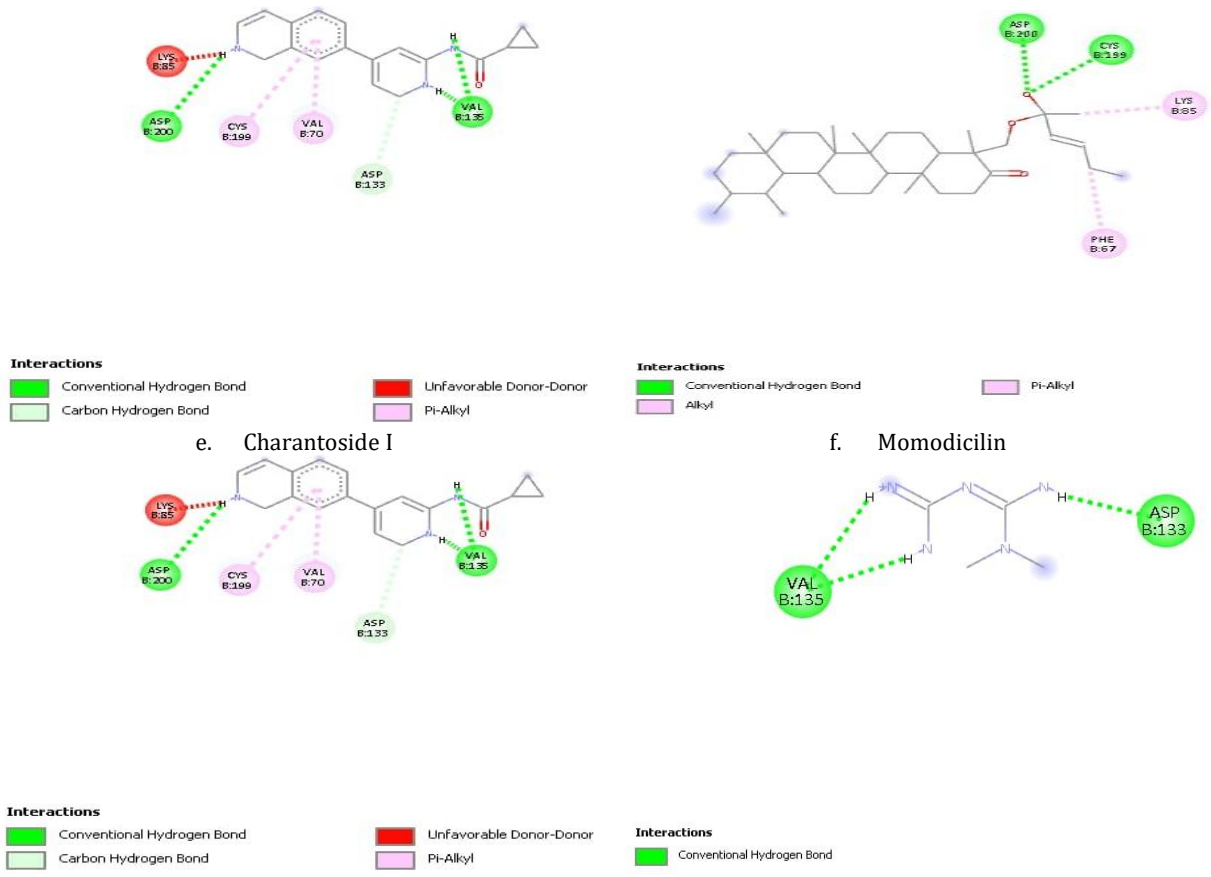
Figure 2. 3D structure of protein ligand interaction with test compound



a. Charantin b. Karaviloside I



c. Quercetin d. Kaempferol



e. Charantoside I f. Momodicilin

g. Native ligand h. Metomin

Figure 3. 2D structure of protein ligand interaction with test compound

The kaempferol compound has the highest binding energy (-6.64 Kcal/mol). followed by quercetin(-6.28 Kcal/mol) and charantoside I (-6.07 Kcal/mol). and forms stable interactions with important residues of the native ligand such as Val 135. Cys 199. Val 70. and Lys 85. The similarity of the interaction location strengthens the assumption that the compounds have equivalent potential in inhibiting the biological activity of the native ligand. as **Table 4** and **Figure 2** (Fauziyyah *et al*.. 2025).

Predicted results of the Absorption

Based on **Table 3**. gastrointestinal (GI) absorption is predicted to be high metformin. kaempferol and quercetin compounds. High absorption of a drug in the intestine can be interpreted as meaning that the drug has good absorption and can be distributed throughout the body (Novianty. 2023). Compounds charantin. quercetin. karaviloside I charantoside I. momordicillin and kaempferol are not recognized by P-gp (not detected) namely negative compounds are not recognized by p-gp. which supports better absorption potential without reflux inhibition. Caco-2 permeability The predicted results of all test compounds have high permeability values and meet the requirements if they have a prediction of > -5.15 (log cm / s) a high permeability value can be interpreted that the drug is completely absorbed (**Figure 3**)(Bitew *et al*.. 2021). High plasma protein binding can limit the amount of free drug available for therapeutic activity (Pires *et al*.. 2015).

Predicted results of the Distribution

Metformin with the symbol + (sufficient/moderate). indicates that it is likely to cause effects on the central nervous system. All compounds from *Momordica charantia* L. bitter melon showed no ability to penetrate the blood-brain barrier (not detected). This indicates that these compounds most likely do not have a direct effect on the brain or central nervous system. and their pharmacological activity is more limited to the peripheral system. The volume distribution of momordicilin (1.113) has a VD value > 0.45 so it is predicted that it can be distributed well in body tissues. except for charantin. karaviloside I. kaempferol. quercetin and charantoside I compounds (Effendi *et al*.. 2023).

Predicted result of the Metabolism

Charantoside I stands out in particular because it does not show strong inhibitory activity against any CYP isoenzymes and is only a limited substrate. namely CYP2C19 which means a stable and safe metabolic profile. as well as a low risk of drug interactions.

Predicted result of the Excretion and Toxicity Test

The clearance value. ranging from 2.477 to 10.596 mL/min/kg indicates that the compound has a varying level of excretion from the body. the momordicillin compound has the highest clearance rate of 10.596 mL/min/kg. A shorter half-life (t ½) indicates rapid elimination for the momordicillin compound (0.291 hours). Meanwhile. charantoside I and karaviloside I compounds have relatively low clearance. each with a value of (4.294 and 2.987 mL/min/kg) and a longer half-life of (1.698 and 1.581 hours) indicating that both compounds are metabolized more slowly and can last longer in the body. This is an advantageous characteristic in drug development. as it allows for a lower frequency of administration (Maulida and Puspitasari. 2020).

Kaempferol. quercetin. and momordicillin compounds that are recorded to have low AMES toxicity scores are mutagenic (Dwi *et al*.. 2020). Charantoside I (0.183) and charantin (0.333) actually show the lowest carcinogenic potential. consideration of the risk of long-term carcinogenicity remains essential in the selection and optimization stage of natural compound-based drug candidates (Seal *et al*.. 2025).

The compounds quercetin and kaempferol showed lower risks indicating that they are relatively safe for the hepatic system (Mohamed *et al*.. 2024). charantoside I (0.46) and momordicilin (0.306) showed relatively low liver injury values. thus having a lower risk of drug-induced liver injury. A crucial finding considering that liver toxicity is one of the main challenges in the process of developing and evaluating the safety of a drug candidate (Bai *et al*.. 2025).

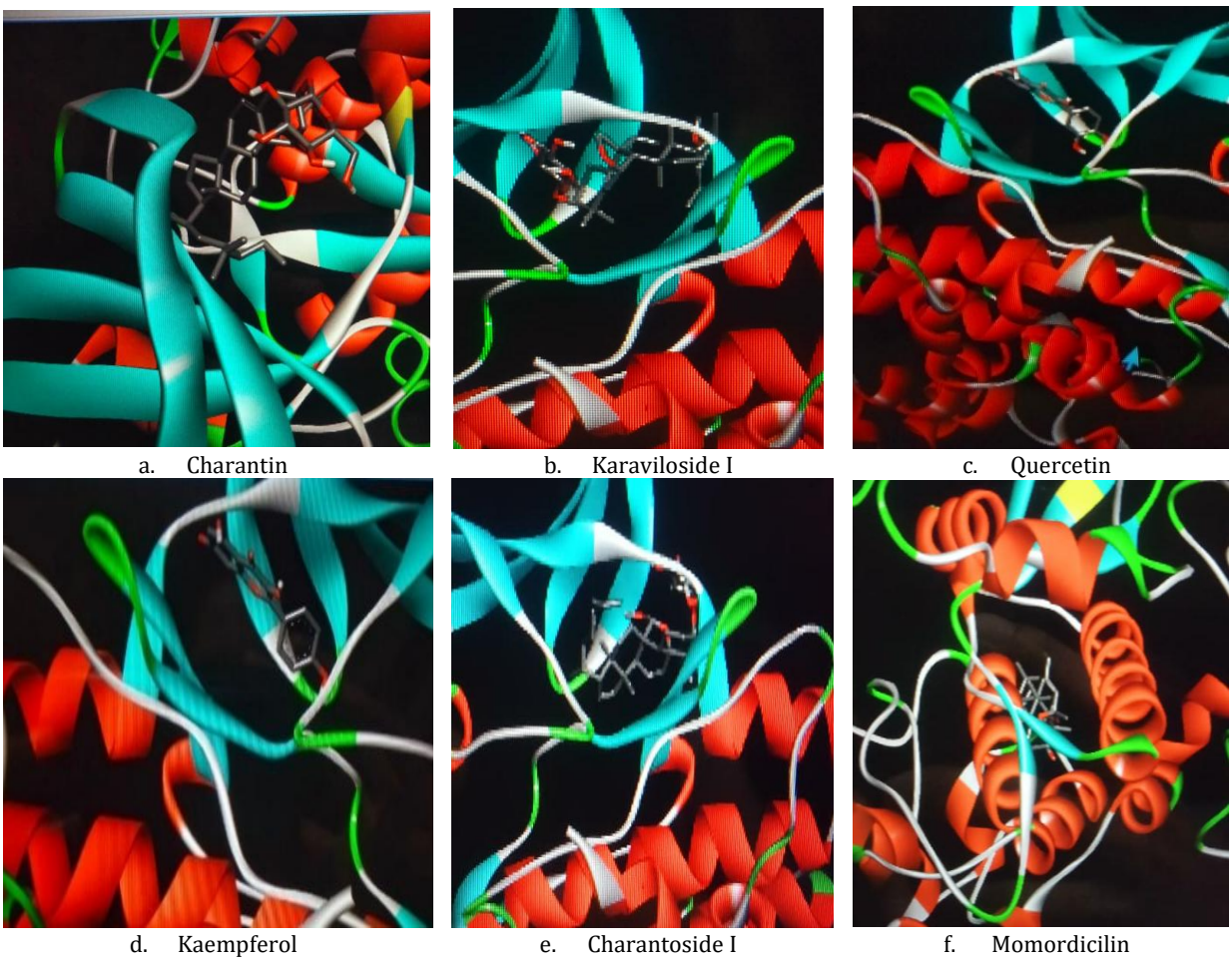
The ability of charantin to inhibit GSK-3β can be associated with its antioxidant activity. which works through two main mechanisms. namely reducing oxidative stress that triggers GSK-3β activation and directly interfering with the interaction of GSK-3β and its ligand. This mechanism supports the potential of charantin as a natural antidiabetic agent through modulation of signaling pathways that are disrupted in hyperglycemic conditions (Xu *et al*.. 2022). Kaempferol and quercetin increase Akt phosphorylation. which will inactivate GSK-3β by improving insulin sensitivity and reducing oxidative stress. thus both compounds have the potential as natural antioxidants and show antidiabetic activity (**Figure 4**). Karaviloside I. momordicillin and charantoside I inhibit GSK-3β as antidiabetic and antioxidant by inhibiting directly (molecular binding) or indirectly through the Akt pathway thereby increasing glycogen synthesis by lowering blood glucose and reducing oxidative stress and pro-inflammatory cytokines from secondary antioxidant effects (Alkhalidy *et al*.. 2018; Andriani and Murtisiwi. 2020; Peng *et al*.. 2017).

The findings of this study support the results of previous studies that have revealed the potential of *Momordica charantia* L as an antidiabetic agent. This is in line with the findings reported in a study (Achmad. 2016) showing the effectiveness of bitter melon (*Momordica charantia*) and green bean (pharseoulus vulgaris) extracts for reducing blood sugar levels and AUC (Area under curve) and research (Syafitri. 2022) showed that the antidiabetic effectiveness test of a combination of bitter melon and rosella flower petals extracts in white male mice had an optimal synergistic effect in lowering blood glucose levels. *Momordica charantia* L and metformin have the same mechanism of action as antidiabetics. namely by lowering blood glucose levels by Facilitating increased insulin signal transduction in target cells Facilitating increased insulin signal transduction in target cells (Bahagia *et al*.. 2019). The data listed show that compounds quercetin. kaempferol and positive controls. consistently meet the Lipinski rule of five criteria and a favorable ADMET profile (**Table 5**). The results of toxicity prediction emphasize the importance of a careful and comprehensive approach in the early stages of drug development. in line with the general pattern found in the scientific literatur.

Table 5. ADMET data parameters of *Momordica charantia* L. compounds

Ligand	Coumpounds						
	Metformin	**Charantin**	**Karaviloside I**	**Quercetin**	**Momordicilin**	**Charantoside I**	**Kaempferol**
Absorption							
Gl absroption	High	Low	Low	High	Low	Low	High
P-glycoprotein inhibitor	---	---	-	---	+++	-	--
P-glycoprotein substrate	+++	---	-	---	---	---	--
Caco-2 Permeability	-5.33	-5.382	-5.508	-6.177	-5.239	-5.705	-5.969
Distribution							
Plasma Protein Binding (PPB) (%)	-8.3%	79.7%	81.0%	99.8%	96.2%	85.3%	97.9%
Blood brain barrier penetration	+	---	---	---	---	---	---
Volume Distribution (VD) (L/Kg)	0.573	0.337	0.41	0.132	1.113	0.344	0.154
Fraction unbound in plasma (Fu) (%)	105.7	16.2%	12.7%	1.1%	4.0%	10.8%	1.4%
Metabolism							
CYP1A2 inhibitor	---	---	---	+++	---	---	+++
CYP2C19 inhibitor	---	---	---	---	---	---	--
CYP2C9 inhibitor	---	---	---	-	--	---	++
CYP2D6 inhibitor	---	---	---	---	---	---	---
CYP2D6 substrate	-	---	---	+++	---	---	+++
CYP3A4 inhibitor	---	---	+++	+++	+++	-	+++
CYP3A4 substrate	+++	+++	+++	---	+++	---	---
Execretion							
Clearance (Cl) (mL/min/kg)	6.3	3.879	4.294	8.289	10.596	2.987	5.694
Half Life (T1/2)	1.897	1.191	1.698	1.586	0.291	1.581	1.388
Compound's Toxicity							
AMES toxicity	0.722	0.623	0.895	0.586	0.186	0.8	0.546
Carcinogenicity	0.636	0.333	0.468	0.6	0.926	0.183	0.716
Genotoxic rule	No Alert	No Alert	No Alert	No Alert	No Alert	No Alert	No Alert
Human hepatotoxicity	0.681	0.577	0.723	0.337	0.711	0.577	0.386
Drug Induced Liver Injury (DILI)	0.167	0.764	0.825	0.783	0.306	0.46	0.703
Respiratory toxicity	0.722	0.316	0.16	0.674	0.822	0.232	0.713

Note: Probability value prediction --- : 0 - 0.1; -- : 0.1 - 0.3; - : 0.3 -0.5; + : 0.5 – 0.9; ++ : 0.7 – 0.9; +++ : 0.9 –1.0



a. Charantin b. Karaviloside I c. Quercetin

d. Kaempferol e. Charantoside I f. Momordicilin

Figure 4. Visualization Overlay comparison of GSK redocking results with test compound docking results

CONCLUSIONS

Momordica charantia L. showed the potential of antidiabetic agent through the mechanism of ligand binding to the active site of native ligand in silico. Kaempferol and quecetin compounds have stable interaction residues and meet the requirements of admet analysis.

ACKNOWLEDGMENT

Financial assistance for this study was generously provided by UMKT. grant number No.039/KEP/SKT.4/C/2025.

AUTHORS' CONTRIBUTIONS

All authors conceptualized the research and conducted literature studies related to the methods. Asri Dwi Endah Dewi Pramesthi evaluated the results and also responsible for data interpretation and analysis. Khairunnisa did the in silico analysis. Aurelia Nabilla Zuliet and Melani Pebriana Putri did the antioxidant assay. Paula Mariana Kustiawan finalized the analysis method. After carefully examining the findings. all authors approved the final draft of the manuscript.

CONFLICT OF INTERESTS

No conflict interest in this publication.

ETHICAL CONSIDERATION

Ethical issues (including plagiarism. data fabrication. double publication. etc) have been completely observed by the author.

BIBLIOGRAPHY

Afriana. D.. & Dewi. C. (2022). Studi In Silico Senyawa Dari Saffron (Crocus sativus L.) Terhadap Reseptor Glikogen Sintase Kinase-3 Beta (GSK-3β) Sebagai Antidiabetes. *Jurnal Pharmacia Mandala Waluya*. 1(5). 188–201. https://doi.org/10.54883/jpmw.v1i5.

Abdullah. S. S.. Antasionasti. I.. Rundengan. G.. & Abdullah. R. P. I. (2022). Aktivitas Antioksidan Ekstrak Etanol Biji dan Daging Buah Pala dengan (Myristica fragrans) Metode DPPH. *Chemistry Progress*. 15(2). 70–75. https://doi.org/10.35799/cp.15.2.2022.4448.

Andriani. D.. & Murtisiwi. L. (2020). Uji Aktivitas Antioksidan Ekstrak Etanol 70% Bunga Telang (Clitoria ternatea L) dari Daerah Sleman dengan Metode DPPH. *Pharmacon: Jurnal Farmasi Indonesia*. 17(1). 70–76. https://doi.org/10.23917/pharmacon.v17i1.9321.

Achmad. A.. Regar. D. N.. & Harwoko. (2016). Efektivitas Ekstrak Buah Pare (*Momordica charantia*) dan Buncis (Phaseolus vulgaris) untuk Penurunan Kadar Gula Darah dan AUC (Area Under Curve). *Pharmaceutical Journal of Indonesia*. 2(1). 25–29. https://doi.org/10.21776/ub.pji.2016.002.01.5

Alkhalidy. H.. Moore. W.. Wang. A.. Luo. J.. McMillan. R. P.. Wang. Y.. Zhen. W.. Hulver. M. W.. & Liu. D. (2018). Kaempferol ameliorates hyperglycemia through suppressing hepatic gluconeogenesis and enhancing hepatic insulin sensitivity in diet-induced obese mice. *J Nutr Biochem*. 58. 90–101. https://doi.org/10.1002/hep.30150.Ductular

Awaluddin. A.. Aksa. R.. & Septiani. H. R. (2018). Studi Potensi Interaksi Farmakodinamik Metformin dan Ekstrak Etanol Daun Kersen(Muntigia calabura L.) Terhadap Perubahan KAdar Glukosa Darah pada Tikus. *Farbal*. 6(2). 44–49.

Akmal. T.. & Sasongko. L. (2023). Influence Of *Momordica charantia* (L.) On The Pharmacokinetics And Pharmacodynamics Of Gliclazide In Alloxan-Induced Diabetic Rats. *Medical Sains : Jurnal Ilmiah Kefarmasian*. 8(3). 1079–1088. https://doi.org/10.37874/ms.v8i3.854

Bakare. R. I.. Magbagbeola. O. A.. Akinwande. A. I.. & Okunowo. O. W. (2010). Nutritional and chemical evaluation of *Momordica charantia*. *Journal of Medicinal Plants Research*. 4(21). 2189–2193.

Bahagia. W.. Kurniawaty. E.. & Mustafa. S. (2018). The Potential of Bitter Melon Extract (Momordhica charantia) to Lower Blood Glucose Levels: The Benefits Behind the Bitter Taste. *Majority*. 7(2). 177–181.

Bai. C.. Wu. L.. Li. R.. Cao. Y.. He. S.. & Bo. X. (2025). Machine Learning-Enabled Drug-Induced Toxicity Prediction. *Advanced Science*. 2413405. https://doi.org/10.1002/advs.202413405

Bitew. M.. Desalegn. T.. Demissie. T. B.. Belayneh. A.. Endale. M.. & Eswaramoorthy. R. (2021). Pharmacokinetics and drug-likeness of antidiabetic flavonoids: Molecular docking and DFT study. *PLoS ONE*. 16(12). https://doi.org/10.1371/journal.pone.0260853

Effendi. N.. Saputri. N. airin. Purnomo. H.. & Aminah. (2023). ADME-T. *Media Farmasi*. 19(1). 10.

Fauziyyah. R. S.. Huang. S. A.. Sholehah. A. M.. Dewi. T. T.. Wulandari. R. P.. Nurdin. H. A.. & Nuwarda. F. (2025). In Silico Study of Secondary Metabolite Compound from Noni fruit (Morinda citrifolia) as Potential Drug Candidates for Type 2 Diabetes Mellitus Targeting PPAR- γ. *Indonesian Journal of Chemical Science*. 14(1).

IDF. (2021). IDF Diabetes Atlas 10 TH Edision. Internasional Diabetes Federation.

Ino Ischak. N.. Musa. W. J.. Ode Aman. L.. Alio. L.. La Kilo. A.. & Deltalia Saleh. S. (2023). Molecular Docking Study and ADME Prediction of Secondary Metabolite Compounds of Gorontalo Traditional Medicinal Plants on HER-2 Receptors as Breast Anticancer Agents. *Jamb.J.Chem*. 5(1). 90–103. https://www.rcsb.org/

Kurniadi. A. (2024). Study Of The Formulation Of Bulldang Pea Flower Extract (*Clitoria Ternatea*) On Antioxidant Activity In Functional Drinks. 3(1). 13–28.

Mahmoud. M. F.. Hassan. N. A.. El Bassossy. H. M.. & Fahmy. A. (2013). Quercetin Protects against Diabetes-Induced Exaggerated Vasoconstriction in Rats: Effect on Low Grade Inflammation. *PLoS ONE*. 8(5). https://doi.org/10.1371/journal.pone.0063784

Mailandari. M. (2012). Uji Aktivitas Antioksidan Ekstrak Daun Garcinia kydia Roxb. Dengan metode DPPH dan IdentfikasiSenyawa Kimia Fraksi Yang Aktif. Fakultas Matematika Dan Ilmu Pengetahuan Alam Program Studi Ekstensi Farmasi. Universitas Indonesia. 13.

Nirnadia. N.. Kamilla. L.. & Djohan. H. (2020). The Potential of Bitter Melon (*Momordica charantia* Linn) as an Antidiabetic. *Jurnal Laboratorium Khatulistiwa*. 4(1). 34. https://doi.org/10.30602/jlk.v4i1.942

Novianty. R. (2023). Innovation of Areca catechu Compounds Combined with Fluoxetine as Antidepressant by In Silico Method. *Photon: Jurnal Sain Dan Kesehatan*. 13(2). 70–77. https://doi.org/10.37859/jp.v13i2.5041.

Octariani. S.. Mayasari. D.. & Ramadhan. A. M. (2021). Optimization of Polyvinyl Alcohol (PVA) as a Base for Anti-Acne Gel Preparations. *Proceeding of Mulawarman Pharmaceuticals Conferences*. 135–138. http://prosiding.farmasi.unmul.ac.id/index.php/mpc/article/view/416/399

Oyelere. S. F.. Ajayi. O. H.. Ayoade. T. E.. Pereira. G. B. S.. Owoyemi. B. C. D.. Ilesanmi. A. O.. & Akinyemi. O. A. (2022). A detailed review on the phytochemical profiles and anti-diabetic mechanisms of *Momordica charantia*. *Heliyon*. 8(4). e09253. https://doi.org/10.1016/j.heliyon.2022.e09253

Peng. J.. Li. Q.. Li. K.. Zhu. L.. Lin. X.. Lin. X.. Shen. Q.. Li. G.. & Xie. X. (2017). Quercetin Improves Glucose and Lipid Metabolism of Diabetic Rats: Involvement of Akt Signaling and SIRT1. *Journal of Diabetes Research*. 2017. https://doi.org/10.1155/2017/3417306

Ramadhani. R.. Baruna. I.. Vedha. G. B.. & Lutfi Chabib. (2023). The Effect of Sambiloto and Ginger Compounds on Covid-19 Target Proteins Using Molecular Docking. *Parapemikir : Jurnal Ilmiah Farmasi.* Vol. 12(2). 157–171.

Rajagopal. P. lakshmi. (2022). Molecular docking analysis of metformin analogues with GSK-3β. *Bioinformation*. 18(3). 269–272.https://doi.org/10.6026/97320630018269

Rantung. O.. Korua. A. I.. & Datau. H. (2021). Metode Spektrofotometer UV untuk Uji Vitamin C dalam Buah-Buahan. Prosiding. 61.

Richter. E.. Geetha. T.. Burnett. D.. Broderick. T. L.. & Babu. J. R. (2023). The Effects of *Momordica charantia* on Type 2 Diabetes Mellitus and Alzheimer's Disease. International Journal of Molecular Sciences. 24(5). https://doi.org/10.3390/ijms24054643

Seal. S.. Mahale. M.. García-Ortegón. M.. Joshi. C. K.. Hosseini-Gerami. L.. Beatson. A.. Greenig. M.. Shekhar. M.. Patra. A.. Weis. C.. Mehrjou. A.. Badré. A.. Paisley. B.. Lowe. R.. Singh. S.. Shah. F.. Johannesson. B.. Williams. D.. Rouquie. D.. … Bender. A. (2025). Machine Learning for Toxicity Prediction Using Chemical Structures: Pillars for Success in the Real World. *Chemical Research in Toxicology*.https://doi.org/10.1021/acs.chemrestox.5c00033

Syafitri. A.. & Mardatillah. H. F. (2022). Antidiabetic Effectiveness Test of a Combination of Bitter Melon Fruit Extract (Momordica charantia L.) and Rosella Flower Petals (Hibiscus sabdariffa L.) on White Male Mice as Experimental Animals. *Jurnal Farmasi Dan Hernal*. 4(2).

Scott. B.. Day. E. A.. O'Brien. K. L.. Scanlan. J.. Cromwell. G.. Scannail. A. N.. McDonnell. M. E.. Finlay. D. K.. & Lynch. L. (2024). Metformin and feeding increase levels of the appetite-suppressing

metabolite Lac-Phe in humans. *Nature Metabolism*. 6(4). 651–658. https://doi.org/10.1038/s42255-024-01018-7

Supringrum. R.. & Jubaidah. S. (2019). Antioxidant Activity Of Ethanol Extract And Fraction Of Tabar Kedayan Roots (*Aristolochia foveolata* Merr.) Using The Dpph (2.2 Diphenyl-1-Picrilhydrazil) Method. *JFL : Jurnal Farmasi Lampung*. 8–14. https://doi.org/10.37090/jfl.v8i1.81

Xu. B.. Li. Z.. Zeng. T.. Zhan. J.. Wang. S.. Ho. C. T.. & Li. S. (2022). Bioactives of *Momordica charantia* as Potential Anti-Diabetic/Hypoglycemic Agents. *Molecules*. 27(7). 1–17. https://doi.org/10.3390/molecules27072175