Investigating Palmatine's inhibitory mechanism on type 2 diabetes via molecular docking

Do Thi Hang[1], Tran Hoang Mai[2], Nguyen Thi Phuong[2], Bui Thanh Tung[3*]

[1]*Phuc Yen Regional General Hospital, Phuc Yen Ward, Phu Tho Province, Vietnam*
[2]*University of Medicine and Pharmacy, Vietnam National University - Hanoi, 144 Xuan Thuy Street, Cau Giay Ward, Hanoi, Vietnam*
[3]*Faculty of Medicine and Pharmacy, Academy of Security Engineering and Technology, Thuan Thanh Ward, Bac Ninh Province, Vietnam*

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Abstract:

Type 2 diabetes mellitus (T2DM) is the most common form, accounting for more than 90% of all individuals with diabetes worldwide. Currently, T2DM is on the rise and is increasingly affecting younger individuals, becoming a serious public health issue. Palmatine is a natural isoquinoline alkaloid belonging to the protoberberine group. The purpose of this study was to evaluate the anti-diabetic properties of Palmatine through molecular docking with several protein targets related to T2DM, such as α-amylase, pyruvate dehydrogenase kinase 4 (PDK4), α-glucosidase, protein tyrosine phosphatase 1B (PTP1B), aldose reductase (AKR1B1), and 11β-hydroxysteroid dehydrogenase (11β-HSD1). Lipinski's rule of five was employed to assess the drug-like characteristics of Palmatine. The pharmacokinetic properties of Palmatine were evaluated using the pkCSM tool, which aids in predicting its absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile. The oral bioavailability of Palmatine was assessed using the SwissADME tool. The results indicated that Palmatine inhibits 11β-HSD1 with the lowest binding energy (-8.4 kcal/mol). According to Lipinski's analysis, Palmatine exhibits properties consistent with drug-like behaviour. The predicted pharmacokinetic parameters suggest that this compound possesses excellent intestinal absorption. Furthermore, Palmatine demonstrated favourable oral bioavailability. Consequently, additional *in vitro* and *in vivo* research is necessary to further explore the potential of this compound as a future treatment for diabetes.

Keywords: **molecular docking, palmatine, protein tyrosine phosphatase 1B, pyruvate dehydrogenase kinase 4, type 2 diabetes, 11β-hydroxysteroid dehydrogenase.**

Classification numbers: **3.2, 3.3, 3.6**

1. Introduction

As reported by the International Diabetes Federation (IDF), approximately 537 million individuals were living with diabetes globally in 2021. This figure is projected to rise to 643 million by 2030 and 783 million by 2045. Type 2 diabetes mellitus (T2DM) is the most prevalent form, accounting for over 90% of all diabetes cases worldwide [1]. The condition is marked by a relative deficiency of insulin, resulting from pancreatic β-cell dysfunction, along with insulin resistance in various organs, which can lead to dangerous chronic complications such as cardiovascular, kidney and eye diseases [2, 3]. Currently, T2DM is on the rise and is increasingly affecting younger individuals, becoming a serious public health problem. Presently, approaches such as metabolic surgery, pharmaceuticals, and lifestyle adjustments are utilised to manage and prevent the disease [4]. Nevertheless, the limited effectiveness and adverse effects of existing medications emphasise a pressing need for new and enhanced treatment alternatives. T2DM exhibits a complex pathophysiological process driven by the coordinated interaction of multiple factors, contributing to disease progression. Therefore, targeting various proteins within the T2DM pathway is crucial [5].

Palmatine is a natural isoquinoline alkaloid of the protoberberine group, with a structure similar to that of berberine, and is found in all berberine-containing plants, albeit in much lower concentrations [6, 7]. In traditional medicine, this substance has been used to treat jaundice, liver diseases, hypertension, inflammation, and dysentery [8]. Numerous studies indicate that Palmatine has anti-cancer, antioxidant, anti-inflammatory, neuroprotective, antibacterial, and antiviral effects [6]. Furthermore, this substance also acts as an agent against metabolic syndrome and its related complications through its antioxidant and anti-inflammatory properties [9].

Corresponding author: Email: tungasia82@gmail.com

Pancreatic α-amylase hydrolyses carbohydrates into oligosaccharides [10, 11]. These oligosaccharides are subsequently broken down into glucose by α-glucosidase. Once released, glucose molecules are absorbed into the bloodstream, leading to an increase in blood sugar levels [12]. Inhibiting α-amylase and α-glucosidase helps to reduce the rate of starch hydrolysis and prevents sudden increases in glucose levels, thereby mitigating postprandial hyperglycaemia. Consequently, these two targets are crucial in the treatment of T2DM. Pyruvate dehydrogenase kinase (PDK) is a potential therapeutic target due to its increased expression in disease states such as diabetes, cancer, and heart failure [13]. Among the PDK isoforms, PDK4 is predominantly produced in muscle and heart tissues in diabetes induced by streptozotocin. In mice lacking hepatic insulin receptor substrates, the deletion of the *Pdk4* gene improves glycaemic control and glucose tolerance [14, 15]. Protein tyrosine phosphatase 1B (PTP1B) reduces insulin phosphorylation, leading to insulin resistance in tissues [16]. During chronic hyperglycaemia, elevated blood glucose concentrations increase flux through the polyol pathway. Aldose reductase (AKR1B1), the first enzyme in the polyol pathway, plays a significant role in the development of microvascular complications in diabetes [17]. The enzyme 11β-Hydroxysteroid dehydrogenase (11β-HSD1) converts cortisone into cortisol [18]. Inhibiting 11β-HSD1 may aid in the treatment of glucocorticoid-related diseases, including diabetes [19]. As a result, the aforementioned targets are essential in the mechanism of T2DM.

Molecular docking is a computational technique used to predict the most favourable positions and orientations in which a ligand can bind to a target protein [20]. Therefore, this study evaluates the ability of Palmatine to inhibit type 2 diabetes-related protein targets, such as α-amylase, PDK4, α-glucosidase, PTP1B, AKR1B1, and 11β-HSD1 through molecular docking.

2. Materials and methods

2.1. Materials

Preparing protein structures: The structures of pancreatic α-amylase (PDB ID: 2QV4), PDK4 (PDB ID: 3D2R), α-glucosidase (PDB ID: 3W37), PTP1B (PDB ID: 2QBS), AKR1B1 (PDB ID: 3G5E), and 11β-HSD1 (PDB ID: 2ILT) were downloaded from a protein data bank (https://www.rcsb.org/). Using Discovery Studio Visualizer 2021, co-crystal and water molecules were eliminated. Next, hydrogen atoms were introduced to the protein, followed by the calculation of Kollman charges and the reconstruction of the active site through MGL Autodock Tools 1.5.6. The selection of reference grid box parameters was based on previously published studies in Web of Science- and Scopus-indexed journals (Table 1) [21-26]. Finally, these proteins were saved in *.pdbqt format to prepare for the docking process.

Preparation of ligands: The 3D structures of Palmatine and the positive controls (Acarbose, PDK4-IN-1, Metformin, Epalrestat, INCB-13739) were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). These compounds were saved in *.sdf format and converted to *.pdb format using Discovery Studio Visualizer 2021 software before being optimised by Avogadro software using the Conjugate Gradient method. Eventually, the ligands were converted to *.pdbqt format using Autodock Tools software.

2.2. Methods

2.2.1. Molecular docking

Molecular docking: The ligands were docked into the active sites of six target proteins utilising Autodock Vina. Interaction energies between ligands and proteins were calculated through Autodock Vina's scoring function. Molecular interactions for compounds with favourable free binding energies were visualised using Discovery Studio Visualizer 2021.

Table 1. Grid box parameters of target proteins.

Target	Protein Data Bank ID	Grid size	Grid spacing	Grid centre		
				X	*Y*	*Z*
Pancreatic α-amylase	2QV4	40x40x40	0.375	12.942	47.17	26.2
PDK4	3D2R	50x50x50	0.375	-25.0	-6.8	6.0
α-glucosidase	3W37	60x60x60	0.375	14.310	-27.101	-42.876
PTP1B	2QBS	60x60x60	0.375	46.535	16.643	5.369
AKR1B1	3G5E	22×22×32	1.000	22.0	-7.0	23.0
11β-HSD1	2ILT	60x60x60	0.375	58.957	105.209	62.493

Evaluation of docking results: To evaluate the docking results, the co-crystal ligand was re-docked into the active site of the target. The process is deemed successful when the root-mean-square deviation (RMSD) value is 1.5 Å or lower [27]. For Palmatine, binding affinity was evaluated by examining its interactions with amino acids located in the active site of the protein, while the interaction energy was determined using Autodock Vina's scoring function. Two crystallised ligands, QV4 for α-amylase (Protein Data Bank ID: 2QV4) and ADP for PDK4 (Protein Data Bank ID: 3D2R) were employed for evaluating and optimising the docking models.

2.2.2. Assessment of Lipinski's rule of five

Lipinski's rule of five was applied to assess the drug-like properties of the compound using an online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) [28, 29].

2.2.3. Estimation of pharmacokinetics and toxicological properties

The properties involving ADMET are essential for evaluating the likelihood of success of developing a new drug. These parameters of the potential compound were assessed using the pkCSM tool (https://biosig.lab.uq.edu.au/pkcsm/prediction) [30].

2.2.4. Evaluation of oral bioavailability

A bioavailability radar was utilised to assess the compound's oral bioavailability through the SwissADME tool (https://www.swissadme.ch/ index.php) [31].

2.2.5. Molecular dynamics simulation

Molecular dynamics (MD) is a technique used to analyse the physical motion of atoms at the atomic level [32]. We used Molecular Operating Environment version 2015.10 to simulate the ligand-protein complex with the least binding energy pose. The Nosé-Poincaré-Andersen (NPA) equations of motion were employed in the Molecular Operating Environment dynamics simulation. The MD default steps and protocols were chosen to optimise the system equilibrium at 600 ps and a 500 ps production run was carried out at 310 K. We determined RMSD for the entire ligand-protein complex to evaluate the overall stability of this system. RMSD was calculated as shown below:

$$\mathrm{RMSD} = \sqrt{\frac{1}{N}\sum_{i=1}^{N} di^2}$$

where di represents the distance between atom i at two different times; N is the total number of atoms in the complex.

3. Results and discussion

3.1. Results of molecular docking

Before docking, the co-crystallised ligands were re-docked into the protein's active site using Chimera software. The RMSD values for 2QV4 and 3D2R are 0.773 and 1.154 Å respectively, both of which are below the 1.5 Å threshold, indicating that the docking process is reliable (Fig. 1).

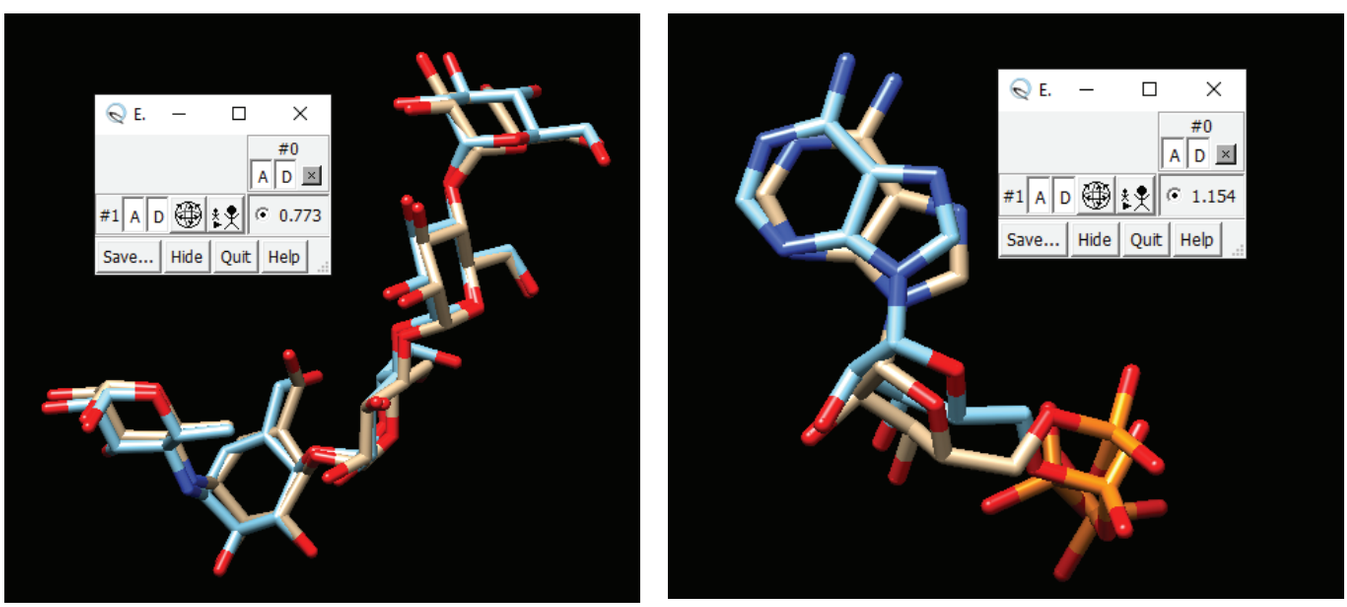

Fig. 1. Co-crystallised ligand re-docking results of 2QV4 (left) and 3D2R (right).

To study the binding ability of Palmatine to targets related to T2DM, we docked this compound with the target proteins and compared the results with positive controls (Acarbose, PDK4-IN-1, Metformin, Epalrestat, INCB-13739). Acarbose is an oral medication that inhibits α-glucosidase and α-amylase, and is used to treat T2DM [33, 34]. PDK4-IN-1 is a potent inhibitor of PDK4, which plays a role in regulating glucose metabolism. Metformin inhibits PTP1B [35]. Epalrestat, a potent inhibitor of AKR1B1, has been used for decades in Japan to treat diabetic peripheral neuropathy [36, 37]. INCB-13739 is a potential inhibitor of 11β-HSD1, which could be used in the treatment of T2DM and metabolic syndrome-related disorders [19].

Table 2. The docking results.

	Compound	PubChem ID	Binding energy (kcal/mol)					
			2QV4	*3D2R*	*3W37*	*2QBS*	*3G5E*	*2ILT*
	Palmatine	19009	-7.8	-6.6	-6.9	-6.6	-7.2	-8.4
	Acarbose	41774	-7.3		-8.1			
	PDK4-IN-1	146026196		-8.8				
+	Metformin	4091				-5.9		
	Epalrestat	1549120					-8.8	
	INCB-13739	66662059						-9.7

Table 2 shows that Palmatine exhibited binding energies of -8.4; -7.8; -7.2; -6.9; -6.6; and -6.6 kcal/mol with 2ILT; 2QV4; 3G5E; 3W37; 3D2R; and 2QBS, respectively. Among the targets, Palmatine binds to 2ILT with the lowest binding energy (-8.4 kcal/mol). When comparing the free binding energy with positive controls, Palmatine exhibited strong binding to the two targets, 2QV4 and 2QBS, with binding energies of -7.8 and -6.6 kcal/mol, respectively. These values are lower than those of the positive controls Acarbose (-7.3 kcal/mol) and Metformin (-5.9 kcal/mol). Binding energy (kcal/mol) serves as an indicator of the binding affinity between different ligands or inhibitors and their corresponding proteins. A lower interaction energy indicates a stronger affinity of the ligand towards the receptor protein. Therefore, the ligand demonstrating the highest affinity may be regarded as a promising candidate for further investigation.

The ligand-amino acid interactions between Palmatine and the six proteins (Fig. 2) show that this compound primarily interacts through alkyl interactions.

The protein-ligand interactions of Palmatine with the respective targets indicated that this substance interacts with numerous amino acids in the active site of the protein, similar to the positive controls. In the 2ILT protein, Palmatine interacts with the amino acids ILE121 and ALA223 via alkyl and pi-alkyl bonds, similar to the positive control INCB-13739. Additionally, Palmatine inhibited 3G5E through interactions with the same amino acids as the positive control Epalrestat, specifically TRP111 and CYS298, via hydrogen bonding. Furthermore, Palmatine forms alkyl bonds with several other amino acids of the respective target proteins. Inhibiting 11β-HSD1 (ID: 2ILT) aids in managing susceptibility to glucocorticoid-related diseases, such as obesity, diabetes, wound healing, and muscle wasting [38]. Conversely, aldose reductase serves as the rate-limiting enzyme in the polyol pathway, facilitating the conversion of excess D-glucose to D-sorbitol, with nicotinamide adenine dinucleotide phosphate acting as a cofactor. This enzyme is essential in the progression of microvascular complications associated with diabetes [39].

Palmatine has been reported to exhibit potent antidiabetic and antioxidant effects in both *in vitro* and *in vivo* studies. *In vitro*, it has been identified as an effective inhibitor of α-amylase, α-glucosidase, and DPP-IV, enzymes involved in postprandial glucose metabolism, thereby contributing to lower blood glucose levels [40]. Specifically, binding energy values of -6.4 and -7.8 kcal/mol for α-amylase and α-glucosidase, respectively, were reported, consistent with our findings. However, our study provides further insights, revealing that Palmatine interacts with amino acid residues of α-amylase, such as TRP59, HIS305, TRP58, HIS299, and TYR62, compared to the limited interaction with TRP59 and TYR62 described in P. Okechukwu, et al. (2020) [40]'s research. Moreover, Palmatine also upregulates the expression of key genes involved in glucose metabolism, including IRS-1, PI3K, AKT2, and GLUT4, while simultaneously downregulating PKC expression, effectively reducing blood glucose levels [41]. Our results align with these observations, demonstrating that Palmatine inhibits the enzymes PTP1B and 11β-HSD1, leading to enhanced insulin signalling via the activation of the PI3K/AKT/GLUT4

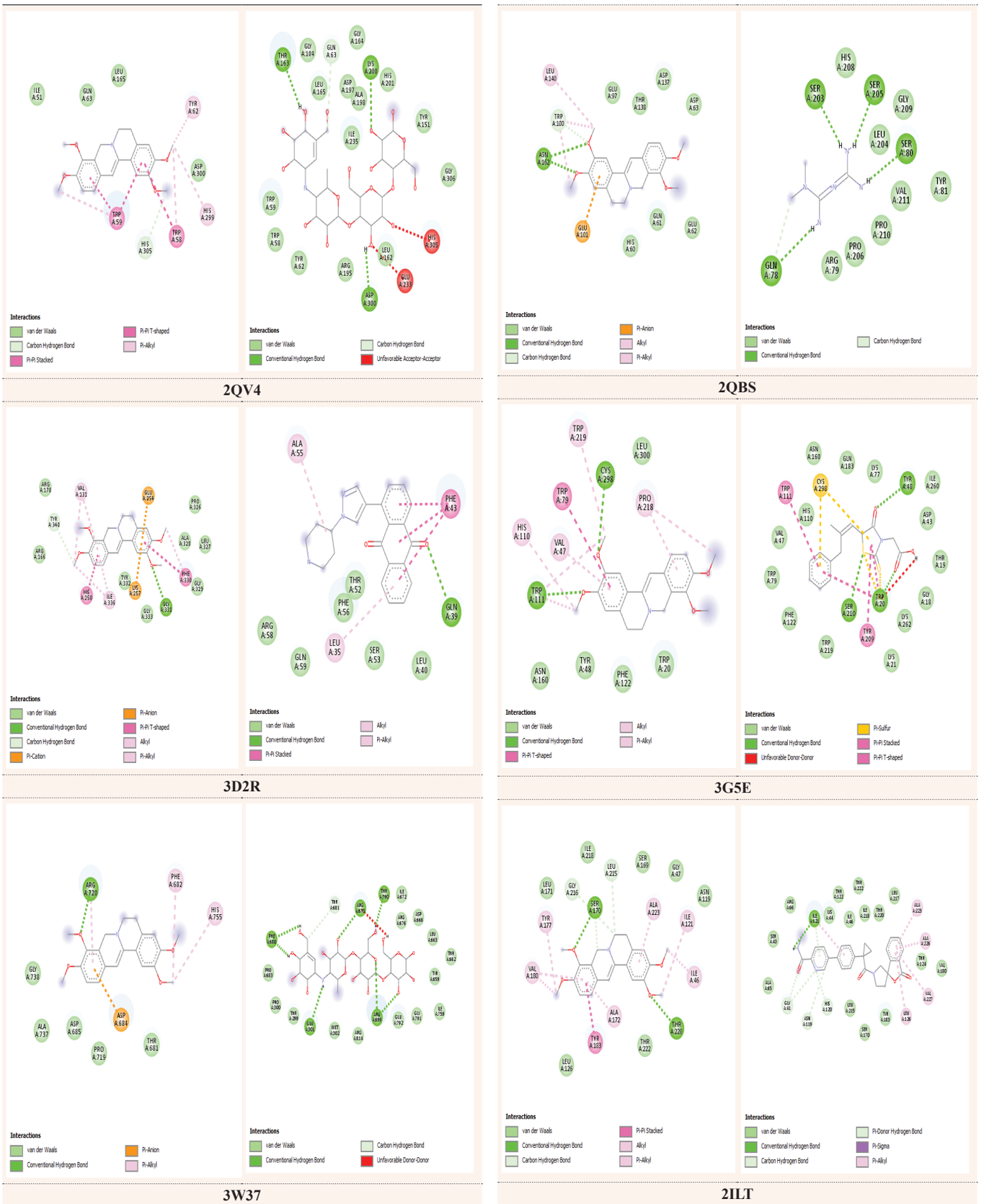

Fig. 2. Interaction of Palmatine (left) and positive controls (right) with their respective targets.

pathway. Additionally, an in vivo study by S.O. Ekeuku, et al. (2015) [42] further supports the therapeutic potential of Palmatine, showing its ability to improve blood glucose levels and reduce oxidative stress. Therefore, these findings underscore Palmatine's potential as an antidiabetic agent.

3.2. Results of Lipinski's rule of five

To be classified as "drug-like", compounds must satisfy at least two of the five conditions specified in Lipinski's rule of five: (1) Molecular weight must be below 500 Daltons; (2) Significant lipophilicity (LogP must not exceed 5); (3) No more than five hydrogen bond donors; (4) No more than ten hydrogen bond acceptors; (5) Molar refractivity should fall between 40 and 130. The results for Palmatine in relation to Lipinski's rule of five are presented in Table 3. Subsequently, Palmatine was further evaluated for its pharmacokinetic and toxicological (ADMET) properties.

Table 3. Results of Lipinski's rule of five.

Compound	Molecular weight	Donors of hydrogen bonding (HBD)	Acceptors of hydrogen bonding (HBA)	logP	Molar refractivity (MR)	Drug-likeness
Palmatine	352.40	0	4	3.3848	101.80	Yes

3.3. Prediction of absorption, distribution, metabolism, excretion, and toxicity

The ADMET prediction results, which include absorption, distribution, metabolism, elimination, and toxicity processes, are summarised in Table 4.

Table 4. Predicted outcomes for pharmacokinetics and toxicity.

Properties		Results
Absorption	Water solubility (log mol/l)	-4.194
	Caco2 permeability (log P_{app} in 10^{-6} cm/s)	0.863
	Human intestinal absorption (%)	97.084
Distribution	VDss (log l/kg)	0.641
	BBB permeability (log BB)	-0.112
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	Yes
	CYP2D6 inhibitor	Yes
	CYP3A4 inhibitor	No
Excretion	Total clearance (log ml/min/kg)	1.246
Toxicity	AMES toxicity	Yes
	Hepatotoxicity	Yes
	Skin sensitisation	No

The absorption capability of the compounds is assessed according to three criteria: water solubility, permeability across the Caco2 membrane, and proportion of intestinal drug absorption. According to Table 4, the compounds exhibit relatively poor water solubility, with a molar concentration of approximately 10^{-4} mol/l. Transmembrane permeability via Caco2 cells (log Papp in 10^{-6} cm/s) is deemed good if it exceeds 0.9; however, Palmatine shows moderate permeability with a log Papp value of 0.863 in 10^{-6} cm/s. In addition, Palmatine reveals high absorption in the intestine, achieving a value of 97.084%.

Regarding distribution, compounds are considered to be effectively distributed to tissues if the log volume of distribution at steady state (log VDss) is greater than 0.45 [43]. A higher VDss indicates that a drug is more extensively distributed into tissues rather than remaining in plasma. Palmatine demonstrates a favourable tissue distribution with a log VDss value of 0.641. The ability of a drug to cross the blood-brain barrier is another important factor, as it can reduce toxicity and side effects or enhance the efficacy of drugs that act on the brain. Compounds are considered capable of crossing the blood-brain barrier if their log BB value exceeds 0.3. However, Palmatine does not cross this barrier, as indicated by its log BB value of -0.112.

With respect to metabolism, the Cytochrome P450 system, which plays a key role in hepatic drug metabolism, can be significantly altered by P450 inhibitors. CYP2D6 and CYP3A4 are the two key polymorphisms of Cytochrome P450 associated with drug metabolism. Metabolic analysis of Palmatine indicates that it is a substrate of CYP3A4.

Regarding excretion, Palmatine may be eliminated via the kidneys, with a total clearance rate of 1.246 (log ml/min/kg). A high clearance rate suggests effective removal from the body.

Concerning toxicity, Palmatine does not induce skin sensitisation; however, it does cause AMES toxicity and liver toxicity.

3.4. Evaluation of oral bioavailability

In the context of efficacy and toxicity, low bioavailability is frequently identified as a major factor contributing to failures in drug development, with oral administration being the most common delivery method. To evaluate oral bioavailability, the Radar plot incorporates six key physicochemical properties: lipophilicity, molecular size, polarity, solubility, flexibility, and saturation. The acceptable ranges for these properties are outlined in Table 5.

Table 5. The specific range of six physicochemical parameters.

Properties	Range
LIPO (Lipophility)	-0.7<XLOGP3<+5.0
SIZE	150 g/mol<MV<500 g/mol
POLAR (Polarity)	20Å²<TPSA<130Å²
INSOLU (Insolubility)	-6<Log S (ESOL)<0
INSATU (Insaturation)	0.25<Fraction Csp3<1
FLEX (Flexibility)	0<Num.rotatable bonds<9

The pink region signifies the ideal range for each characteristic. To be considered drug-like, a compound must exhibit all six physicochemical properties within this pink region (Fig. 3).

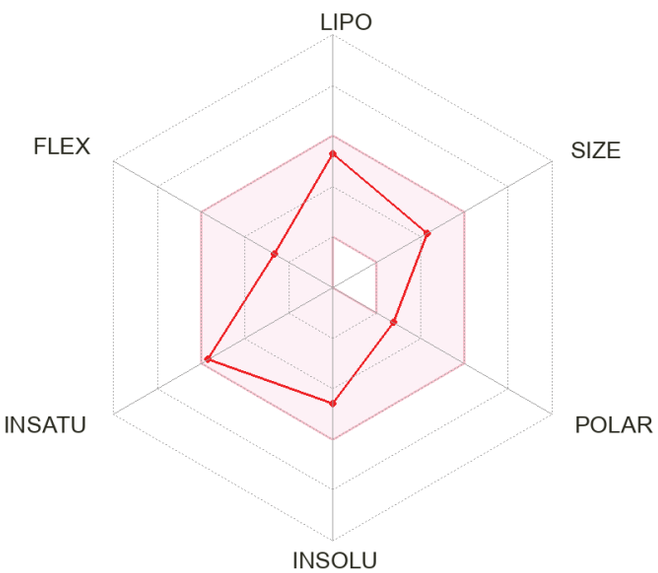

Fig. 3. Bioavailability radar.

Palmatine meets the criteria outlined in the radar chart, indicating its potential for oral bioavailability. Our study demonstrated that Palmatine may inhibit these enzymes including amylase, PDK4, α-glucosidase, PTP1B, AKR1B1, and 11β-HSD1, which may contribute to its anti-diabetic activity. Our study is consistent with previous research findings. X. Tian, et al. (2020) [44] demonstrated that Palmatine can mitigate impaired glucose tolerance and enhance insulin resistance in diabetes rats with a high-fat diet. Additionally, Palmatine improved the function of pancreatic islets, significantly increasing the mass of β cells. Their research revealed that Palmatine could reduce β cell apoptosis, which is a key factor in the loss of β cell mass in the models of impaired glucose tolerance. Furthermore, Palmatine influenced the Mitogen-activated protein kinase (MAPK) signalling pathway by inhibiting the ERK and JNK cascades [44]. P. Okechukwu, et al. (2020) [40] demonstrated that Palmatine can inhibit the enzymes alpha-amylase, alpha-glucosidase, and dipeptidyl peptidase-IV (DPP-IV) *in vitro* with IC50 values of 1.31, 9.39, and 8.7 µM, respectively. P.N. Okechukwu, et al. (2021) [45] demonstrated that Palmatine decreased the expression of chaperone proteins CALR and GRP78. It also increased the expression of peroxiredoxin 4, protein disulfide isomerase (PDIA2/3), glutathione-S-transferase, and serum albumin in diabetic Sprague Dawley rats. Moreover, this compound also showed the activated antioxidant protein ability, by protecting cells against reactive oxygen species and endoplasmic reticulum stress. S.O. Ekeuku, et al. (2015) [42] demonstrated that administering Palmatine at a dose of 2 mg/kg body weight for 90 days significantly decreased blood plasma glucose levels and lipid peroxidation in a streptozotocin-induced diabetic rat model, compared to the positive control, Tolbutamide.

3.5. Molecular dynamics results

Based on docking results, Palmatine demonstrated the strongest binding affinity with the two proteins 2ILT (-8.4 kcal/mol) and 2QV4 (-7.8 kcal/mol). However, its docking score with 2QV4 is lower than that of the positive control, Acarbose (-7.3 kcal/mol), suggesting that Palmatine could be a potential 2QV4 inhibitor. Therefore, we selected these two targets for molecular dynamics evaluation. The RMSD and free energy of the complexes are presented in the Figs. 4 and 5.

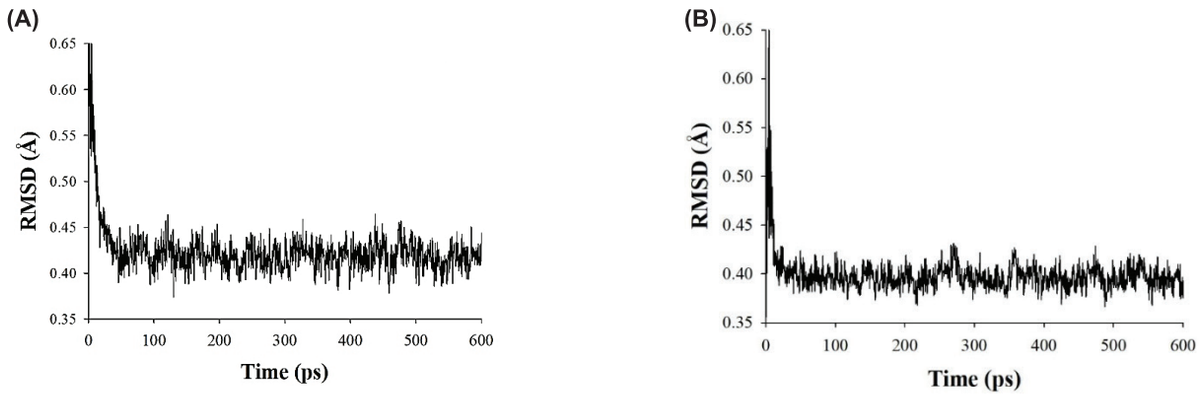

Fig. 4. Root-mean-square deviation of 2ILT - Palmatine complex (A) and 2QV4 - Palmatine complex (B) during 600 ps of molecular dynamics simulation.

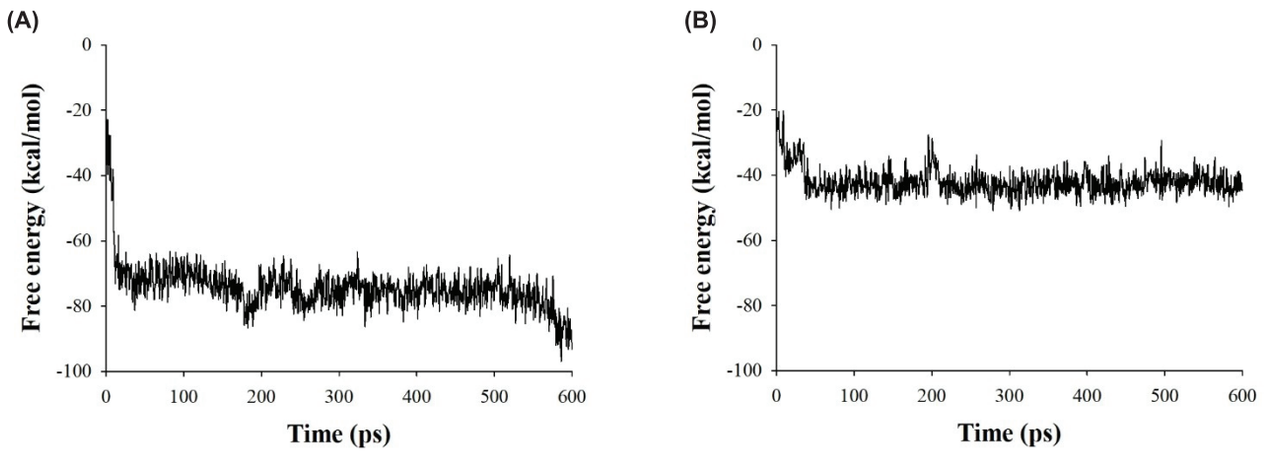

Fig. 5. Free energy of 2ILT - Palmatine complex (A) and 2QV4 - Palmatine complex (B) during 600 ps of molecular dynamics simulation.

The molecular dynamics simulation results of both complexes demonstrated stability, with the free energy reaching equilibrium. The RMSD values of the complexes quickly stabilised at 0.4-0.45 Å after approximately 50 ps for the 2ILT-Palmatine complex and at 0.38-0.42 Å after about 30 ps for the 2QV4-Palmatine complex, respectively. This indicates that the overall structure of both complexes maintained stability throughout the 600 ps simulation period. Although the 2ILT-Palmatine complex exhibited stronger fluctuations, it displayed lower binding free energy, suggesting that it binds more readily compared to the 2QV4-Palmatine complex. This finding is fully consistent with the docking results presented above, which demonstrated that the binding free energy of Palmatine with 2ILT is lower than that with 2QV4. However, to draw more accurate conclusions, further evaluations of the stability of these complexes over a longer simulation period are necessary.

4. Conclusions

This research employs virtual screening through molecular docking to identify potential targets for diabetes therapy. The docking scores of Palmatine ranged from -8.4 to -6.6 kcal/mol across several key synthetic pathways involved in diabetes. Among these, Palmatine exhibited the strongest inhibitory activity against 11β-HSD1, with the lowest binding energy recorded at -8.4 kcal/mol. The results indicate that Palmatine is an effective inhibitor, binding well to various targets related to type 2 diabetes. Furthermore, this compound demonstrates drug-like properties, as it meets the criteria of Lipinski's rule of five, and the predicted ADMET results suggest good absorption, acceptable oral bioavailability, but indicate potential genotoxicity and hepatotoxicity that warrant further investigation. In addition, the results of molecular dynamics simulations of the

Palmatine-target complexes are quite stable. Consequently, further *in vitro* and *in vivo* research is necessary to advance the development of this promising compound as a treatment for diabetes.

CRediT author statement

Do Thi Hang: Resources, Literature search, Writing; Tran Hoang Mai: Investigation, Methodology, Software, Writing; Nguyen Thi Phuong: Software, Validation; Bui Thanh Tung: Conceptualisation, Design, Supervision, Critical reviews.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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