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Research Article

Molecular Docking and ADMET Profiling of Human DPP-IV Inhibitors from *Dalbergia sissoo*: *In-silico* Assessment of Antidiabetic Potential

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ABSTRACT

In the quest for efficient treatment for diabetes mellitus (DM), human dipeptidyl peptidase-IV (DPP-IV) inhibitors have shown potential oral antidiabetic medications. Despite their potential, many existing medications are associated with adverse effects, highlighting the need for novel and safer alternatives. Type 2 diabetes mellitus (T2DM) treatment often relies on incretin hormones (GLP-1 and GIP), which play crucial roles in metabolism, such as enhancing the secretion of insulin. However, the DPP-IV enzyme deactivates these incretins, necessitating the identification of effective DPP-IV inhibitors as potential antidiabetic agents. Although synthetic inhibitors like vildagliptin, sitagliptin, and saxagliptin are available, they can have adverse effects. Conversely, several natural plants and products inhibit the DPP-IV enzyme, offering safer and more effective alternatives for diabetes treatment. This research uses a multifaceted strategy involving pharmacokinetic/toxicity assessment and *in-silico* molecular docking to explore the potential of phytochemicals from *Dalbergia sissoo* as DPP-IV inhibitors with antidiabetic properties. An investigation of 21 (more negative) specific phytoconstituents from *D. sissoo* using molecular docking shows that six of them have a higher binding affinity ($\Delta G \geq -7.3$ kcal/mol) and significantly lower inhibition constants ($Ki \leq 3.17$ μM) compared to the well-established drug vildagliptin ($\Delta G = -7.3$ kcal/mol, $Ki = 4.45$ μM). Among the top-performing compounds, sissotrin, isocaviudin, tectoridin, caviunin 7-O-glucoside, biochanin A, 6, 7-dimethoxy-4-phenylcoumarin, tectorigenin, nordalbergin, 5-hydroxy-6,7,4'-trimethoxyisoflavone, and dalbergin, additional study utilizing pharmacophore/ADMET profiling validates their drug-like characteristics. These phytochemicals follow Lipinski's rule of five, showing desirable drug qualities and having high oral availability. The results indicate that phytochemicals from *D.sissoo*, especially the specific compounds identified, show potential as DPP-IV inhibitors. These compounds show strong *in-silico* properties and deserve more experimental testing, suggesting they could be safer and more efficient options for developing new antidiabetic drugs.

Introduction

Globally, approximately 537 million individuals aged between 20 and 79 are diabetic, accounting for 10.5% of the total population in that age range. It is estimated that 643 million adults will be diabetic by 2030 and 783 million by 2045. This reflects a 46% increase in diabetic individuals, compared to a 20% growth in the global population over the same period.[1] Diabetes mellitus, commonly referred to as diabetes, results from high levels of blood sugar caused by a lack of production of insulin in T1DM or inadequate use of insulin in T2DM. This severe, persistent (chronic) condition has been termed the "epidemic of the 21st century" and presents significant challenges in modern drug discovery efforts, particularly in the development of novel therapies for T2DM.[2] Although increasing insulin secretion has shown therapeutic benefits for T2DM patients, these medications often have unwanted adverse effects like weight gain and hypoglycemia.[3] Thus, there is an urgent need for the development of better medications to treat T2DM.

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Inhibiting human DPP-IV has been posed as a novel therapeutic avenue for T2DM.[4] DPP-IV is a conserved exopeptidase involved in protein regulation, and it can be tethered to the plasma membrane or move around unrestricted space outside the cells. It impacts glucose metabolism, oxidative stress and the immune system.[5] This enzyme, which is a member of the serine protease group, selectively eliminates N-terminal dipeptides from substrates with alanine or proline as the second residue. Because DPP-IV inhibition prolongs incretin half-lives, inhibitors have been developed to improve glucose tolerance in diabetics. DPP-IV has a major substrate in incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[6] Following a meal, intestinal L-cells release GLP-1, decreasing glucagon secretion, delaying stomach emptying and decreasing appetite, promoting islet β-cell differentiation and regeneration, and increasing insulin biosynthesis and secretion.[7] GIP, generated by duodenal K-cells, plays a major role in the process of glucose metabolism by boosting the release of insulin.[8] Both peptides are rapidly degraded by DPP-IV, resulting in very short half-lives (4 minutes for GIP and 1-2 minutes for GLP-1). Inhibiting DPP-IV enhances glucose homeostasis and reduces the risk of hypoglycemia by extending the impacts of GLP-1 and GIP.[9] This has garnered significant interest from the pharmaceutical industry, leading to the development and market introduction of DPP-IV inhibitors such as sitagliptin, saxagliptin, alogliptin, linagliptin, and vildagliptin.[10] However, extensive research indicates that CD26/DPP-IV is also crucial for the immune system, particularly for T cell activation.[11] Consequently, synthetic DPP-IV inhibitors may have side effects, making DPP-IV inhibition a double-edged sword.

The modern era is witnessing a rapid increase in the use of plants for medicinal purposes. With a lower risk of side effects and higher acceptance, these natural remedies have shown promising effects in the administration of diabetes and its associated issues.[12-14] In light of their capacity to elevate plasma GLP-1 and GIP levels, which ultimately boosts insulin secretion and improves blood sugar management, DPP-4 inhibitors are prescribed for the treatment of T2DM.[15] Bioactive compounds found in medicinal plants that inhibit DPP-4 activity have been extensively studied; examples of highly potent DPP-4 inhibitors include resveratrol, quercetin, and coumarins, with IC_{50} values measured in the nanomolar range. [16] The potential for inhibiting DPP-4 in *G. uralensis* and its bioactive constituents, licochalcone A and licochalcone B, has been investigated both *in-vitro* and *in-silico*, with findings indicating that licochalcone A is a better DPP-4 inhibitor.[17] Herbal DPP-4 inhibitors have demonstrated antidiabetic potential, and proven plant-based antidiabetic formulations have been studied to manage diabetes and its related complications.[18] A comprehensive study of medicinal plants and their active phytoconstituents that inhibit the DPP-IV enzyme has been reviewed, and proposed an alternative approach for the treatment of T2DM.[19]

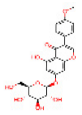
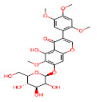
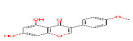
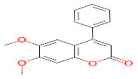
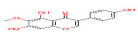
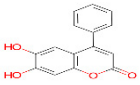
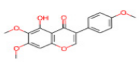
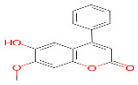
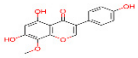
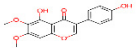
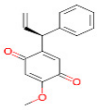
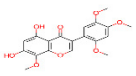
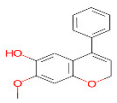
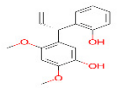
Dalbergia sissoo, an Indian rosewood, belongs to the Fabaceae family. This plant demonstrates significant pharmacological potential across various ailments, with numerous studies highlighting its anti-inflammatory, anthelmintic, anti-diarrheal, anti-termite, neuroprotective, antioxidant, analgesic, antipyretic, anti-nociceptive, and osteogenic properties.[20,21] A molecular docking (MD) study (*in-silico*) was performed to investigate the anti-wrinkling effects of *D. sissoo* extract ingredients lupeol, botulin and phytol by inhibiting MMP-1. It is found that the binding energy (ΔG) of lupeol is lower than that of doxycycline, showing that it is a more effective inhibitor of MMP-1.[22] Extensive *in-silico* studies, including molecular docking and MD simulations, revealed that Biorobin is the top phytochemical in *D. sissoo* leaves for inhibiting the c-Abl kinase receptor in leukemia cells, indicating to develop of new bioactive drugs to target cancer diseases.[23] Recent molecular docking studies have characterized plant-derived inhibitors of DPP-IV as potential antidiabetic agents.[24, 25] Because of the many uses of phytochemicals found in *D. sissoo*, we intend to explore its potential through *in-silico* methods in treating T2DM in order to uncover the potential of its phytochemicals as DPP-4 inhibitors via the application of computational molecular docking technique. A study comparing the binding properties, DPP-IV inhibition activity, and glucose-reduction effects of alogliptin (Pdb id: 3G0B), linagliptin (Pdb id: 2RGU), saxagliptin (Pdb id: 3BJM), sitagliptin (Pdb id: 1X70) and vildagliptin (Pdb id: 6B1E) in mice reveals that these DPP-4 inhibitors are a varied group of oral antihyperglycemic drugs with similar binding interactions with the enzyme.[26] However, when evaluating the efficiency and safety of vildagliptin, sitagliptin, and linagliptin in treating T2DM patients taking a combination of insulin and oral medications, all three DPP-4 inhibitors seem to be both safe and effective, but vildagliptin was found to be more successful in reducing insulin needs and managing blood sugar levels compared to sitagliptin and linagliptin.[27] Thus, we have chosen the DPP-IV enzyme complexed with vildagliptin (Pdb id: 6B1E) for our investigation.

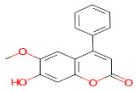
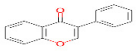
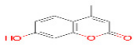
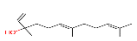
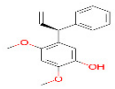
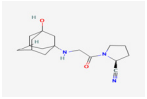
Materials and Methods

Target Protein Retrieval and Preparation

The DPP-IV enzyme (Pdb id: 6B1E) was obtained from the protein data bank (PDB) database.[28] In order to obtain a processed protein structure devoid of duplicate chains, the ligand groups, heteroatoms, and water molecules pre-bound were removed, along with any unwanted interference from the aforementioned groups, by opening the PDB file with the BIOVIA Discovery Studio Visualizer.[29]

Table 1: Selected phytochemicals from *D. sissoo* and drug molecule (Vildagliptin)

S. No.	*Compound*	*PubChem CID*	*Mol. formula*	*Mol. weight (g/mol)*	*Structure*
1	Sissotrin	5280781	$C_{22}H_{22}O_{10}$	446.4	
2	Isocaviudin	44257371	$C_{25}H_{28}O_{13}$	536.5	
3	Tectoridin	5281810	$C_{22}H_{22}O_{11}$	462.4	
4	Caviunin 7-O-glucoside	44257363	$C_{25}H_{28}O_{13}$	536.5	
5	Biochanin A	5280373	$C_{16}H_{12}O_5$	284.26	
6	6,7-Dimethoxy-4-phenylcoumarin	1235191	$C_{17}H_{14}O_4$	282.29	
7	Tectorigenin	5281811	$C_{16}H_{12}O_6$	300.26	
8	Nordalbergin	5320203	$C_{15}H_{10}O_4$	254.24	
9	5-Hydroxy-6,7,4'-trimethoxyisoflavone	10830108	$C_{18}H_{16}O_6$	328.3	
10	Dalbergin	442768	$C_{16}H_{12}O_4$	268.26	
11	psi-Tectorigenin	5353911	$C_{16}H_{12}O_6$	300.26	
12	7-O-Methyltectorigenin	5487785	$C_{17}H_{14}O_6$	314.29	
13	(S)-4-Methoxydalbergione	10400054	$C_{16}H_{14}O_3$	254.28	
14	Isocaviunin	15559891	$C_{19}H_{18}O_8$	374.3	
15	Dalbergichromene	5316291	$C_{16}H_{14}O_3$	254.28	
16	Latifolin	340211	$C_{17}H_{18}O_4$	286.32	

17	7-Hydroxy-6-methoxy-4-phenylcoumarin	5318543	$C_{16}H_{12}O_4$	268.26	
18	Isoflavone	72304	$C_{15}H_{10}O_2$	222.24	
19	Hymecromone	5280567	$C_{10}H_8O_3$	176.17	
20	trans-Nerolidol	5284507	$C_{15}H_{26}O$	222.37	
21	Dalbergiphenol	44446855	$C_{17}H_{18}O_3$	270.32	
22	Vildagliptin	6918537	$C_{17}H_{25}N_3O_2$	303.4	

Finally, this processed structure is converted into pdbqt format by making it a macromolecule (by use of Open Babel software) in-built in PyRx software.[30]

Ligand Retrieval and Preparation

Twenty-one phytochemicals from *D. sissoo* (Table 1) obtained by the IMPPAT website[31] and were downloaded from PubChem Data Bank.[32] The use of Open Babel software did energy minimization and conversion into .pdbqt format of these compounds in-built in PyRx software.

Docking Procedure and Analysis of Docked Results

Employing Vina Wizard from the PyRx Software, the docking operation was started. The Grid box was set to cover all residues in the receptor protein's active site (center at x: 37.2806, y: 51.6115, z: 34.2562, and dimension (in A^0) at x: 31.3072, y: 29.9228, z: 26.0155). The Vina Run exhaustiveness was set to value 8, and the docking procedure was started, showing binding affinity (kcal/mol) and rmsd values. The protein-ligand complexes that had docked best pose (having zero rmsd values) were selected for forward analysis. The binding sites of the docked complexes were visualized (in 2D and 3D) using the BIOVIA DSV software.

Evaluation of Inhibition Constant

The MD analysis predicts binding energies and H-bond modifications with the residues of the protein's active site, as well as the inhibition constant (Ki), which is employed to assess the effectiveness of the interaction. The dissociation constant (Kd) is the inhibition constant, also known as the Ki value of the docked complex. Smaller Ki values are related to higher inhibition and a lower dissociation probability. It is calculated by the formula Ki =exp(ΔG/(RT), where ΔG is the free energy of binding, gas constant R=1.987 Kcal/K/mol, and temperature T=298.15 K.[33]

Assessment of Molecular Properties and Bioactivity Score

The vildagliptin drug molecule (standard medication for DPP-4 inhibition) and ligand molecules were examined by the online screening server Molinspiration Cheminformatics.[34] SMILES of the compounds were utilized to create a three-dimensional structure. The bioavailability scores and molecular properties were computed using the mol file. The likelihood that a given molecule will be active increases with the bioactivity scores value.

ADME-TOX Prediction

The pharmacokinetics and toxicity of potential molecules determine their suitability as a drug molecule. In the initial phases of CADD, the significance of ADMET evaluation of chemicals has been acknowledged. The SwissADME[35] admetSAR 2.0[36] and ADMETLAB2.0[37] online platforms were employed to assess the pharmacokinetics and drug-like behavior of these compounds. Predicting compound toxicities is a vital part of the drug design process, with computational estimations offering a faster alternative to animal testing in determining toxic doses, ultimately reducing the need for animal experiments. In order to predict the toxicity of ligand molecules, ProTox 3.0[38] a virtual lab has been utilized. The ADMET properties of these molecules were evaluated using the SMILES format. Crucial factors for a medication molecule consist of pharmacokinetics traits such as P-glycoprotein, HIA, Lipinski Ro5 drug-likeness prediction, Pfizer, GSK, and Golden Triangle drug rule criteria, as well as BBB penetration. To assess drug-likeness and determine the

potential bioactivity of a compound, various key factors such as MW, LogP, and the number of HBA and HBD were taken into consideration. Lipinski's "Rule of 5"[39] states that the majority of compounds considered "drug-like" have a logP of ≤ 5, MW of ≤ 500, a number of nHA of ≤ 10, and nHD of ≤ 5. If a molecule doesn't adhere to several principles, it could encounter problems with its bioavailability. The ideal descriptor, LogP, and TPSA can be used to explain HIA, bioavailability, Caco-2 permeability and BBB penetration. These elements are crucial in forecasting the characteristics of a drug.

Results and Discussion

Investigation of Molecular Interactions (2D and 3D)

Molecular docking is a dependable, fast, and cost-effective approach used to discover new drugs (lead compounds) and potential drug-target proteins. After conducting an extensive study of the literature and examining the crystal structures of proteins significant in T2DM's biosynthetic pathways[40,41] our choice is dipeptidyl peptidase-IV (DPP-IV) with Pdb id: 6B1E. This virtual study explored the potential interactions between 21 selected phytochemicals and the DPP-IV enzyme. The results were compared with the existing T2DM medication vildagliptin. Six out of the 21 compounds showed better binding energies (in Kcal/mol) ranging from -8.8 to -7.5, compared to the binding energy of vildagliptin (-7.3) (Table 2). Other compounds that were analyzed also showed superior affinities for binding. The binding affinity of the inhibitor is a valuable metric for correlating and investigating the specific receptor protein. Lower binding energies are commonly related to stronger ligand affinities or to more favorable interactions with the protein. The ligand with the greatest affinity emerges as a potential prospective deserving of additional assessment. Twenty-one phytochemicals obtained from *D. sissoo* were screened against 6B1E, with ten compounds showing the strongest binding affinities to this receptor protein and chosen for further analysis after docking. The following compounds sissotrin, isocaviudin, tectoridin, caviunin 7-O-glucoside, biochanin A, 6,7-dimethoxy-4-phenylcoumarin, tectorigenin, nordalbergin, 5-hydroxy-6,7,4'-trimethoxyisoflavone and dalbergin shown considerably higher binding affinity with receptor protein 6B1E. The DPP-IV binding site exhibits high druggability, meaning that small molecules possessing physicochemical properties similar to those of drugs can be used to achieve precise and tight binding to the enzyme.[42, 43] DPP-IV ligands utilize different interaction motifs, such as Ser630 (part of the enzyme's catalytic triad with Asp708 and His740), the hydrophobic S1 pocket (composed of Tyr631, Val656, Trp659, Tyr662, Tyr666, and Val711), the hydrophobic S2 pocket (comprised of Arg125, Phe357, Arg358, Tyr547, Pro550, and Asn710), and the N-terminal recognition region (consisting of Glu205, Glu206, and Tyr662).[42-45] Co- crystalized structure of DPP-4 enzyme with vildagliptin (6B1E) exhibits hydrogen bonding (H-bonds) with residues Arg125, Glu205, Tyr547, Tyr631, Tyr662 and Asn710 and hydrophobic interactions with residues Phe357, Val656, Tyr662, Tyr666 and Val711.[26] Interestingly, in this docking investigation, vildagliptin forms H- bonds with residues Glu205 and Arg358 along with Hydrophobic interactions with residues Arg356, Phe357 and Arg358, confirming the validity of this docking experiment.

Compound sissotrin, having the highest binding affinity (-8.8 Kcal/mol and inhibition constant 0.35 μM), forms nine H- bonds with residues Arg125, Glu205, Glu206, Ser209, Arg358, Tyr547, Ser630, and Tyr662. Besides these, it also showed 2 more π-π stacked bonds with Phe357, which provide the highest binding affinity (Table 2, Fig. 1a-1c). Isocaviudin having binding affinity (-8.4 Kcal/mol and inhibition constant 0.69μM) formed ten H- bonds with residues Arg125, Glu205, Glu206, Ser209, Arg358, Tyr547, Ser630 and Tyr662, two π-π stacked bonds with residue Phe357 and One π-Alkyl bond with residue Arg358 (Table 2, Fig. 2a-2c). Tectoridin, having binding affinity (-8.4 Kcal/mol, inhibition constant 0.69 μM)), also binds efficiently with six H- bonds with Arg125, Glu205, Glu206, Tyr547 and Gln553A and one π-π stacked, one π-sigma and five other bonds with residues Glu206, Tyr456, Asp556, Asn710 and His740 (of the type unfavorable donor-donor and unfavorable acceptor-acceptor) (Table 2, Fig. 3a-3c). Caviunin 7-O-glucoside having binding affinity (-8.3 Kcal/mol and inhibition constant 0.82 μM) formed five H- bond with residue Arg125, Glu206, Ser630, Arg669 and His740 and two π-π stacked with residue Tyr547 and two π-π T-shaped bonds with residue Trp629 two π-Alkyl bond with residue Trp629. Besides these bonds, it also forms three (π-cation, π- Anion) bonds with residues Glu205 and Trp629, which strongly stabilize the binding (Table 2, Fig. 4a-4c). Biochanin A, having binding affinity (-7.6 Kcal/mol and inhibition constant 2.68 μM) formed three H-bonds with residues Tyr547, Tyr631 and Tyr666, including one π-π stacked one π-Alkyl with residue Phe357 and one unfavorable donor-donor bond with Asn710. (Table 2, Fig. 5a-5c). 6,7-dimethoxy-4-phenylcoumarin having binding affinity (-7.5 Kcal/mol and inhibition constant 3.17 μM) formed three H-bond with residues Arg358 and Tyr547 including three π-π stacked bonds with Phe357 and one π-Alkyl with Tyr666. (Table 2, Fig. 6a-6c).

Another compound tectorigenin having binding affinity (-7.2 Kcal/mol and inhibition constant 5.27 μM) formed six H- bonds with residues Arg125, Tyr547, Tyr631, Tyr662 and Asn710 including one π-π stacked with residue Phe357 and three (Alkyl and π-Alkyl bonds) with residues Val656, Trp659 and Trp666 (Table 2, Fig. 7a-7c).

All other remaining ligands also have significant binding affinity with active site residues and biding patterns resembling with control drug molecule vildagliptin.

Pharmacodynamics and Bioactivity Score of Compounds and Vildagliptin

The bioactivity score has been determined for ligands and drug molecules (Table 3) to assess their efficacy for various parameters. Upon investigation, it is evident that the majority of ligands exhibit a greater level of kinase inhibition. Five ligands, namely sissotrin, tectoridin, caviunin 7-O-glucoside, biochanin A and 6,7-dimethoxy-4-phenylcoumarin (comp. 1-6 except comp. 2) show higher values for enzyme inhibition in comparison to control drug Vildagliptin (0.17).

ADME-TOX Prediction

Table 4 displays the anticipated physical and chemical properties, drug-likeness, and molecular characteristics of ligands and drug compounds. Druglikeness was also

Table 2: Binding affinities, inhibition constants, hydrogen bonding of ligands with 6B1E

S. No.	*Ligand name*	*Binding affinity (ΔG) (kcal/mol)*	*Inhib. Const. Ki (μM)*	*H-bonds (no.)*	*H-bonded residues*	**Other types of bonds (No. of Other bonds)*
1	Sissotrin	-8.8	0.35	9	Arg125, Glu205, Glu206, Ser209, Arg358, Tyr547, Ser630, Tyr662	Pi-Pi Stacked (2)
2	Isocaviudin	-8.4	0.69	10	Arg125, Glu205, Glu206, Ser209 Arg358, Tyr547, Ser630, Tyr662	Pi-Pi Stacked (2), Alkyl (1)
3	Tectoridin	-8.4	0.69	6	Arg125, Glu205, Glu206, Tyr547 Gln553	Pi-Pi Stacked (1), Pi-Sigma (1)
4	Caviunin 7-O-glucoside	-8.3	0.82	5	Arg125, Glu206, Ser630, Arg669 His740	Pi-Pi Stacked (2), Pi-Pi T – shaped (1), Pi-Alkyl (2)
5	Biochanin A	-7.6	2.68	3	Tyr547, Tyr631, Tyr666	Pi-Pi Stacked (1), Pi-Alkyl (1)
6	6,7-Dimethoxy-4-phenylcoumarin	-7.5	3.17	3	Arg358, Tyr547	Pi-Pi Stacked (3), Pi-Alkyl (1)
7	Tectorigenin	-7.2	5.27	6	Arg125, Tyr547, Tyr631, Tyr662 Asn710	Pi-Pi Stacked (1), Pi-Alkyl (3) Alkyl (1)
8	Nordalbergin	-7.2	5.27	3	Ser630, His740, Gly741	Pi-Pi Stacked (2)
9	5-Hydroxy-6,7,4'-trimethoxyisoflavone	-7.1	6..24	3	Arg125, Tyr547, Tyr662	Pi-Pi Stacked (1), Pi-Alkyl (1)
10	Dalbergin	-7.0	7.38	4	Lys122, Arg125, Glu205, Asp709	Am Pi-Stacked (1) Pi-Alkyl (5)
11	psi-Tectorigenin	-7.0	7.38	2	Tyr662, His740	Pi-Pi Stacked (1), Pi-Alkyl (2), Pi-Anion (2)
12	7-O-Methyltectorigenin	-7.0	7.38	3	Arg125, Tyr547	Pi-Pi Stacked (1), Pi-Alkyl (2) Pi-Anion (1)
13	(S)-4-Methoxydalbergione	-6.8	10.35	3	Ser630, His740	Pi-Pi- Stacked (2)
14	Isocaviunin	-6.8	10.35	3	Glu205, Glu206, Tyr547	Pi-Pi Stacked (2), Pi-Alkyl (5)
15	Isocaviunin	-6.8	10.35	2	Arg125, Glu205	Am Pi-Stacked (1), Pi-Alkyl (1), Alkyl (1), Pi-Cation (1), Pi-Anion (1)
16	Latifolin	-6.7	12.25	---	---	Pi-Pi- Stacked (1) Pi-Alkyl (1) Pi-Anion (1)
17	7-Hydroxy-6-methoxy-4-phenylcoumarin	-6.7	12.25	2	Arg358, Tyr547	Pi-Pi- Stacked (2)
18	Isoflavone	-6.6	14.51	---	---	Pi-Pi- Stacked (3)
19	Hymecromone	-6..5	17.18	4	Glu206, Arg358, Arg669	Pi-Pi- Stacked (3)
20	trans-Nerolidol	-6.3	24.07	2	Arg356, Arg358	Pi-Alkyl (3), Alkyl (2)
21	Dalbergiphenol	-6.1	33.74	1	Tyr662	Pi-Pi T-Shaped (1), Pi-Alkyl (5), Pi-Sigma (1)
22	Vildagliptin (control drug)	-7.3	4.45	3	Glu205, Arg358	Pi-Alkyl (2), Alkyl (1)

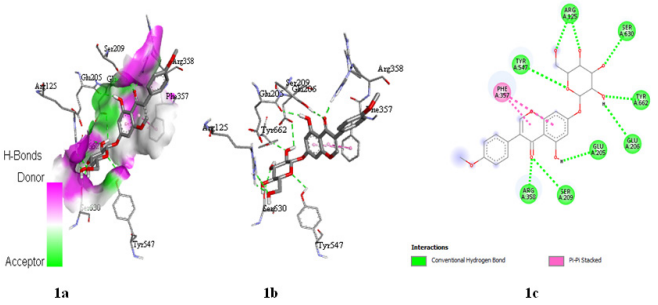


Fig. 1: Sissotrin

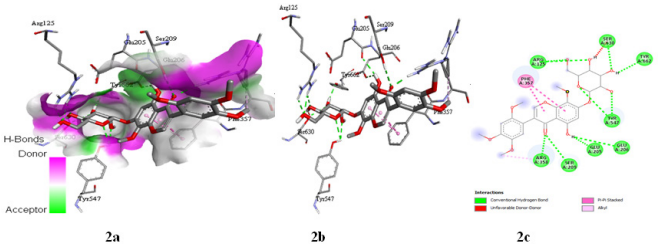


Fig. 2: Isocaviudin

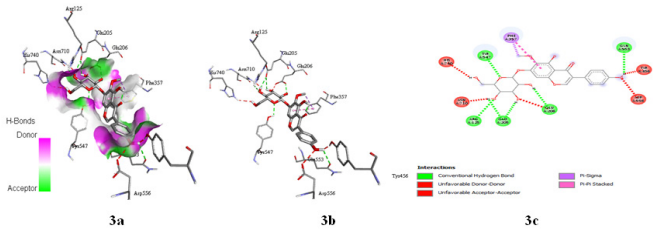


Fig. 3: Tectoridin

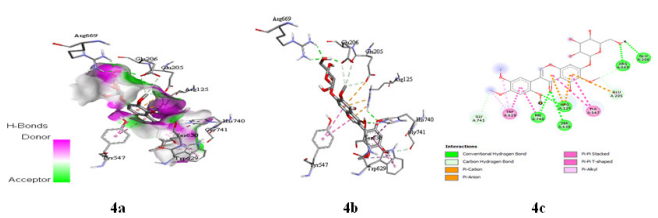


Fig. 4: Caviunin 7-O-glucoside

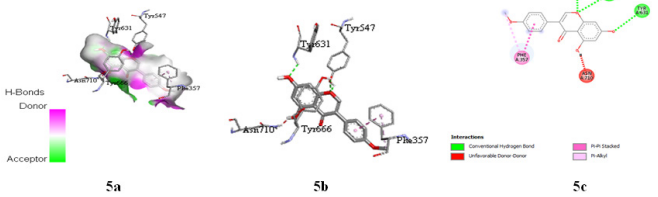


Fig. 5: Biochanin A

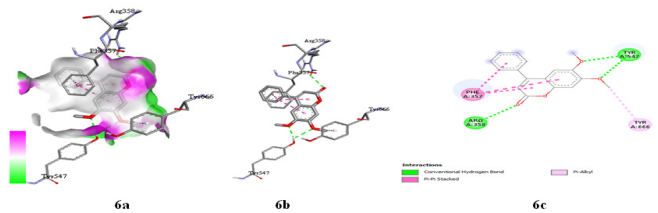


Fig. 6: 6,7-Dimethoxy-4-phenylcoumarin

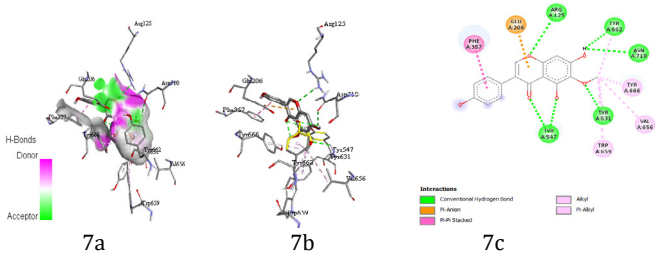


Fig. 7: Tectorigenin

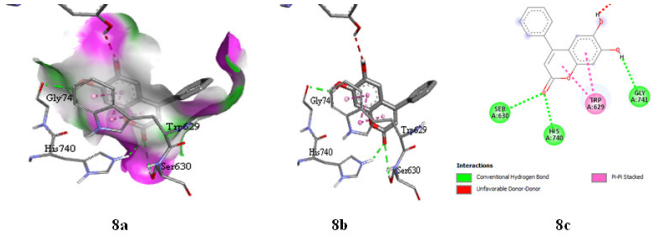


Fig. 8: Nordalbergin

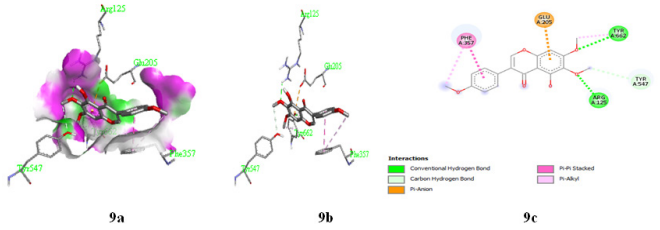


Fig. 9: 5-Hydroxy-6,7,4'-trimethoxyisoflavone

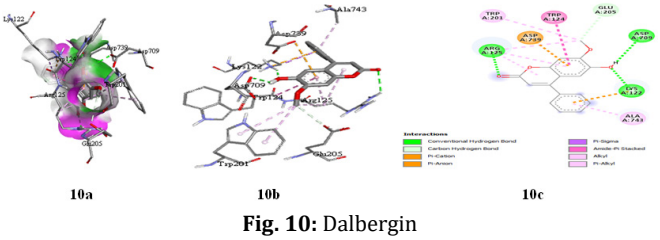


Fig. 10: Dalbergin

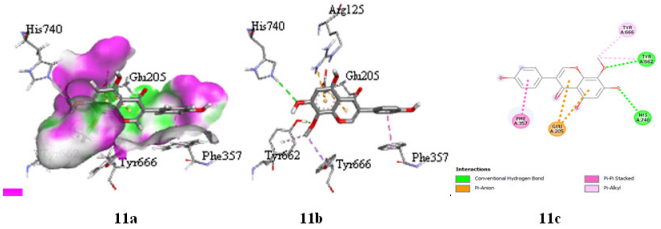


Fig. 11: psi-Tectorigenin

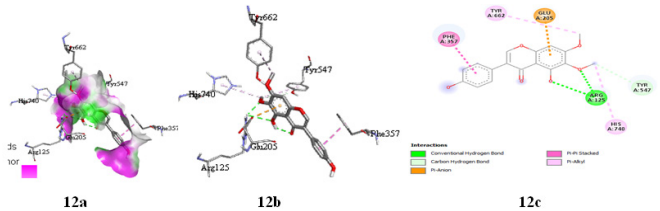


Fig. 12: 7-O-Methyltectorigenin

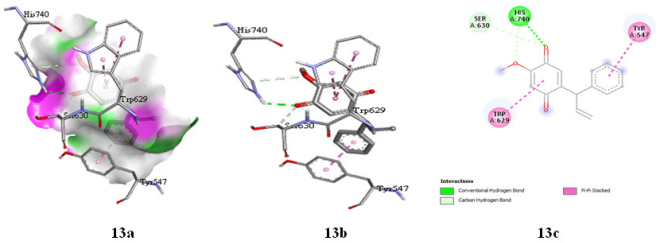


Fig. 13: (S)-4-Methoxydalbergione

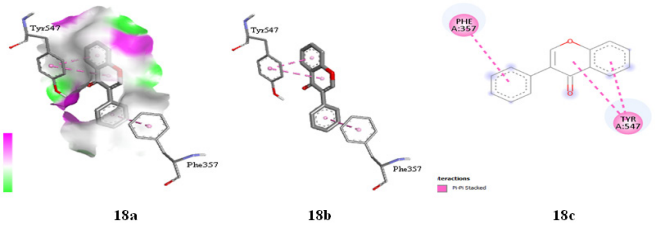


Fig. 18: Isoflavone

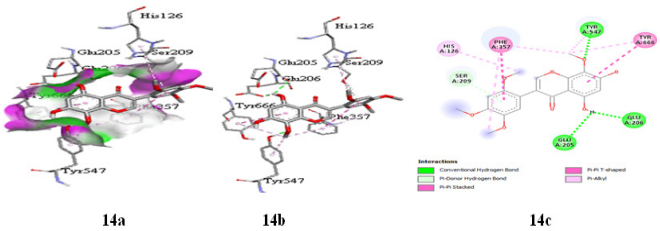


Fig. 14: Isocaviunin

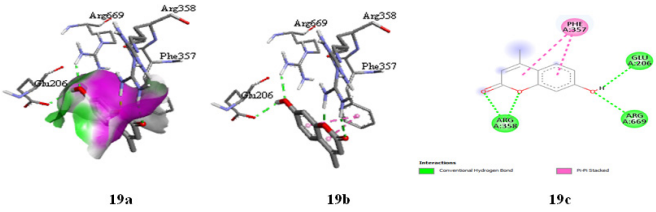


Fig. 19: Hymecromone

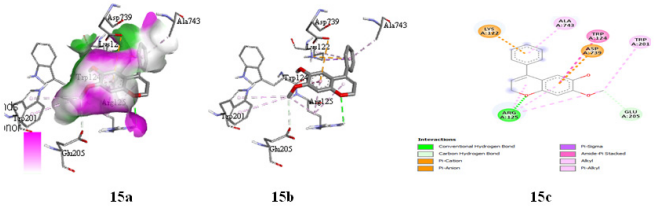


Fig. 15: Isocaviunin

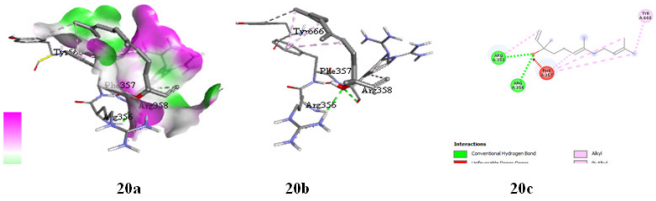


Fig. 20: trans-Nerolidol

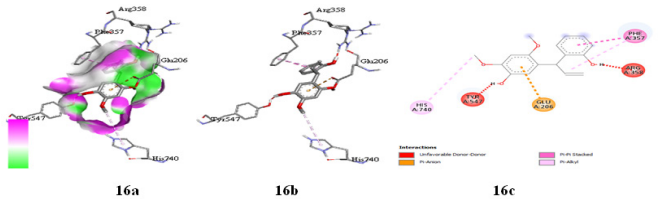


Fig. 16: Latifolin

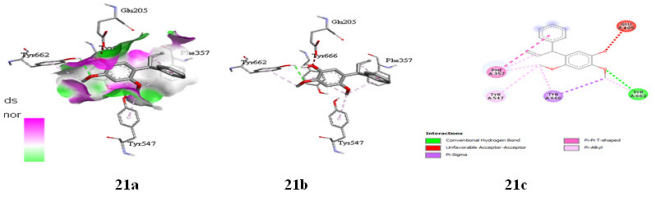


Fig. 21: Dalbergiphenol

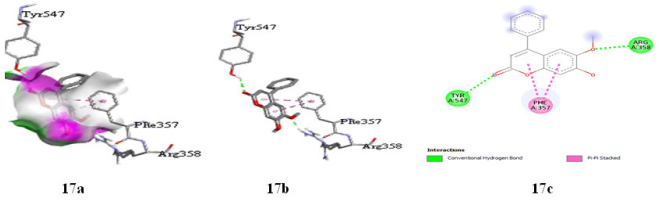


Fig. 17: 7-Hydroxy-6-methoxy-4-phenylcoumarin

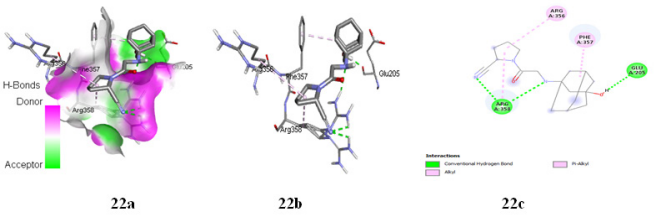


Fig. 22: Vildagliptin (control drug)

Fig. 1 (a, b, c) – Fig. 22 (a, b, c): Showing all 21 phytochemicals and vildagliptin (in Table 1, S. No. 1-22) docked with 6B1E. (a) The 3D interactions (depicting donor and accepter H– bonds regions) (b) The 3D image showing significant interactions with binding-pocket residues (c) The molecular level interactions (2D) of the ligands

predicted using different drug rules. All ten compounds were found to comply with lipinski RO5 except isocaviudin, tectoridin and caviunin 7-O-glucoside (1 violation, which may be ignored). All compounds accept the Pfizer rule; likewise, GSK and Golden Triangle rules are also violated by some compounds. But compounds Biochanin A, 6,7-dimethoxy-4-phenylcoumarin, tectorigenin, nordalbergin, 5-hydroxy-6,7,4'-trimethoxyisoflavone and dalbergin accepted all the four drug rules. QED value for most of the compounds is greater than 0.5, showing positive characteristics for drug suitability of these compounds except sissotrin,

Table 3: Predicted bioactivity score of ligands and vildagliptin

S/N	*Parameter*	**Comp. 1*	*Comp. 2*	*Comp. 3*	*Comp. 4*	*Comp. 5*	*Comp. 6*	*Comp. 7*	*Comp. 8*	*Comp.9*	*Comp.10*	*Vildagliptin*
1	GPCR ligand	-0.04	-0.19	-0.07	0.08	0.11	0.28	-0.21	-0.51	-0.24	-0.50	0.04
2	Ion channel mod,	-0.35	-0.58	-0.09	-0.22	0.10	-0.01	-0.64	-0.47	-0.65	-0.54	-0.04
3	Kinase inhibitor	-0.04	-0.20	0.18	-0.22	0.93	0.76	-0.01	-0.28	-0.05	-0.25	-0.26
4	Nuclear receptor	0.16	0.34	0.34	0.28	0.19	0.24	0.10	0.02	0.04	-0.02	-0.19
5	Protease inhibitor	-0.29	-0.39	-0.25	-0.05	-0.20	0.02	-0.72	-0.67	-0.65	-0.69	1.02
6	Enzyme inhibitor	0.29	0.01	0.26	0.37	0.21	0.35	0.05	0.12	0.00	0.07	0.17

*Comp. (1-10) from Table 1

Table 4: Predicted properties (Druglikeness and Molecular) of phytochemicals and drug molecule

S/N	*Parameter*	*#Comp. 1*	*Comp. 2*	*Comp. 3*	*Comp. 4*	*Comp. 5*	*Comp. 6*	*Comp. 7*	*Comp. 8*	*Comp.9*	*Comp.10*	*Vildagliptin*
1	miLogP	1.02	0.38	0.27	0.38	2.80	3.36	2.28	2.75	3.13	3.05	1.42
2	TPSA	159.05	186.75	179.28	186.75	79.90	48.68	100.13	70.67	78.14	59.67	76.36
3	natoms	32	38	33	38	21	21	22	19	24	20	22
4	MW	446.41	536.49	463.41	536.49	284.27	282.30	300.27	254.24	328.32	268.27	303.41
5	nON (HBA*)	10	13	11	13	5	4	6	4	6	4	5
6	nOHNH (HBD**)	5	5	6	5	2	0	3	2	1	1	2
7	Lipinski Ro5	+A	++R	R	R	A	A	A	A	A	A	A
	Pfizer	A	A	A	A	A	A	A	A	A	A	A
	GSK	R	R	R	R	A	A	A	A	A	A	A
		A	R	A	R	A	A	A	A	A	A	A
8	nrotb	5	2	5	8	2	0	2	1	4	2	3
9	volume	373.70	450.33	381.72	450.33	241.58	251.09	249.59	216.03	284.65	233.56	289.82
10	QED	0.37	0.266	0.302	0.266	0.756	0.69	0.672	0.517	0.792	0.725	0.821

Note: *HBA: Hydrogen Bond Acceptors, +A-Accepted, ++R-Rejected

**HBD: Hydrogen Bond Donors

#Comp. (1-10) from Table 1

Table 5: Estimation of absorbtion and distribution of ligands and control drug

		Absorption						*Distribution*			
S. No	*Ligand name*	*Solubility logS*	*logP*	*Coca-2*	*HIA*	*Skin Log Kp*	*PPB (%)*	*VDss*	*BBB*	*Fu (%)*	*Pgp- sub*
1	Sissotrin	-3.047	0.349	-6.286	Low	-8.18	78.4	0.669	No	20.7	Yes
2	Isocaviudin	-2.367	-0.237	-6.236	Low	-8.79	73.8	0.635	No	24.4	Yes
3	Tectoridin	-3.032	-0.331	-6.307	Low	-8.53	79.7	0.781	No	20.2	Yes
4	Caviunin 7-O-glucoside	-2.43	-0.005	-6.196	Low	-8.79	74.4	0.636	No	24.4	Yes
5	Biochanin A	-3.725	2.411	-5.009	High	-5.91	97.2	0.829	No	2.1	No
6	6,7-Dimethoxy-4-phenylcoumarin	-4.374	2.919	-4.566	High	-5.87	98.6	0.385	Yes	0.8	No
7	Tectorigenin	-3.297	1.808	-5.032	High	-6.26	95.6	0.207	No	4.3	No
8	Nordalbergin	-3.889	2.491	-4.828	High	-6.16	98.6	0.216	Yes	0.9	No
9	5-Hydroxy-6,7,4'-trimethoxyisoflavone	-3.572	2.429	-4.961	High	-5.97	95.5	0.262	Yes	4.3	No
10	Dalbergin	-4.302	2.935	-4.956	High	-6.02	98.9	0.288	Yes	0.7	No
11	Vildagliptin	-1.128	0.28	-4.713	High	-7.53	93.2	0.957	No	4.9	Yes

isocaviudin, tectoridin and caviunin 7-O-glucoside, showing their less druggability.

Above discussed properties (in Table 4) of ligands (comp.1-10) and drug molecules are depicted in Figs 23 - 33. Almost all the compounds show these properties within the upper and lower domains of the drug-likeness.

Fig. 23 – 33: Showing upper and lower domain of drug-likeness including compound's properties for compounds (1-10) and drug molecule

Table 6: Estimation of metabolism and excretion of ligands and control drug

		CYP- Metabolism							*Excretion*	
S. No.	*Ligand name*	*2D6 Substrate*	*3A4 Substrate*	*1A2 Inhib.*	*2C19 Inhib.*	*2C9 Inhib.*	*2D6 Inhib.*	*3A4 Inhib.*	*CLp*	*CLr*
1	Sissotrin	++*	---	---	---	---	---	---	0.105	0.628
2	Isocaviudin	---	--	---	---	---	---	---	0.359	0.71
3	Tectoridin	-	---	---	---	---	---	---	0.578	0.684
4	Caviunin 7-O-glucoside	---	--	---	---	---	---	---	0.214	0.712
5	Biochanin A	+++	---	+++	+++	--	+++	+++	0.809	0.597
6	6,7-Dimethoxy-4-phenylcoumarin	+++	+++	+++	+++	++	---	---	0.638	0.217
7	Tectorigenin	+++	---	+++	+++	-	-	+++	0.868	0.656
8	Nordalbergin	+++	---	+++	+++	+++	--	---	0.819	0.541
9	5-Hydroxy-6,7,4'-trimethoxyisoflavone	+++	---	+	++	--	--	-	0.345	0.26
10	Dalbergin	+++	++	+++	+++	++	+	---	0.593	0.411
11	Vildagliptin	---	--	---	---	---	---	---	0.634	0.698

* Prediction probability values are converted into six symbols for the classification endpoints: 0-0.1 (---), 0.1-0.3 (--), 0.3-0.5 (-), 0.5-0.7 (+), 0.7-0.9 (++), and 0.9-1.0 (+++).

The absorption and distribution properties of the studied compounds is depicted in Table 5. For evaluating a drug's bioavailability, the LogS value is crucial. For optimal absorption and distribution within the body, a higher solubility (higher LogS>-4) is typically desired. All the studied compounds fulfill this criteria. The pharmaceutical industries use LogP to comprehend how drug molecules behave within the body. In order to aid in drug selection and analog optimization, drug candidates are frequently screened using logP in addition to other factors. This is due to the fact that a compound's lipophilicity plays an important role in determining its absorption, distribution within the body, ability to pass through biological barriers and essential membranes, metabolism, and excretion (ADME properties). The logP of a compound meant for oral administration should be less than 5, according to "Lipinski's RO5". All the studied compounds show positive LogP values between 2 and 3, showing lipophilic character, except isocaviudin, tectoridin and caviunin 7-O-glucoside (-LogP), showing their hydrophilic nature. The Caco-2 cell line serves as a representation of drug absorption in the human intestine. The Caco-2 Permeability determined for all these molecules was to be almost identical to that of the drug molecule. The first four compounds show low HIA and no BBB permeation except all other compounds. Predicted skin permeability, log Kp is within range for all the compounds (acceptable range: −8.0 to −1.0).

A medication's pharmacodynamic behavior is strongly influenced by its ability to bind to proteins in plasma, which is one of the main mechanisms of drug uptake and distribution. Due to the fact that when a drug binds to serum proteins, its free concentration is at risk, PPB has a direct impact on oral bioavailability. A compound is deemed to have a proper PPB if its predicted value is less than 90%. Sissotrin, isocaviudin, tectoridin and caviunin 7-O-glucoside show PPB value less than 90% and tectorigenin (95.6%) slightly higher than control drug vildagliptin (93.2%). The extent to which a drug binds blood proteins may have an impact on its efficacy because the more bound the protein, the less effectively it can diffuse or cross cellular membranes. A medication that has ≥ 5% Fu is regarded as excellent. Sissotrin, isocaviudin, tectoridin, and caviunin 7-O-glucoside exhibit around 20% Fu. Other compounds exhibit a lower value.

CYP-mediated metabolism for Substrates (2D6, 3A4) and for Inhibitors (1A2, 2C19, 2C9, 2D6 and 3A4) behave as the key enzymes involved in the metabolism of drugs (Table 6). CYP-mediated metabolism not only helps drugs be eliminated, but it additionally results in toxic metabolites and unfavorable drug-drug interactions. Sissotrin, isocaviudin, tectoridin and caviunin 7-O-glucoside show approximately the same value as the control drug vildagliptin apart from the other compounds studied. Excretion parameters for plasma clearance (CLp) and renal clearance (CLr) are given in Table 6. Sissotrin, isocaviudin and caviunin 7-O-glucoside have lower CLp values in comparison to other compounds. Other compounds except 6,7-dimethoxy-4-phenylcoumarin have better CLr values. Predicting the toxicities of compounds is a vital step in the creation of novel drugs. Evaluating toxicity computationally is quicker and can also lessen the number of experiments with animals. A detailed toxicities evaluation of the studied compounds is presented in Table 7. LD_{50} values, expressed as mg/kg body weight, are frequently used to indicate toxic doses. The dose at which 50% of test subjects pass away after being exposed to a compound is known as the median

Table 7: Estimation of toxicity of ligands and control drug

			Toxicity							
S. No.	*Ligand name*	*LD_{50} (mg/kg)*	*Toxicity Class*	*Hepato (dili)*	*Neuro*	*Nephro*	*Resp*	*Cardio*	*Carcinogen*	*Ames*
1	Sissotrin	2500	5	*i	i	**a	a	i	i	0.681
2	Isocaviudin	5000	5	i	i	a	a	a	a	0.547
3	Tectoridin	5000	5	i	i	a	a	i	i	0.515
4	Caviunin 7-O-glucoside	5000	5	i	I	a	a	a	i	0.532
5	Biochanin A	2500	5	i	i	a	a	a	i	0.661
6	6,7-Dimethoxy-4-phenylcoumarin	2000	4	i	i	a	a	i	i	0.463
7	Tectorigenin	2500	5	i	i	a	a	a	i	0.461
8	Nordalbergin	2850	5	i	i	a	a	i	a	0.545
9	5-Hydroxy-6,7,4'-trimethoxyisoflavone	2500	5	i	i	a	a	i	i	0.52
10	Dalbergin	2850	5	i	i	a	a	i	a	0.493
11	Vildagliptin	80	3	i	i	i	a	i	i	0.108

*i- inactive **a-active

lethal dose, or LD_{50}. The compounds are categorized as follows based on their LD_{50} values: Class 3 becomes toxic if ingested (LD_{50} between 50 and 300), Class 4 is considered harmful (LD_{50} between 300 and 2000), and class 5 may cause harm if ingested (LD_{50} between 2000 and 5000). All the compounds (Class 5) except 6,7-Dimethoxy-4-phenylcoumarin (Class 4) are less toxic in comparison to the control drug molecule vildagliptin (Class 3). All the compounds are inactive for hepatotoxicity (Drug Induced Liver Injury-dili) and neurotoxicity. All the compounds show active responses for nephrotoxicity and respiratory toxicity. Most of the compounds show inactive responses towards cardiotoxicity and carcinogenicity. Ames test is a short-term bacterial test used to identify carcinogens by assessing the end point of mutagenicity in bacteria. All the compounds show higher ames toxicity than vildagliptin. Studies suggest that sissortin[46] and Biochanin A[46,47] have been investigated against neuroinflammatory markers and pharmaceutical applications as potent therapeutic targets. Research has demonstrated that Biochanin A has a range of impacts like anti-inflammatory and estrogen-like effects, including modulation of glucose and lipid metabolism.[47] It also has properties related to cancer prevention, neuroprotection, and drug interactions.[48] Tectoridin effectively stops acute ethanol-induced liver fat accumulation in mice.[49] Additionally, it enhances the function of papilla cells on human skin and encourages hair shaft growth in mice.[50] Caviunin 7-O-glucoside has the potential to treat the clinical symptoms of osteoarthritis.[51] The neuroinflammatory impacts of tectorigenin were assessed in both LPS-treated BV2 microglial cells and mouse models.[52] Anti-neuroinflammatory effect of nordalbergin[53] and the antidiabetic effect of dalbergin[54] have also been studied extensively. Natural phenolic compounds such as rutin, antroquinonol, curcumin, quercetin, berberine, resveratrol, etc., were studied by molecular docking approach and found that these are good inhibitors of the DPP-IV enzyme.[55]

Conclusion

Investigating low-toxicity phytoconstituents is a promising research direction due to the global threat of diabetes and the side effects of ongoing diabetes medications. The major objective of this study is the screening of phytochemicals extracted from the *D. sissoo* plant, with a specific focus on targeting the DPP-IV enzyme (6B1E). This enzyme acts as an oral antihyperglycemic agent by avoiding the inactivation of GLP-1 and GIP incretin hormones, impacting glucose regulation through various pathways such as increased insulin secretion, slowed stomach emptying, and decreased glucagon levels and food consumption after meals. Molecular docking studies found six plant compounds - Sissotrin, isocaviudin, tectoridin, caviunin 7-O-glucoside, Biochanin A, and 6,7-dimethoxy-4-phenylcoumarin - with better binding affinity to protein. Pharmacophore (PDB ID: 6B1E) than vildagliptin, a typical DPP-IV inhibitor pharmacophore and ADMET investigations validated their drug-like attributes with no immediate toxicity. Furthermore, tectorigenin, nordalbergin, 5-hydroxy-6,7,4'-trimethoxyisoflavone, and dalbergin showed notable binding affinities for DPP-IV and have been investigated for different medical benefits. These results indicate that phytochemicals from *D. sissoo* could possibly be transformed into antidiabetic drugs that are both more efficient and safer. The next important phase includes putting these phytoconstituents through extensive clinical trials to confirm their effectiveness

and help integrate them into regular diabetes treatment plans. There is great potential in the future to use these natural compounds to tackle the worldwide health issues of diabetes mellitus.

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