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RESEARCH ARTICLE

In silico ADMET profiling and PTP1B molecular docking of phytochemicals from the desert medicinal plant *Pergularia tomentosa* L.

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Abstract

This study presents an *in silico* profiling of phytochemical compounds derived from *Pergularia tomentosa* L. against the protein tyrosine phosphatase 1B (PTP1B), a key regulator in type 2 diabetes mellitus (T2DM). With the aid of computational assessment, the phytochemicals were examined for their drug-likeness, absorption, distribution, metabolism, excretion and toxicity (ADMET) properties and molecular interactions with the target protein PTP1B. A total of 40 phytochemical compounds derived from *P. tomentosa* were evaluated using ADMET tools and molecular docking against PTP1B, a central enzyme involved in the negative regulation of insulin signalling and thus a critical target in T2DM. Molecular docking analysis identified six top phytochemical compounds from *P. tomentosa* with binding affinities ranging from -6.8 to -7.9 kcal/mol relative to the reference inhibitor and exhibiting satisfactory ADMET profiles with no major toxicity. These findings suggest that phytochemicals from *P. tomentosa* possess promising antidiabetic potential by potentially inhibiting PTP1B, as indicated by *in silico* studies.

Keywords: ADMET; molecular docking; *Pergularia tomentosa*; phytochemicals; PTP1B; T2DM

Introduction

One of the most significant global health issues, type 2 diabetes mellitus (T2DM), affects more than 500 million people and leads to substantial healthcare costs and mortality. T2DM is a metabolic disease characterized by continual hyperglycemia and impaired metabolic processes of fats, carbohydrates and proteins (1). T2DM growth is associated with serious health issues, such as retinopathy, nephropathy, neuropathy and heart disease (2).

The pharmacological treatments utilized for the management of diabetes mellitus include primarily oral anti-diabetic medicines or insulin therapy (3). Therefore, there is growing interest in the investigation of medicinal herbs, traditionally used as therapeutic agents to manage diabetes mellitus (4). These issues highlight an urgent demand for safer, more effective and low-cost therapeutic alternatives, especially those obtained from natural medicinal origins (5).

This research investigates the type 2 anti-diabetes mellitus potential of phytochemical compounds derived from *Pergularia tomentosa* L., an evergreen annual shrub belonging to the family Apocynaceae, characterized by a distinctive odor (6). It is a hairy plant and green in colour and widely dispersed in the outgrowth of Africa (Niger, Egypt, Ethiopia, Algeria, Jordan, North Sudan and Kenya) and the Middle East (Saudi Arabia, Iran, Oman, Pakistan and Afghanistan). The presence of bioactive phytochemical compounds, including cardenolide, glycosides, flavone glycosides, which exhibit antioxidant properties (7). *P. tomentosa* plays an important role in reducing blood glucose levels and demonstrates antihyperglycemic, hypolipidemic, antioxidant and triglyceride-lowering effects in diabetic models (8).

Ethnobotanically, *P. tomentosa* has been used in traditional medicine for treating different types of diseases, such as gastrointestinal problems, inflammation, fever, wounds, respiratory disorders and parasitic infections (9). According to *in vivo* studies, phytochemical compounds of *P. tomentosa* have been identified as diverse bioactive secondary metabolites, such as cardenolides (e.g., pergularosides), which are best known for their potent biological action; flavonoids and flavone glycosides, which exhibit antioxidant and metabolic regulatory characteristics (10). Steroidal glycosides, phenolic compounds, alkaloids, saponins and triterpenoids, which contribute to its antioxidant, enzyme-modulating potential and anti-inflammatory properties, encouraging the plant's traditional utilization and giving a biochemical rational for evaluating its components in antidiabetic drug discovery (11).

Through an *in silico* computational method, we screened the phytochemical for drug-likeness and their binding affinities with the target protein. PTP1B, a regulatory enzyme implicated in impaired insulin signaling, plays a critical inhibitory role in T2DM (12). The essential function of the PTP1B serves as a central antagonistic

control of the tyrosine phosphorylation cascade intrinsic to the signalling pathway of insulin (13). The development of PTP1B function as an "insulin sensitiser" in T2DM (14). Extensive molecular, genetic and pharmacological work has validated PTP1B as alterative target in metabolic disorders and its hyperactivity contributes immediately to insulin opposition and broken glucose homeostasis (15).

ADMETlab 2.0 is an integrated platform for the identification of pharmacokinetics and toxicity constants of bioactive phytochemical compounds with the help of ADMET-related endpoints (16). ProTox-II is a web server to identify toxicity and multiple toxicological endpoints for different bioactive phytochemical compounds and has four models, like the oral acute toxicity prediction model, the organ toxicity model and the carcinogenicity model endpoint, among others (17). The present work aimed to measure the T2DM potential of *P. tomentosa* phytochemicals through with an *in silico* investigation combining ADMETlab 2.0 screening and molecular docking against the validated insulin-signaling regulator PTP1B. We hypothesised that the reported phytochemicals of *P. tomentosa* would display favourable pharmacokinetic (ADMET) properties and significant binding affinity toward PTP1B, comparable to or better than the reference inhibitor trodusquemine.

Materials and Methods

Identification of bioactive phytochemicals of *P. tomentosa*

As this was an entirely *in silico* investigation, no physical plant material was collected. We identified 40 phytochemicals, selecting only well-characterized, structurally defined compounds with available 3D canonical SMILES structures were reported antidiabetic activity, with the help of peer-reviewed literature and databases such as PubChem (https://pubchem.ncbi.nlm.nih.gov), Scopus, Google Scholar and phytochemical/ethnobotanical databases (18).

Pharmacokinetic categorization (ADMET studies)

To evaluate toxicity and pharmacokinetic profiles of the selected phytochemicals, we utilized ADMETlab 2.0 (version 2020; accessed on 12 March 2024) (https://admetmesh.scbdd.com). ADMETlab 2.0 provide several key predictive parameters, including:

Human intestinal absorption (HIA)

compounds with predicted HIA ≥ 70 % were considered well absorbed.

Metabolism (CYP450 inhibition)

compounds were flagged if identified to inhibit CYP3A4, CYP2D6 or CYP2C9, major isoforms involved in drug metabolism.

Distribution like blood-brain barrier permeability (logBB)

values between -1.0 and +0.3 reasoned satisfactory for non-CNS drugs, indicating controlled but not excessive penetration.

Toxicity alerts

hepatotoxicity (0 = non-toxic, 1 = toxic), hERG inhibition, AMES mutagenicity and acute oral toxicity were evaluated according to thresholds outlined in the ADMETlab documentation (19).

Prediction of target proteins of bioactive phytochemicals *P. tomentosa*

Swiss Target Prediction was utilized for the prediction of human target protein of *P. tomentosa*. The tool was executed using 3-dimensional canonical SMILES as input and restricted to the "*Homo sapiens*" species filter. Predicted targets with a probability score ≥ 0.10 were considered for further study (20). Therefore, the occurrence of predictions toward PTP1B-combined with strong biological credibility was utilized to confirm the selection of PTP1B as the essential molecular target for resultant molecular docking and ADMET evaluation.

After identifying the target protein, we utilized the PDB database to obtain its 3-D structure and downloaded. Subsequently, Biovia Discovery Studio Visualizer [Dassault Systems, BIOVIA Corp USA, v21.1] was used to view the 3-D structures of the target protein (21).

Target protein preparation

The three-dimensional structure of target Protein Tyrosine Phosphatase 1B (PTP1B) (PDB ID: 4IN8), was obtained from the Protein Data Bank, Research Collaboratory for Structural Bioinformatics (RCSB). The 4IN8 structure was resolved by X-ray crystallography at 1.65 Å resolution and selected for molecular docking. The resulting structure was prepared by eliminating water molecules, cofactors and ligands. Afterwards, polar hydrogen atoms were added and AutoDock Vina v1.2.3 (http://vina.scripps.edu/) was utilized to execute molecular docking study and evaluate possible interactions (22).

Phytochemical compound preparation

The phytochemical compounds derived from *P. tomentosa* were obtained from PubChem in 3-dimensional canonical SMILES format. This procedure was refined by converting SMILES to 3D structures using OpenBabel v3.1.1. Energy minimization was performed using the MMFF94 force field until the gradient reached < 0.0001 kcal/mol·Å, followed by setting rotatable bonds and generating a single optimized low-energy conformation. Final PDBQT files were prepared. All phytochemical compounds were standardised at pH 7.4 and processed with characteristics that are accurate for molecular docking studies (23).

Molecular docking study

Binding site selection

The 4IN8 protein binding pocket was selected to obtain biologically important outcomes. This investigation focused on the docking pocket because trodusquemine (MSI-1436) is a well-characterized synthetic aminosterol derivative modelled after the squalamine inhibitor of PTP1B (24). The docking grid was centred on the trodusquemine-binding region using the following coordinates: x = -9.14, y = 46.22, z = 48.38, with a sphere of 12.13 Å. Molecular docking was carried out using AutoDock Vina v1.2.3, with the following parameters: exhaustiveness = 8, number of modes = 9 and energy range = 3 kcal/mol. All ligands were prepared as described above and docked into the PTP1B binding site to identify binding affinity and intermolecular interactions. The resulting protein-ligand complexes were visualized and analyzed using BIOVIA Discovery Studio Visualizer to evaluate π-stacking, hydrophobic interactions and hydrogen bonding (25).

Docking analysis

Docking analysis was carried out using a single Vina run per ligand with the default nine generated poses, from which the best-scoring position was chosen for analyzing the interaction between phytochemical compounds derived from *P. tomentosa* and target PTP1B (PDB ID: 4IN8). This process involved evaluating parameters such as conformational changes, intermolecular interactions and binding energies. The resulting ligand-protein complexes were analyzed to determine phytochemical compounds with strong binding energy and favorable interactions with target PTP1B protein. Therefore, no statistical significance testing was applied in this research (26).

Results

Pharmacokinetics and bioavailability of phytochemical compounds

ADMET analysis revealed that the bio-active phytochemical compound derived from *P. tomentosa* fell within acceptable ADMET evaluation ranges, supporting their possible suitability as promising drug candidates (27). The bioactivity values for each phytochemical compound obtained from *P. tomentosa,* as predicted using the Molinspiration tool (Table 1; Fig. 1). These values were calculated for different target categories, such as kinase inhibitor (KI), nuclear receptor ligand (NRL), protease inhibitor (PI), G protein-coupled receptor (GPCR) ligand, ion channel modulator (ICM) and enzyme inhibitor (EI). These values represent the ability of each phytochemical compound to modulate action of particular biological targets (28).

Phytochemical compounds with values greater than zero are considered to exhibit significant biological activity, while values between -0.5 to 0 indicate moderate activity. Phytochemical compounds with values below -0.5 are considered inactive (28). Particularly CIDs 73170, 12302399, 162876281, 155554459 and 163106525 showed strong interactions with nuclear receptors (scores ranging from 0.35 to 0.45) and demonstrated balanced engagement with enzymes (≥ 0.23) and nuclear receptors (≥ 0.33), indicating their potential to modulate enzymatic targets such as PTP1B, an antagonistic controller of insulin signaling (29). Their predicted activity on nuclear receptors, GPCRs and metabolic enzymes highlights their potential to control pathways in glucose homeostasis, insulin sensation and lipid metabolism.

Out of the 40 phytochemicals screened from *P. tomentosa*, 16 compounds were found to violate two or more factor of Lipinski's rule of five (Table 2). These violations included excessive molecular weight (> 500 g/mol), high lipophilicity (LogP > 5) or an excessive number of hydrogen bond acceptors/ donors. The remaining 24 compounds complied with Lipinski criteria, indicating drug-likeness potential. The compounds (PubChem IDs: 73170, 5280450, 6324619, 162909502, 162918230, 162971157 and 162988003) exhibit LogP values greater than 5, indicating excessive lipophilicity, which is negatively associated with solubility and oral bioavailability. High LogP values can

Table 1. Bioactivity scores of phytochemical compound

PubChem CID	GPCR	Ion channel	Kinase	Nuclear receptor	Protease	Enzyme
73170	0.38	0.1	-0.18	0.45	0.12	0.38
92760	0.05	-0.05	-0.02	0.1	0.08	0.2
148124	-0.12	-0.09	-0.25	0.3	0.05	0.21
159559	0.02	-0.12	-0.03	0.2	0.11	0.28
441849	0.12	-0.1	-0.05	0.12	0.02	0.14
5280450	0.25	0.08	-0.15	0.1	0.01	0.28
5343381	0.28	0.1	-0.15	0.15	0.01	0.28
6324619	0.32	-0.05	-0.18	0.42	0.12	0.35
11876182	0.38	-0.05	-0.18	0.42	0.12	0.35
12302399	0.38	-0.12	-0.25	0.38	0.08	0.24
14859018	0.15	-0.1	-0.18	0.35	0.02	0.2
15558779	0.1	-0.08	-0.12	0.31	0.01	0.18
16086565	0.28	-0.05	-0.1	0.28	0.01	0.22
16086566	0.25	-0.05	-0.1	0.26	0.01	0.2
16086567	0.25	-0.05	-0.1	0.28	0.01	0.2
42601447	0.18	-0.05	-0.12	0.35	0.01	0.2
44179785	0.32	-0.1	-0.25	0.35	0.01	0.25
44179786	0.38	-0.12	-0.25	0.38	0.08	0.24
44559134	0.15	-0.05	-0.18	0.28	0.02	0.2
44573470	0.12	-0.1	-0.2	0.25	0.01	0.18
45267296	0.25	-0.08	-0.18	0.3	0.01	0.22
45269892	0.28	-0.1	-0.2	0.3	0.01	0.22
45270717	0.25	-0.08	-0.15	0.32	0.01	0.22
56677566	0.3	-0.1	-0.18	0.32	0.02	0.24
155537105	0.3	-0.08	-0.2	0.36	0.02	0.22
155541548	0.28	-0.1	-0.12	0.35	0.01	0.24
155546078	0.25	-0.09	-0.18	0.33	0.01	0.2
155554341	0.27	-0.07	-0.15	0.32	0.02	0.21
155554459	0.32	-0.12	-0.22	0.38	0.03	0.25
162817524	0.2	-0.06	-0.17	0.3	0	0.18
162817558	0.22	-0.05	-0.16	0.28	0.01	0.19
162876281	0.35	-0.11	-0.14	0.37	0.02	0.26
162878840	0.18	-0.09	-0.19	0.31	0.01	0.2
162895926	0.24	-0.08	-0.13	0.33	0.02	0.22
162909502	0.26	-0.1	-0.21	0.34	0	0.21
162918230	0.23	-0.07	-0.2	0.32	0.01	0.2
162971157	0.29	-0.11	-0.19	0.36	0.02	0.23
162988003	0.19	-0.06	-0.12	0.29	0	0.18
163106525	0.33	-0.09	-0.17	0.35	0.03	0.24
5280343	0.31	-0.08	-0.16	0.34	0.01	0.23

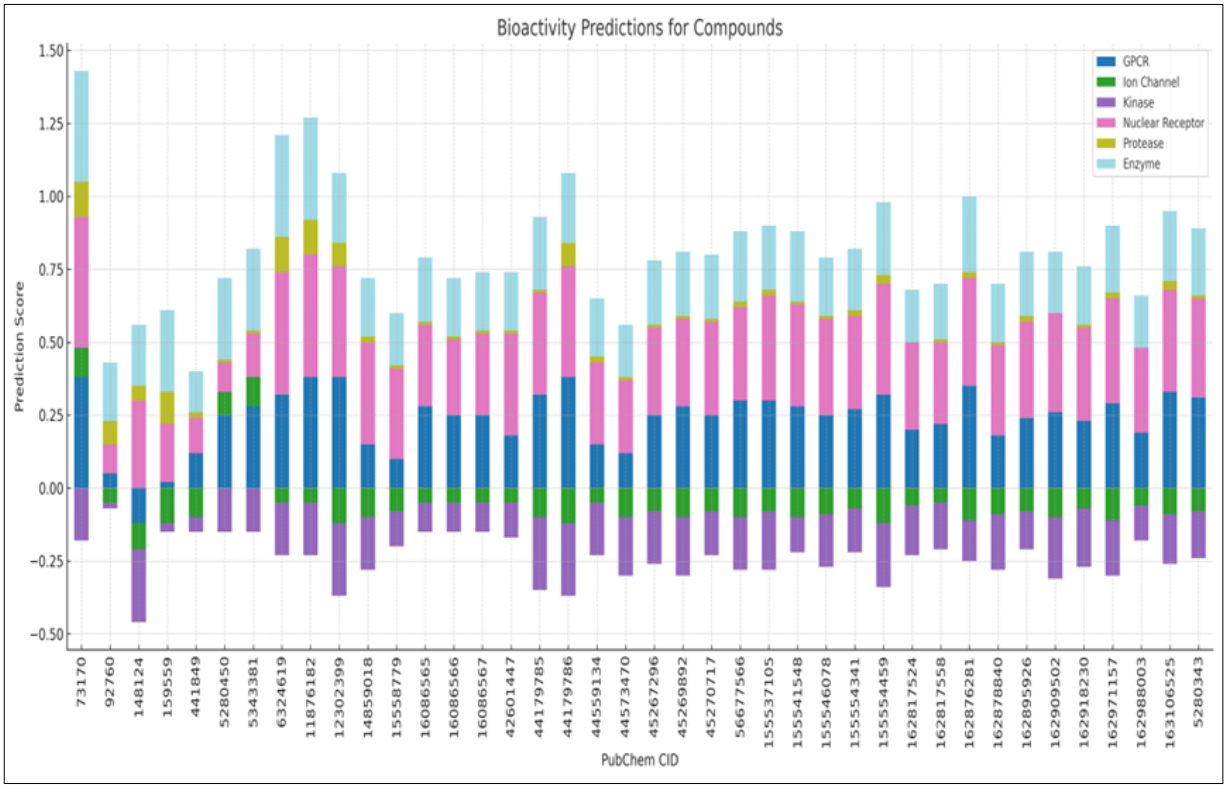

Fig. 1. Selection of optimal compounds: balancing bioactivity and ADMET.

Table 2. Physicochemical properties and bioavailability properties of phytochemical compounds

PubChem id	Molecular weight (g/mol)	LogP	nHA (H-bond acceptors)	nHD (H-bond donors)	nRot (rotatable bonds)	PSA (Å²)
73170	426.39	7.35	1	1	0	20.23
92760	374.25	2.71	4	2	1	66.76
148124	807.35	3.19	15	5	14	224.45
159559	566.27	-0.42	11	6	3	175.37
441849	532.27	1.26	9	3	2	131.75
5280450	280.24	6.65	2	1	14	37.3
5343381	425.09	4.83	5	2	4	78.61
6324619	352.25	6.13	3	2	14	48.65
11876182	406.24	0.49	6	4	2	107.22
12302399	390.24	1.49	5	3	2	86.99
14859018	552.29	-0.63	10	6	5	166.14
15558779	536.3	0.59	9	5	4	145.91
16086565	694.32	-0.44	14	6	5	210.9
16086566	550.28	0.73	10	5	2	155.14
16086567	550.28	0.57	10	5	3	155.14
42601447	548.26	0.52	10	4	2	151.98
44179785	606.27	0.2	12	4	5	178.28
44179786	548.26	0.34	10	4	3	151.98
44559134	566.27	-0.43	11	6	3	175.37
44573470	712.35	2.97	12	5	9	181.44
45267296	548.26	0.52	10	4	2	151.98
45269892	694.32	-0.44	14	6	5	210.9
45270717	548.26	0.62	10	4	2	151.98
56677566	694.32	-0.44	14	6	5	210.9
155537105	564.26	-0.39	11	5	3	172.21
155541548	606.27	0.42	12	4	4	178.28
155546078	548.26	0.34	10	4	3	151.98
155554341	564.26	-0.39	11	5	3	172.21
155554459	564.26	-0.17	11	5	2	172.21
162817524	710.31	-0.52	15	7	5	231.13
162817558	458.29	3.42	8	5	18	136.68
162876281	426.35	4.95	2	2	0	40.46
162878840	566.27	-0.43	11	6	3	175.37
162895926	308.13	1.76	6	3	2	96.22
162909502	470.38	6.11	3	1	2	46.53
162918230	522.44	8.34	2	0	4	26.3
162971157	468.4	7.43	2	0	2	26.3
162988003	426.39	7.12	1	1	0	20.23
163106525	550.28	1.02	10	5	3	155.14
5280343	302.04	2.15	7	5	1	131.36

nHA = number of hydrogen bond acceptors; nHD = number of hydrogen bond donors; nRot = number of rotatable bonds; PSA = polar surface area (specifically, TPSA: total polar surface area.

result in poor absorption and enhanced metabolic instability due to increased affinity for plasma proteins and lipophilic tissues (30). These results supports further experimental validation and structural optimization for T2D therapy development.

ADMET properties of compounds

A total of forty phytochemicals were screened using ADMET profiling via the ADMET tool with key thresholds: human intestinal absorption (HIA > 70 %), blood-brain barrier penetration (logBB < -1.0), plasma protein binding (PPB < 90 %) and non-carcinogenicity (31). A summary of the most promising candidates is given here, while detailed results are given in Table 2, 3. The phytochemical compounds CIDs 162895926, 14859018, 16086565, 6324619, 15558779, 16086567, 155554459, 16086566, 162817524 and 159559 demonstrated good solubility. Most compounds showed high predicted intestinal absorption, with values of '1' indicating favorable bioavailability. For example, compounds like PubChem ID 92760, 5343381 and 15558779 exhibited high absorption (1), whereas compounds like 73170 and 6324619 showed poor absorption (0), potentially limiting their oral bioavailability.

Several compounds, CID 441849 (0.99), CID 12302399 (0.96) and CID 92760 (0.96), demonstrated high BBB permeability, showing potential for central nervous system (CNS) exposure. Compounds like CID 5343381 (0.02) and CID 148124 (0.04) exhibit negligible permeability, suggesting limited CNS penetration (32). The implications of BBB permeability are critical for both therapeutic targeting and the prediction of off-target CNS-related side effects (33).

A total of 8 compounds have CYP2D6-substrate scores ≥ 0.5, raising concerns for drug-drug interactions and metabolic instability. Most of these compounds also show PPB > 95 %, indicating limited free drug availability and potential displacement effects shown in Table 2. High plasma protein binding reflects more affinity for plasma proteins, which can restrict the free active fraction of the compound in systemic circulation (34). The LogS values reportable in Table 2 for some compounds, including CID 73170 (-6.35) and CID 162918230 (-7.31), fall well below the acceptable threshold for drug-like molecules (typically LogS > -5) and indicate very poor aqueous solubility, which could significantly hinder oral bioavailability and systemic absorption.

The compounds that evaluated by ADMET showed a lower level of toxicity (Table 2, 3; Fig. 2). Almost all phytochemical compounds exhibited some toxicity factors, like the Ames test (mutagenicity) and hERG inhibition (35). However, several compounds demonstrated acceptable safety margins, enhancing their potential for advancement in drug development.

Investigation of the ADMET profiles for phytochemical compounds derived from *P. tomentosa* showed that many phytochemical compounds fall inside marked ADMET range, indicating its possible usage as drug (36). These results suggest that phytochemical compounds derived from *P. tomentosa* have the potential to be used in the development of new medicines.

Table 3. ADMET Properties of compounds

PubChem id	Solubility	BBB (blood-brain barrier)	CYP2D6-sub	PPB (plasma protein binding)	Absorption	Hepatotoxicity
73170	-6.35	0.76	0.50	98.7	0	Inactive
92760	-4.5	0.96	0.39	95.03	1	Inactive
148124	-4.02	0.04	0.11	94.7	0	Inactive
159559	-2.94	0.53	0.12	19.38	0	Inactive
441849	-3.79	0.99	0.14	67.27	0	Inactive
5280450	-5.23	0.19	0.08	98.39	1	Inactive
5343381	-6.05	0.02	0.50	97.8	1	Inactive
6324619	-2.70	0.26	0.02	100.4	0	Inactive
11876182	-3.13	0.97	0.13	17.68	1	Inactive
12302399	-3.81	0.96	0.17	91.06	1	Inactive
14859018	-1.98	0.15	0.12	83.97	0	Inactive
15558779	-2.73	0.34	0.19	91.28	0	Inactive
16086565	-2.71	0.86	0.10	48.92	0	Inactive
16086566	-3.34	0.87	0.16	22.64	0	Inactive
16086567	-3.15	0.91	0.15	86.57	0	Inactive
42601447	-3.40	0.99	0.11	24.15	0	Inactive
44179785	-3.11	0.98	0.09	34.86	0	Inactive
44179786	-3.23	0.99	0.11	59.56	0	Inactive
44559134	-2.93	0.53	0.12	19.39	0	Inactive
44573470	-4.07	0.67	0.40	99.87	0	Inactive
45267296	-3.40	0.99	0.11	24.15	0	Inactive
45269892	-2.71	0.86	0.10	48.92	0	Inactive
45270717	-3.28	0.99	0.10	40.8	0	Inactive
56677566	-2.71	0.86	0.10	48.92	0	Inactive
155537105	-3.03	0.97	0.09	21.94	0	Inactive
155541548	-3.29	0.95	0.09	23.8	0	Inactive
155546078	-3.23	0.99	0.11	59.56	0	Inactive
155554341	-3.03	0.97	0.09	21.94	0	Inactive
155554459	-3.09	0.92	0.09	22.16	0	Inactive
162817524	-2.27	0.93	0.09	46.2	0	Inactive
162817558	-3.14	0.25	0.07	95.27	0	Inactive
162876281	-5.09	0.88	0.6	90.59	1	Inactive
162878840	-2.93	0.53	0.12	19.39	0	Inactive
162895926	-1.96	0.27	0.34	69.32	0	Inactive
162909502	-6.22	0.94	0.53	97.59	0	Inactive
162918230	-7.31	0.24	0.54	95.6	0	Inactive
162971157	-6.93	0.6	0.75	99.93	0	Inactive
162988003	-6.06	0.79	0.51	99.22	0	Inactive
163106525	-3.47	0.78	0.13	80.15	0	Inactive
5280343	-3.67	0	0.64	95.49	1	Inactive

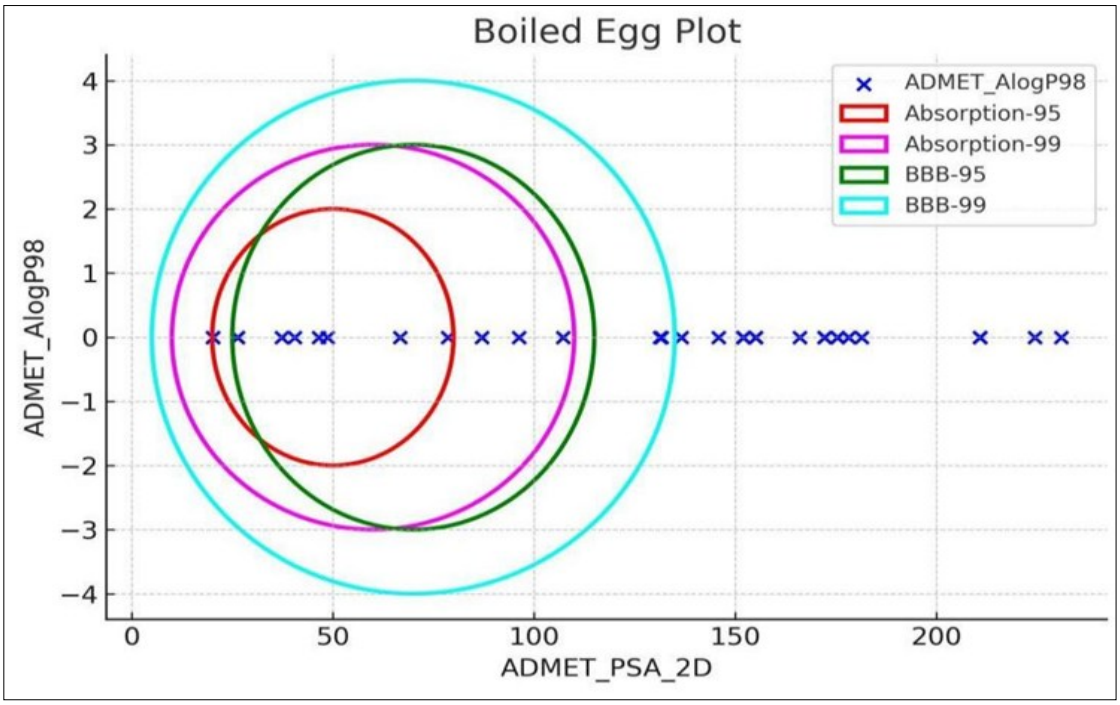

Fig. 2. ADMET profile: correlation between 2D polar surface area (PSA_2D) and octanol-water partition coefficient (AlogP98) for *Pergularia tomentosa* compounds.

Target protein prediction

Swiss target prediction tool was used to predict the potential target protein of phytochemical compounds (37). Compound CID 73170 was found to interact with PTP1B, T-cell protein-tyrosine phosphatase (TCPTP) and phosphodiesterase 4D (PDE4D) (Table 4). Compound CID 92760 showed interactions with PTP1B, potassium transporting ATPase and protein kinase C alpha (PKCα). Compound CID 148124 exhibited binding affinity toward growth hormone-releasing hormone receptor (GHRHR), PTP1B and 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1).

Compounds with PubChem CIDs 159559, 16086565, 16086567, 42601447, 44179786, 44559134, 45269892, 45270717, 56677566, 155537105, 155554459, 162817524 and 162878840 showed interactions with key target proteins, sodium/potassium-transporting ATPase alpha-1 chain (ATP1A1), nuclear receptor ROR-gamma (RORC), signal transducer and activator of transcription 3 (STAT3). The phytochemical compound 5280343 was found to interact with target proteins PTP1B, tyrosine-protein kinases receptor FLT3 and 11- β-HSD1.

STAT3 was the most often predicted target, associated with 22 different compounds, indicating its potential role as a common signaling node. The sodium/potassium-transporting ATPase alpha-1 chain, another target, was associated with 21 compounds, proposing a continual interaction motif that may connect to ion transport modulation. Similarly, the nuclear receptor ROR-gamma (ROR-γ) was linked to 19 compounds, indicating a connection in transcriptional regulation pathways.

The predicted target proteins sodium/potassium-transporting ATPase alpha-1 chain plays an important role in insulin signaling, glucose metabolism and cellular ion balance. Nuclear receptors ROR-gamma a key controllers of biological processes that cause the development and progression of T2DM, like adipogenesis and hepatic glucose production (38). STAT3 serve as a critical mediator in the development of insulin resistance and β-cell dysfunction in T2DM. The well-established anti-diabetic target, Protein Tyrosine Phosphatase 1B (PTP1B), was predicted in 16 compounds, reinforcing its pharmacological importance. Lastly, 11β -HSD1 was connected with five compounds, highlighting a possible role in glucocorticoid metabolism (39). PTP1B was chosen as a target protein because of its important function in insulin signaling regulation and other targets like DPP4 and SGLT2 were also considered due to their roles in insulin resistance modulation (40).

Phytochemical compounds with rigid hydrophobic polycyclic backbones (CIDs 73170, 162876281, 162988003) mapped to PTP1B, 11β-HSD and ABL-family kinases. Their structural similarity to aminosterol scaffolds supports their affinity for allosteric pockets like those found in PTP1B. Other phytochemical compounds with highly oxygenated (e.g., CIDs 148124, 159559) interacted with STAT3, ROR-γ and Na^+/K^+-ATPase, with their polar surfaces and H-bonding capacity.

Some phytochemical Compounds with moderately sized aromatic or heterocyclic compounds (e.g., CIDs 5280450, 5343381, 162895926) often targeted kinases (Chk1, CDK2, Src, IGF1R) and PTP1B, reflecting similarities with ATP-competitive kinase pharmacophores and PTP1B inhibitors. Other phytochemical Compounds with multiple donor/acceptor functions (e.g., CIDs 16086565-16086567) showed affinity for Na^+/K^+-K-ATPase, STAT3 and ROR-γ, showing functions in immunometabolic modulation. This classification of core scaffold types demonstrates that the bioactivity of phytochemicals derived from *P. tomentosa* support rational prioritization of candidate molecules for experimental validation (41).

Docking analysis

Docking analysis showed that study of molecular interactions between top six phytochemicals PubChem CIDs 162876281, 5343381, 92760, 12302399, 11876182 and 5280343 revealed binding affinities of -7.9, -7.7, -7.1, -7.0, -6.9 and -6.8 kcal/mol, respectively and demonstrated important interactions within the binding site of target PTP1B (PDB ID:4IN8). Molecular docking analysis revealed that six bioactive compounds bound strongly to the PTP1B binding pocket, particularly in the region where trodusquemine binds (42). The outcomes showed that some phytochemical were capable of

Table 4. Target identification phytochemical compounds

PubChem iD	Predicted target 1	Predicted target 2	Predicted target 3
73170	PTP1B	T-cell protein-tyrosine phosphatase	Phosphodiesterase 4D
92760	PTP1B	Potassium-transporting ATPase alpha chain 2	Protein kinase C alpha
148124	Growth hormone-releasing hormone receptor	Protein Tyrosine Phosphatase 1B (PTP1B)	11-beta-hydroxysteroid dehydrogenase 1
159559	Sodium/potassium-transporting ATPase alpha-1 chain	Signal transducer and activator of transcription 3	Nuclear receptor ROR-gamma
441849	Sodium/potassium-transporting ATPase alpha-1 chain	Glycine receptor subunit alpha-1	Proteinase-activated receptor 2
5280450	PTP1B	Fatty acid binding protein adipocyte	Peroxisome proliferator-activated receptor delta
5343381	PTP1B	MAP kinase p38 alpha	Tyrosine-protein kinase JAK1
6324619	C-C chemokine receptor type 5	Tyrosine-protein kinase ABL	Phosphodiesterase 10A (by homology)
11876182	PTP1B	Potassium-transporting ATPase alpha chain 2	Not found
12302399	PTP1B	Tyrosine-protein kinase ABL	Progesterone receptor
14859018	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Proteinase-activated receptor 2
15558779	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Proteinase-activated receptor 2
16086565	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
16086566	Sodium/potassium-transporting ATPase alpha-1 chain	Protein Tyrosine Phosphatase 1B (PTP1B)	Signal transducer and activator of transcription 3
16086567	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
42601447	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
44179785	PTP1B	Protein kinase C epsilon	Signal transducer and activator of transcription 3
44179786	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
44559134	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
44573470	Sodium/potassium-transporting ATPase alpha-1 chain	Aldo-keto reductase family 1 member B10	Carbonic anhydrase II
45267296	PTP1B	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
45269892	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
45270717	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
56677566	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
155537105	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
155541548	Sodium/potassium-transporting ATPase alpha-1 chain	Protein kinase C eta	Signal transducer and activator of transcription 3
155546078	PTP1B	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
155554341	Sodium/potassium-transporting ATPase alpha-1 chain	Protein kinase C eta	Signal transducer and activator of transcription 3
155554459	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
162817524	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
162817558	Glucocorticoid receptor	Protein Tyrosine Phosphatase 1B (PTP1B)	Signal transducer and activator of transcription 3
162876281	PTP1B	11-beta-hydroxysteroid dehydrogenase 1	UDP-glucuronosyltransferase 2B7
162878840	Sodium/potassium-transporting ATPase alpha-1 chain	Nuclear receptor ROR-gamma	Signal transducer and activator of transcription 3
162895926	Serine/threonine-protein kinase Chk1	Cyclin-dependent kinase 2	Signal transducer and activator of transcription 3
162909502	PTP1B	Insulin-like growth factor I receptor	Tyrosine-protein kinase SRC
162918230	Cyclin-dependent kinase 2	Phosphodiesterase 10A	Protein-tyrosine phosphatase 1B
162971157	Acetylcholinesterase	11-beta-hydroxysteroid dehydrogenase 1	Nuclear receptor ROR-gamma
162988003	UDP-glucuronosyltransferase 2B7	11-beta-hydroxysteroid dehydrogenase 1	Protein-tyrosine phosphatase 1B
163106525	Sodium/potassium-transporting ATPase alpha-1 chain	11-beta-hydroxysteroid dehydrogenase 2	Signal transducer and activator of transcription 3
5280343	PTP1B	Tyrosine-protein kinase receptor FLT3	11-beta-hydroxysteroid dehydrogenase 1

forming stable complexes through H-bonding and hydrophobic interaction to a significant part of the binding site. The bioactive phytochemical and trodusquemine exhibited corresponding binding interactions, suggesting their potential therapeutic advantages in targeting PTP1B for antidiabetic activity (43).

The consistency of phytochemical binding within target PTP1B binding site, similar to trodusquemine, further supports their inhibitory potential. Several intramolecular interactions were known by molecular docking studies, as shown in Fig. 3. The results of molecular docking interactions between the bioactive phytochemical with target PTP1B (44). The molecular docking studies of top six phytochemical against PTP1B revealed multiple important interactions within the binding site.

Compound CID 162876281

showed binding energy of (-7.9 kcal/mol), strongest binder, showed alkyl interaction with LEU204 (3.92 Å) and Pi-alkyl interactions with VAL108 (5.26 Å), MET253 (4.94 Å), ILE72 (3.92 Å) and TYR81 (4.71 Å).

Compound CID 5343381

showed a binding energy of (-7.7 kcal/mol), showing alkyl interactions with LEU204 (2.33 Å), PHE225 (2.33 Å), CYS226 (4.02 Å) and TYR81 (5.04 Å), alongside hydrogen bonds involving VAL108 and ASP229 at distances of 3.60 Å and 2.03 Å, respectively.

Compound CID 92760

showed a binding affinity of -7.1 kcal/mol and formed Pi-alkyl interactions with residues VAL108 (5.24 Å), MET74 (3.90 Å), ILE72 (3.68 Å) and TYR81 (4.18 Å), as well as alkyl interactions with CYS226 (4.67 Å), PHE225 (4.89 Å) and LEU260 (4.09 Å).

Compound CID 12302399

showed a binding affinity of (-7.0 kcal/mol), formed alkyl interactions with PHE225 (3.98 Å) and LEU195 (3.86 Å), hydrogen bonding with ARG105 (3.54 Å) and Pi-alkyl interactions with TYR81 (3.50 Å) and VAL108 (3.86 Å).

Compound CID 11876182

showed a binding affinity of (-6.9 kcal/mol) interacted hydrophobically through alkyl contacts with LEU195 (4.62 Å), ARG105 (2.84 Å) and CYS226 (4.12 Å), as well as Pi-alkyl interaction with VAL108 (4.99 Å) and hydrogen bonds were observed with ASP229 (2.25 Å), PHE225 (1.72 Å) and TYR81 (3.08 Å).

Compound CID 5280343

showed a binding affinity of (-6.8 kcal/mol) engaged in Pi-alkyl interaction with VAL198 (3.94 Å), Pi-sigma interaction with LEU204 (3.43 Å), Pi-cation interaction with ARG199 (4.83 Å) and hydrogen bonding with CYS226 (3.74 Å).

The docking analysis highlights key intermolecular interactions, such as π-alkyl and hydrogen bonds, between the ligands and residues like VAL108, PHE225, CYS226 and TYR81 (Table 5; Fig. 3). These compounds exhibited strong binding affinities and formed key interactions with critical catalytic residues such as cysteine (Cys), arginine (Arg) and aspartic acid (Asp) and key interactions considering hydrogen bonding, alkyl, π-alkyl, π-σ and π-cation contacts were identified within the binding pocket (PDB ID: 4I8N) as observed through visual review using PyMOL and Discovery Studio Visualizer (44).

Compound CID 162876281 (-7.9 kcal/mol) and CID 5343381 (-7.7 kcal/mol) showed strong interactions with functionally important residues such as VAL108, MET253, LEU204 and TYR81, indicating high binding complementarity. For example, quercetin PubChem CID 5280343 well-studied natural PTP1B inhibitor, has docking scores -6.8 kcal/mol and interacts with similar residues such as CYS226, ARG199, VAL198 and ASP199. The presence of multiple stabilising interactions across all six compounds reinforces their potential as PTP1B inhibitors, supporting their predicted binding affinities and biological connection (45).

The binding structure of the six bioactive phytochemical compounds shows strong similarity to PTP1B inhibitors, which interact with residues like Asp181, Arg221, Cys215 and Tyr46 within or close to the catalytic pocket. Some of the bioactive phytochemical compounds involved key residues such as Tyr81, Phe225, Cys226, Val108 and Leu204, with a binding site for inhibitors that target the secondary hydrophobic pocket of the enzyme (46).

Comparative docking analysis showed that cimigenol (CID 162876281) and neriifolin (CID 5343381) bind more strongly to target protein PTP1B with ΔΔG values of -0.4 and -0.2 kcal/mol, than the reference inhibitor trodusquemine (Table 6). The remaining phytochemical compounds showed slightly weaker affinities (ΔΔG +0.4 to +0.7 kcal/mol).

Discussion

These phytochemicals showed higher oral bioavailability, which is essential in the development of new medicine (47). Based on the bioactivity prediction data, some compounds demonstrated promising potential toward the management of T2DM (Table 1; Fig. 1). Compounds such as PubChem CIDs 73170, 11876182, 6324619, 12302399 and 162876281 exhibited high predicted activity across target classes specifically relevant to T2DM-namely enzymes, GPCRs and nuclear receptors. Compound CID 73170 displayed strong activity in all three classes (GPCR: 0.38, nuclear receptor: 0.45, enzyme: 0.38), indicating potential multi-target efficacy, possibly through inhibition of enzymes like PTP1B or modulation of GPCRs related to incretin signalling (e.g., GLP-1R). Similarly, CID 11876182 and 6324619 also showed high scores and may act through similar pathways (48). Therefore, these compounds warrant further investigation through molecular docking, pharmacokinetic profiling and potential *in vitro* validation against T2DM-related targets.

Most of the phytochemicals show acceptable drug-like properties (Table 2; Fig. 2). Molecular weights ranged from 280-807 g/mol, LogP from -0.63 to 8.34 and PSA from 20 to 231 $Å^2$. Most compounds had appropriate H-bond donors/acceptors and rotatable bonds, suggesting good bioavailability, though some may have moderate or controlled absorption (49). Most phytochemicals exhibited drug-like properties, supporting their potential for drug development.

Some compounds showed good solubility, along with high plasma binding, no hepatotoxicity and moderate to good BBB permeability, showing favourable drug-like profiles (Table 3) (50). Table 4 shows that target prediction discovered that some phytochemicals interact with important proteins involved in metabolic, inflammatory and signalling pathways. PTP1B was often targeted, showing potential antidiabetic or anti-obesity effects (51). The Na^+/K^+-K-ATPase alpha-1 chain was identified, indicating a connection in ion regulation. Some compounds targeted ROR-γ and STAT3, which play roles in immune

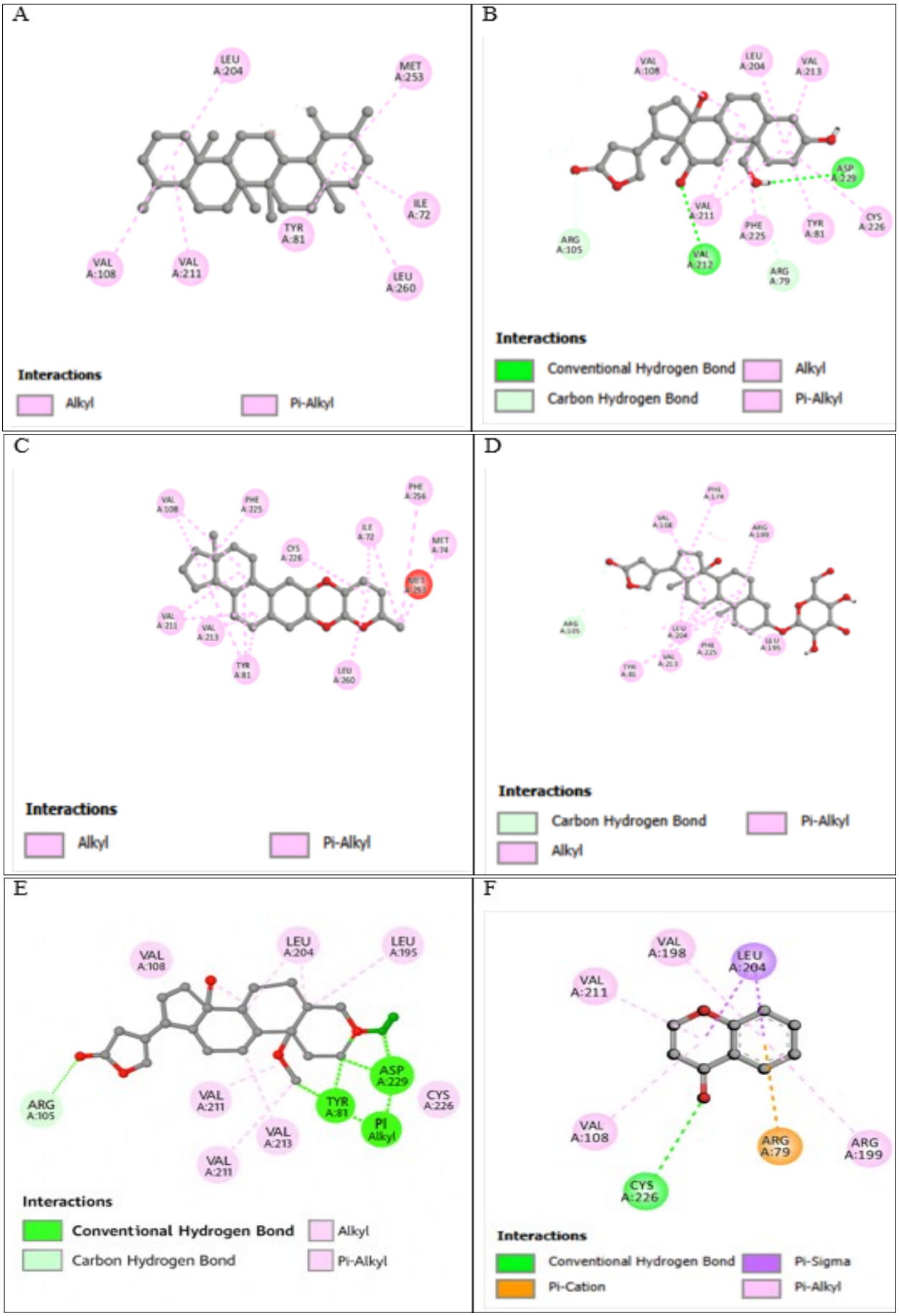

Fig. 3. *Molecular docking poses of the top six bioactive phytochemical ligands within the active site of protein tyrosine phosphatase 1B (PTP1B).* The ligands, represented in ball-and-stick format, are docked in the active site of PTP1B, while key binding site residues are shown as sticks. The top six compounds-PubChem CIDs: (A) 162876281, (B) 5343381, (C) 92760, (D) 12302399, (E) 11876182 and (F) 5280343 demonstrate favorable binding orientations and close intra-molecular interactions within the catalytic pocket. Green dashed lines represent *hydrogen bonds*, pink dashed lines denote *hydrophobic interactions* and purple dashed lines indicate *additional non-covalent interactions* (e.g., π-π stacking or electrostatic interactions), contributing to the overall binding affinity.

Table 5. Intra-molecular interactions defined by the phytochemical compounds with target protein tyrosine phosphatase PTP1B (PDB ID:4I8N)

PubChem iD	Binding affinity (kcal/mol)	Interacting group(s)	Intramolecular interaction(s)	Distance (Å)
92760	-7.1	VAL 108	PI-ALKYL	5.24
		CYS 226	ALKYL	4.67
		PHE 225	ALKYL	4.89
		LEU 260	ALKYL	4.09
		MET 74	PI-ALKYL	3.9
		ILE 72	PI-ALKYL	3.68
		TYR 81	PI-ALKYL	4.18
		LEU 204	ALKYL	2.33
5343381	-7.7	VAL 108	HYDROGEN BONDING	3.6
		PHE 225	ALKYL	2.33
		CYS 226	ALKYL	4.02
		TYR 81	ALKYL	5.04
		ASP 229	HYDROGEN BONDING	2.03
		LEU 195	ALKYL	4.62
		VAL 108	PI-ALKYL	4.99
11876182	-6.9	ASP 229	HYDROGEN BONDING	2.25
		ARG 105	ALKYL	2.84
		CYS 226	ALKYL	4.12
		PHE 225	HYDROGEN BONDING	1.72
		TYR 81	HYDROGEN BONDING	3.08
12302399	-7	PHE 225	ALKYL	3.98
		LEU 195	ALKYL	3.86
		ARG 105	HYDROGEN BONDING	3.54
		TYR 81	PI-ALKYL	3.5
		VAL 108	PI-ALKYL	3.86
		LEU 204	ALKYL	3.92
162876281	-7.9	VAL 108	PI-ALKYL	5.26
		MET 253	PI-ALKYL	4.94
		ILE 72	PI-ALKYL	3.92
		TYR 81	PI-ALKYL	4.71
		VAL 198	PI-ALKYL	3.94
5280343	-6.8	LEU 204	PI-SIGMA	3.43
		ARG 199	PI-CATION	4.83
		CYS 226	HYDROGEN BONDING	3.74

Table 6. Comparative docking scores of top six phytochemicals compounds against target protein PTP1B relative to trodusquemine

Compound name	PubChem iD	Binding affinity ΔG (kcal/mol)	ΔΔG relative to trodusquemine (kcal/mol)
Trodusquemine (reference)	9917968	-7.5	0.00
Cimigenol	162876281	-7.9	-0.4
Neriifolin (cardenolide)	5343381	-7.7	-0.2
Frugoside (cardenolide)	92760	-7.1	+0.4
α-Buforin analogue	12302399	-7.0	+0.5
Compound	11876182	-6.9	+0.6
Quercetin (literature comparator)	5280343	-6.8	+0.7

modulation and cancer.

The docking results show some of the phytochemicals that interact with key catalytic and binding site residues of PTP1B, which are important for enzyme activity (Table 5; Fig. 3) (52). These interactions suggests that the compounds could inhibit PTP1B by occupying the active sites involved in substrate identification. Table 4 indicates that phytochemicals exhibited strong binding to PTP1B (-6.8 to -7.9 kcal/mol), involving key residues such as VAL 108, TYR 81, CYS 226 and PHE 225 through hydrogen bonding and hydrophobic interactions (53). A more negative score indicates a stronger binding affinity, implying that phytochemical compounds are more likely to effectively inhibit the target protein (54).

The binding affinities of six selected compounds against Protein Tyrosine Phosphatase 1B (PTP1B, PDB ID: 4IN8) were analysed to assess comparative significance. The binding energies were as follows:

CID 162876281: -7.9 kcal/mol,

CID 5343381: -7.7 kcal/mol,

CID 92760: -7.1 kcal/mol,

CID 12302399: -7.0 kcal/mol,

CID 11876182: -6.9 kcal/mol,

CID 5280343: -6.8 kcal/mol.

These phytochemical compounds may act as natural PTP1B inhibitors, supporting their potential antidiabetic activity (55). Among these, compound CID 162876281 demonstrated the strongest expected binding (-7.9 kcal/mol) connected with favorable ADMET properties, considering good solubility and non-toxicity, suggesting a likely balance of potency and pharmacokinetics (55). Compounds 5343381 and 92760 also showed strong binding affinities and acceptable predicted absorption and metabolism profiles (56).

The molecular docking analysis showed that these phytochemicals interact with key residues in the PTP1B binding pocket, which helps in substrate identification and catalysis (57). Molecular interactions, including hydrogen bonding with residues such as ASP229 and ARG105, may contribute to binding particularity and stability (58). Hydrophobic interactions, especially alkyl and Pi-alkyl contacts with LEU260 and MET253, likely improve compound affinity by stabilizing the complex within the

hydrophobic cavity next to the catalytic site (59).

Asp181 is a key catalytic residue within the active site of PTP1B and plays a crucial role in the enzymatic mechanism, often stabilizing the transition state or interacting with substrates and inhibitors. The top six compounds exhibited strong binding affinity toward PTP1B, indicating potential inhibitory activity against the regulator of insulin signaling. Overall, these results highlight the potential of *P. tomentosa*-derived phytochemicals as promising lead compounds for PTP1B inhibition and the management of type 2 diabetes.

Conclusion

Selected phytochemical compounds from *P. tomentosa* showed promising binding affinities toward PTP1B, indicating potential inhibitory action. Among them, CID 162876281 and CID 5343381 showed the strongest interactions, with favorable docking scores and stable binding within the active site. Toxicity profiles identified using ProTox-II and ADMETlab 2.0 indicated that most compounds have low to moderate toxicity risks along with satisfactory pharmacokinetic properties. CID 162876281 showed low predicted hepatotoxicity and high absorption potential, making it a promising lead candidate. This *in silico* study highlights the therapeutic potential of phytochemicals from *P. tomentosa* as putative anti-diabetic agents.

Furthermore, several *P. tomentosa* phytochemicals demonstrated docking scores comparable to or better than trodusquemine and formed interactions with catalytically relevant residues. These phytochemicals show docking affinities and interaction profiles consistent with PTP1B modulation. These phytochemical compounds warrant further cell-based studies and *in vivo* evaluation to validate their potential as potential PTP1B-targeting candidates and to assess their suitability as natural alternatives for managing type 2 diabetes and associated metabolic diseases.

Future directions

With the help of these silico results, experimental work should relate an *in vitro* enzymatic assay to confirm PTP1B inhibition and the results of cytotoxicity testing. These steps will help in assessing the pharmacodynamic properties and therapeutic efficacy of the most promising phytochemicals and finally advance them towards drug discovery.

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Authors' contributions

SN carried out the experimental work and data collection. AK supervised the project, designed the study and revised the manuscript. MS contributed to data analysis and manuscript preparation. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflicts of interest.

Ethical issues: None

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