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In Silico Evaluation of Flavonoids from *Imperata cylindrica* as Potential Antidiabetic Agents

Evaluasi In Silico Flavonoid dari *Imperata cylindrica* sebagai Agen Potensial Antidiabetes

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by impaired insulin secretion and disrupted blood-glucose homeostasis. Novel therapies targeting the incretin system, such as dipeptidyl peptidase 4 (DPP-4) inhibitors, enhance insulin secretion, protect β-pancreatic cells, and restore glucose balance. *Imperata cylindrica* (reeds) has shown antidiabetic effects, including improved insulin release and reduced blood glucose, but its molecular mechanism remains unclear. This study investigated flavonoid compounds from *I. cylindrica* as potential DPP-4 inhibitors using molecular docking. The target protein (PDB: 6B1E) and drug-like flavonoids were evaluated via PyRx and visualized with Discovery Studio 2021. The results indicate that tricin binds strongly to DPP-4 (−8.4 kcal/mol) and forms stable interactions with residues ILEB102, ILEB76, and ILEB529. These findings suggest that tricin from *I. cylindrica* may inhibit DPP-4 and serve as a potential antidiabetic agent *in silico*.

ABSTRAK

Diabetes mellitus adalah gangguan metabolik yang ditandai oleh sekresi insulin yang terganggu dan ketidakseimbangan glukosa darah. Terapi baru yang menargetkan sistem inkretin, seperti inhibitor dipeptidyl peptidase 4 (DPP-4), dapat meningkatkan sekresi insulin, melindungi sel β-pankreas, dan mengembalikan keseimbangan glukosa. *Imperata cylindrica* (ragi) menunjukkan efek antidiabetik, termasuk peningkatan sekresi insulin dan penurunan kadar glukosa darah, namun mekanisme molekulernya belum jelas. Penelitian ini mengevaluasi senyawa flavonoid dari *I. cylindrica* sebagai calon inhibitor DPP-4 menggunakan metode docking molekuler. Protein target (PDB: 6B1E) dan flavonoid dengan karakteristik drug-likeness dianalisis melalui PyRx dan divisualisasikan menggunakan Discovery Studio 2021. Hasil menunjukkan bahwa tricin berikatan kuat dengan DPP-4 (−8,4 kcal/mol), membentuk interaksi stabil dengan residu ILEB102, ILEB76, dan ILEB529. Temuan ini menunjukkan bahwa tricin dari *I. cylindrica* berpotensi menghambat DPP-4 dan menjadi kandidat agen antidiabetik secara *in silico*.

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1. INTRODUCTION

Diabetes mellitus is a metabolic disorder resulting from defects in secretion and insulin that cause an imbalance in blood glucose homeostasis, which then impacts increasing blood glucose levels (Nkonge et al., 2023). In recent years, diabetes mellitus has been mentioned as being very risky as a factor causing cardiovascular diseases and neurological disorders (July et al., 2022). In this case, over the past few decades, many researchers, especially in medicine, have been synthesizing future drugs using natural ingredients whose efficacy is not well known, so their use is still minimal. One of them is using *I. cylindrica* leaf extract (Ruan et al., 2022).

The molecular synthesis of diabetes drugs requires a receptor, dipeptidyl peptidase 4 (DPP-4), an inhibitor that can lower blood sugar levels (Stoian et al., 2020). DPP-4 inhibits the degradation of peptides 1 and 2 (GLP-1 and GLP-2) and activates insulinotropic peptides that are highly dependent on glucose, which function in pancreatic beta cells to produce more insulin (Florentin et al., 2022). On the other hand, the comparator drug used is vildagliptin, which is an oral hypoglycemic agent (OHA) for diabetics that has been widely used as a DPP-4 inhibitor with two main functions, namely treating diabetic patients directly and suppressing the release of glucagon in the pancreas (Pariyar et al., 2022). However, there is a concomitant occurrence of adverse effects, including, but not limited to, nausea, peripheral edema, weight gain, headaches, dizziness, upper respiratory tract infections, back pain, and diarrhea (Wang et al., 2021).

The medicinal plant reeds (*I. cylindrica*) are native to Southwest Asia and tropical and subtropical regions and have the main components of saponins, flavonoids, phenols, and glycosides (Kato-Noguchi, 2022). These substances can be used as ingredients with potential immunomodulatory, antibacterial, anticancer, anti-inflammatory, and antidiabetic properties. Several studies found that the content of polyphenols, flavonoids, and tannins in *I. cylindrica* can lower blood glucose levels through the antioxidant pathway process (Jung & Shin, 2021). By using the DPP-4 receptor as a target protein in diabetes and the binding of flavonoid chemical components in *I. cylindrica* using the molecular docking method, a drug design reference will be found that can be used as a natural diabetes drug candidate.

Molecular docking is an *in silico* method that is used to compile the basis of a drug or compound. This process involves the stimulation of molecular interactions that predict the binding method and affinity between receptors and ligands (Stanzione et al., 2021). This method uses a database of compounds on a website that researchers can use to synthesize pharmacological compound tests efficiently and cost-effectively (Rashid et al., 2023). This technology can significantly improve the predictive capacity of the desired drug target and understand the molecular-level mechanisms related to drug design. In recent years, this method has been widely applied in research on preparing components for drug design (Deshpande et al., 2020). Using molecular docking techniques, this study aimed to identify potential flavonoid compounds from *I. cylindrica* capable of binding to DPP-4 and providing inhibitory effects, thereby supporting their potential use as *in silico* antidiabetic drug candidates.

2. METHODS

2.1. Ligand-protein preparation

The chemical compound from *I. cylindrica* was obtained based on the literature review, is 5-Hydroxy-2-styrylchromone, Tricin, 5,7-Dihydroxy-8-methoxyflavone, Jaceidin, Caryatin (Jung & Shin, 2021) (**Table 1**). In particular, hydroxylated 2-styrylchromones, including 5-hydroxy-2-styrylchromone, have been shown to exhibit potent inhibitory activity against α-glucosidase and moderate activity against α-amylase. These compounds act primarily as non-competitive inhibitors of α-glucosidase and competitive inhibitors of α-amylase, suggesting their strong therapeutic potential for regulating postprandial blood glucose levels in type 2 diabetes mellitus (Santos et al., 2024). Tricin has been investigated both *in vitro* and *in vivo*, showing protective effects against diabetic complications through the Sestrin2/Nrf2 pathway and enhancement of antioxidant enzymes such as SOD and GSH-Px (Yang & Li, 2023; Zhang et al., 2017). Jaceidin, which is structurally related to luteolin, has also been identified as a potential α-glucosidase inhibitor (Elhady et al., 2020). Although direct studies on 5,7-dihydroxy-8-methoxyflavone and caryatin remain limited, their classification as flavones with structural similarities to bioactive flavonoids provides a strong rationale for *in silico* evaluation. Overall, the combination of enzyme inhibition, antioxidant activity, and metabolic modulation supports the scientific basis for investigating these compounds as potential antidiabetic agents using computational approaches.

The 3D structures of the chemical compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). This study used DPP-4 as the target protein, which was retrieved from the Protein Data Bank (https://www.rcsb.org) with the PDB code 6B1E. Protein preparation was performed using AutoDock 4.2 software to separate the protein structure from its native ligand. The OpenBabel plugin in PyRx 0.9.3 was used to process the ligand files and increase the molecular flexibility through energy minimization (Astuti et al., 2024).

2.2. Druglikeness prediction

Druglikeness is a qualitative assessment used to ascertain the degree of similarity between a natural compound and a drug molecule. This evaluation is done by evaluating several specific parameters. The Rule of Five (RO5) is used to evaluate the compounds in this study with the provisions of RO5, having a molecular weight of around 150-500 g/mol, the number of hydrogen bond acceptors is less than <10, the number of hydrogen bond donors is less than <5, measures lipophilicity with a logP partition coefficient value of less than <5 and molar refractivity beetwen 40-130 (Suhargo et al., 2023).

2.3. Molecular docking analysis

Molecular docking was performed to simulate the interactions between the active compounds of *Imperata cylindrica* and the DPP-4 protein using the Vina Wizard plugin in PyRx 0.9.3. The binding affinity value indicates the strength of the interaction, the more negative the binding affinity, the stronger the binding between the ligand and the target protein (Guzmán-Flores et al., 2023).

2.4. Ligand-protein interaction and Network Pharmacology Analysis

The molecular docking results were used to determine the binding position and type of chemical interactions between the ligand and target protein. Visualization of the ligand–protein complex was carried out using Discovery Studio 2021, which enabled detailed observation of the interaction sites, including hydrogen bonds, hydrophobic interactions, and other non-covalent forces. These molecular interactions are critical in determining the ligand's potential to modulate the biological activity of the target protein, in this case DPP-4, where a greater number of stable interactions may correspond to a higher inhibitory potential (Afnani et al., 2024; Anggarani et al., 2025).

To further elucidate the mechanism of action, a network pharmacology analysis was conducted to explore protein–protein interactions associated with DPP-4. The analysis was performed using Cytoscape version 3.10.1, based on interaction data obtained from publicly available databases (Wang et al., 2021). The resulting network visualizes both direct and indirect protein interactions, allowing the identification of potential downstream targets and signaling pathways influenced by the ligand, particularly those relevant to glucose metabolism and incretin signaling.

3. RESULTS AND DISCUSSION

3.1. Identification of flavonoid compounds in *I. cylindrica*

One of the contents in the extract of *I. cylindrica* leaves is flavonoids, which have the potential to lower blood glucose levels through the antioxidant pathway. Some of the flavonoid compounds found in the research by Jhung & Shin (2021) have Simplified Molecular Input Line Entry System (SMILES) variations that are used as compounds.

Table 1. Identification results of compounds obtained from *I. cylindrica*

No	Compounds	PubChem	SMILES
1.	5-Hydroxy-2-styrylchromone	497595	C1=CC=C(C=C1)C=CC2=CC(=O)C3=C(C=CC=C3O2)O
2.	Tricin	5281702	COC1=CC(=CC(=C1O)OC)C2=CC(=O)C3=C(C=C(C=C3O2)O)O
3.	5,7-Dihydroxy-8-methoxyflavone	5281703	COC1=C(C=C(C2=C1OC(=CC2=O)C3=CC=CC=C3)O)O
4.	Jaceidin	5464461	COC1=C(C=CC(=C1)C2=C(C(=O)C3=C(O2)C=C(C(=C3O)OC)O)OC)O
5.	Caryatin	5489501	COC1=CC(=CC2=C1C(=O)C(=C(O2)C3=CC(=C(C=C3)O)O)OC)O

3.2. Characteristics of druglikeness in *I. cylindrica* flavonoid compounds

Drug-likeness is a parameter used in the preparation of compounds before molecular docking to assess the feasibility of a compound as a drug candidate (Jia et al., 2020). This assessment includes an evaluation based on the Lipinski rules, which include molecular weight, lipophilicity (log P), the number of hydrogen donors and acceptors, and other pharmacokinetic properties, such as cell membrane permeability, solubility, and stability (Suhargo et al., 2023).

The identification of flavonoid compounds in the Jhung & Shin (2021) study was conducted to look at several flavonoid compounds with antidiabetic potential. These compounds were identified based on the Simplified Molecular Input Line Entry System (SMILES) variations used as compounds shown in **Table 1**. Some of these compounds met the drug-likeness characteristics based on Lipinski's Rule of Five (RO5) (**Table 2**). In addition, druglikeness also ensures that the compound has low toxicity potential, making it safer to develop. Thus, compounds that meet the druglikeness criteria are predicted to be more likely to interact with the target protein and provide relevant results in molecular docking tests (Zhu et al., 2023).

Table 2. Druglikeness results based on Lipinski's Rules of Five (RO5)

Compounds	Molecular weight (g/mol)	H-bond acceptor (<10)	H-bond donor (<5)	LogP (<5)	Molar Refractivity (40-130)
5-Hydroxy-2-styrylchromone	264.28	3	1	2.90	79.88
Tricin	330.29	7	3	2.58	86.97
5,7-Dihydroxy-8-methoxyflavone	284.26	5	2	2.55	78.46
Jaceidin	360.31	8	3	3.07	93.47
Caryatin	330.29	7	3	1.99	86.97

3.3. Molecular docking simulation

In this study, molecular docking was employed to identify ligand interactions with receptor molecules. The affinity binding value was determined, and a comparison was made with the affinity binding results of generic diabetes drugs (Jia et al., 2020). It has been demonstrated that the magnitude of the standard free energy

charge value is directly proportional to the extent of the ligand's binding affinity to the receptor. Residual interactions have been demonstrated to reveal the specific binding of the ligand to certain amino acids of the protein (Paggi et al., 2024).

The addition of a control test for comparison, namely a generic drug for diabetes whose interaction with the target protein (DPP-4) will be examined, is vildagliptin (Pariyar et al., 2022). Receptor preparation entails the removal of water molecules not associated with the active site, regeneration of the original status, and addition of hydrogen atoms (Pavlovicz et al., 2020). The most accurate method for evaluating the accuracy of the docking procedure is to determine the proximity of the lowest-energy pose predicted by the object scoring function (Jakhar et al., 2020). The calculation of results is contingent upon three parameters: The following three factors must be considered: G score, H-bond energy, and residual interaction. These parameters form the basis of ligand affinity binding to the binding receptors (Raval & Ganatra, 2022).

Table 3. The result of molecular docking of *I. cylindrica* leaf extract compound with DPP-4 target protein

Compounds	Binding Affinity (Kcal/mol)
5-Hydroxy-2-styrylchromone	-7.8
Tricin	-8.4
5,7-Dihydroxy-8-methoxyflavone	-7.8
Jaceidin	-7.4
Caryatin	-7.6
Vildagliptin (control)	-7.8

The phytochemicals derived from the leaf extract of *I. cylindrica* were analyzed by comparing their binding affinities to the receptor (**Table 3**). The type of bond that occurred in **Table 4**, and the visualization of the bond formed in **Table 5**. **Table 3** shows that tricin has a high affinity binding value of -8.4 kcal/mol, which identifies it as a strong candidate for a strong antidiabetic target. In confirming the potential of the flavonoid compound from the extract of *I. cylindrica* leaves with the generic drug vildagliptin, which is docked with the DPP-4 receptor, the affinity binding result is -7.8 kcal/mol **Table 3**. From the five types of flavonoid compounds reported in the literature review by Jung and Shin (2021), namely 5-hydroxy-2-styrylchromone, tricin, 5,7-dihydroxy-8-methoxyflavone, jaceidin, and caryatin. Docking has been carried out which shows that the tricin compound has potential for affinity binding to the DPP-4 receptor. The DPP-4 receptor itself is a proteolytic enzyme that is on the surface of a cell, so with the presence of an inhibitor of this enzyme, it is hoped that it can maintain glucose balance by inactivating incretin proteolytic enzymes, which will then increase its tolerance to glucose and the function of islet cells in the pancreas of people with diabetes (Rendi et al., 2021). In addition, the use of DPP-4 receptors is chosen because DPP-4 is one of the pathogenesis of diabetes mellitus type 2, so it is important to design drugs that will be used by inhibiting the performance of DPP-4 to increase insulin secretion and restore normal glucose metabolism (Deacon, 2020).

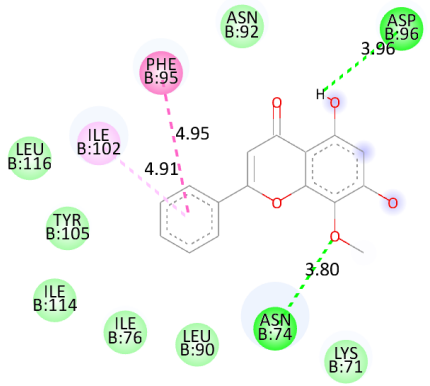
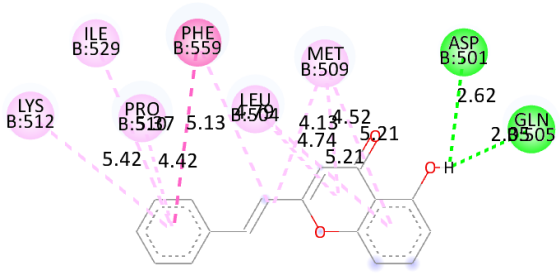
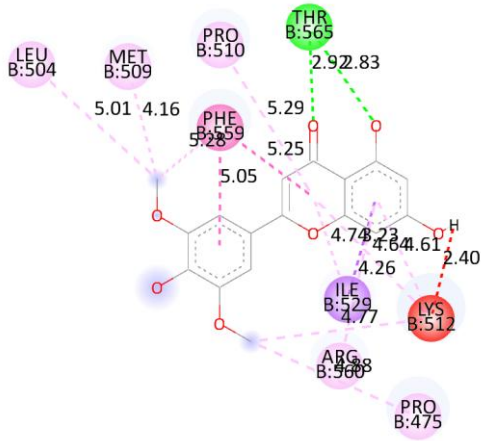
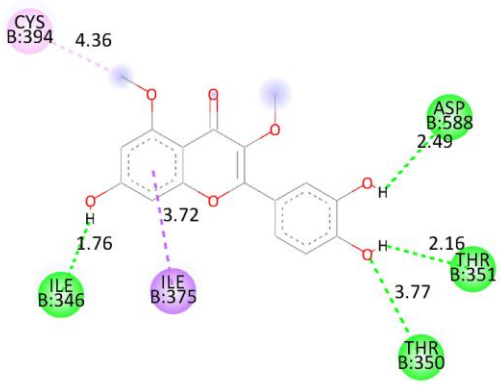
3.4. Ligand-protein interaction and Network Pharmacology Analysis

All selected compounds were evaluated for their potential to interact with Dipeptidyl Peptidase-4 (DPP-4), a serine protease responsible for the degradation of incretin hormones, such as GLP-1. Inhibition of DPP-4 prolongs incretin activity, thereby enhancing insulin secretion, reducing glucagon release, and contributing to improved glycemic control in individuals with type 2 diabetes mellitus (Florentin et al., 2022; Stoian et al., 2020). Based on the molecular docking results, all compounds demonstrated a favorable binding affinity toward the active site of DPP-4, indicating their potential inhibitory roles.

To further explore the interaction profile, visualization was performed using Discovery Studio 2021, which allowed the identification of amino acid residues involved in ligand–receptor binding. The analysis revealed that these flavonoids formed various molecular interactions with DPP-4 residues, including hydrogen bonding, hydrophobic contacts, and electrostatic interactions. These binding interactions are crucial, as the active site of DPP-4 is known to undergo conformational changes upon ligand attachment, which in turn may affect enzymatic function (Gu et al., 2021). The identification of specific residues at the binding site also supports the mechanistic plausibility of DPP-4 inhibition through direct molecular contact (Ji et al., 2020). Although direct experimental validation of these specific compounds remains limited, their structural similarities to known DPP-4 inhibitors suggest that these ligands may exert antidiabetic effects by modulating the incretin pathway and suppressing postprandial hyperglycemia.

Visualization in **Table 4**, shows the similarity of the binding structure with the comparator drug vildagliptin, namely the tricin compound, which means that the molecules in the compound and the peptide show inhibition activity on the DPP-4 receptor *in vitro* by binding to the active side or the allosteric side of the protein (Sun et al., 2020). **Table 5** shows that the hydrogen bond formed between vildagliptin and the tricin compound is one bond with the amino acid residue in tricin, namely GluB91, against vildagliptin. The bond formed is also hydrophobic, which is an essential bond in the process of combining the nonpolar region of the drug molecule with the nonpolar region of the biological receptor. In this case, the nonpolar part of the drug molecule, which cannot dissolve in water, will combine with the surrounding water molecules through hydrophobic bonds to form a quasi-crystalline structure. This hydrophobic bond plays a pivotal role in determining the strength of the bond between the protein and ligand (Chen et al., 2020).

Table 4. Visualization of the bond between the compound of *I. cylindrica* leaf extract and the target protein DPP-4

Compounds	Visualization
5,7-Dihydroxy-8-methoxyflavone	
5-Hydroxy-2-styrylchromone	
Tricin	
Caryatin	

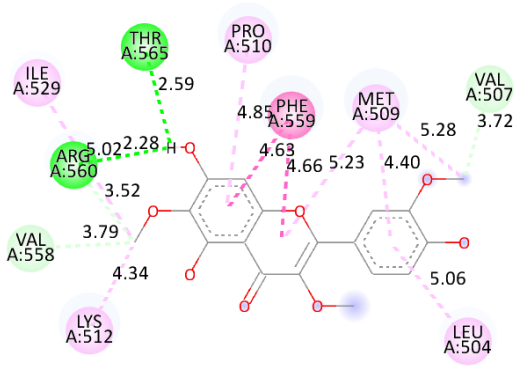
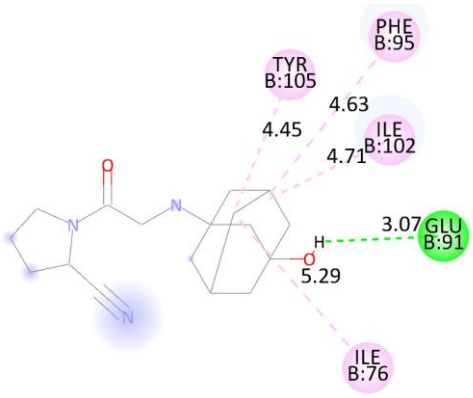
Compounds	Visualization
Jaceidin	
Vildagliptin (Control)	

Table 5. The type of bond formed between the compound of *I. cylindrica* leaf extract and the target protein DPP-4

Compounds	Amino Acid Residue		Type of Bond Formed
5,7-Dihydroxy-8-methoxyflavone	ASN	B:74	Hydrogen
	ASP	B:96	
	PHE	B:95	Hydrophobic
	ILE	B:102	
5-Hydroxy-2-styrylchromone	ASP	B:501	Hydrogen
	GLN	B:505	
	LEU	B:504	Hydrophobic
	MET	B:509	
	PHE	B:559	
	PRO	B:510	
	ILE	B:529	
	LYS	B:512	
Tricin	THR	B:565	Hydrogen
	LEU	B:504	Hydrophobic
	MET	B:509	
	PRO	B:510	
	PHE	B:559	
	ILE	B:529	
	LYS	B:512	
	ARG	B:560	
	PRO	B:475	
Caryatin	ILE	B:346	Hydrogen
	ASP	B:588	
	THR	B:350	
	THR	B:351	
	CYS	B:394	Hydrophobic

Compounds	Amino Acid Residue		Type of Bond Formed
	ILE	B:375	
Jaceidin	THR	A:565	Hydrogen
	ARG	A:560	
	VAL	A:507	
	VAL	A558	
	ILE	A:529	Hydrophobic
	PRO	A:510	
	PHE	A:559	
	MET	A:509	
	LYS	A:512	
	LEU	A:504	
Vildagliptin (control)	GLU	B:91	Hydrogen
	TYR	B:105	Hydrophobic
	PHE	B:95	
	ILE	B:102	
	ILE	B:76	

The molecular docking results indicate that the tricin compound exhibits the strongest binding affinity and approaches the binding affinity of the natural ligand, vildagliptin. The condition is influenced by the presence of two residues, ILEB102 and ILEB76, in the hydrophobic interaction between tricin and vildagliptin, along with ILEB529. In contrast, the different hydrophobic bonds with vildagliptin produced by tricin are amino acid residue interactions that are made possible by the contact between the ligand and the DPP-IV receptor to have inhibitory activity (Yang et al., 2020). A comparison of the results of the affinity binding of vildagliptin with five test compounds reveals that the tricin compound has the greatest potential as an antidiabetic drug candidate compared to the other test compounds because it has the closest affinity bond to the vildagliptin affinity bond. To further elucidate the mechanism of action of tricin as a potential DPP-4 inhibitor, network pharmacology analysis was conducted using Cytoscape, revealing that tricin may influence not only DPP-4 directly but also a network of related proteins such as GLP1R, GIP, ACE2, ADA, and GCG (**Figure 1**). These proteins are involved in key biological pathways associated with glycemic regulation, including incretin signaling, glucose homeostasis, and vascular functions. Inhibition of DPP-4 by tricin is expected to prolong the activity of GLP-1 and GIP, enhancing insulin secretion and reducing postprandial glucose levels (Hira et al., 2021). The indirect modulation of additional proteins further supports tricin's role in improving metabolic balance and preventing diabetic complications, highlighting its potential for multi-targeted antidiabetic activity. However, further examination is necessary to ascertain whether the compound has the potential to serve as an antidiabetic drug candidate, which would involve conducting *in vitro*, *in vivo*, and clinical trials.

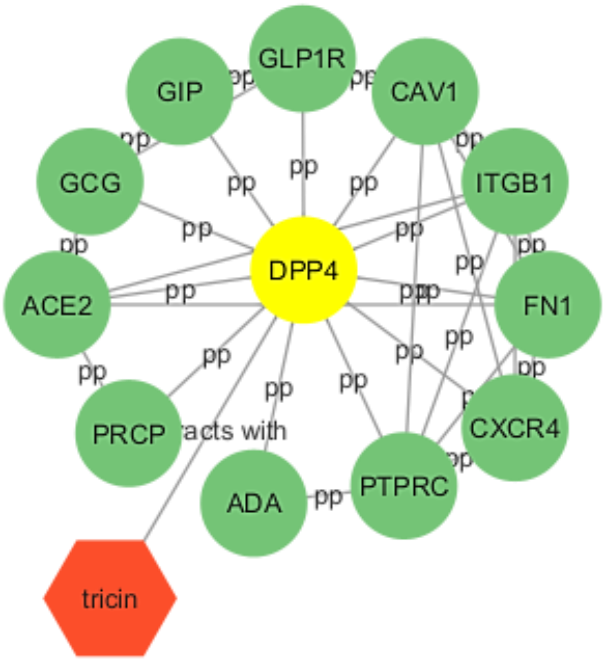


Figure 1. Interaction of the tricin compound (red) with the direct target protein DPP-4 (yellow) and indirect interaction between DPP-4 and other proteins (green)

4. CONCLUSION

Based on the results of the research conducted, it can be concluded that the flavonoid derivative tricin, found in the extract of *I. cylindrica* leaves, shows potential as a candidate for a type 2 antidiabetic drug to replace vildagliptin. This potential is indicated by its mechanism of action as an inhibitor of the DPP-4 protein receptor, with a binding affinity score of − 8.4 kcal/mol. However, these findings require further validation through *in vitro* and *in vivo* studies to strengthen the evidence for the antidiabetic potential of *I. cylindrica*.

AUTHOR CONTRIBUTIONS

M.R.A. and R.A.S.; conceptualization, writing, and original draft preparation, M.R.A.; designed the methodology, prepared the sample and software, and visualization data, A.R.M.A.; review, editing, and project administration. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable. The research did not require ethical approval because the study did not involve humans or animals.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ROLE OF FUNDERS

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

The authors declare that no generative AI or AI-assisted technologies were used in the preparation or writing of this manuscript. All contents were produced entirely by the authors without any automated assistance.

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