HYDROGEN
JURNAL KEPENDIDIKAN KIMIA
https://e-journal.undikma.ac.id/index.php/hydrogen/index

October 2025. 13(5)
e-ISSN: 2656-3061
p-ISSN: 2338-6487
pp. 985-995

In Silico Study of Antidiabetic Activity Mikania Cordata as PPAR-γ Agents

Dian Oktavianti[1], Masriani[1*], Ihsanul Arief[2]
[1] Department of Chemistry Education, Faculty of Teacher Training and Education, Tanjungpura University, Pontianak, Indonesia
[2] Yarsi Academy of Pharmacy, Pontianak, Indonesia
[*] Corresponding Author e-mail: masriani@fkip.untan.ac.id

Article History
Received: 21-10-2025
Revised: 04-11-2025
Published: 19-11-2025

Keywords: antidiabetic, *M. cordata*, PPAR-γ

Abstract
Diabetes mellitus remains a significant global health problem, requiring safer and more effective therapeutic agents. Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) plays a crucial role in regulating glucose metabolism by enhancing insulin sensitivity, making it a key target in the development of antidiabetic drugs. Pioglitazone, a PPAR-γ agonist from the thiazolidinedione class, has long been used as a conventional therapy; however, its long-term use is associated with side effects such as fluid retention, weight gain, and an increased risk of heart failure. The World Health Organization recommends the development of natural-based drugs with minimal adverse effects. One promising plant candidate is *Mikania cordata*, which has been reported to possess antidiabetic activity and contains various bioactive compounds, including terpenoids, flavonoids, sterols, and sesquiterpenoids. This study aimed to evaluate the bioactive compounds of *Mikania cordata* as potential natural PPAR-γ agonists using a molecular docking approach. A total of 36 ligands from *M. cordata* were docked to the PPAR-γ protein (PDB ID: 2PRG), with Pioglitazone serving as the positive control. Docking was performed using PyRx with the AutoDock Vina system after ligand and protein preparation with UCSF Chimera 1.16. The docking results were analyzed using BIOVIA Discovery Studio Visualizer to identify the interactions between the ligand–protein complexes. The results showed that Cordatolide exhibited the lowest binding affinity (–9.1 kcal/mol), followed by Stigmasterol (–8.9 kcal/mol), both of which were better than Pioglitazone (–8.8 kcal/mol). Interaction analysis revealed that Cordatolide formed two hydrogen bonds with key residues ARG288 and GLY284, accompanied by stable hydrophobic interactions without any unfavorable contacts. Meanwhile, Stigmasterol also showed competitive affinity, although its stability relied solely on hydrophobic interactions without hydrogen bonding. Therefore, Cordatolide demonstrates strong potential as a natural PPAR-γ agonist with fewer side effects compared to conventional therapies. This study provides a novel finding on the potential of *M. cordata* as a natural PPAR-γ agonist; however, further *in vitro* and *in vivo* evaluations are required to confirm its pharmacological activity.

How to Cite: Oktavianti, D., Masriani, & Arief, I. (2025). In Silico Study of Antidiabetic Activity Mikania Cordata as PPAR- γ Agents. Hydrogen: Jurnal Kependidikan Kimia, 13(5), 985–955. https://doi.org/10.33394/hjkk.v13i5.18110

https://doi.org/10.33394/hjkk.v13i5.18110

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INTRODUCTION

Diabetes mellitus, often referred to as a silent killer, occurs due to an unhealthy lifestyle that leads to elevated blood glucose levels above the normal threshold (>70–150 mg/dL) (Anisa & Indarjo, 2021). According to the International Diabetes Federation, there are approximately 537 million individuals with diabetes mellitus worldwide within the 20–79 age group, and this number is projected to increase to 643 million by 2030 and 783 million by 2045. Indonesia ranks fifth among countries with the highest number of diabetes cases, following China, India, Pakistan, and the United States (IDF, 2021). This condition arises from insufficient insulin production, resulting in increased blood glucose levels (hyperglycemia) (Wartana & Cindrayana, 2022). If left untreated, hyperglycemia can progress into severe complications such as retinopathy, nephropathy, and peripheral neuropathy (Sabuncu et al., 2021). One of the

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key factor involved in the regulation of glucose metabolism and closely associated with diabetes mellitus is PPAR-γ.

Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) is highly expressed in adipose tissue, muscle, and liver, and functions as a transcription factor that regulates the expression of genes related to glucose and lipid metabolism (Medina-Gomez et al., 2007). Structurally, PPAR-γ consists of two main domains: the DNA Binding Domain (DBD), which binds to response elements on DNA to regulate gene transcription, and the Ligand Binding Domain (LBD), which becomes active upon ligand binding. Ligand binding to the LBD induces a conformational change that enables PPAR-γ to form a heterodimer with the retinoid X receptor (RXR), allowing the complex to interact with DNA and activate target genes (Ahmadian et al., 2013). Activation of PPAR-γ enhances insulin sensitivity by increasing the expression of glucose transporters such as GLUT4 and modulating adipokines like adiponectin, while also suppressing pro-inflammatory cytokines involved in insulin resistance (Marx et al., 2003).

A prevalent therapeutic approach involves the administration of pioglitazone, a thiazolidinedione-class drug that acts as a PPAR-γ agonist to enhance insulin sensitivity in adipose tissue, muscle, and liver (Soccio et al., 2014). Although effective in improving glycemic control, long-term use of pioglitazone is frequently associated with side effects such as fluid retention, weight gain, and an increased risk of congestive heart failure (Sheikh et al., 2023). Therefore, alternative PPAR-γ agonists with fewer adverse effects are urgently needed.

A plant with notable antidiabetic potential is Mikania cordata, which contains various secondary metabolites such as terpenes, diterpenes, sesquiterpene lactones, and sterols. Stigmasterol, in particular, is known to exhibit anti-inflammatory and antioxidant activities, as well as the ability to modulate glucose metabolism through its influence on GLUT4 expression and the PPAR-γ pathway (Bakrim et al., 2022). Other studies have reported that M. cordata extract exerts anti-inflammatory effects by inhibiting the NF-κB pathway and activating Nrf2, and it also demonstrates wound-healing activity relevant to diabetes-related complications (Kang et al., 2023). In addition, Jayatilake & Munasinghe (2020) noted that the ethyl acetate extract of M. cordata can enhance glucose uptake in yeast cells more effectively than the conventional antidiabetic drug metformin. However, the specific compounds responsible for the glucose-lowering mechanism have not yet been clearly identified.

As a strategy to identify potential active compounds, the molecular docking approach is widely used because it can rapidly and efficiently predict interactions between ligand molecules and target proteins (Pradani et al., 2021). This method not only provides binding affinity values but also visualizes the orientation of ligands within the active site, identifies amino acid residues involved in complex stability, and predicts the potential biological activity of compounds (Meng et al., 2011). This approach offers significant advantages by reducing the use of experimental animals, lowering research costs and time, and enabling detailed visualization of molecular binding patterns (Ferreira et al., 2015). Molecular docking also allows the evaluation of a compound's ability to interact with the receptor's Ligand Binding Domain (LBD) and mimic the agonistic mechanism of drugs such as pioglitazone (Feng et al., 2016). Based on these considerations, this study aims to evaluate the potential of compounds from *Mikania cordata* as PPAR-γ agonists through molecular docking analysis and to compare their binding affinities and interaction profiles with those of the pioglitazone as positive controls.

METHOD

Preparation of Compounds and Target Protein

The compounds investigated in this study consisted of 36 constituents identified in *Mikania cordata*, namely: 3,5-Dihydroxy-4',6,7-trimethoxyflavone (Mikanin), Epifriedelanol,

Friedelin, Stigmasterol, Mikanolide, Dihydromikanolide, Sesquiterpene Lactone, Sterol, α-thujene, β-thujene, Limonene, Linalool, α-terpineol, δ-elemene, β-elemene, α-humulene, γ-murolene, Germacrene D, Bicyclogermacrene, α-muuroolene, Germacrene A, γ-cadinene, cis-calamenene, δ-cadinene, Germacrene B, Germacrene D-4-ol, α-cadinol, Scandenolide (sesquiterpene lactone), Scandenolide, Germacranolide, Cordatolide, 6α-hydroxycordatolide (Sajid et al., 2019), Deoxymikanolide, α-pinene, β-pinene (Singh, 2022), 16-hydroxy betulinic acid (Siddiqui et al., 2018), and pioglitazone as a positive control. All compounds were retrieved from PubChem and prepared using Dockprep in Chimera 1.16 by adding hydrogen atoms and saving the structures in .pdb format (Pettersen et al., 2004). The target protein used was Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), PDB code: 2PRG, downloaded from the Protein Data Bank (https://www.rcsb.org/). The protein was then separated from non-essential residues and optimized using Chimera 1.16.

Molecular Docking

Molecular docking was performed using the PyRx software with the AutoDock Vina engine (Dallakyan & Olson, 2015), involving 36 test ligands, the native ligand, and pioglitazone docked into the PPAR-γ protein. A grid box measuring 25.0000 × 25.0000 × 25.0000 Å was adjusted to cover the active site of the protein at coordinates x = 48.2583, y = -35.5090, and z = 18.8336. Each ligand was docked to obtain its binding affinity value in kcal/mol, and the docking quality was evaluated using RMSD, with successful results defined by an RMSD ≤ 2 Å (Zheng et al., 2022).

Visualization and Analysis

Docking results were visualized using Discovery Studio Visualizer, displaying ligand-protein interactions in both 2D and 3D formats, including hydrogen bonds, hydrophobic interactions, and other types of non-covalent interactions (Yahaya et al., 2021). Through visualization, binding patterns and interaction distances were clearly observed. The analysis phase involved evaluating the binding affinity of ligand-protein complexes, interaction types, number of hydrogen bonds, bond distances, and the similarity of amino acid residues interacting with each compound (Rasyid et al., 2023).

RESULTS AND DISCUSSION

Molecular docking was conducted on compounds derived from *Mikania cordata* using PPAR-γ as the target protein, and the entire process was executed in a single computational run to ensure that the grid box was consistently positioned at the same location. This setup was intended to guarantee that each ligand was evaluated at an identical binding site, allowing for objective and accurate comparison of binding affinity values. PPAR-γ was selected as the target protein due to its crucial role in regulating glucose metabolism and enhancing insulin sensitivity in body cells. Activation of PPAR-γ is known to reduce insulin resistance by modulating the expression of genes involved in glucose storage and utilization. As a comparative reference, pioglitazone a thiazolidinedione class PPAR-γ agonist widely used as a standard therapy for type 2 diabetes mellitus was employed.

Table 1. Molecular docking results and ligand-protein interactions

No	Ligand	Binding affinity	Hydrogen bond	Other
1	Mikanin	-7.7	GLN271, ARG280, SER A342	PHE287, GLN283, GLY284, GLU343, LEU340, LEU270, LEU330, ARG288, ILE341, CYS285, LEU333.

No	Ligand	Binding affinity	Hydrogen bond	Other
2	epifridelanol	-8.1	-	GLN271, GLY284, ARG280, GLU259, PHE287, SER342, GLU343, LYS365, THR268, ILE262, LEU270
3	friedelin	-7.9	-	THR268, ILE262, LEU270, ILE341, MET348, GLY284, ILE281, CYS285, PHE287, ARG288, SER342, GLU291, GLU343
4	stigmasterol	-8.9	-	SER342, GLU343, ILE 341, LEU340, VAL339, LEU333, LEU353, LEU270, PHE287, GLY284, ILE326, SER289, LEU330, MET364, CYS285, LYS367, TYR327, ARG288
5	mikanolide	-7.9	GLN271	SER342, ILE341, ILE262, ILE249, GLU259, MET348, LEU255, ILE281, ARG280, GLY284, LEU270, PHE287
6	dihydromikanolide	-7.8	GLN271	ILE341, ILE262, ILE249, GLU259, MET348, LEU255, ILE281, ARG280, GLY284, LEU270, PHE287
7	sesquiterpene lactone	-8.1	ARG288	LEU255 MET348, SER342, ILE249, ILE341, ILE262, GLU259, ARG280, GLN271, GLN283, GLY284, LEU270, PHE287
8	Sterol	-7.3	-	LEU340, LEU333, SER289, HIS323, HIS449, TYR473, PHE363, MET364, ILE341, VAL339, ARG288, LEU330, ILE326, TYR327, CYS285
9	α-thujene	-5.5	-	SER289, HIS323, GLN286, HIS449, PHE363, LEU469, TYR473, LEU330, CYS285, TYR327, ILE326
10	β-thujene	-5.4	-	SER289, HIS323, GLN286, HIS449, PHE363, LEU469, TYR473, LEU330, ILE326, CYS285, TYR327
11	limonene	-5.4	-	TYR327, LYS367, PHE363, GLN286, LEU465, SER289, ILE326, CYS285, MET364, LEU330, HIS449, LEU469, HIS323, TYR473
12	Linalol	-5.6	TYR473	ILE326, HIS449, LEU453, GLN286, LYS367, SER289, PHE363, CYS285, LEU330, MET364, HS323, LEU469, TYR327
13	α-terpineol	-5.6	GLU259	ARG280, GLN271, GLN283, GLY284, ILE281, PHE287, LEU270
14	δ-elemene	-6	-	LEU333, SER342, LEU340, ILE341, CYS285, SER289, ALA292, ILE326, LEU330, ARG288, VAL339, TYR327
15	β-elemene	-6.2	-	SER342, GLU343, LEU228, LEU333, LEU340, CYS285, GLY284, ARG288, ILE341, MET364, LEU330. VAL339
16	α-humulene	-6.7	-	ILE341, VAL339, LAU340, LEU333, MET329, ALA292, SER289, ILE326, TYR327, CYS285, ARG288, LEU330

No	Ligand	Binding affinity	Hydrogen bond	Other
17	γ-murolene	-6.6	-	ALA292, GLY344, LEU333, LEU228, GLU343, SER342, LEU340, ILE326, LEU330, ILE341, VAL339, ARG288
18	Germacrene D	-6.5	-	PHE287, LEU270, GLY284, ILE341, GLU259, LEU255, ILE281, ARG280, GLN283, GLN271
19	bicyclogermacrene	-6.4	-	PHE287, LEU270, GLY284, CYS285, SER342, ILE262, ARG288, ILE341
20	α-muuroolene	-6.7	-	MET364, VAL339, SER342, GLU343, LEU340, LEU333, ARG288, CYS285, LEU330, ILE341
21	germacrene A	-6.4	-	PHE287, GLY284, GLN283, GLN271, ILE262, SER342, ARG288, LEU270
22	γ-cadinene	-6.8	-	GLY284, GLN283, GLN271, ARG280, ILE262, ARG288, PHE287, LEU270
23	cis-calamenene	-7.3	-	ARG280, ILE281, ARG288, GLY284, GLN271, PHE287, GLN283, LEU270
24	δ-cadinene	-6.9	-	MET343, VAL339, PHE363, SER289, GLN286, LEU330, ARG288, ALA292, TYR327, HIS323, ILE326, CYS285
25	germacrene B	-6.9	-	TYR327, HIS449, PHE363, LYS367, MET364, ARG288, LEU330, ILE326, SER289, HIS323, CYS285, GLN286
26	germacrene D-4-ol	-6.4	-	PHE287, LEU270, GLY284, GLN271, ARG280, ILE281, GLU259, LEU255, ILE262, MET348, ILE341, SER342
27	α-cadinol	-6.9	-	ILE262, GLU259, ARG280, GLN271, GLY284, GLN283, ARG288, LEU270, PHE287
28	Scandenolide (sesquiterpene lactone)	-8	SER342, ILE341, GLY284	LEU340, CYS285, ARG288, PHE287, LEU270, ILE262, GLU259, LEU255, ILE281, MET348
29	Scandenolide	-7.6	GLN271	SER342, ARG288, GLY284, ILE262, GLN283, LEU270, PHE287, ARG280, GLU259, LEU255, ILE281, MET348, ILE341, CYS285
30	germacranolide	-6.9	-	GLY284, ARG280, GLN271, LEU270, ILE262, SER342, GLU259, ILE249, LEU255, CYS285, ILE341, MET348, ILE281
31	cordatolide	-9.1	GLY284, ARG288	PHE287, LEU270, ILE281, MET348, LEU353, LEU330, LEU333, LEU340, GLU343, SER342, CYS285, ILE341
32	6α-hydroxycordatolide	-8.7	ARG288, SER342, ILE341	LEU333, LEU340, LEU330, VAL339, MET348, ILE281, ARG280, GLU343, CYS285, GLY284

No	Ligand	Binding affinity	Hydrogen bond	Other
33	deoxymikanolide	-7.8	GLN271	ILE341, ILE262, ILE249, GLU259, MET348, LEU255, ILE281, ARG280, GLY284, LEU270, PHE287, SER342
34	α-pienene	-5	-	VAL290, HIS466, GLN286, SER464, LEU465, GLN283, GLN271, LEU270, PHE287
35	β-pienene	-4.9	-	GLN283, LEU270, GLN286, GLN271, PHE287, HIS466
36	16-hydroxy betulinic acid	-7.3	GLU291, GLY284	GLN271, ARG288, LEU270, PHE287, THR268, GLU343, SER342, ILE262, ILE249, ILE341, GLU259, MET348, LEU255, ILE281, ARG280, GLN283
37	ligan native	-8.7	HIS323, SER289, TYR473, GLN286, CYS285	LEU330, VAL339, LEU353, ILE341, MET348, MET364
38	Pioglitazone	-8.8	HIS449, GLN286, TYR473, SER289	PHE363, LEU453, LEU465, LEU469, TYR327, ILE326, ARG288, GLU295, LEU333, LEU330, PHE226, ILE296, MET329, ALA292, CYS285, MET364, HIS323

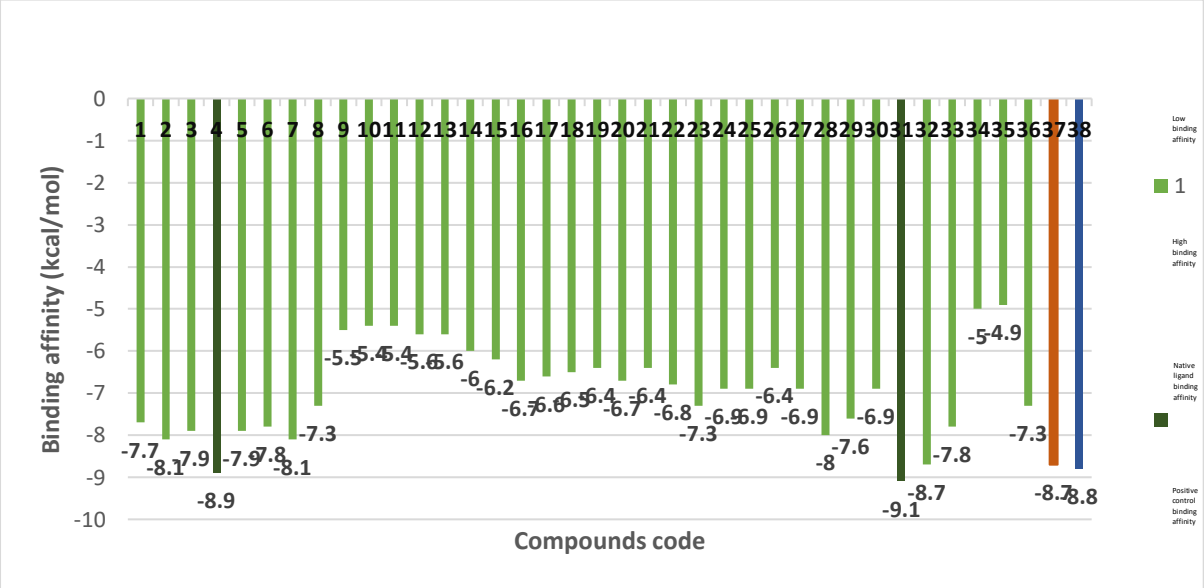
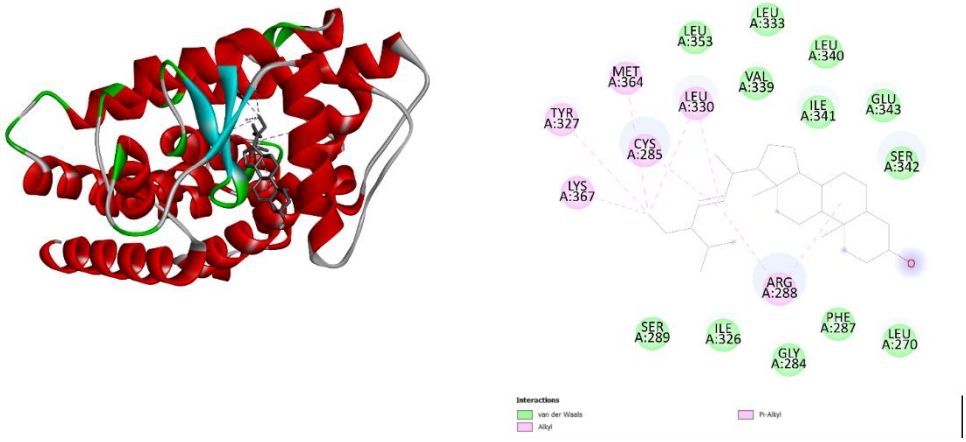


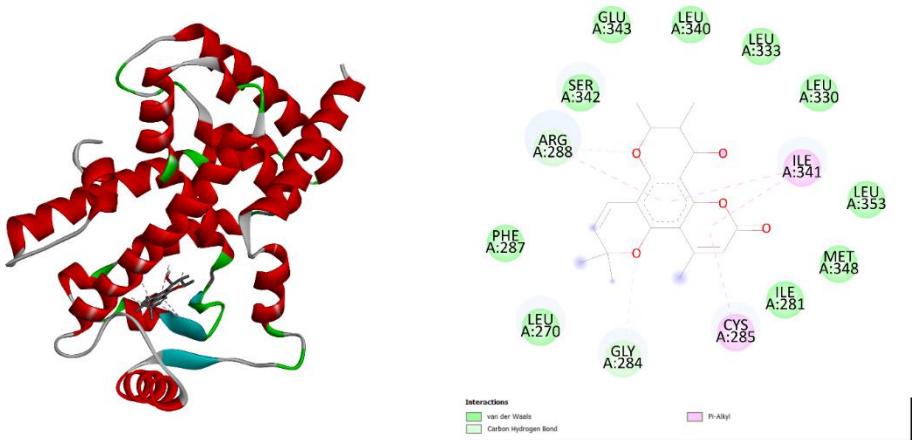
Figure 1. Comparison of binding affinity

Based on the molecular docking results, compounds from Mikania cordata demonstrated competitive affinity toward the PPAR-γ target protein. Pioglitazone, used as the positive control, showed a binding affinity of −8.8 kcal/mol, while the native ligand exhibited a value of −8.7 kcal/mol. Among all tested compounds, cordatolide displayed the lowest affinity value at −9.1 kcal/mol, indicating a more stable interaction compared to both pioglitazone and the native ligand. Stigmasterol also showed promising potential with an affinity of −8.9 kcal/mol, slightly lower than that of pioglitazone. Lower affinity values generally correspond to stronger ligand–protein interactions and greater complex stability (Alsedfy et al., 2024). Thus, the lower the affinity value, the stronger and more stable the resulting ligand–protein complex. Both stigmasterol and cordatolide demonstrated the potential for more effective binding, suggesting

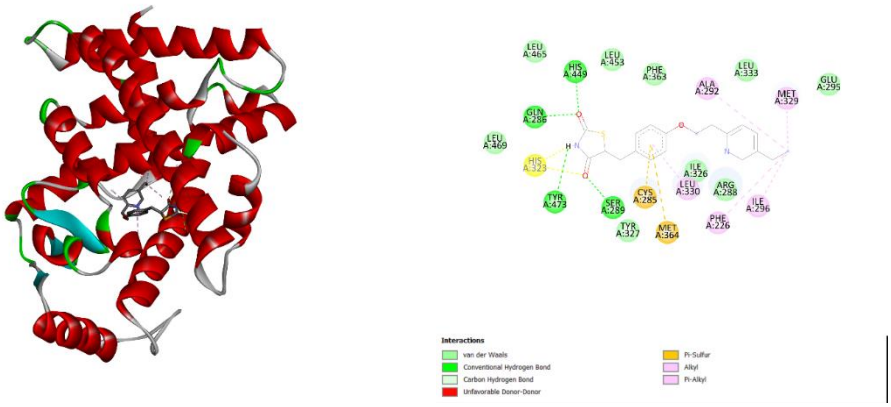
that they may activate PPAR-γ more optimally. This is consistent with previous reports stating that natural compounds, particularly sesquiterpene lactones and sterols, can function as PPAR-γ modulators and possess potential antidiabetic activity (Bakrim et al., 2022; Feng et al., 2016; Salazar-Gómez et al., 2020).



(a)



(b)



(c)

Figure 2. Visualization of ligand–receptor complexes of (a) Stigmasterol, (b) Cordatolide, and (c) Pioglitazone.

When compared to Stigmasterol (−8.9 kcal/mol), Cordatolide exhibits a superior interaction profile. Stigmasterol is known to interact with residues such as SER342, GLU343, LEU340,

ILE341, LEU333, and ARG288, all of which are hydrophobic or van der Waals in nature without the presence of hydrogen bonds. Consequently, the stability of the Stigmasterol–PPAR-γ complex relies primarily on non-polar forces, which are generally weaker and less directional than hydrogen bonds (Du et al., 2016). Despite a broad contact surface, Stigmasterol's binding affinity is lower than Cordatolide's.

In contrast, Cordatolide forms two strong hydrogen bonds with the GLY284 and ARG288 residues, which serve as the primary stabilizing interactions within the ligand–receptor complex. Hydrogen bonds are known to contribute greater and more specific binding energy than hydrophobic interactions due to their directional and selective nature (Kumar et al., 2020). In addition, Cordatolide also exhibits hydrophobic interactions with several key residues, including ILE341, LEU340, LEU333, PHE287, CYS285, and ARG288, which are similarly involved in the hydrophobic interactions of pioglitazone (Devchand et al., 2018; Jang et al., 2018). The presence of unfavorable donor–donor interactions in the positive control ligand causes electrostatic repulsion and reduces the stability of the complex, resulting in weaker binding affinity for pioglitazone (Spassov et al., 2023). Therefore, although pioglitazone forms a greater number of hydrogen bonds, these detrimental contacts contribute to its slightly lower binding affinity compared to the natural ligand.

CONCLUSION

Cordatolide shows strong potential as a PPAR-γ agonist candidate and a possible alternative to Pioglitazone due to its more favorable interaction profile. The novelty of this study lies in the finding that cordatolide exhibits superior and more stable binding affinity toward PPAR-γ, despite never having been previously reported as a PPAR-γ agonist. This compound forms two specific hydrogen bonds with the key residues ARG288 and GLY284, along with stable hydrophobic interactions involving CYS285 and LEU330 that contribute to receptor activation. The absence of detrimental interactions, such as unfavorable donor–donor contacts, further enhances the stability of the ligand–receptor complex. These findings provide a new scientific basis indicating that natural compounds from Mikania cordata, particularly cordatolide, have promising potential to be developed as natural PPAR-γ agonists with high affinity and possibly fewer side effects compared to conventional therapies. This study opens opportunities for further investigations, including in vitro and in vivo assays, as well as the broader development of natural product–based antidiabetic drug candidates with improved safety profiles.

RECOMMENDATIONS

In vitro and in vivo validation is required to confirm the PPAR-γ agonistic activity of Cordatolide and Stigmasterol that has been predicted computationally. Furthermore, advanced analyses such as molecular dynamics simulations and ADMET profiling are essential to assess the stability of interactions and the pharmacological safety of both compounds. These steps will establish a strong foundation for further development as natural antidiabetic therapies.

BIBLIOGRAPHY

Ahmadian, M., Suh, J. M., Hah, N., Liddle, C., Atkins, A. R., Downes, M., & Evans, R. M. (2013). PPARγ signaling and metabolism: The good, the bad and the future. *Nature Medicine, 19*(5), 557–566. https://doi.org/10.1038/nm.3159

Alsedfy, M. Y., Ebnalwaled, A. A., Moustafa, M., & Said, A. H. (2024). Investigating the binding affinity, molecular dynamics, and ADMET properties of curcumin-IONPs as a

mucoadhesive bioavailable oral treatment for iron deficiency anemia. *Scientific Reports*, *14*(1), 22027. https://doi.org/10.1038/s41598-024-72577-8

Anisa, N. A., & Indarjo, S. (2021). *Perilaku Sehat Pasien Diabetes Mellitus Tipe 2 yang Mengalami Gangren di Puskesmas Halmahera Kota Semarang*.

Bakrim, S., Benkhaira, N., Bourais, I., Benali, T., Lee, L.-H., El Omari, N., Sheikh, R. A., Goh, K. W., Ming, L. C., & Bouyahya, A. (2022). Health Benefits and Pharmacological Properties of Stigmasterol. *Antioxidants*, *11*(10), 1912. https://doi.org/10.3390/antiox11101912

Dallakyan, S., & Olson, A. J. (2015). Small-Molecule Library Screening by Docking with PyRx. In J. E. Hempel, C. H. Williams, & C. C. Hong (Eds.), *Chemical Biology* (Vol. 1263, pp. 243–250). Springer New York. https://doi.org/10.1007/978-1-4939-2269-7_19

Devchand, P. R., Liu, T., Altman, R. B., FitzGerald, G. A., & Schadt, E. E. (2018). The Pioglitazone Trek via Human PPAR Gamma: From Discovery to a Medicine at the FDA and Beyond. *Frontiers in Pharmacology*, *9*, 1093. https://doi.org/10.3389/fphar.2018.01093

Du, X., Li, Y., Xia, Y.-L., Ai, S.-M., Liang, J., Sang, P., Ji, X.-L., & Liu, S.-Q. (2016). Insights into Protein–Ligand Interactions: Mechanisms, Models, and Methods. *International Journal of Molecular Sciences*, *17*(2), 144. https://doi.org/10.3390/ijms17020144

Feng, S., Reuss, L., & Wang, Y. (2016). Potential of Natural Products in the Inhibition of Adipogenesis through Regulation of PPARγ Expression and/or Its Transcriptional Activity. *Molecules*, *21*(10), 1278. https://doi.org/10.3390/molecules21101278

Ferreira, L., Dos Santos, R., Oliva, G., & Andricopulo, A. (2015). Molecular Docking and Structure-Based Drug Design Strategies. *Molecules*, *20*(7), 13384–13421. https://doi.org/10.3390/molecules200713384

IDF. (2021). *IDF diabetes atlas* (10th edition). International Diabetes Federation.

Jang, J. Y., Bae, H., Lee, Y. J., Choi, Y. I., Kim, H.-J., Park, S. B., Suh, S. W., Kim, S. W., & Han, B. W. (2018). Structural Basis for the Enhanced Anti-Diabetic Efficacy of Lobeglitazone on PPARγ. *Scientific Reports*, *8*(1), 31. https://doi.org/10.1038/s41598-017-18274-1

Jayatilake, P. L., & Munasinghe, H. (2020). In Vitro Determination of Antimicrobial and Hypoglycemic Activities of Mikania cordata (Asteraceae) Leaf Extracts. *Biochemistry Research International*, *2020*, 1–7. https://doi.org/10.1155/2020/8674708

Kang, E., Lee, J., Seo, S., Uddin, S., Lee, S., Han, S. B., & Cho, S. (2023). Regulation of anti-inflammatory and antioxidant responses by methanol extract of Mikania cordata (Burm. F.) B. L. Rob. Leaves via the inactivation of NF-κB and MAPK signaling pathways and activation of Nrf2 in LPS-induced RAW 264.7 macrophages. *Biomedicine & Pharmacotherapy*, *168*, 115746. https://doi.org/10.1016/j.biopha.2023.115746

Marx, N., Froehlich, J., Siam, L., Ittner, J., Wierse, G., Schmidt, A., Scharnagl, H., Hombach, V., & Koenig, W. (2003). Antidiabetic PPARγ-Activator Rosiglitazone Reduces MMP-9 Serum Levels in Type 2 Diabetic Patients With Coronary Artery Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *23*(2), 283–288. https://doi.org/10.1161/01.ATV.0000054195.35121.5E

Medina-Gomez, G., Gray, S., & Vidal-Puig, A. (2007). Adipogenesis and lipotoxicity: Role of peroxisome proliferator-activated receptor γ (PPARγ) and PPARγcoactivator-1 (PGC1).

Public Health Nutrition, *10*(10A), 1132–1137. https://doi.org/10.1017/S1368980007000614

Meng, X.-Y., Zhang, H.-X., Mezei, M., & Cui, M. (2011). Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery. *Current Computer Aided-Drug Design*, *7*(2), 146–157. https://doi.org/10.2174/157340911795677602

Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., & Ferrin, T. E. (2004). UCSF Chimera—A visualization system for exploratory research and analysis. *Journal of Computational Chemistry*, *25*(13), 1605–1612. https://doi.org/10.1002/jcc.20084

Pradani, T. C., Fatimawali, ., Manampiring, A. E., Kepel, B. J., Budiarso, F. D., & Bodhi, W. (2021). Molecular Docking Terhadap Senyawa Kurkumin dan Arturmeron pada Tumbuhan Kunyit (Curcuma Longa Linn.) yang Berpotensi Menghambat Virus Corona. *Jurnal e-Biomedik*, *9*(2). https://doi.org/10.35790/ebm.v9i2.31888

Rasyid, H., Mardiyanti, R., Arief, I., & Saputri, W. D. (2023). An Insight of Cryptocarya Secondary Metabolites as Anticancer P388: Study of Molecular Docking and ADMET Properties. *Molekul*, *18*(1), 89. https://doi.org/10.20884/1.jm.2023.18.1.6364

Sabuncu, T., Sonmez, A., Eren, M. A., Sahin, I., Çorapçioğlu, D., Üçler, R., Akin, Ş., Haymana, C., Demirci, İ., Atmaca, A., Ersöz, H. Ö., Satman, I., Bayram, F., Güldiken, S., Aytürk, S., Yilmaz, M., Aşik, M., Dinççağ, N., Satman, İ., … Araz, M. (2021). Characteristics of patients with hypertension in a population with type 2 diabetes mellitus. Results from the Turkish Nationwide SurvEy of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus (TEMD Hypertension Study). *Primary Care Diabetes*, *15*(2), 332–339. https://doi.org/10.1016/j.pcd.2020.11.001

Sajid, S. S., Anika, A. K., Jahan, M. A. N., & Dash, P. R. (2019). A Comprehensive Review of *Mikania Cordata* (Asteraceae). . . *ISSN*, *5*(4), 49–59.

Salazar-Gómez, A., Ontiveros-Rodríguez, J. C., Pablo-Pérez, S. S., Vargas-Díaz, M. E., & Garduño-Siciliano, L. (2020). The potential role of sesquiterpene lactones isolated from medicinal plants in the treatment of the metabolic syndrome – A review. *South African Journal of Botany*, *135*, 240–251. https://doi.org/10.1016/j.sajb.2020.08.020

Sheikh, I. M., Hassan, O. A., Adam, S. M., Ali, A. I., Ogedegbe, O. J., Tabowei, G., Barbarawi, A., Yussuf, F. M., & Nor, M. A. (2023). Association of Pioglitazone With Major Adverse Cardiovascular Events, All-Cause Mortality, and Heart Failure Hospitalizations: A Systematic Review. *Cureus*. https://doi.org/10.7759/cureus.46911

Siddiqui, S. A., Rahman, A., Oliur Rahman, M., Akbar, M. A., Shamsur Rouf, A. S., Ali, M. A., Al-Hemaid, F. M. A., & Farah, M. A. (2018). Evaluation of anti-nociceptive, anti-inflammatory and antipyretic potential of Mikania cordata (Burm. F.) Robinson in experimental animal model. *Saudi Journal of Biological Sciences*, *25*(6), 1049–1055. https://doi.org/10.1016/j.sjbs.2018.01.009

Singh, M. K. (2022). A Comprehensive Review on some Species of Mikania. *YMER Digital*, *21*(04), 299–309. https://doi.org/10.37896/YMER21.04/27

Soccio, R. E., Chen, E. R., & Lazar, M. A. (2014). Thiazolidinediones and the Promise of Insulin Sensitization in Type 2 Diabetes. *Cell Metabolism*, *20*(4), 573–591. https://doi.org/10.1016/j.cmet.2014.08.005

Spassov, D. S., Atanasova, M., & Doytchinova, I. (2023). A role of salt bridges in mediating drug potency: A lesson from the N-myristoyltransferase inhibitors. *Frontiers in Molecular Biosciences*, *9*, 1066029. https://doi.org/10.3389/fmolb.2022.1066029

Wartana, I. K., & Cindrayana, R. S. (2022). Hubungan Pola Makan dan Aktivitas Fisik dengan Hiperglikemia pada Pasien Diabetes Mellitus di Desa Tinggede. *Jurnal Kesmas Untika Luwuk:Public Health Journal*, *13*(1), 20–28.

Yahaya, M. A. F., Bakar, A. R. A., Stanslas, J., Nordin, N., Zainol, M., & Mehat, M. Z. (2021). Insights from molecular docking and molecular dynamics on the potential of vitexin as an antagonist candidate against lipopolysaccharide (LPS) for microglial activation in neuroinflammation. *BMC Biotechnology*, *21*(1), 38. https://doi.org/10.1186/s12896-021-00697-4

Zheng, L., Meng, J., Jiang, K., Lan, H., Wang, Z., Lin, M., Li, W., Guo, H., Wei, Y., & Mu, Y. (2022). Improving protein–ligand docking and screening accuracies by incorporating a scoring function correction term. *Briefings in Bioinformatics*, *23*(3), bbac051. https://doi.org/10.1093/bib/bbac051