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Original Article

Mechanism of Inhibitory Effects of Phellodendrine on Diabetes Mellitus Using Molecular Docking Method

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Abstract: Diabetes mellitus is a common non-communicable disease globally, one of the leading causes of cardiovascular mortality compared to other causes. Phellodendrine is an isoquinoline alkaloid derived from the cortex of the *Phellodendron chinense* Schneid or *Phellodendron amurense* Rupr, which has therapeutic potential in diabetes mellitus. This study evaluates the inhibitory effect of phellodendrine on 10 receptors and enzymes that play an important role in the mechanism of diabetes mellitus using the molecular docking method. The 3D structures of the receptors and enzymes were obtained from the RCSB Protein Data Bank. The phellodendrine structure was obtained from the PubChem database (https://PubChem.ncbi.nlm.nih.gov/). The molecular docking screening was conducted using Autodock Vina software (https://vina.scripps.edu/). Lipinski's rule of five was used to evaluate the drug-like properties of phellodendrine. Pharmacokinetic parameters of phellodendrine were evaluated using the pkCSM tool. The oral bioavailability of phellodendrine was assessed using the SwissADME tool. The results showed that phellodendrine with PTP1B, aldose reductase, and 11β-HSD had significantly low binding energies (ΔG = -8.7 kcal/mol, -8.5 kcal/mol, and -8.4 kcal/mol, respectively). Lipinski analysis showed that phellodendrine had drug-like properties. Prediction results of pharmacokinetic parameters showed that this compound had good intestinal absorption and toxicity. In addition, phellodendrine showed an oral bioavailability response, thus phellodendrine is a potential compound that can become an antidiabetic drug.

Keywords: Diabetes Mellitus; Molecular Docking; Phellodendrine; Lipinski; ADMET.

1. Introduction

Diabetes mellitus (DM) is a chronic disease that occurs when the pancreas does not produce sufficient insulin to regulate blood glucose levels or when the body cannot effectively use the insulin it produces. According to the International Diabetes Federation (IDF) in 2021,

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approximately 537 million adults (aged 20-79) worldwide are affected by diabetes. This number is projected to rise to 643 million by 2030, accounting for 11.3% of the global population. By 2045, the number of people with diabetes is expected to increase to about 783 million, meaning that 12 out of every 100 individuals will be affected by DM [1].

The receptors and enzymes involved in the pathogenesis of diabetes mellitus (DM) include α-amylase (AA), α-glucosidase (AG), protein tyrosine phosphatase 1B (PTP1B), aldose reductase (AR), peroxisome proliferator-activated receptor-γ (PPARγ), glycogen synthase kinase-3β (GSK-3β), pyruvate dehydrogenase kinase isoforms (PDKs 1–4), glucokinase (GK), 11β-hydroxysteroid dehydrogenase (11β-HSD), and glutamine: fructose-6-phosphate amidotransferase (GFAT). Inhibition of these receptors and enzymes plays a crucial role in the treatment of DM.

The two enzymes α-amylase (AA) and α-glucosidase (AG) play a role in breaking down glycosidic bonds in starch molecules and converting carbohydrates into smaller molecular weight substances [2, 3]. Inhibiting α-glucosidase and α-amylase enzymes helps slow the breakdown of carbohydrates into glucose, thereby reducing blood glucose levels. Protein tyrosine phosphatase 1B (PTP1B), one of the central protein tyrosine phosphatases (PTPs), is a key factor in several human diseases and disorders, such as diabetes, obesity, and hematopoietic malignancies, through modulation of various signaling pathways [4]. Aldose reductase (AR) is an aldo-keto reductase that catalyzes the first step in the polyol pathway, converting glucose to sorbitol. Under normal glucose homeostasis, this pathway represents a minor glucose metabolic route operating in parallel with glycolysis [5]. It plays a crucial role in the microvascular complications of diabetes [6]. Peroxisome proliferator-activated receptor-γ (PPARγ) regulates the expression of genes involved in inflammation, redox balance, nutrient production, insulin sensitivity, and lipid and glucose metabolism. Synthetic PPARγ agonists (e.g., thiazolidinediones) are used to treat Type II diabetes and have the potential to reduce the risk of developing brain injuries, such as stroke, by mitigating the impact of comorbid conditions [7]. Glycogen synthase kinase-3 (GSK-3) is a multifunctional serine/threonine kinase found in all eukaryotic organisms. In humans, two genes encode two closely related but distinct forms of GSK-3, known as GSK-3α and GSK-3β. GSK-3β is a key enzyme that activates protein kinases and acts as a negative regulator in the control of hormonal glucose homeostasis, Wnt signaling, and the regulation of transcription factors and microtubules [8]. Pyruvate dehydrogenase kinase isoenzymes (PDKs 1–4) negatively regulate the activity of the mitochondrial pyruvate dehydrogenase complex through reversible phosphorylation. PDK isoenzymes are upregulated in obesity, diabetes, heart failure, and cancer, and are potential therapeutic targets for these significant human diseases [9]. Glucose metabolism in humans is tightly regulated by the activity of glucokinase (GK). GK is primarily produced in the pancreas to control the rate of insulin secretion and in liver cells to participate in glycogen synthesis. Numerous pathogenic mutations in the GK gene have been identified. Gain-of-function mutations manifest clinically as congenital hyperinsulinism, while loss-of-function mutations result in various forms of diabetes [10]. 11β-Hydroxysteroid dehydrogenase is an enzyme that catalyzes the conversion of inactive 11-ketosteroids into biologically active 11β-hydroxy derivatives and vice versa. Inhibition of 11β-HSD1 helps control susceptibility to diseases associated with glucocorticoids, including obesity, diabetes, wound healing, and muscle wasting [11]. Glutamine: fructose-6-phosphate amidotransferase (GFAT), also known as GFPT1 and GFAT1, catalyzes the initial step of the hexosamine biosynthesis pathway in mammals and thus plays a crucial role in type 2 diabetes [12].

This study aims to evaluate the inhibitory effects of phellodendrine on ten targets related to

the mechanisms of diabetes mellitus using the molecular docking method.

2. Materials and Methods

2.1. Materials

Preparing protein structures: The 3D structures of the following enzymes were obtained from the RCSB Protein Data Bank (https://www.rcsb.org): α-amylase (PDB ID: 2QV4) [13]; α-glucosidase (PDB ID: 3W37) [14]; protein tyrosine phosphatase 1B (PDB ID: 2QBS) [15]; aldose reductase (PDB ID: 3G5E) [16]; peroxisome proliferator-activated receptor-γ (PPARγ) (PDB ID: 3DZY) [17]; glycogen synthase kinase-3β (PDB ID: 3F7Z) [18]; pyruvate dehydrogenase kinase isoforms (PDB ID: 2BU8) [19]; glucokinase (PDB ID: 1V4S) [20]; 11β-hydroxysteroid dehydrogenase (PDB ID: 2ILT) [21]; glutamine: fructose-6-phosphate amidotransferase (PDB ID: 6SVO) [22]. Two crystallized ligands, QV4 for α-amylase (ID: 2QV4) and NAG for α-glucosidase (ID: 3W37), were used to evaluate and optimize the docking models. The active site of the proteins was identified using Discovery Studio Visualizer 4.0 software. Before docking, all protein molecules were stripped of water molecules and co-crystallized ligands using Discovery Studio Visualizer 4.0 software. Hydrogen molecules were added using Autodock Vina software before re-establishing the active site of the protein using MGL Autodock Tools 1.5.7 software. The active sites of α-amylase (AA), α-glucosidase (AG), protein tyrosine phosphatase 1B (PTP1B), aldose reductase (AR), peroxisome proliferator-activated receptor-γ (PPARγ), glycogen synthase kinase-3β (GSK-3β), pyruvate dehydrogenase kinase isoforms (PDKs 1–4), glucokinase (GK), 11β-hydroxysteroid dehydrogenase (11β-HSD), and glutamine: fructose-6-phosphate amidotransferase (GFAT) were identified in Table 1.

Table 1. The active sites of 10 important protein targets

PDB ID	Grid box size (Å)	Grid spacing	(x; y; z)
2QV4	70x70x70	0.375	(16.11; 49.57; 25.06)
3W37	60x60x70	0.375	(14.103; -27.101; -42.876)
2QBS	60x60x46	0.375	(46.535; 16.643; 5.369)
3G5E	22×22×32	1.000	(22; -7; 23)
3DZY	40x40x40	0.375	(-11; 19.5; 15)
3F7Z	40x40x40	0.375	(-0.025; 13.328; 17.837)
2BU8	50x50x50	0.375	(55.7; 46.5; 81)
1V4S	30x44x24	0.375	(40.144; 14.796; 62.039)
2ILT	60x60x60	0.375	(58.957; 105.209; 62.493)
6SVO	60x60x60	0.375	(-3.21; 50.14; -45.43)

Preparing ligand structures: The 3D structure of phellodendrine (PubChem ID: 3081405), with the IUPAC name - (7S,13aS)-3,10-dimethoxy-7-methyl-6,8,13,13a-tetrahydro-5H-isoquinolino[2,1-b]isoquinolin-7-ium-2,11-diol, was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) (accessed on: April 3rd, 2024) in sdf format and then converted to pdb format using UCSF Chimera 1.17.3 software. Subsequently, the ligands were optimized using Avogadro 1.1.0 software using the Conjugate Gradients method and then converted to pdbqt format using Autodock Tools 1.5.7 software.

2.2. Methods

Molecular docking

Performing molecular docking: The ligands were docked into the active site of the protein using Autodock Vina software. The Discovery Studio Visualizer 4.0 software was used to

observe the interactions between the protein and phellodendrine.

Evaluation of docking results: To evaluate the docking results, we redocked the co-crystallized ligands into the active site of the target. The process was considered successful if the root mean square deviation (RMSD) value was less than or equal to 1.5 Å. For phellodendrine, the binding affinity was assessed by its interaction with amino acids in the protein active site, and the interaction energy was calculated using the scoring function of Autodock Vina.

Prediction of inhibition constant calculation: Numerical and complex analyses *in silico* algorithms have been proposed to calculate inhibition constants (Ki), as Ki primarily depends on the association (or binding) constant (Kb) and the dissociation constant (Kd) of the enzyme-inhibitor complex, occurring in opposite directions (ln Kb = -ln Kd) [23].

$\Delta G = (R \times T) \ln Ki$

Therefore, Ki is calculated using the following formula:

$Ki = e^{\Delta G/(R \times T)}$

The binding energy ΔG is calculated in kcal/mol, the universal gas constant R = 1.987 kcal/mol·K, at room temperature (25 °C) T = 273 + 25 = 298 K. Ki is expressed in units of μM.

Evaluation of Lipinski's Rule of Five

Lipinski's Rule of Five criteria are used to evaluate the drug-like properties of a compound [24] using an online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) [25].

Prediction of pharmacokinetic and toxicity

The predicted results of pharmacokinetic parameters, including absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the compound, are evaluated using the pkCSM tool (https://biosig.lab.uq.edu.au/pkcsm/prediction) [26].

Evaluation of oral bioavailability

A bioavailability radar is used to evaluate the oral bioavailability of the compound using the SwissADME tool (https://www.swissadme.ch/index.php) [27].

3. Results and Discussion

3.1. Results of Molecular Docking

Before screening the compounds, the accuracy of the docking model needs to be evaluated. After redocking the co-crystallized ligands, the results yielded RMSD values of 0.721 and 0.678 Å, respectively (Figure 1). These two values satisfy the condition of RMSD being less than 1.5 Å, indicating that the molecular docking results for the targets are reliable.

(A) (B)

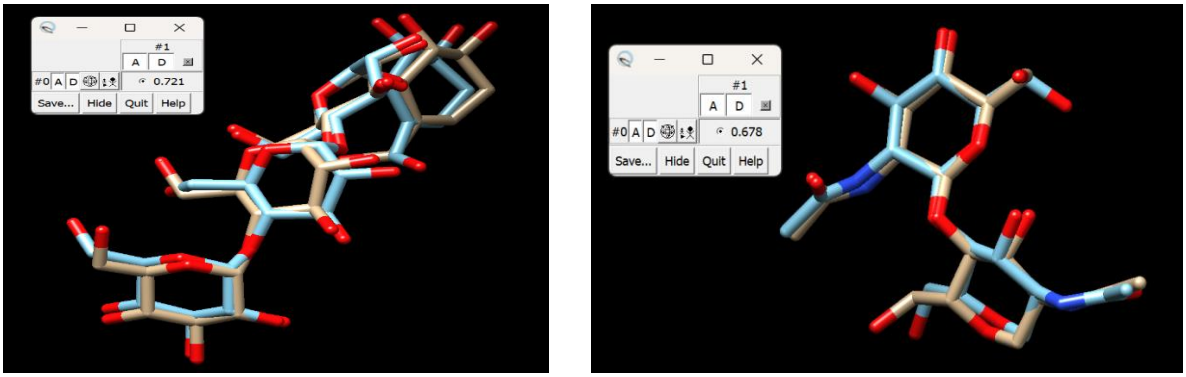


Figure 1. Results of re-docking the co-crystallized ligand and 2QV4 (A) and 3W37 (B).

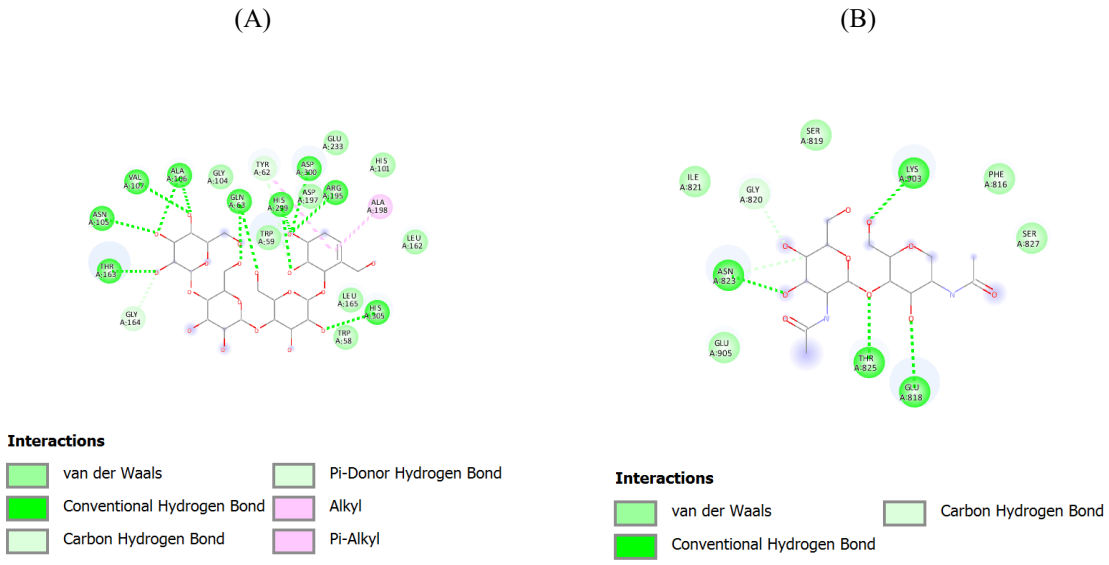


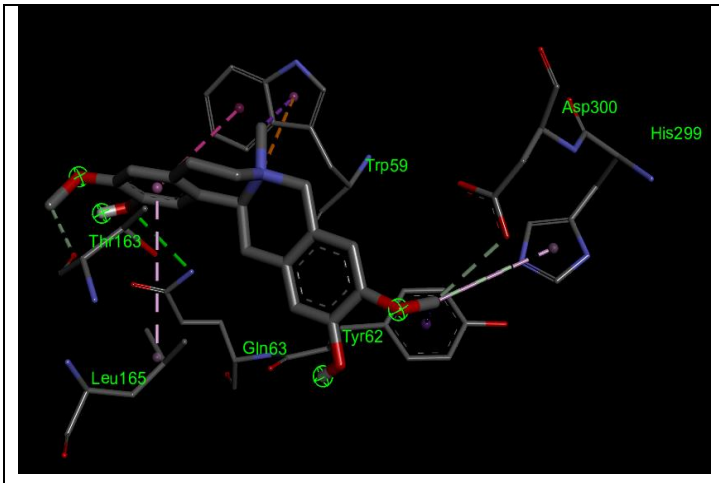
Figure 2. 2D interactions between QV4 and 2QV4 (A), NAG and 3W37 (B).

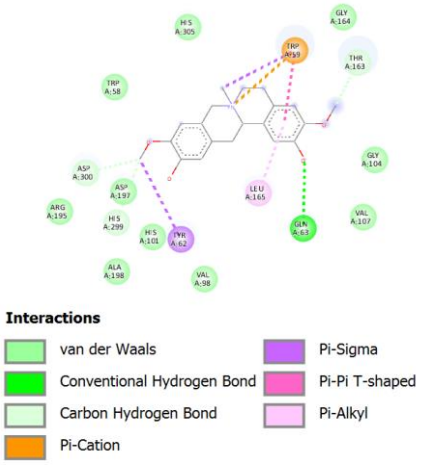
The interactions between the co-crystallized ligand and 2QV4 and 3W37 are shown in Figure 2.

After preparing the ligands, phellodendrine was docked to screen for inhibitory activity against the target proteins of diabetes. Phellodendrine exhibited binding energies of -8.7 kcal/mol; -8.5 kcal/mol; -8.4 kcal/mol; -8.1 kcal/mol; -7.7 kcal/mol; -7.7 kcal/mol; -7.5 kcal/mol; -7.4 kcal/mol; -7.3 kcal/mol; -6.6 kcal/mol with PTP1B; aldose reductase; 11β-HSD; α-amylase; PDKs 1-4; GSK-3β; GFAT; α-glucosidase; glucokinase; PPARγ, respectively. Binding energy (kcal/mol) is used to correlate the binding affinity of various ligands or inhibitors with their respective target proteins. Generally, the lower the binding energy, the greater the affinity of the ligand for the receptor protein. Therefore, the ligand with the highest affinity can be considered a candidate for further study. The results are presented in Table 2.

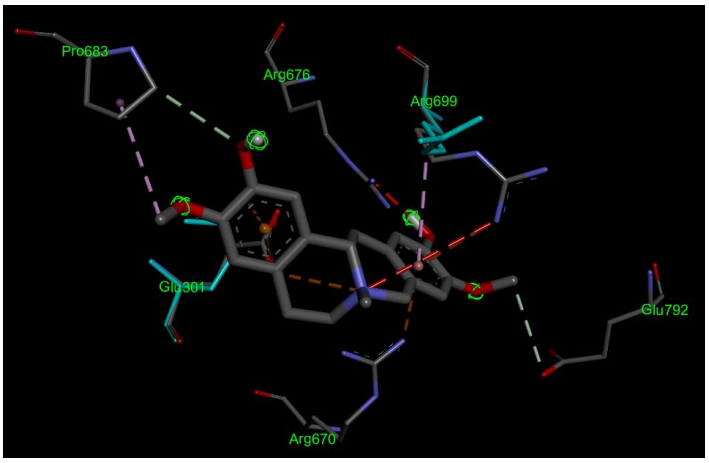
Table 2. The docking results of phellodendrine and the predicted inhibition constants with various proteins related to diabetes

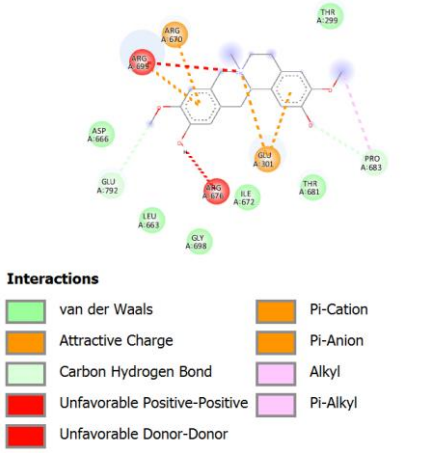
No.	Protein	Binding energy (ΔG) (kcal/mol)	Predicted inhibition constant (pKi) (μM)	H-Bond Forming Residues
1	2QV4	-8.1	5.94	GLN63
2	3W37	-7.4	5.43	-
3	2QBS	-8.7	6.38	ASP48
4	3G5E	-8.5	6.23	LYS21; CYS298; SER214
5	3DZY	-6.6	4.84	-
6	3F7Z	-7.7	5.65	ILE62
7	2BU8	-7.7	5.65	-
8	1V4S	-7.3	5.35	TYR215; ARG250
9	2ILT	-8.4	6.16	THR220
10	6SVO	-7.5	5.50	GLU31



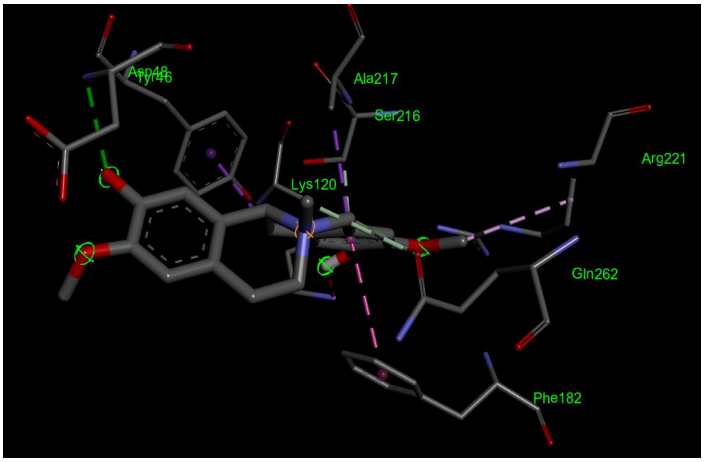


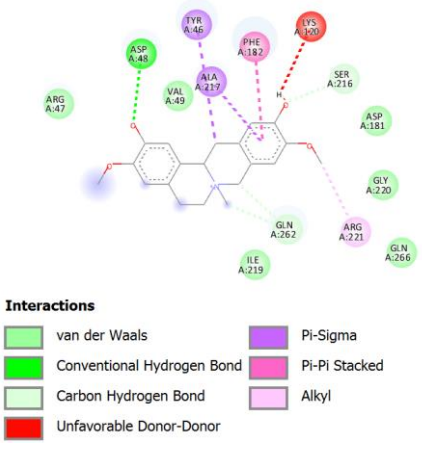
α-amylase (PDB ID: 2QV4).



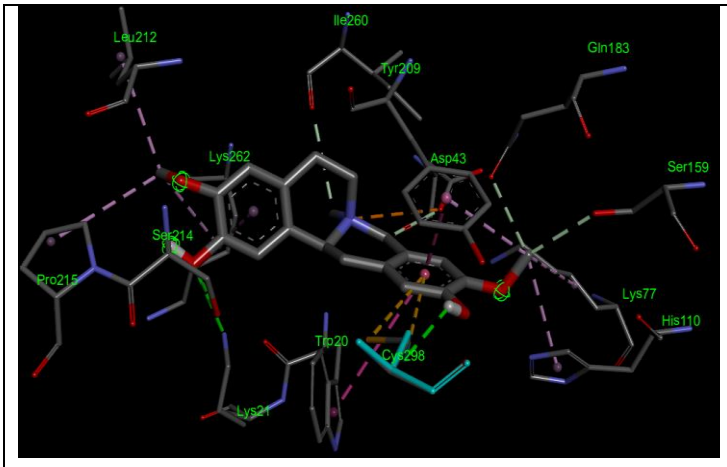


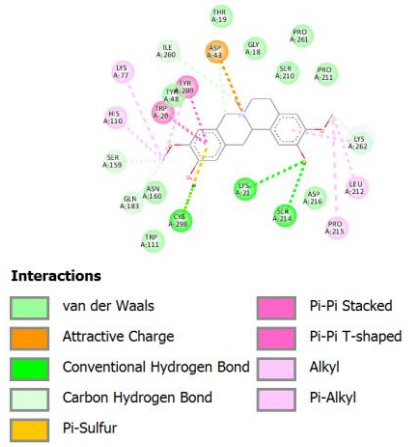
α-glucosidase (PDB ID: 3W37).



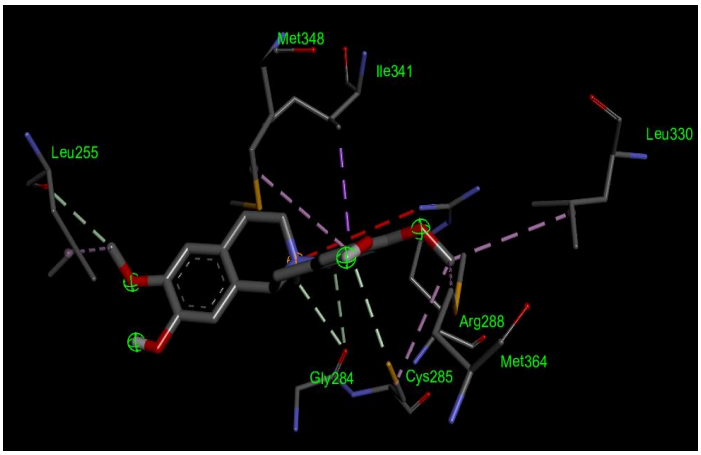


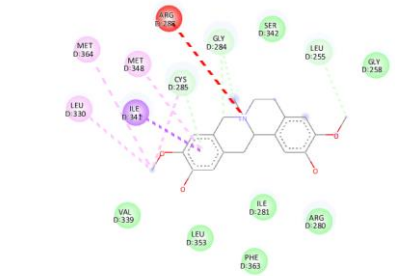
Protein tyrosine protease 1B (PDB ID: 2QBS).



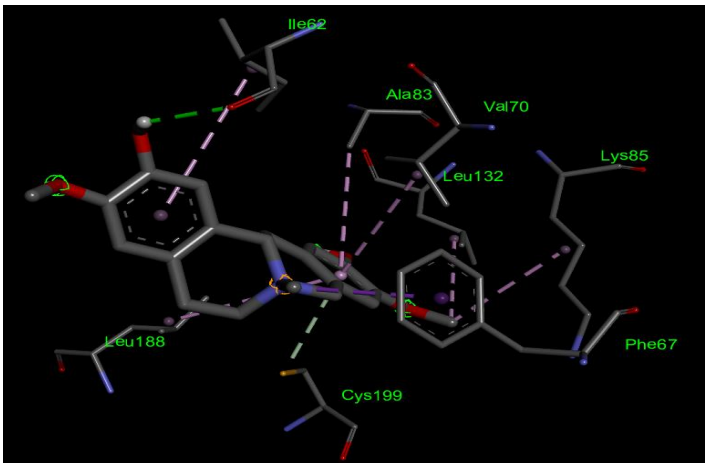


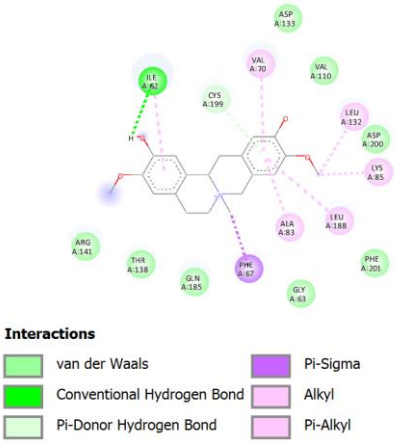
Aldose reductase (PDB ID: 3G5E).



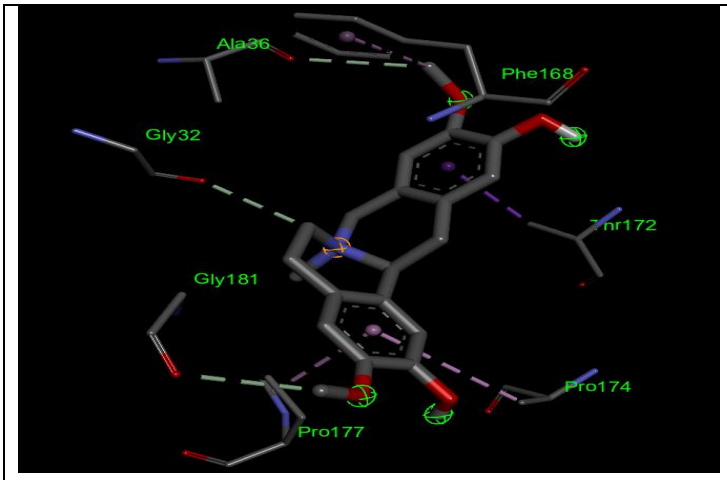


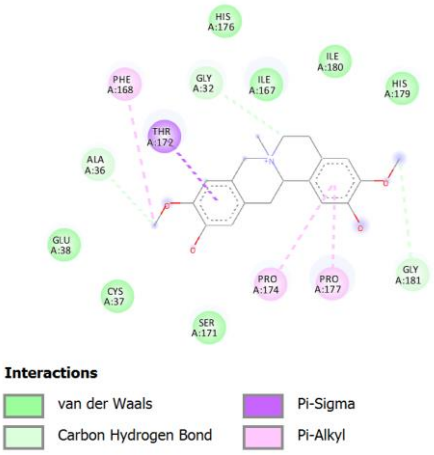
Peroxisome proliferator-activated receptor-γ (PPARγ) (PDB ID: 3DZY).



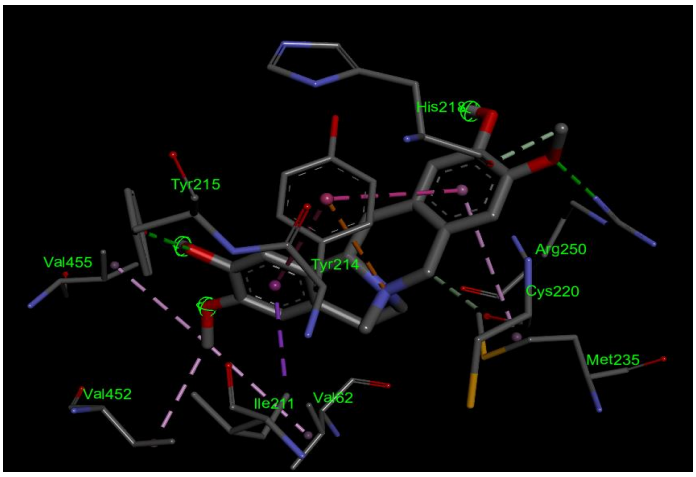


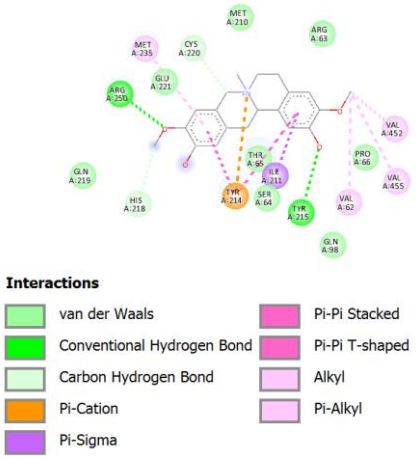
Glycogen synthase kinase-3β (PDB ID: 3F7Z).



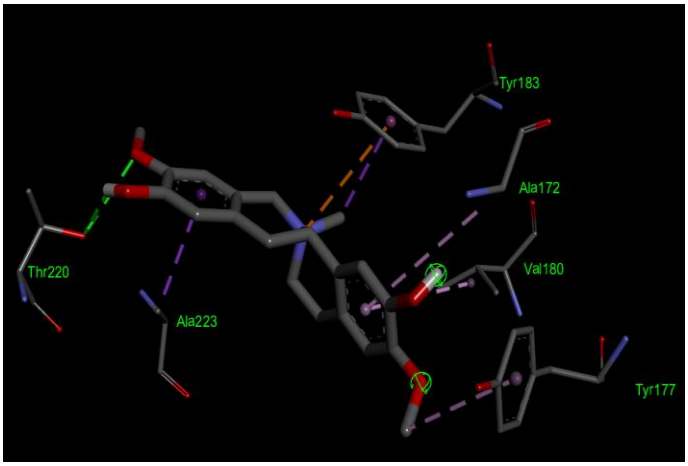


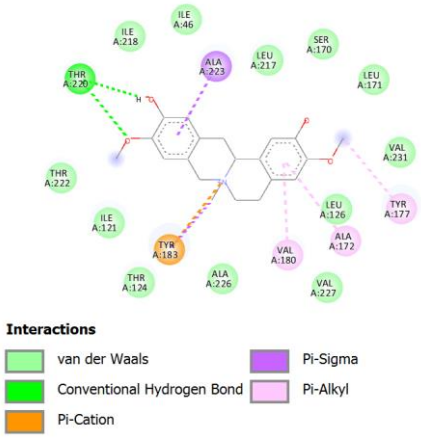
Pyruvate dehydrogenase kinase isoforms (PDB ID: 2BU8).



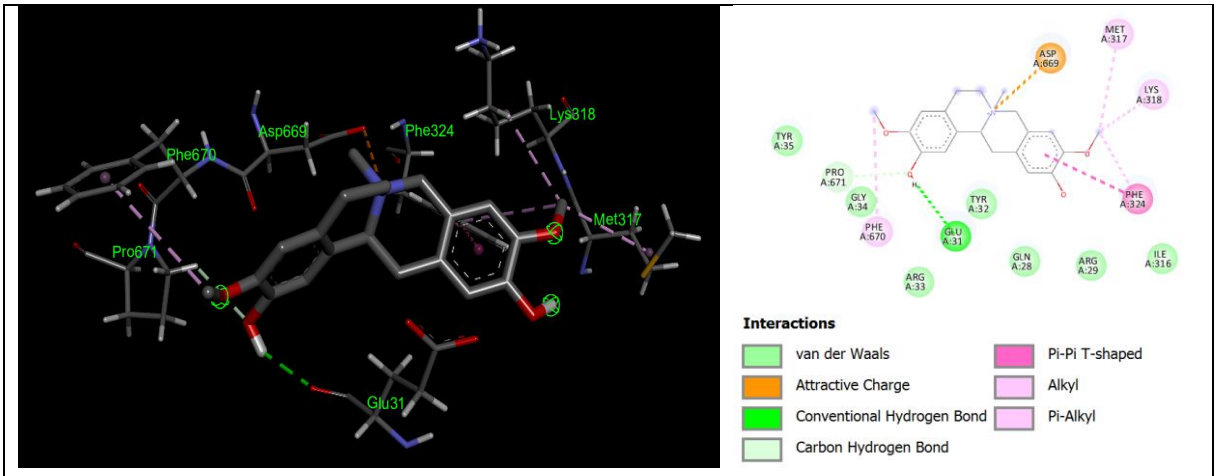


Glucokinase (PDB ID: 1V4S).





11β-Hydroxysteroid dehydrogenase (PDB ID: 2ILT).



Glutamine: fructose-6-phosphate amidotransferase (PDB ID: 6SVO)

Figure 3. Representation of the interaction of phellodendrine with 10 protein targets shown in 2D (right) and 3D (left).

The results indicate that phellodendrine is a potent inhibitor of protein tyrosine phosphatase 1B (PTP1B). PTP1B plays a crucial role in regulating insulin signaling, and several protein tyrosine phosphatases have been reported to regulate insulin receptor (IR) signaling both under normal conditions and in insulin-resistant states [28]. PTP1B has been demonstrated to act as a negative regulator of the phosphorylation process of IR and IR (IRS)-1 [29; 30]. Furthermore, several studies have demonstrated that increased expression of PTP1B occurs in insulin-resistant states associated with obesity [31; 32]. Phellodendrine exhibits binding to PTP1B through a hydrogen bond with ASP48 and six van der Waals bonds ARG47; VAL49; ASP181; GLY220; GLN266 and ILE219. The ARG221 forms a π-alkyl bond; PHE182 forms a π-π bond, and two π-sigma bonds TYR46 and ALA217 stabilize phellodendrine's binding to the active site of PTP1B (Figure 3). With a minimum binding energy of -8.7 kcal/mol and the highest predicted inhibition constant of 6.38 μM, phellodendrine is forecasted to be a genuine inhibitor of human protein tyrosine phosphatase 1B, thus potentially aiding in controlling diabetes and blood lipid levels.

Aldose reductase is the rate-limiting enzyme in the polyol pathway. It converts excess D-glucose to D-sorbitol with NADPH as the co-factor [33]. It plays a crucial role in treating microvascular complications caused by diabetes [6]. Aldose reductase also participates in lipid metabolism. Phellodendrine binds to aldose reductase through three hydrogen bonds LYS21; CYS298; SER214 and nine van der Waals bonds ASN160; TRP111; TYR48; THR19; GLY18; PRO261; SER210; PRO211; ASP216 (Figure 3). With a binding energy of -8.5 kcal/mol, a predicted inhibition constant of 6.23 μM, and four π-alkyl bonds and two π-π bonds involving TYR209 and TRP20, phellodendrine is stabilized at the active site. Consequently, it can be concluded that phellodendrine is an effective aldose reductase inhibitor.

Phellodendrine binds and significantly inhibits 11β-HSD. The conversion of inert cellular cortisone to active cortisol by NADPH as a cofactor is catalyzed by the enzyme 11β-HSD. Cortisol increases hepatic glucose production by inducing genes related to gluconeogenesis and glycogenolysis in the liver. Cortisol promotes the differentiation of preadipocytes into mature adipocytes, leading to increased fat tissue production. By modulating

the cortisone/cortisol concentration, selective inhibition of this enzyme could be a novel therapeutic approach for diabetes and elevated blood lipids [11; 34]. Obesity, diabetes, wound healing, and muscle atrophy are disorders associated with glucocorticoids, and inhibition of 11β-HSD1 holds therapeutic value, including for diabetes and hyperlipidemia. Phellodendrine establishes a hydrogen bond with THR220 and with eleven amino acids ILE121; ILE218; ILE46; THR124; LEU217; LEU171; LEU126; SER170; VAL231; VAL227; ALA226 through van der Waals forces (Figure 1). With a binding energy of -8.4 kcal/mol, an inhibition constant of 6.16 μM, and π-alkyl; π-sigma; π-cation bonds stabilizing phellodendrine at the active site.

Phellodendrine binds to α-amylase; GSK-3β; GFAT and glucokinase with binding energies of -8.1 kcal/mol; -7.7 kcal/mol; -7.5 kcal/mol; -7.3 kcal/mol, respectively; and predicted inhibition constants of 5.94 μM; 5.65 μM; 5.50 μM; 5.35 μM through hydrogen bonds, van der Waals forces; π-alkyl; π-sigma, and π-π interactions, suggesting potential inhibitory effects on these proteins for glycemic control. Phellodendrine binds to α-amylase through a hydrogen bond with GLN63 and ten van der Waals bonds TRP58; HIS305; GLY164; GLY104; VAL107; VAL98; HIS101; ASP197; ALA198 and ARG195. Phellodendrine with GSK-3β establishes a hydrogen bond with ILE62 and eight van der Waals bonds ASP133; ASP200; VAL110; PHE201; GLY63, GLN185; THR138; ARG141. Similarly, phellodendrine binds to GFAT through a hydrogen bond with GLU31 and seven van der Waals bonds TYR35; TYR32; GLY34; ARG33; ARG29; GLN28; and ILE316.

The pyruvate dehydrogenase kinase isoforms; α-glucosidase and peroxisome proliferator-activated receptor gamma (PPARγ) did not exhibit strong binding with phellodendrine (binding energies ΔG = -7.7 kcal/mol; -7.4 kcal/mol; -6.6 kcal/mol, respectively). Without associated hydrogen bonds, only via van der Waals forces, π-alkyl interaction, and π-sigma interaction, phellodendrine stabilizes at the active site

A molecular docking investigation of phellodendrine with ten different protein targets relevant to diabetes mellitus revealed three potential target proteins perfectly dock with phellodendrine. Docking analysis also revealed that based on binding energy (ΔG) and predicted inhibition constant (pKi), PTPB1 (2QBS) showed best binding with phellodendrine, followed by aldose reductase (3G5E) and 11β-HSD (2ILT). The docking and interaction pattern of ligands were fantastically able to interact with the key residues of the catalytic cavity of the enzyme or located in very close proximity to the active sites of these proteins.

3.2. Results of Lipinski's Rule of Five

Compounds are termed "drug-like" when they satisfy at least 2 of the 5 criteria of Lipinski's Rule of 5: i) Molecular weight < 500 Da; ii) High lipophilicity (LogP does not exceed 5); iii) No more than 5 hydrogen bond donors of hydrogen bonding; iv) No more than 10 hydrogen bond acceptors of hydrogen bonding; and v) Molar refractivity should be between 40-130. The results of phellodendrine with Lipinski's Rule of 5 are presented in Table 3. Next, phellodendrine was further predicted as pharmacokinetic-toxicological (ADMET).

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
Phellodendrine	342.415	4	2	2.9151	100.92	Yes

The results in Table 3 demonstrate that phellodendrine satisfies all 5 Lipinski criteria, very high drug-like properties. Therefore, this compound continues to be evaluated for

pharmacokinetic properties including absorption, distribution, metabolism, excretion, and toxicity.

3.3. Prediction of ADMET

ADMET prediction results including absorption, distribution, metabolism, elimination, and toxicity processes are presented in Table 4.

The absorption potential of compounds is evaluated based on three properties: water solubility, permeability through the Caco2 membrane, and percentage of drug absorption in the intestine. The results in Table 4 show that the water solubility of the compounds is quite poor with a molar concentration of only about 10^{-4} mol/L. Permeability through the Caco2 membrane (logPapp in 10^{-6} cm/s) greater than 0.9 is considered good permeability, and phellodendrine exhibits high permeability with a logPapp value of 1.595 in 10^{-6} cm/s. Additionally, phellodendrine also demonstrates good intestinal absorption with a value of 94.978%.

Regarding distribution, compounds are considered to be well distributed to tissues if logVDss > 0.45 [10]. The higher the VDss, the more the drug is distributed into tissues rather than plasma. Phellodendrine has a good volume of distribution to tissues (VDss = 1.01). The ability of a drug to pass through the blood-brain barrier is a factor to consider in helping reduce toxicity, and side effects or to improve the effectiveness of pharmacologically active drugs in the brain. Compounds can penetrate the blood-brain barrier if a logBB is greater than 0.3. Phellodendrine doesn't cross the blood-brain barrier with the logBB value of -0.392.

In terms of metabolism, the cytochrome P450 system is crucial in hepatic drug metabolism. P450 inhibitors may significantly alter the pharmacokinetics of these drugs. The two main polymorphisms of cytochrome p450 responsible for drug metabolism are CYP2D6 and CYP3A4. Assessment of phellodendrine metabolism with CYP2D6 and CYP3A4 reveals that phellodendrine is a substrate of CYP3A4.

Phellodendrine may be excreted through the kidneys with a total clearance rate of 1.188 (logml/min/kg). High total clearance indicates its efficient elimination from the body.

Regarding toxicity, phellodendrine does not cause skin sensitization, AMES toxicity, or liver toxicity.

Table 4. Pharmacokinetic and toxicological prediction results

Properties		Results
Absorption	Water solubility (logmol/l)	-3.606
	Caco2 permeability ($logP_{app}$ in 10^{-6} cm/s)	1.595
	Intestinal absorption human (%)	94.978
Distribution	VDss (log L/kg)	1.01
	BBB permeability (logBB)	-0.392
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	Yes
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
Excretion	Total clearance (logml/min/kg)	1.188
Toxicity	AMES toxicity	No
	Hepatotoxicity	No
	Skin sensitization	No

3.4. Evaluation of Oral Bioavailability

According to efficacy and toxicity, poor bioavailability is often cited as a major cause of drug development failures, and oral administration is the most common route of administration. Therefore, the Radar plot of oral bioavailability utilizes six physicochemical properties: lipophilicity, size, polarity, insolubility, flexibility, and saturation to assess oral bioavailability. The range of these properties is detailed in Table 5.

Table 5. The specific range of six physicochemical properties

Properties	Range
LIPO (Lipophility)	− 0.7 < XLOGP3 < + 5.0
SIZE	150 g/mol < MV < 500 g/mol
POLAR (Polarity)	20Å^2 < TPSA < 130Å^2
INSOLU (Insolubility)	-6 < Log S (ESOL) < 0
INSATU (Insaturation)	0.25 < Fraction Csp3 < 1
FLEX (Flexibility)	0 < Num.rotatable bonds < 9

The pink area represents the optimal range for each attribute. A compound must have a range of six physicochemical properties that lie entirely in the pink region to be considered drug-like (Figure 4).

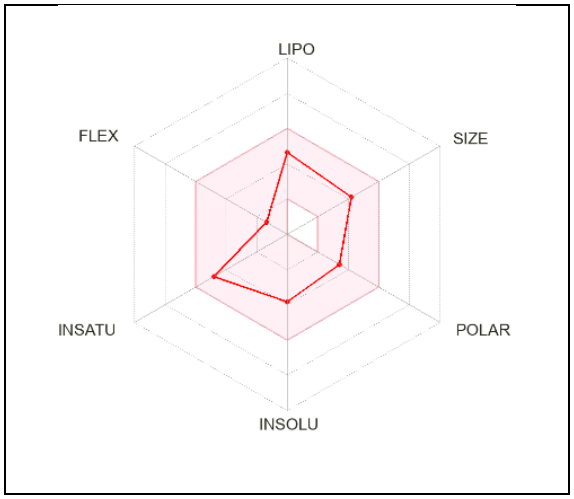


Figure 4. Bioavailability Radar.

Phellodendrine was shown to satisfy the radar chart criteria and is therefore expected to have oral bioavailability.

4. Conclusion

This study applies virtual screening based on molecular docking to identify promising targets for diabetes treatment. The docking scores ranged of phellodendrine with several key synthetic pathways in diabetes including α-amylase; α-glucosidase; protein tyrosine phosphatase 1B; aldose reductase; peroxisome proliferator-activated receptor- γ; glycogen synthase kinase-3β; pyruvate dehydrogenase kinase isoforms; glucokinase; 11β-hydroxysteroid dehydrogenase, and glutamine: fructose-6-phosphate amidotransferase from -8.7 to -6.6 (kcal/mol). The binding affinities of the ligands to the receptors were clearly explained by 2D and 3D interaction analyses. Furthermore, this compound also exhibits drug-like properties by evaluating Lipinski's rule of 5; predicted ADMET suggests good absorption, low toxicity, and oral bioavailability. Therefore, further *in vitro* and *in vivo* studies are needed to develop this potential compound into a diabetes therapeutic.

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