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Original Article

Assessment of Izalpinin Inhibitory Effect on Diabetes via Molecular Docking Method

Nguyen Thuy Tien[1], Nguyen Tuan Minh[2], Nguyen Minh Trang[3], Bui Thanh Tung[3,*]

[1]*VNU University of Medicine and Pharmacy, 144 Xuan Thuy, Cau Giay, Hanoi, Vietnam*
[2]*Hai Phong University of Medicine and Pharmacy, 72A Nguyen Binh Khiem, Gia Vien, Hai Phong, Vietnam*
[3]*Academy of Security Engineering and Technology, Thuan Thanh, Bac Ninh, Vietnam*

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Abstract: Diabetes mellitus is a common non-communicable disease globally and one of the leading causes of death due to cardiovascular diseases compared to other causes. Izalpinin is a flavonoid compound found in several medicinal plants with potential antidiabetic effects. This study evaluates the inhibitory effects of Izalpinin on three targets (α-glucosidase, Aldose reductase, Dipeptidyl-peptidase IV) involved in the pathogenesis of diabetes using molecular docking methods. The 3D structures of the targets were obtained from the RCSB Protein Data Bank. The structure of Izalpinin was retrieved from the PubChem database. Molecular docking screening was performed using AutoDock Vina. Lipinski's Rule of Five was applied to assess the drug-like properties of Izalpinin. The pharmacokinetic parameters of Izalpinin were evaluated using the pkCSM tool. Oral bioavailability was assessed using the SwissADME tool. The results showed that Izalpinin had a significantly low binding energy with Aldose reductase (ΔG = −10.3 kcal/mol). Lipinski analysis indicated that Izalpinin possesses drug-like properties. Predicted pharmacokinetic parameters showed that the compound has good absorption and low toxicity. However, Izalpinin does not meet the criteria for oral bioavailability. Therefore, further studies are needed to develop this compound as a potential diabetes treatment.

Keywords: Diabetes, Izalpinin, Molecular Docking, Lipinski, ADMET.

1. Introduction

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose (or blood sugar) levels, which, over time, can lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves [1]. According

* Corresponding author.
E-mail address: tungbt.ump@vnu.edu.vn

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to the International Diabetes Federation (IDF) in 2021, approximately 537 million adults (aged 20-79) are living with diabetes, and around 6.7 million deaths occurred due to diabetes in 2021 [2]. The prevalence of diabetes in Vietnam is approximately 5.76 million people, accounting for about 6% of the population (data from 2017) [3].

α-glucosidase is an enzyme that catalyzes hydrolysis reactions and is found in the epithelium of the small intestine [4]. This enzyme catalyzes the cleavage of the 1,4-α-D-glucosidic bond from the substrate to form α-D-glucose [5]. By inhibiting α-glucosidase, the absorption of carbohydrates from the small intestine is reduced, thereby decreasing the postprandial rise in blood glucose levels by approximately 3 mmol/L [6]. Aldose reductase (AR) is an aldo-keto reductase that catalyzes the first step in the polyol pathway, converting glucose into sorbitol. Under normal glucose homeostasis conditions, this pathway represents a secondary metabolic route for glucose, operating alongside glycolysis [7]. AR is believed to be involved in the pathogenesis of secondary complications of diabetes, such as retinopathy, neuropathy, nephropathy, and cataracts [8]. Dipeptidyl-peptidase IV (DPP-IV) is a cell surface protease belonging to the prolyloligopeptidase family. It plays a role in glucose homeostasis by inactivating the breakdown of incretin proteins. DPP-IV inhibitors improve glucose tolerance and pancreatic islet cell function in animal models of Type II diabetes and in diabetic patients [9].

Izalpinin, a flavonoid isolated from the fruit of *Alpinia oxyphylla*, is widely used to treat ulcerations, gastralgia, diarrhea, dementia, diabetes, and Alzheimer's disease [10]. In addition, Izalpinin is also found in the leaves of *Muntingia calabura* L., research has shown that extracts from the *Muntingia calabura* L. plant exhibit analgesic, anti-inflammatory, antipyretic, anti-ulcer, antidiabetic, and antihypertensive activities, among others [11]. According to research by Le Huu Tho et al., Izalpinin is one of the flavonoid compounds in the leaves of *Muntingia calabura* L. that exhibit strong α-glucosidase inhibitory activity [12]. In this study, the inhibitory effects of Izalpinin on several other targets of diabetes will be further evaluated.

Molecular docking is a modeling technique that helps predict the favorable binding position and configuration of a substrate molecule (ligand) to a protein molecule (target). This *in silico* method saves significant time and costs in compound screening compared to experimental methods [13]. This study will evaluate the inhibitory effect of the Izalpinin compound on diabetes using molecular docking.

2. Materials and Methods

2.1. Materials

Preparing protein structures: The 3D structures of the targets were obtained from the RCSB Protein Data Bank (https://www.rcsb.org): Aldose reductase (AR) (PDB ID: 3G5E) [14]; α-Glucosidase (PDB ID: 3W37) [14]; Dipeptidyl Peptidase IV (DPP-IV) (PDB ID: 3F8S) [15]. Three co-crystallized ligands, NDP for Aldose reductase (AR) (PDB ID: 3G5E), NAG for α-Glucosidase (PDB ID: 3W37), and PF2 for Dipeptidyl Peptidase IV (DPP-IV) (PDB ID: 3F8S) were used to evaluate and optimize the docking models. The active sites of the proteins were determined using Discovery Studio 2021 Client. Prior to docking, all protein molecules were stripped of water molecules and co-crystallized ligands using Discovery Studio Visualizer 4.0 software. Hydrogen atoms were added using AutoDock Vina software, and the protein's active site was re-established using MGL AutoDock Tools 1.5.7. The active sites of Aldose reductase (AR), α-Glucosidase, and Dipeptidyl Peptidase IV (DPP-IV) were determined in Table 1.

Table 1. The active sites of 4 protein targets

ID PDB	Grid box size (Å)	Grid spacing	(XYZ)
3G5E	22x22x32	0,375	(22; −7; 23)
3W37	60x60x70	0,375	(14.103; −27.101; −42.876)
3F8S	60x60x70	0,375	(34.36; 48.98; 40.19)

Preparing ligand structures: The 3D structure of Izalpinin (PubChem ID: 5318691), with the IUPAC name 3,5-dihydroxy-7-methoxy-2-phenylchromen-4-one, was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) (accessed on November 4, 2024) in .sdf format and then converted to .pdb format using UCSF Chimera 1.17.3 software. The ligands were then optimized using Avogadro 1.1.0 with the Conjugate Gradients method and subsequently converted to. pdbqt format using Autodock Tools 1.5.7.

2.2. Methods

i) Molecular docking

Performing molecular docking: The ligands were docked into the active site of the protein using AutoDock Vina software with an exhaustiveness value of 8 (default setting). For each ligand–protein complex, multiple binding poses were generated, and the top-ranked poses were retained for further analysis. Discovery Studio 2021 Client software was used to visualize the interactions between the protein and Izalpinin.

Evaluation of docking results: To validate the docking protocol, the co-crystallized ligands were re-docked into the active site of the target proteins. The docking procedure was considered reliable when the root mean square deviation (RMSD) between the docked pose and the experimental structure was ≤ 1.5 Å. For all docked compounds, binding affinity was evaluated based on the predicted binding energy and key interactions with amino acid residues in the binding pocket. The optimal binding pose was selected based on the lowest binding energy and acceptable RMSD values.

Prediction of inhibition constant calculation: The inhibition constant (Ki) is dependent on the binding constant (Kb) and the dissociation constant (Kd) of the enzyme-inhibitor complex, in an inverse relationship (ln Kb = −ln Kd) [16].

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

Therefore, Ki is calculated using the following formula:

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

$$(pKi = -\log_{10} Ki)$$

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

ii) Evaluation of Lipinski's Rule of Five

The Lipinski's Rule of Five criteria are used to evaluate the drug-like properties of a compound [17] using an online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) [18].

iii) Prediction of pharmacokinetics and toxicity

The predicted results of the 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) [19].

iv) 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) [20].

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 re-docking the co-crystallized

ligands, the results yielded RMSD values of 0.527 Å, 0.584 Å, and 0.574 Å (Figure 1). These three values satisfy the RMSD criterion of less than 1.5 Å, indicating that the molecular docking results for the targets are reliable. Besides, the interactions between the co-crystallized ligand and 3G5E, 3W37, and 3F8S are shown in Figure 2.

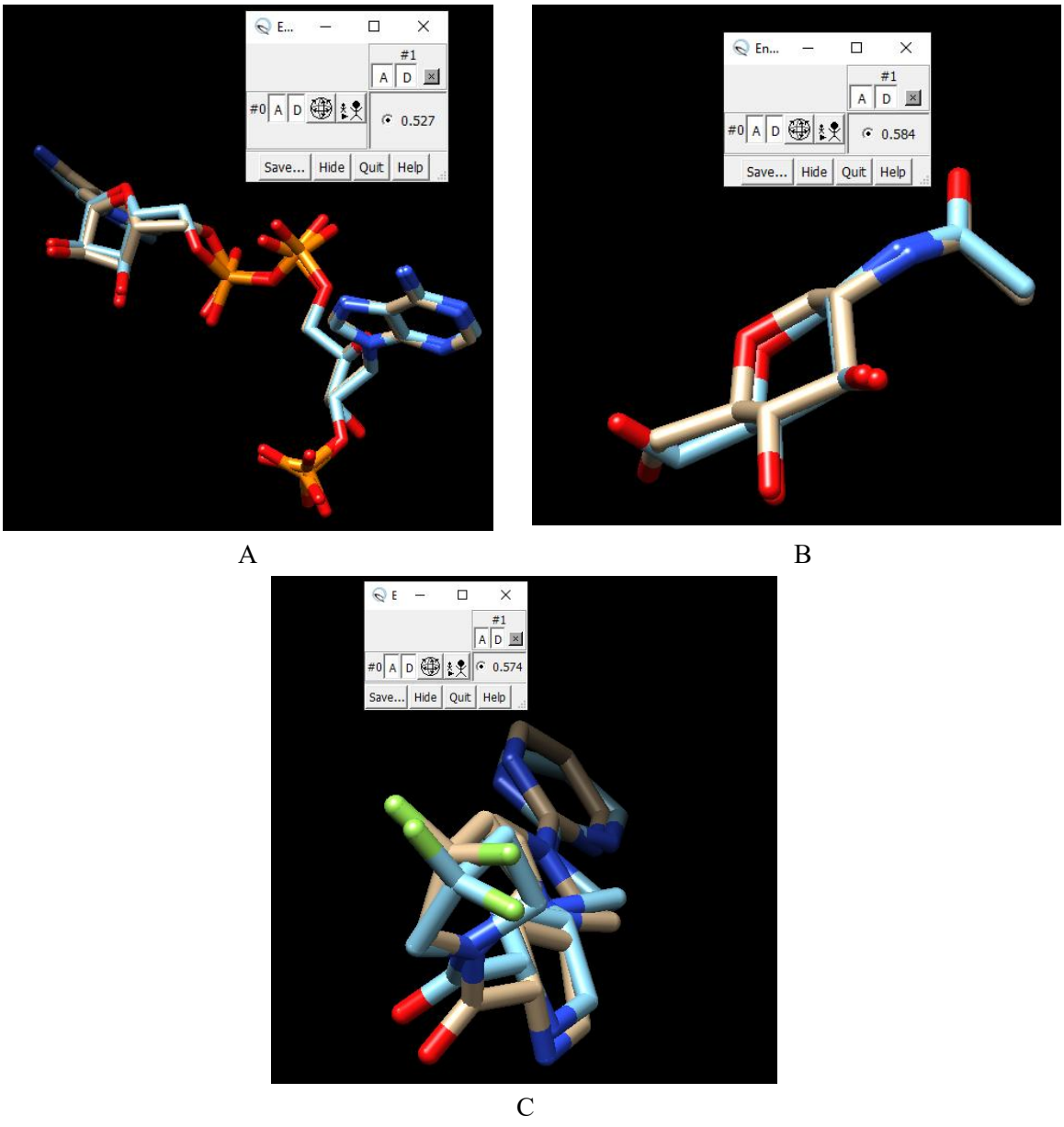


Figure 1. Results of re-docking the co-crystallized ligand and 3G5E (A); 3W37 (B); 3F8S (C).

After preparing the ligands, Izalpinin was docked onto the base to screen its inhibitory activity against diabetes-related target proteins (Figure 2). Izalpinin exhibited binding energies of −10.3 kcal/mol, −7.3 kcal/mol, and −7.6 kcal/mol with Aldose reductase, α-glucosidase, and DPP-IV, respectively. The binding energy (kcal/mol) is used to correlate the binding

affinity between the ligands or other inhibitors and their corresponding target proteins. The lower the binding energy, the higher the affinity of the ligand for the target protein. Therefore, the ligand with the highest affinity can be considered a candidate for further study. The results are presented in Table 2.

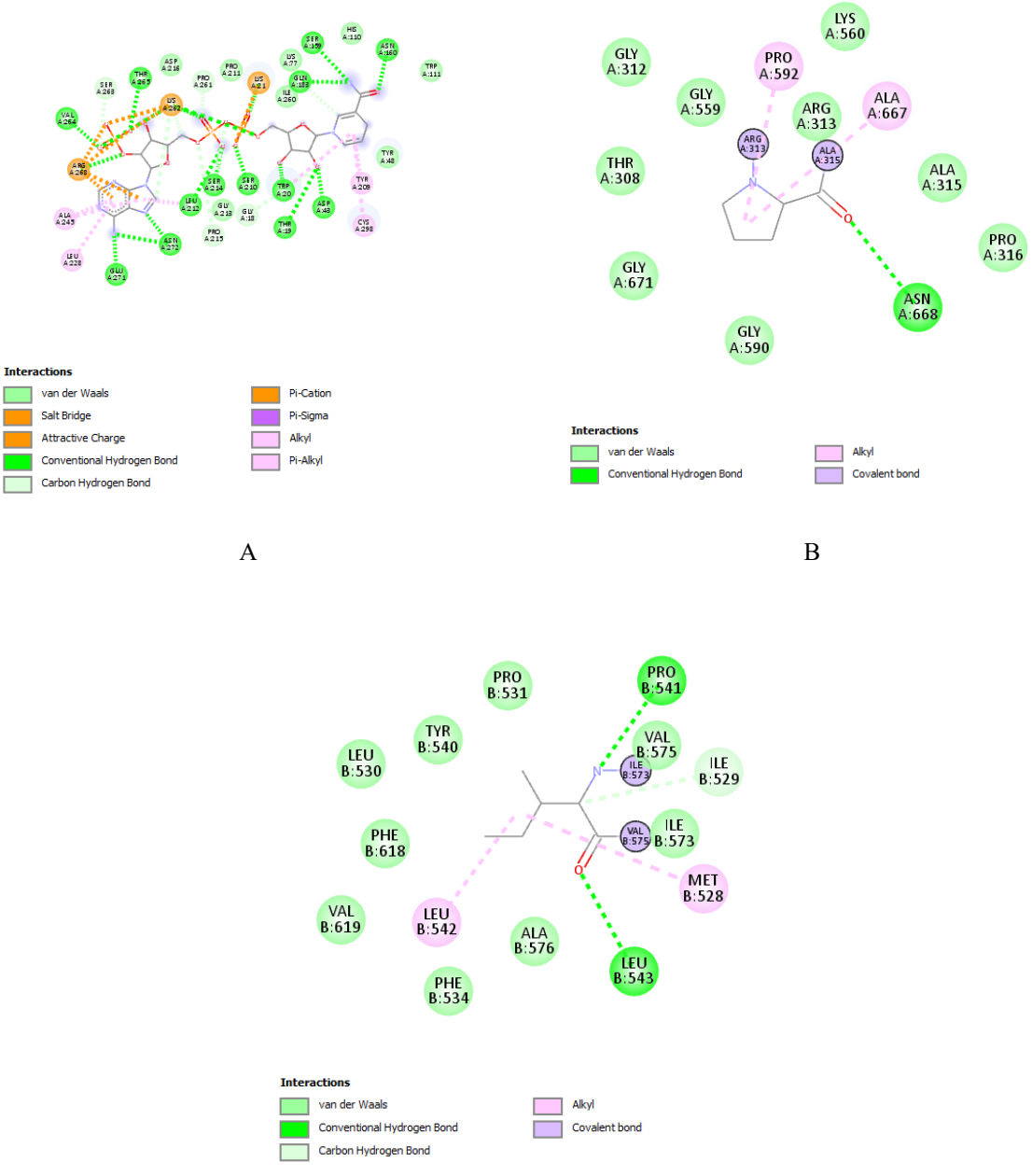
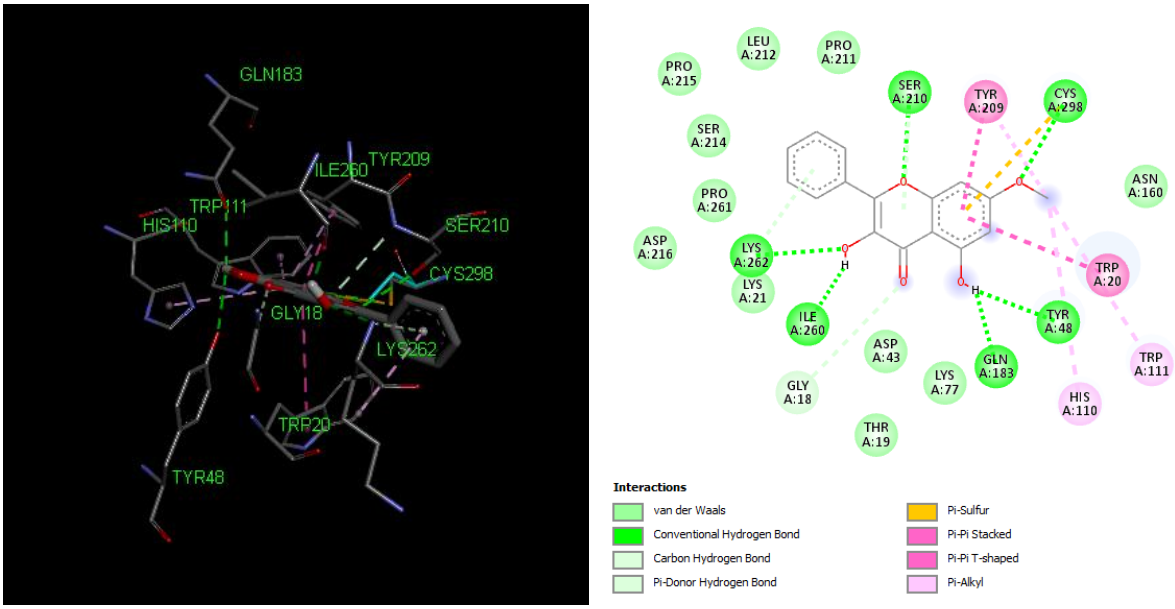


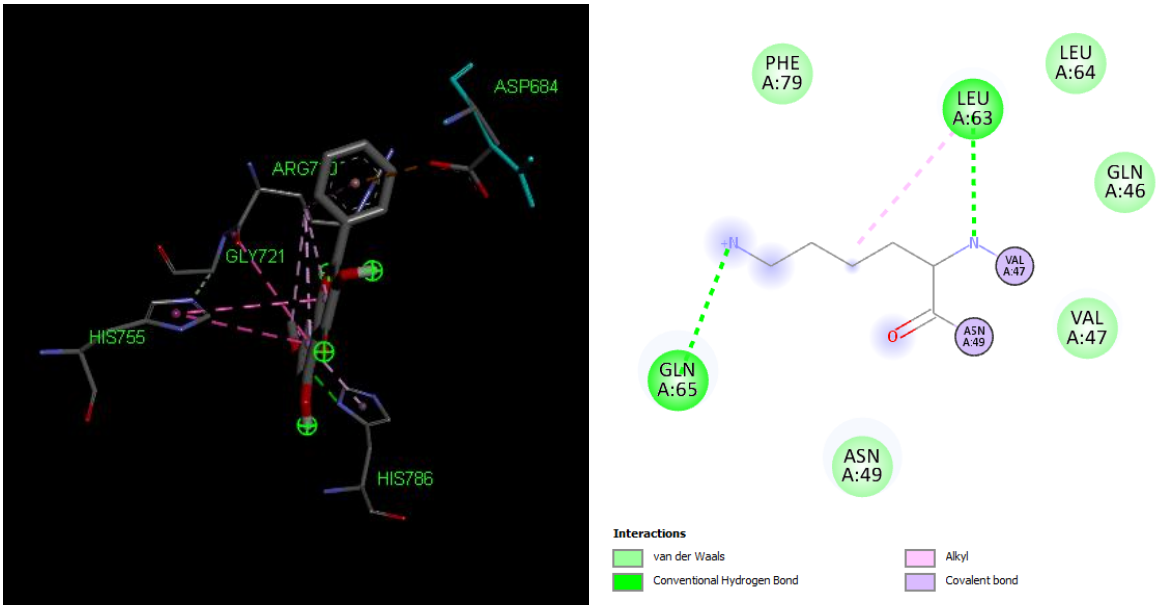
Figure 2. 2D interactions between NDP and 3G5E (A); NAG and 3W37 (B); PF2 and 3F8S (C).

Table 2. The docking results of Izalpinin and the predicted inhibition constants with proteins

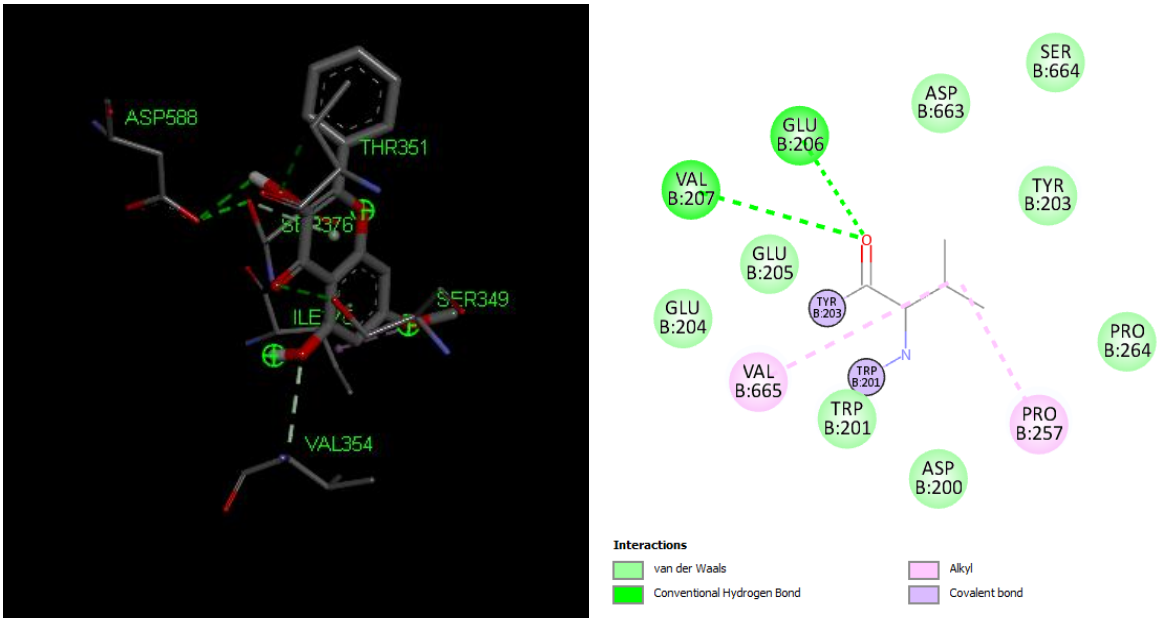
Protein	Binding energy (ΔG) (kcal/mol)	Predicted inhibition constant (pKi)	H-Bond Forming Residues
3G5E	−10.3	7.56	SER210; CYS298; LYS262; ILE260; GLN183; TYR48
3W37	−7.3	5.35	LEU63; GLN65
3F8S	−7.6	5.57	GLU206; VAL207



Aldose reductase (AR) (ID PDB: 3G5E)



α-Glucosidase (ID PDB: 3W37)



Dipeptidyl Peptidase IV (DPP-IV) (ID PDB: 3F8S)

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

The results suggest that Izalpinin has potential inhibitory activity against Aldose reductase (AR). Aldose reductase is the rate-limiting enzyme in the polyol pathway. It converts excess D-glucose to D-sorbitol with NADPH as a cofactor [21]. It plays a crucial role in the treatment of microvascular complications caused by diabetes [22]. Aldose reductase is also involved in lipid metabolism. Izalpinin binds to AR through six hydrogen bonds with SER210, CYS298, LYS262, ILE260, GLN183, and TYR48, and 11 van der Waals interactions with PRO211, LEU212, PRO215, SER214, PRO261, ASP216, LYS21, ASP43, THR19, LYS77, and ASN160. GLY18 forms a hydrogen bond with π. TYR209 and TRP20 form π-π interactions. HIS110 and TRP111 form π-alkyl interactions, stabilizing Izalpinin's binding to the AR active site (Figure 3). With a binding energy of −10.3 kcal/mol, Izalpinin shows a favorable predicted binding affinity toward human aldose reductase. The predicted inhibition constant (pKi) of 7.56 suggests that Izalpinin may act as a potential aldose reductase inhibitor. However, it should be noted that the binding energies obtained from computational docking are derived from empirical scoring functions and do not represent true thermodynamic free energy. Therefore, the calculated pKi values are approximate and should be used primarily for relative comparisons rather than absolute predictions of inhibitory activity.

Izalpinin binds to α-Glucosidase through 2 hydrogen bonds with LEU63 and GLN65, and 5 van der Waals interactions with PHE79, ASN49, VAL47, GLN46, and LEU64, along with two hydrophobic bonds with ASN49 and VAL47.

Izalpinin binds to Dipeptidyl Peptidase IV (DPP-IV) through 2 hydrogen bonds with GLU206 and VAL207, and 8 van der Waals interactions with GLU205, GLU204, TRP201, ASP200, PRO264, TYR203, ASP663, and SER664. Additionally, tuo alkyl bonds with VAL665 and PRO257, and two hydrophobic bonds with TYR203 and TRP201 are formed.

Based on molecular docking analysis, including binding energy (ΔG) and predicted inhibition constant (pKi), Izalpinin exhibits the most favorable interaction with aldose reductase (AR) (3G5E). However, these values are

approximate and primarily useful for comparative purposes.

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 Izalpinin with Lipinski's Rule of 5 are presented in Table 3. Next, Izalpinin 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	Druglikeness
Izalpinin	284.000	2	5	2.9026	75.608	Yes

The results in Table 3 indicate that Izalpinin satisfies all five of Lipinski's criteria, suggesting favorable drug-like properties. Therefore, this compound was further evaluated for its pharmacokinetic profile, including absorption, distribution, metabolism, excretion, and toxicity (ADMET).

3.3. Prediction of ADMET

ADMET prediction results, including absorption, distribution, metabolism, elimination, and toxicity processes, are presented in Table 4. In particular, the absorption potential of the compounds was evaluated based on water solubility (logS), Caco-2 permeability (logPapp, in 10^{-6} cm/s), and intestinal absorption. The results indicate that Izalpinin has relatively low aqueous solubility, as reflected by its logS value, suggesting limited solubility in water. The Caco-2 permeability (logPapp) value of 0.955 (10^{-6} cm/s) indicates good membrane permeability. Furthermore, Izalpinin shows high intestinal absorption, with a predicted value of 94.905%.

Regarding distribution, compounds are considered to distribute well to tissues if logVDss > 0.45 [23]. The higher the VDss, the more the drug is distributed to tissues rather than plasma. Izalpinin has a distribution volume in plasma greater than in tissues (VDss = −0.186). The ability of a drug to cross the blood-brain barrier is a factor to consider in reducing toxicity and side effects, or in improving the effectiveness of drugs with pharmacological effects in the brain. Compounds can penetrate the blood-brain barrier if logBB is greater than 0.3. Izalpinin does not cross the blood-brain barrier, with a logBB value of −0.093.

Table 4. Pharmacokinetic and toxicological prediction results

Properties		Results
Absorption	Water solubility (logS)	−3.469
	Caco2 permeability (logPapp, 10^{-6} cm/s)	0.955
	Human intestinal absorption (%)	94.905
Distribution	VDss (log L/kg)	−0.186
	BBB permeability (logBB)	−0.093
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	Yes
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	Yes
Excretion	Total clearance (log mL/min/kg)	0.323
Toxicity	AMES toxicity	No
	Hepatotoxicity	No
	Skin sensitization	No

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 Izalpinin's metabolism with CYP2D6 and CYP3A4 reveals that Izalpinin is a substrate of CYP3A4 and also an inhibitor of CYP3A4. Besides, assessment of Izalpinin's metabolism with CYP2D6 and CYP3A4 reveals that Izalpinin is both a substrate and an inhibitor of CYP3A4, suggesting a potential risk of drug–drug interactions, as co-administration with other CYP3A4 substrates or inhibitors may affect its metabolic profile.

Izalpinin has the potential to be eliminated through the kidneys, with a total clearance of 0.323 (log ml/min/kg).

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

3.4. Evaluation of Oral Bioavailability

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

According to efficacy and toxicity, poor bioavailability is often considered the main cause of failure in drug development, with oral administration being 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.

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).

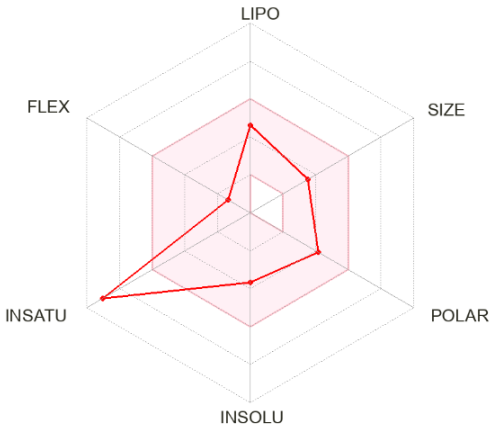


Figure 4. Bioavailability Radar.

Izalpinin meets 5 criteria regarding lipophilicity, size, polarity, insolubility, and flexibility, but does not meet the criterion for saturation (Figure 4). This may be attributed to the structural characteristics of flavonoids, which often exhibit low saturation due to their planar aromatic systems, potentially affecting their oral bioavailability. Therefore, it cannot be concluded that Izalpinin has favorable oral bioavailability.

4. Conclusion

This study applies virtual screening using molecular docking to determine the extended inhibitory effects of Izalpinin on the targets α-glucosidase, Aldose reductase (AR), and Dipeptidyl-peptidase IV (DPP-IV) in the treatment of diabetes. The results suggest that Izalpinin has potential inhibitory activity against Aldose reductase (AR), with a binding energy of −10.3 kcal/mol and a predicted highest inhibition constant of 7.56 μM. 2D and 3D interaction analyses clearly revealed the ligand-receptor

binding affinities. This compound also exhibits drug-like properties as evaluated by Lipinski's Rule of Five; ADMET predictions indicate good absorption and low toxicity. However, Izalpinin does not meet the criterion for saturation; therefore, its oral bioavailability cannot be concluded. Hence, further *in vitro* and *in vivo* studies are needed to develop this compound into a therapeutic drug for diabetes.

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