TiS Trends in Sciences
TRENDS IN SCIENCES 2027; 24(2): 14127
SPRINT Scholarly Publishing and Repository Integration Center
https://doi.org/10.48048/tis.2027.14127
RESEARCH ARTICLE

Network Pharmacology-Based Investigation and Molecular Docking Validation of the Therapeutic Targets of *Moringa Oleifera* Against Diabetes Through Network Approach

Wahyudin Rauf[1], Hasnah Natsir[1,*], Nur Umriani Permatasari[1] and Anita Anita[2]

[1]*Chemistry Department, Faculty of Mathematics and Natural Science, Hasanuddin University, Makassar 90132, Indonesia*
[2]*Medical Laboratory Technology, Polytechnic of Muhammadiyah Makassar, Makassar 90132, Indonesia*

([*]Corresponding author's e-mail: hasnahnatsir@unhas.ac.id)

Received: 18 April 2026, Revised: 28 May 2026, Accepted: 7 June 2026, Published: 10 October 2026

Abstract

This study investigates the antidiabetic potential of *Moringa oleifera* through an integrated network pharmacology and molecular docking approach to elucidate its multi-target therapeutic mechanisms. An initial screening of 30 phytochemical compounds resulted in the identification of 11 bioactive molecules exhibiting high gastrointestinal absorption and favorable drug-likeness properties, indicating strong oral bioavailability. Network pharmacology analysis revealed 14 common protein targets shared between the selected compounds and diabetes-related pathways, highlighting key regulatory roles in glucose metabolism, insulin signaling, and inflammatory modulation. Protein-protein interaction and pathway enrichment analyses further supported the involvement of these targets in critical metabolic processes associated with diabetes pathogenesis. Molecular docking simulations confirmed stable ligand-target interactions, with binding affinities ranging from −5.0 to −9.3 kcal/mol. Among the identified compounds, ellagic acid demonstrated the strongest binding affinity and structural stability, suggesting its potential as a promising lead compound. In addition, *in silico* toxicity assessment indicated favorable safety profiles for all screened compounds, with LD_{50} values exceeding 2,500 mg/kg and classification within Toxicity Classes IV and V. Overall, these findings provide a robust theoretical basis for the development of *Moringa oleifera*-derived bioactive compounds as safe and effective candidates for diabetes management and support further experimental and clinical investigations.

Keywords: *Moringa oleifera*, Network pharmacology, Molecular docking, Antidiabetic potential, Bioactive compounds, Ellagic acid, Phytochemical screening, Glucose metabolism, *In silico* toxicity, Drug-likeness

Introduction

Diabetes mellitus is a group of chronic metabolic disorders characterized by persistent hyperglycemia resulting from impaired insulin secretion, impaired insulin action, or a combination of both [1,2]. Based on etiology and underlying pathophysiological mechanisms, diabetes mellitus is broadly classified into 2 major types, namely Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) [2]. T1DM is an autoimmune disorder characterized by the progressive destruction of pancreatic β-cells, leading to absolute insulin deficiency, whereas T2DM is primarily characterized by insulin resistance accompanied by relative impairment of insulin secretion. Both types of diabetes contribute substantially to the global disease burden and continue to show an increasing prevalence worldwide, including among individuals of productive age [3].

Both T1DM and T2DM are associated with a high risk of developing severe chronic complications, such as diabetic neuropathy, retinopathy, nephropathy, and cardiovascular diseases, which collectively lead to reduced quality of life and increased morbidity and

mortality [4,5]. Although the fundamental pathogenic mechanisms of T1DM and T2DM differ, chronic hyperglycemia and oxidative stress represent shared pathogenic pathways that play a critical role in the progression of diabetic complications. Consequently, therapeutic strategies that not only focus on glycemic control but also emphasize cellular protection and metabolic pathway modulation are urgently needed.

Current standard diabetes management includes insulin therapy, which is essential for T1DM and frequently required in advanced stages of T2DM, as well as the use of oral antidiabetic agents such as metformin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors for T2DM [6]. Although these treatments are effective in reducing blood glucose levels, long-term use is often associated with adverse effects, including hypoglycemia, gastrointestinal disturbances, weight gain, and diminished therapeutic responsiveness. These limitations have driven the search for alternative or adjunctive therapeutic agents that are safer, more effective, and possess broader mechanisms of action [7,8].

In recent decades, herbal plants rich in natural bioactive compounds have been increasingly investigated as complementary therapies for diabetes. This approach is considered promising due to its relative safety, accessibility, and multicomponent pharmacological activity. One such plant that has gained considerable attention is *Moringa oleifera*, traditionally used in the treatment of various diseases across Asia and Africa [9]. Experimental and preclinical studies have demonstrated that *Moringa oleifera* leaves contain bioactive compounds such as quercetin, kaempferol, chlorogenic acid, and niazirin, which exhibit antidiabetic properties through multiple mechanisms, including enhancement of insulin sensitivity, inhibition of carbohydrate-digesting enzymes such as α-glucosidase, modulation of inflammatory responses, and protection against oxidative stress.

Nevertheless, the comprehensive molecular mechanisms underlying the combined effects of multiple bioactive compounds in *Moringa oleifera* within the context of diabetes, encompassing both T1DM and T2DM, remain incompletely understood. The complex interactions between herbal compounds, biological targets, and cellular signaling pathways necessitate a systematic and integrative analytical approach. In this regard, network pharmacology, which integrates systems pharmacology and bioinformatics, enables the comprehensive mapping of compound-target-signaling pathway interactions to elucidate the synergistic effects of multicomponent therapies [10,11].

Therefore, this study aims to explore potential molecular targets and signaling pathways involved in the pathogenesis of diabetes mellitus in general, encompassing both Type 1 and Type 2 Diabetes Mellitus, in order to elucidate the molecular mechanisms of *Moringa oleifera* as a potential antidiabetic agent using a network pharmacology approach, and the overall research design and analytical workflow are schematically illustrated in **Figure 1**.

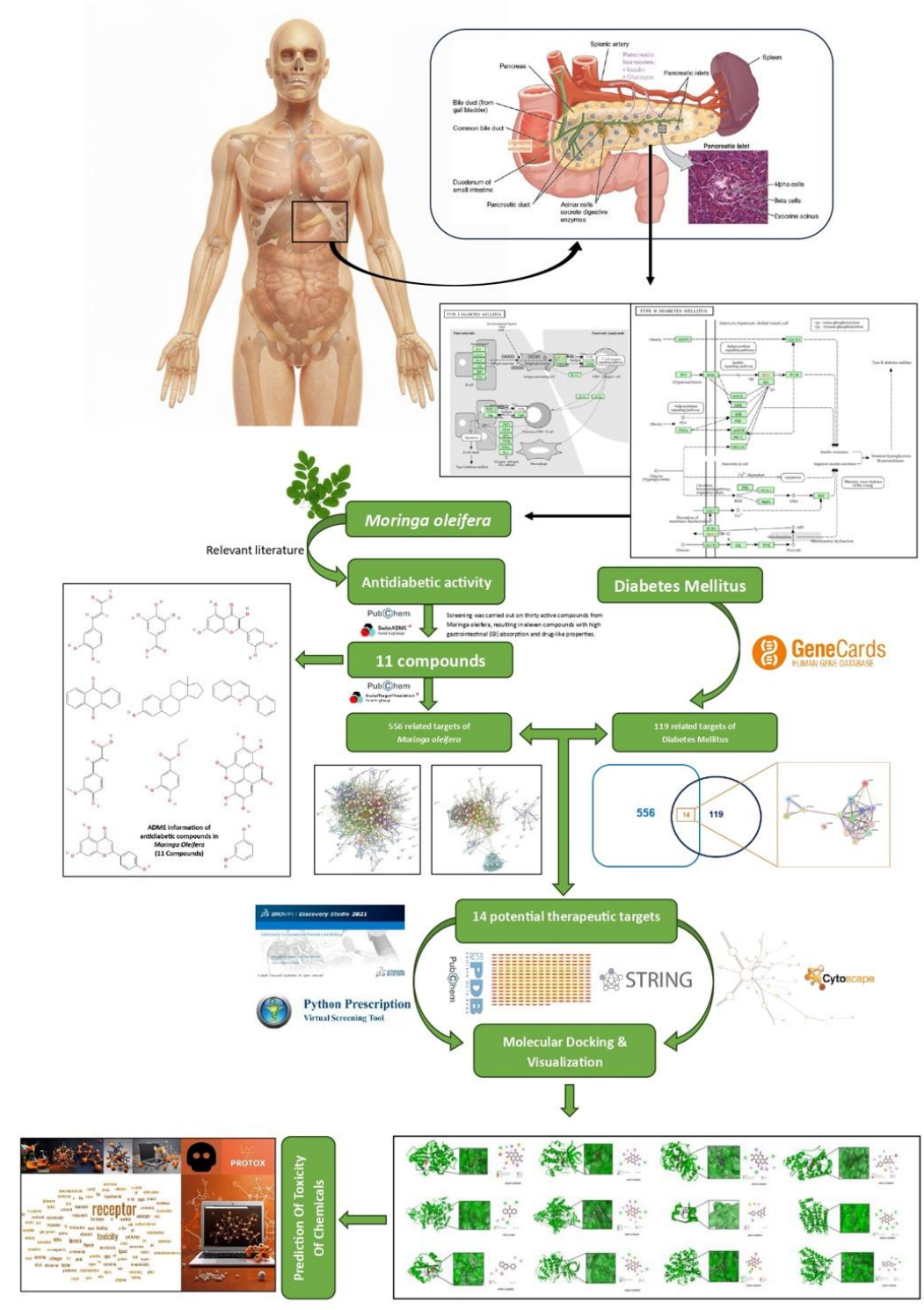


Figure 1 The research design and workflow of this study are schematically illustrated.

Materials and methods

Experimental

Chemical candidates and Moringa oleifera-related targets

All compounds from *Moringa oleifera* reported to possess antidiabetic activity were identified through a comprehensive review of relevant literature. These compounds were subsequently screened using the SwissADME database (http://www.swissadme.ch/) (accessed on 16 October 2025) based on 2 key ADME parameters, namely gastrointestinal (GI) absorption and drug-likeness [13,14]. GI absorption reflects the ability

of a compound to be digested and absorbed through the gastrointestinal tract following oral administration, whereas drug-likeness evaluates the potential of a molecule to be developed as an oral drug based on its bioavailability-related properties. Accordingly, only compounds exhibiting high GI absorption and favorable drug-likeness were selected as potential candidates.

The selected active candidate compounds were then submitted to the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) (accessed on 16 October 2025) to obtain their chemical structures in the Simplified Molecular Input Line Entry System (SMILES) format [14,15]. Subsequently, protein targets associated with *Moringa oleifera* were predicted using the SwissTargetPrediction database (http://www.swisstargetprediction.ch) (accessed on 16 October 2025), with only targets showing a prediction probability greater than zero being included for further analysis [16,17].

Identification of Diabetes Mellitus (DM)-related targets

The identification of targets associated with diabetes mellitus (DM) was conducted using 3 major databases. The GeneCards database (https://www.genecards.org/) (accessed on 25 October 2025) was utilized as the primary resource, as it provides comprehensive and easily accessible information on all annotated and predicted human genes [17]. This database automatically integrates diverse gene-centered data, including genomic, transcriptomic, proteomic, genetic, clinical, and functional information, collected from approximately 150 online sources. In addition, the Online Mendelian Inheritance in Man (OMIM) database (https://omim.org/) (accessed on 25 October 2025) was employed as a reliable reference source containing extensive information on human genes and genetic phenotypes. This open-access database is updated daily and documents all known Mendelian disorders, encompassing more than 16,000 genes. All targets obtained from these databases were subsequently integrated and designated as diabetes mellitus (DM)-related targets for further analysis.

Construction and analysis of the Protein–Protein Interaction (PPI) network

STRING (https://string-db.org/) (accessed on 11 November 2025) is a database that integrates all known and predicted protein associations, including both physical and functional interactions. In this study, the STRING database was used to analyze the relationships between *Moringa oleifera*–related targets and diabetes mellitus (DM)-associated targets, which were considered potential therapeutic targets.The PPI network of these potential therapeutic targets was constructed under the following conditions: The selected species was Homo sapiens, and the confidence score was set to a medium confidence level (≥0.4). A confidence score of 0.4 is commonly used as an indicator of moderate reliability in predicting protein-protein interactions. This threshold was chosen because it provides a balance between sensitivity and specificity and serves as a reliable cutoff for identifying potential interactions. Accordingly, only proteins with an interaction score ≥0.4 were included in the PPI network [17,18,20].

Subsequently, the PPI network was analyzed using Cytoscape software version 3.8.0 to obtain topological parameters of the network nodes, including degree, betweenness centrality (BC), and closeness centrality (CC). The degree value represents the number of nodes that directly interact with a given node and is often used to assess the importance of a node within the network. Meanwhile, BC and CC values are employed to evaluate the significance of a node based on its ability to interact with other nodes or to act as a connector facilitating information flow within the network. Hub genes within the PPI network were then identified based on the following screening criteria: first, genes with degree (≥28), BC (≥0.00144074408), and CC (≥0.485611511) values greater than the overall median were selected; subsequently, genes with degree (≥40), BC (≥0.016190014), and CC (≥0.5625) values exceeding the median within this gene set were further filtered. The MCODE plugin was used to perform module clustering analysis on the PPI network.

Functional and pathway enrichment analysis

All potential therapeutic targets were further analyzed to identify relevant biological functions and signaling pathways using Gene Ontology (GO) and KEGG pathway enrichment analyses via the DAVID database (https://david.ncifcrf.gov/) (accessed on 10 December 2022). This analysis encompassed 3 main categories, namely biological processes (BP), molecular functions (MF), and cellular components (CC). Only GO terms and pathways with a significance level of $p < 0.05$ were retained as meaningful results. Subsequently, the GO and KEGG enrichment results were visualized using the Bioinformatics platform (http://www.bioinformatics.com.cn/) (accessed on 13 December 2022), presented as bar charts for signaling pathways and bubble plots for GO categories. Furthermore, the relationships among active compounds, potential targets, and signaling pathways were visualized using Cytoscape software version 3.8 to clearly illustrate the biological interactions among these components.

Verification using molecular docking

Preparation of receptor and ligand structures

The initial step in molecular docking simulations is the identification of the receptor and ligand to be evaluated. The receptor used in this study was a diabetes-related target protein obtained based on the results of the protein–protein interaction (PPI) analysis and retrieved from the Protein Data Bank (https://www.rcsb.org/structure/). The receptor structure was subsequently prepared using BIOVIA Discovery Studio 2021. Ligand structures were obtained by searching the PubChem database (https://www.ncbi.nlm.nih.gov/pccompound) [14,21,22].

Docking simulation and visualization of results

To initiate the docking simulation, the PyRx application was opened and the Vina Wizard mode was selected as the main interface for the docking process. The target protein and ligand files were then uploaded by clicking the Load Molecules button. The protein file was required to be in .pdb format, and the same procedure was applied for uploading the ligand file. After uploading, PyRx automatically converted both the protein and ligand files into PDBQT format, which is the standard format required by AutoDock Vina for docking simulations [14]. Following file preparation, a grid box was defined to serve as the search space around the protein's active site where ligand binding occurs. The grid box was configured via the Grid tab, with its size and position adjusted based on active site information obtained from the literature or the position of the native ligand within the PDB structure. The grid box dimensions (X, Y, and Z) were set to adequately cover the target region to ensure optimal and accurate docking results.

Once the grid box was properly defined, the target protein and ligand were selected from the available molecule list, and the docking simulation was initiated by clicking the Start button using AutoDock Vina. After completion of the simulation, PyRx displayed the binding affinity values for each ligand pose within the protein's active site. These values are typically expressed in energy units (kcal/mol), where more negative values indicate stronger and more stable interactions between the ligand and the protein.

The final step involved saving the docking results. The best binding pose from the simulation was saved in PDBQT format and exported to PDB format for further analysis using additional software, such as BIOVIA Discovery Studio. This software enabled detailed visualization and interpretation of the molecular interactions between the ligand and the target protein.

Toxicity prediction

Toxicity prediction of the tested compounds was conducted using the ProTox-3.0 web server (https://tox.charite.de/protox_3) through an *in silico* approach (accessed on 20 January 2026). The chemical structures of the selected bioactive compounds were retrieved from the PubChem database in SMILES or SDF format and subsequently uploaded to the ProTox-3.0 platform for analysis. Toxicity assessment was performed by activating multiple relevant parameters to obtain a comprehensive safety profile of each compound. Organ toxicity evaluation was carried out to predict potential adverse effects on vital organs, including hepatotoxicity, neurotoxicity, nephrotoxicity, and cardiotoxicity. In addition, key toxicity endpoints such as immunotoxicity, mutagenicity, and cytotoxicity were assessed to examine possible effects on the immune system, genetic material, and cellular viability.

Furthermore, toxicity related to Tox21 nuclear receptor signaling pathways was analyzed by selecting receptors associated with metabolic and endocrine regulation, including the aryl hydrocarbon receptor (AhR), androgen receptor (AR), estrogen receptor alpha (ER-α), and peroxisome proliferator-activated receptor gamma (PPAR-γ). The Tox21 stress response pathways were also evaluated, encompassing nuclear factor erythroid-derived 2-like 2/antioxidant responsive element (Nrf2/ARE), heat shock response element (HSE), mitochondrial membrane potential (MMP), and tumor suppressor protein p53, to predict potential cellular stress and oxidative damage induced by the compounds. In addition, molecular initiating events were examined by assessing acetylcholinesterase (AChE) interaction to identify possible neurotoxic effects. Drug metabolism was further predicted by evaluating interactions with major cytochrome P450 isoenzymes, including CYP2C19, CYP2C9, CYP2D6, and CYP3A4, which play a crucial role in xenobiotic metabolism and potential drug–drug interactions. After all parameters were selected, toxicity prediction was initiated using the "Start Tox-Prediction" function, and the resulting data, including acute toxicity class (LD_{50}) and specific toxicity profiles, were analyzed to determine the overall safety and suitability of the compounds as potential antidiabetic candidates [23-25].

Results and discussion

Identification and ADME profiling of antidiabetic compounds from *Moringa oleifera*

This study aims to identify active compounds from *Moringa oleifera* with potential antidiabetic properties using an *in-silico* approach, with particular emphasis on pharmacokinetic characteristics and drug-likeness properties. Of the 30 compounds reported in the literature to exhibit antidiabetic activity, a screening process was conducted using the PubChem database and the SwissADME tool, resulting in the identification of 11 compounds that met the criteria of high gastrointestinal (GI) absorption and favorable drug-likeness. These findings indicate that not all bioactive compounds of *Moringa oleifera* have equal potential to be developed as oral drug candidates, underscoring the importance of ADME-based screening as a critical step in network pharmacology-based research [17].

High GI absorption observed in all selected compounds suggests good potential for oral bioavailability. In the context of diabetes mellitus therapy, oral bioavailability is a crucial consideration, as treatment is generally long-term and requires convenient administration. Compounds such as caffeic acid, gallic acid, and resorcinol exhibit very high-water solubility, which supports efficient absorption in the gastrointestinal tract [26-28]. This property also facilitates their distribution within biological systems, although it must be balanced with adequate metabolic stability to prevent rapid elimination.

Flavonoids such as quercetin and apigenin identified in this study have been widely reported to possess antihyperglycemic activity through multiple mechanisms [29], including enhancement of insulin sensitivity, inhibition of α-glucosidase activity, and modulation of oxidative stress and inflammatory pathways. The presence of flavonoid compounds with favorable drug-like properties strengthens the hypothesis that the antidiabetic effects of *Moringa oleifera* are multitarget in nature and not dependent on a single molecular mechanism. This observation is consistent with the complex pathophysiology of diabetes mellitus, which involves multiple interconnected molecular pathways.

Other phenolic compounds, including ferulic acid, ellagic acid, and protocatechuic acid ethyl ester, are known for their strong antioxidant activity [30-32]. Oxidative stress plays a significant role in the pathogenesis of diabetes mellitus, particularly in pancreatic β-cell dysfunction and the development of insulin resistance. Therefore, the presence of these compounds supports the potential role of *Moringa oleifera* in mitigating metabolic complications of diabetes through cellular protective mechanisms. In addition, the good solubility and relatively low molecular weight of most selected compounds may facilitate efficient interactions with target proteins.

Anthraquinone and anthocyanin (2-phenylchromenylium) identified in this study also exhibit favorable pharmacokinetic profiles. These compounds have been reported to participate in the regulation of glucose and lipid metabolism, although their precise molecular mechanisms require further investigation. Phenolic steroids, characterized by moderate solubility and good drug-likeness, show

potential interactions with nuclear receptors involved in glucose and lipid homeostasis [33], such as peroxisome proliferator-activated receptors (PPARs), which are key therapeutic targets in type 2 diabetes mellitus.

Overall, the results of ADME screening indicate that the antidiabetic effects of *Moringa oleifera* are likely mediated by the synergistic action of multiple bioactive compounds with supportive pharmacokinetic characteristics. The pharmacokinetic profiles and drug-likeness properties of the 11 *Moringa oleifera* active compounds that passed the ADME screening are summarized in **Table 1**.

Table 1 ADME information of antidiabetic compounds in *Moringa Oleifera*.

Molecular formula	Molar mass (Da)	Identification	GI	Water Solubility	Druglikeness
$C_9H_8O_4$	180.2	Caffeic acid	High	Very soluble	Yes
$C_7H_6O_5$	170.1	Gallic acid	High	Very soluble	Yes
$C_{15}H_{10}O_7$	302.2	Quercetin	High	Soluble	Yes
$C_{14}H_8O_5$	252.21	Anthraquinone	High	Soluble	Yes
$C_{19}H_{30}O_2$	290.4	Phenolic steroid	High	Moderately soluble	Yes
$C_{15}H_{11}O_5$	271	2-phenylchromenylium (anthocyanin)	High	Moderately soluble	Yes
$C_{10}H_{10}O_4$	194.2	Ferulic acid	High	Soluble	Yes
$C_9H_{10}O_5$	198.2	Protocatechuic acid ethyl ester	High	Soluble	Yes
$C_{14}H_6O_8$	302.2	Ellagic acid	High	Soluble	Yes
$C_{15}H_{10}O_5$	270.2	Apigenin	High	Soluble	Yes
$C_6H_6O_2$	110.1	Resorcinol	High	Very soluble	Yes

This approach reinforces the concept of network pharmacology, in which a single medicinal plant exerts therapeutic effects through multiple compounds acting on multiple targets simultaneously. These findings provide a strong foundation for subsequent analyses, including protein target prediction, construction of compound-target-disease networks, and validation through molecular docking and *in silico* toxicity assessment, prior to further *in vitro* and *in vivo* experimental studies.

Potential therapeutic targets of Moringa oleifera in the treatment of diabetes mellitus

The identification of potential therapeutic targets of *Moringa oleifera* in the treatment of diabetes mellitus was conducted by retrieving diabetes-related data using the keyword “diabetes mellitus” across several major and relevant databases. Through this process, a total of 556 targets associated with the pathogenesis of diabetes mellitus were collected. Meanwhile, protein targets related to the active compounds of *Moringa oleifera* were obtained through target prediction using bioinformatics databases, resulting in the identification of 119 targets potentially interacting with the plant’s bioactive compounds.

Subsequently, an intersection analysis was performed between diabetes mellitus–related targets and *Moringa oleifera*-related targets. The results revealed 14 common targets, representing shared targets between the disease and the active compounds of *Moringa oleifera*. These overlapping targets were therefore defined as potential therapeutic targets of *Moringa oleifera* in the treatment of diabetes mellitus, as illustrated in the Venn diagram and interaction network visualization (**Figure 2**), with detailed target protein information summarized in **Table 2**.

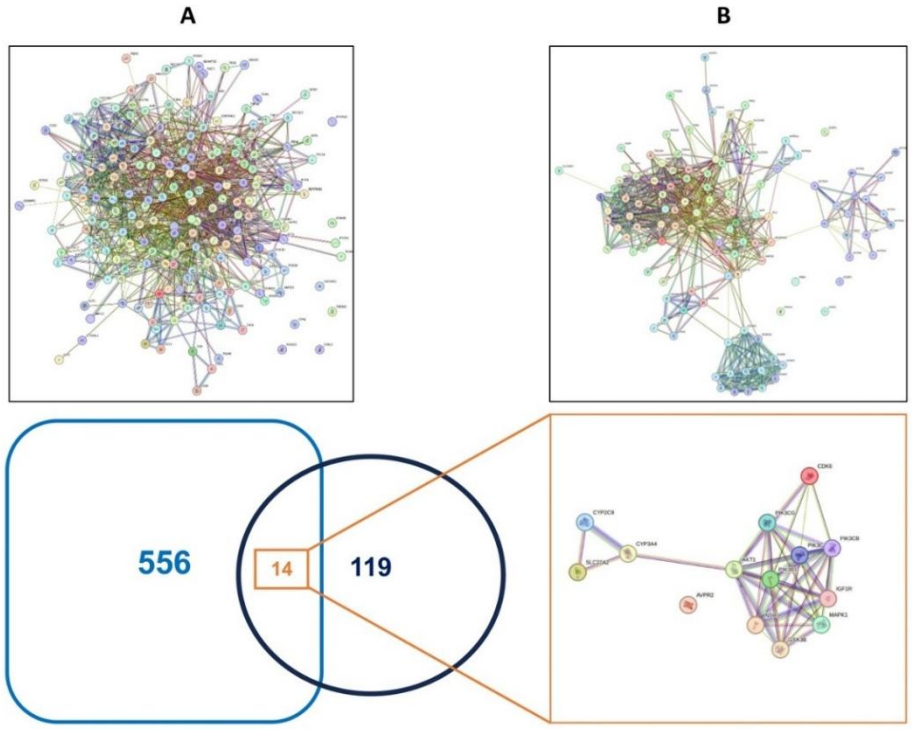


Figure 2 Venn diagram illustrating the intersection between diabetes mellitus-related targets and *Moringa Oleifera*-related targets. A total of 556 targets associated with diabetes mellitus and 119 targets related to the active compounds of *Moringa oleifera* were identified, with 14 overlapping targets representing potential therapeutic targets of *Moringa oleifera* in the treatment of diabetes mellitus.

Table 2 Protein targets and PDB codes (RCSB) involved in diabetes-related pathways.

No.	Protein	Protein name	Example PDB Code (RCSB)	Biological function
1	AKT1	RAC-alpha serine/threonine-protein kinase	3OCB	A key protein in the PI3K/AKT signaling pathway that regulates glucose uptake, energy metabolism, and cell survival; plays a crucial role in insulin sensitivity.
2	INSR	Insulin receptor	4ZXB	The primary insulin receptor that initiates activation of the PI3K/AKT and MAPK pathways; dysfunction of INSR is directly associated with insulin resistance.
3	IGF1R	Insulin-like growth factor 1 receptor	3LVP	A receptor tyrosine kinase involved in the regulation of cell growth and glucose metabolism; closely interacts with insulin signaling pathways.
4	PIK3CA	PI3K catalytic subunit alpha	5DXT	The catalytic subunit of PI3K responsible for PIP3 production; plays a central role in insulin signal transduction and glucose homeostasis.
5	PIK3CB	PI3K catalytic subunit beta	2Y3A	Regulates insulin responses and cellular metabolism; contributes to glucose and lipid regulation.
6	PIK3CG	PI3K catalytic subunit gamma	1E8X	Involved in metabolic and inflammatory signaling; associated with immune-mediated diabetic complications.

No.	Protein	Protein name	Example PDB Code (RCSB)	Biological function
7	PIK3R1	PI3K regulatory subunit	1H9O	A regulatory subunit of PI3K that stabilizes and controls the activity of the catalytic subunits within the insulin signaling pathway.
8	GSK3B	Glycogen synthase kinase 3 beta	1Q5K	Inhibits glycogen synthesis; inhibition of GSK3B enhances glucose storage and improves insulin sensitivity.
9	MAPK1 (ERK2)	Mitogen-activated protein kinase 1	2OJJ	Involved in cell proliferation and signal transduction; plays a role in diabetic complications and oxidative stress responses.
10	CDK6	Cyclin-dependent kinase 6	1XO2	Regulates the cell cycle; associated with altered cell proliferation and metabolic dysregulation in diabetes.
11	INS	Insulin	4INS	The primary hormone regulating blood glucose levels by promoting cellular glucose uptake.
12	SLC2A2 (GLUT2)	Glucose transporter 2	5EQG	A major glucose transporter in the liver and pancreas; involved in glucose sensing and glycemic regulation.
13	CYP3A4	Cytochrome P450 3A4	1TQN	A key drug-metabolizing enzyme; involved in the biotransformation of herbal bioactive compounds and antidiabetic drugs.
14	CYP2C9	Cytochrome P450 2C9	1OG5	Regulates the metabolism of various antidiabetic drugs; important in herb–drug interaction considerations.

The identification of these common targets suggests that the antidiabetic effects of *Moringa oleifera* may be mediated through the direct modulation of key proteins involved in glucose metabolism regulation, insulin signaling, oxidative stress, and inflammatory processes. These findings provide a strong biological basis for subsequent analyses, including protein–protein interaction (PPI) network construction, signaling pathway enrichment analysis, and molecular interaction validation using molecular docking and *in silico* toxicity assessment.

Molecular docking results of selected bioactive compounds with target proteins

The molecular docking analysis provides an integrated overview of binding affinity, structural stability, and interaction characteristics between the selected bioactive compounds and their respective target proteins. Overall, the binding affinity values ranged from −5.0 to −9.3 kcal/mol, indicating that all ligands were able to form energetically favorable complexes, albeit with varying binding strengths. More negative binding affinity values reflect higher thermodynamic stability and a stronger ability of the ligands to bind within the active sites of the target proteins. In this context, ellagic acid consistently exhibited the best docking performance across several target proteins, including 1E8X, 5EQG, 2OJJ, and 1Q5K, with binding affinity values approaching or exceeding −9.0 kcal/mol. The selection of these specific target proteins is consistent with established methodologies in recent pharmacological studies [34-37], which have identified these receptors as critical nodes in the regulation of metabolic pathways.

The relibility of the predicted docking poses is further supported by the RMSD values, particularly the low RMSD lower bound observed in several ligand–protein complexes, indicating good convergence and consistency of the binding conformations. The visualization of ligand–protein interactions is presented in **Figure 3**, while the complete quantitative data on binding affinity, RMSD values, and types of interactions are summarized in **Table 3**. Low RMSD values suggest that the predicted ligand orientations within the protein active sites are stable and reproducible, whereas relatively higher RMSD upper bound values in some complexes likely reflect conformational flexibility of the ligand or protein rather than instability of the

docking results. Thus, the combined evaluation of binding affinity and RMSD parameters supports the structural validity and reliability of the predicted interactions.

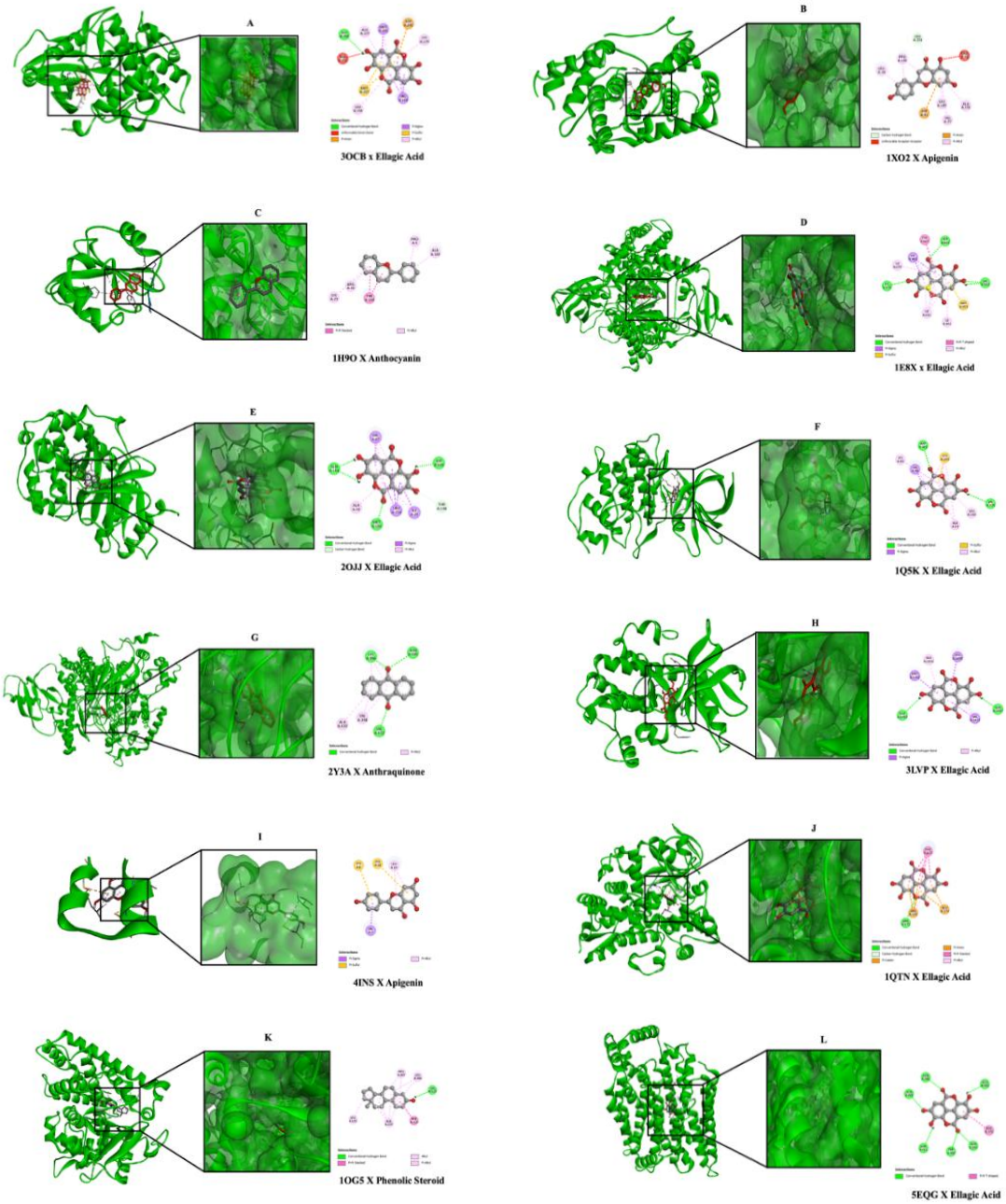


Figure 3 Molecular docking poses of bioactive compounds with protein targets. (A) Ellagic acid bound to protein 3OCB, stabilized by hydrogen bonds and hydrophobic interactions within the active site. (B) Apigenin docked to protein 1XO2, showing moderate binding through hydrogen bonding and π-type interactions. (C) Anthocyanin interacting with protein 1H9O, forming limited stabilizing contacts in the binding pocket. (D) Ellagic acid–protein 1E8X complex, exhibiting strong binding supported by multiple non-covalent interactions. (E) Binding mode of ellagic acid in protein 2OJJ, indicating a stable ligand–protein interaction. (F) Ellagic acid docked to protein 1Q5K, maintained by hydrogen bonds and hydrophobic contacts. (G) Anthraquinone bound to protein 2Y3A, showing moderate interaction stability within the active site. (H) Ellagic acid–protein 3LVPX complex, with a well-accommodated ligand in the binding pocket. (I) Apigenin interacting with protein 4INS, displaying moderate binding affinity. (J) Ellagic acid docked to protein 1QTN, characterized by extensive stabilizing interactions. (K) Phenolic steroid bound to protein 1OG5, dominated by hydrophobic interactions with limited hydrogen bonding. (L) A major glucose transporter in the liver and pancreas; involved in glucose sensing and glycemic regulation.

At the molecular interaction level, the ligand–protein complexes are stabilized by a complementary network of non-covalent interactions. Conventional hydrogen bonds involving polar and charged residues, such as GLU, ASP, ASN, GLN, ARG, and LYS, play a crucial role in anchoring the ligands within the active sites and enhancing binding specificity. In addition, extensive hydrophobic interactions, including Pi–alkyl, Pi–sigma, and Pi–Pi interactions with residues such as VAL, LEU, ILE, PHE, and TYR, contribute significantly to the overall stability of the complexes by strengthening van der Waals forces within hydrophobic regions of the binding pockets. In several target proteins, the presence of Pi–sulfur interactions with cysteine and methionine residues further reinforces ligand binding within the active sites.

Comparative analysis among the ligands demonstrates that ellagic acid forms the most extensive and diverse interaction networks, which is consistent with its high binding affinity and low RMSD values. Anthraquinone and apigenin exhibit moderate binding potential, characterized by the formation of essential hydrogen bonds and hydrophobic interactions, although these interactions are less extensive than those observed for ellagic acid. In contrast, anthocyanin shows relatively weaker binding affinity, as indicated by less negative binding affinity values and a more limited number of stabilizing interactions.

In conclusion, the integrated analysis of binding affinity, RMSD parameters, and molecular interaction profiles clearly identifies ellagic acid as the most promising ligand candidate among the tested compounds. Its strong and stable interactions with multiple target proteins suggest a high potential for biological activity. These docking results provide a robust theoretical foundation for subsequent studies, including further evaluation through toxicity prediction of the most promising compound to support its potential development as a bioactive agent.

Table 3 Molecular docking results of selected bioactive compounds with target proteins.

No.	Ligand x protein target	Binding affinity (kcal/mol)	RMSD UB / RMSD LB	Hydrogen bonds (Å)	Hydrophobic & Other interactions
1	3OCB x Ellagic Acid	−7.8	6.185/0.264	GLU228 (2.50)	VAL164, MET281, LYS179, LEU156, ALA177, ASP292, MET227
2	3LVP x Ellagic Acid	−7.9	3.518/1.387	GLN1007 (1.88), GLU1080 (2.82)	VAL1013, MET1142, LEU1005, ALA1031
3	2Y3A x Anthraquinone	−8.9	5.416/0.042	VAL432 (2.46), ASN335 (2.81), LYS336 (2.83)	LYS336, VAL398, ALA433 (Pi-Alkyl)
4	1E8X x Ellagic Acid	−9.3	3.698/1.141	LYS833 (2.17), VAL882 (2.39; 2.42), ASP964 (2.65)	ILE963, ILE831, ILE879, ILE881 (Pi-Sigma/Alkyl), TYR867 (Pi-Pi T-shaped), MET953 (Pi-Sulfur)
5	1H9O x Anthocyanin	−5.6	6.13/0.977	None	TYR104 (Pi-Pi Stacked), LYS29, ARG30, PRO5, ALA108 (Pi-Alkyl)
6	1Q5K x Ellagic Acid	−9.0	6.179/0.326	VAL135 (2.72), ASP200 (2.78)	VAL70 (Pi-Sigma/Alkyl), CYS199 (Pi-Sulfur/Alkyl), ALA83, LYS85, LEU188 (Pi-Alkyl)
7	2OJJ x Ellagic Acid	−9.1	6.183/0.032	GLN103 (1.84; 2.72), ASP109 (1.92),	ILE29, VAL37, LEU154 (Pi-Sigma/Alkyl), ALA50 (Pi-Alkyl)

No.	Ligand x protein target	Binding affinity (kcal/mol)	RMSD UB / RMSD LB	Hydrogen bonds (Å)	Hydrophobic & Other interactions
				MET106 (1.99), THR108 (3.42)	
8	1XO2 x Apigenin	−8.2	2.955/1.242	LEU151 (3.68)	PRO195, VAL77, LEU185, ALA191, LEU34 (Pi-Alkyl), ASP81 (Pi-Anion)
9	4INS x Apigenin	−5.0	1.119/0.312	UNK1 (2.50)	VAL3 (Pi-Sigma), LEU16 (Pi-Alkyl), CYS6, CYS20 (Pi-Sulfur)
10	5EQG x Ellagic Acid	−9.2	6.183/0.079	GLU380 (2.05), TRP388 (2.39), ASN288 (2.61), GLN282 (2.67), ASN415 (2.70), ASN411 (2.75)	PHE379 (Pi-Pi T-shaped)
11	1TQN x Ellagic Acid	−9.0	6.184/0.089	ARG372 (2.94), ARG372 (3.45)*	PHE215 (Pi-Pi Stacked), ARG106 (Pi-Cation/Alkyl), GLU374 (Pi-Anion)
12	1OG5 x Phenolic Steroid	−9.1	2.608/0.912	VAL113 (2.24)	PHE114 (Pi-Pi Stacked/Pi-Alkyl), ALA103, LEU366, PRO367, LEU102 (Alkyl/Pi-Alkyl)

Acute toxicity analysis using ProTox 3.0 indicates that all 5 compounds generally exhibit favorable safety profiles, with the majority falling into Toxicity Class 5 [23,24]. Acute toxicity analysis using ProTox 3.0 indicates that all 5 compounds generally exhibit favorable safety profiles, with the majority falling into Toxicity Class 5 [23,24]. As presented in **Table 4**, ellagic acid, anthraquinone, and phenolic steroid were selected as the 3 best candidate compounds from several identified antidiabetic bioactive compounds based on their superior molecular docking performances. These compounds demonstrated the most favorable binding affinities, stable docking conformations, and significant molecular interactions with the active sites of the target proteins compared to other tested compounds such as apigenin and anthocyanin. Ellagic acid exhibited the strongest binding affinity among all compounds, indicating a highly stable ligand–protein complex formation. Anthraquinone showed excellent docking stability, reflected by its very low RMSD value, while Phenolic Steroid demonstrated strong hydrophobic interaction potential due to its high lipophilicity. The combination of strong binding energy, stable molecular orientation, and favorable interaction profiles suggests that these 3 compounds may possess higher inhibitory potential against diabetes-related target proteins.

Toxicity prediction analysis further supported the selection of these compounds. Anthraquinone and phenolic steroid exhibited the highest safety margins, with predicted oral LD_{50} values reaching 5,000 mg/kg, indicating relatively low acute toxicity. In contrast, Ellagic Acid showed a predicted LD_{50} value of 2,991 mg/kg, which remains within an acceptable safety range for further investigation. Interestingly, Ellagic Acid was classified in Toxicity Class 4 (harmful if swallowed), whereas anthraquinone and phenolic steroid belonged to the safer Toxicity Class 5 category. From the physicochemical perspective, phenolic steroid demonstrated the highest lipophilicity with a WLOGP value of 4.64, suggesting strong membrane permeability and enhanced hydrophobic interaction capability. Anthraquinone also exhibited favorable lipophilic characteristics that may facilitate passive diffusion through biological membranes. Meanwhile, Ellagic

Acid showed more hydrophilic properties, reflected by its lower LogP value and higher topological polar surface area (TPSA), indicating better aqueous solubility but comparatively lower membrane permeability. Overall, these findings suggest that the selected compounds possess promising antidiabetic potential supported by strong molecular interactions, acceptable toxicity profiles, and favorable physicochemical characteristics for further drug development studies.

Table 4 Toxicity prediction ellagic acid, anthraquinone and phenolic steroid.

Classification	Target	Shorthand	Prediction	Probability
Prediction of Toxicity of chemicals (Anthroqunone)				
Organ toxicity	Hepatotoxicity	dili	Inactive	0.72
Organ toxicity	Neurotoxicity	neuro	Active	0.59
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.69
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.69
Toxicity end points	Immunotoxicity	immuno	Inactive	0.98
Toxicity end points	Mutagenicity	mutagen	Active	0.83
Toxicity end points	Cytotoxicity	cyto	Inactive	0.85
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.65
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.78
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Active	0.93
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Active	1
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.95
Molecular Initiating Events	Achetylcholinesterase (AChE)	mie_ache	Inactive	0.72
Metabolism	Cytochrome CYP2C19	CYP2C19	Active	0.83
Metabolism	Cytochrome CYP2C9	CYP2C9	Active	0.87
Metabolism	Cytochrome CYP2D6	CYP2D6	Inactive	0.69
Metabolism	Cytochrome CYP3A4	CYP3A4	Inactive	0.92

Classification	Target	Shorthand	Prediction	Probability
Prediction of Toxicity of chemicals (Ellagic Acid)				
Organ toxicity	Hepatotoxicity	dili	Inactive	0.83
Organ toxicity	Neurotoxicity	neuro	Inactive	0.91
Organ toxicity	Nephrotoxicity	nephro	Active	0.58
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.76
Toxicity end points	Immunotoxicity	immuno	Inactive	0.81
Toxicity end points	Mutagenicity	mutagen	Inactive	0.84
Toxicity end points	Cytotoxicity	cyto	Inactive	0.90
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.87
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.94
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.86
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.95
Molecular Initiating Events	Achetylcholinesterase (AChE)	mie_ache	Inactive	0.83
Metabolism	Cytochrome CYP2C19	CYP2C19	Inactive	0.98
Metabolism	Cytochrome CYP2C9	CYP2C9	Active	0.64
Metabolism	Cytochrome CYP2D6	CYP2D6	Inactive	0.82
Metabolism	Cytochrome CYP3A4	CYP3A4	Inactive	0.95
Prediction of Toxicity of chemicals (Phenolic Steroid)				
Organ toxicity	Hepatotoxicity	dili	Inactive	0.83
Organ toxicity	Neurotoxicity	neuro	Inactive	0.54
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.92
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.62
Toxicity end points	Immunotoxicity	immuno	Active	0.87
Toxicity end points	Mutagenicity	mutagen	Inactive	0.87

Classification	Target	Shorthand	Prediction	Probability
Toxicity end points	Cytotoxicity	cyto	Inactive	0.82
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.89
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Active	0.66
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Active	0.87
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.95
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.94
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.94
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Active	0.82
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.83
Molecular Initiating Events	Achetylcholinesterase (AChE)	mie_ache	Inactive	0.79
Metabolism	Cytochrome CYP2C19	CYP2C19	Inactive	0.71
Metabolism	Cytochrome CYP2C9	CYP2C9	Active	0.70
Metabolism	Cytochrome CYP2D6	CYP2D6	Inactive	0.76
Metabolism	Cytochrome CYP3A4	CYP3A4	Inactive	0.85

Regarding biological target interactions based on toxicity prediction data in **Table 4**, the 3 selected candidate compounds ellagic acid, anthraquinone, and phenolic steroid, exhibit distinct interaction profiles across nuclear receptor signalling pathways. Phenolic steroid poses the broadest risk for endocrine disruption, as it is predicted to actively bind to both the Androgen Receptor (AR) and Estrogen Receptor Alpha (ER) with probabilities of 0.66 and 0.87, respectively, while remaining inactive toward other nuclear receptors such as AhR and PPAR-Gamma. In contrast, Anthraquinone demonstrates a notably different receptor interaction pattern, showing active binding only to the Estrogen Receptor Alpha (ER) with a high probability of 0.93, without predicted interactions with the Androgen Receptor. Meanwhile, Ellagic Acid presents the cleanest nuclear receptor profile among the 3, with all nuclear receptor pathways predicted as inactive, suggesting a minimal risk of hormone-mediated adverse effects.

Furthermore, although all 3 compounds maintain good acute safety profiles, significant differences exist in their cellular stress response and organ toxicity predictions. Anthraquinone exhibits potential neurotoxicity (Active, 0.59) and mutagenicity (Active, 0.83), which warrants careful consideration in long-term application contexts. It also shows active disruption of mitochondrial membrane potential (MMP, probability 1.00), a finding shared with phenolic steroid (MMP Active, 0.82), suggesting that both compounds may exert mitochondrial stress at the cellular level. Ellagic acid, however, demonstrates the most favorable cellular safety profile among the 3, with all stress response pathways including p53, nrf2/ARE, HSE, and MMP

predicted as inactive, and no neurotoxicity or mutagenicity activity detected. The sole concern for ellagic acid lies in its predicted nephrotoxicity activity (Active, 0.58), indicating a potential mild risk to renal tissue. Phenolic steroid uniquely demonstrates active immunotoxicity (Active, 0.87), distinguishing it from the other 2 compounds and raising considerations regarding its effects on immune system modulation.

Regarding hepatic metabolism, anthraquinone undergoes the most active biotransformation, with predicted activity on both CYP2C19 (0.83) and CYP2C9 (0.87) cytochrome enzymes, consistent with its lipophilic characteristics that necessitate Phase I hepatic metabolism for elimination. Ellagic acid shows partial metabolic activity, being predicted active only on CYP2C9 (0.64), while phenolic steroid similarly shows activity limited to CYP2C9 (0.70), suggesting more selective hepatic processing for both compounds. Consequently, it can be concluded that the 3 selected compounds ellagic acid, anthraquinone, and phenolic steroid possess favorable acute safety profiles, with Anthraquinone and phenolic steroid demonstrating the maximum safety margin of 5,000 mg/kg (Toxicity Class 5), while ellagic acid remains within an acceptable range at 2,991 mg/kg (Toxicity Class 4). Physicochemical characterization reveals significant differences in lipophilicity, ranging from the highly lipophilic phenolic steroid (WLOGP 4.64) to the more hydrophilic ellagic acid, which directly influences their membrane permeability and distribution mechanisms within the body. While systemically safe, specific cellular risks exist: Phenolic steroid acts as a potential endocrine disruptor through dual AR and ER receptor activation and presents immunotoxicity activity, anthraquinone carries neurotoxicity and mutagenicity concerns alongside broad cytochrome enzyme involvement, and ellagic acid raises mild nephrotoxicity considerations. Nevertheless, the consistent inactivity of critical cellular stress response pathways particularly p53 and nrf2/ARE across all 3 compounds ensures a low risk of hazardous DNA damage or systemic oxidative stress. Overall, Ellagic Acid emerges as the compound with the most favorable and specific safety profile at the cellular level, while anthraquinone and phenolic steroid offer strong molecular docking performance supported by acceptable, though more complex, toxicity profiles for further antidiabetic drug development investigation.

Conclusions

This study successfully identified the therapeutic potential of *Moringa oleifera* against diabetes mellitus using an integrated bioinformatics approach. Based on ADME screening, 11 active compounds were identified with high gastrointestinal absorption and favorable drug-likeness properties, suggesting strong oral bioavailability for long-term treatment. Network pharmacology analysis further revealed 14 common protein targets intersecting the plant's bioactive compounds and diabetes pathogenesis, supporting the hypothesis that the antidiabetic effects of *Moringa oleifera* are mediated through a multi-target mechanism involving glucose regulation, insulin signaling, and inflammatory pathways. Molecular docking validation reinforced these findings, with all ligands demonstrating stable binding affinities ranging from −5.0 to −9.3 kcal/mol. Ellagic acid consistently emerged as the most prominent candidate, exhibiting the strongest binding affinity and the most reliable structural stability across various target proteins. Regarding safety, toxicity predictions indicated that all compounds possess favorable acute safety profiles (Class 4 and 5) with LD_{50} values exceeding 2,500 mg/kg. While specific risks such as potential endocrine disruption or mild neurotoxicity were noted for certain compounds, the low activation of cellular stress response pathways (p53 and nrf2) confirms the overall systemic safety of these bioactive candidates. Based on the comprehensive evaluation integrating molecular docking performance, physicochemical properties, and toxicity prediction profiles, 3 bioactive compounds from *Moringa oleifera* were identified as the most promising antidiabetic candidates: Ellagic acid, anthraquinone, and phenolic steroid. Ellagic acid demonstrated the strongest binding affinity across diabetes-related target proteins alongside the most favorable cellular safety profile, making it the lead candidate for further drug development. Anthraquinone exhibited excellent docking stability with a very low RMSD value and the highest acute safety margin (LD_{50} 5,000 mg/kg, Class 5), while Phenolic Steroid demonstrated strong hydrophobic interaction potential attributed to its high lipophilicity (WLOGP 4.64), supporting enhanced membrane permeability and target engagement. Collectively, these results provide a robust theoretical foundation for the development of *Moringa oleifera*, particularly its 3 lead

compounds, as an effective antidiabetic agent, warranting further *in vitro* and *in vivo* validation studies.

Declaration of generative AI in scientific writing

During the preparation of this work, the authors used Gemini and Grammarly to improve the language, clarity, and overall readability of the manuscript. Additionally, the AI tool was utilized to provide a conceptual framework and visual suggestions for the development of the graphical abstract. Following the use of these technologies, the authors carefully reviewed and edited the content to ensure scientific accuracy and take full responsibility for the integrity of the final publication.

CRediT author statement

Wahyudin Rauf: Contributed to the conceptualization and design of the study and conducted the network pharmacology and molecular docking analyses, compound screening, and toxicity prediction analysis. **Hasnah Natsi**r: Contributed to the study design, supervised the analytical process, and critically reviewed the scientific content of the manuscript. **Anita Anita**: was responsible for data curation. **Nur Umriani Permatasari**: Assisted in data interpretation, results visualization, and manuscript drafting. All authors contributed to revising the manuscript, approved the final version, and take responsibility for all aspects of the research.

References

[1] OA Ojo, HS Ibrahim, DE Rotimi, AD Ogunlakin and AB Ojo. Diabetes mellitus: From molecular mechanism to pathophysiology and pharmacology. *Medicine in Novel Technology and Devices* 2023; **19**, 100247.

[2] F Siddiqui and V Bakshi. Hydroalcoholic extraction, phytoconstituent profiling by LC-HRMS, and computational analysis of *Lantana camara* as potential glucokinase, alpha amylase, alpha glucosidase, and DPP-IV inhibitors. *Chemical Methodologies* 2025; **9(12)**, 1189-1220.

[3] MAB Khan, MJ Hashim, JK King, RD Govender, H Mustafa and J Al-Kaabi. Epidemiology of type 2 diabetes—global burden of disease and forecasted trends. *Journal of Epidemiology and Global Health* 2020; **10(1)**, 107-111.

[4] L Sacchetta, M Chiriacò, L Nesti, S Leonetti, G Forotti, A Natali, A Solini and D Tricò. Synergistic effect of chronic kidney disease, neuropathy, and retinopathy on all-cause mortality in type 1 and type 2 diabetes: A 21-year longitudinal study. *Cardiovascular Diabetology* 2022; **21(1)**, 233.

[5] BS Modjtahedi, J Wu, TQ Luong, NK Gandhi, DS Fong and W Chen. Severity of diabetic retinopathy and the risk of future cerebrovascular disease, cardiovascular disease, and all-cause mortality. *Ophthalmology* 2021; **128(8)**, 1169-1179.

[6] BA Perkins, JL Sherr and C Mathieu. Type 1 diabetes glycemic management: Insulin therapy, glucose monitoring, and automation. *Science* 2021; **373(6554)**, 522-527.

[7] J Blahova, M Martiniakova, M Babikova, V Kovacova, V Mondockova and R Omelka. Pharmaceutical drugs and natural therapeutic products for the treatment of type 2 diabetes mellitus. *Pharmaceuticals* 2021; **14(8)**, 806.

[8] X Tian, W Wang, L Zhang, L Wang, K Zhang, X Ge, Z Luo, Y Zhao, X Zhai and C Li. Acupuncture and drug combination therapy for abnormal glucose metabolism: Exploring synergistic enhancement and reduced toxicity mechanisms. *Diabetes, Metabolic Syndrome and Obesity* 2024; **17**, 4525-4537.

[9] D Meireles, J Gomes, L Lopes, M Hinzmann and J Machado. A review of properties, nutritional and pharmaceutical applications of *Moringa oleifera*: Integrative approach on conventional and traditional Asian medicine. *Advances in Traditional Medicine* 2020; **20(4)**, 495-515.

[10] FS Owens III, O Dada, JW Cyrus, OO Adedoyin and G Adunlin. The effects of *Moringa oleifera* on blood glucose levels: A scoping review of the literature. *Complementary Therapies in Medicine* 2020; **50**, 102362.

[11] E Nova, N Redondo-Useros, RM Martínez-García, S Gómez-Martínez, LE Díaz-Prieto and A Marcos. Potential of *Moringa oleifera* to improve glucose control for the prevention of diabetes and related metabolic alterations: A systematic review of animal and human studies. *Nutrients* 2020; **12(7)**, 2050.

[12] A Leone, SD Lello, S Bertoli, S Ravasenghi, RD Amicis, F Menichetti, G Fico, L Santogistini, B Mohamed-Iahdih, SML Saleh and A Battezzati. *Moringa oleifera* leaf powder enhances glycemic control in Sahrawi women with type 2 diabetes: Findings from a 3-month unblinded randomized controlled trial. *PharmaNutrition* 2025; **31**, 100434.

[13] MB Afridi, H Sardar, G Serdaroğlu, SWA Shah, KF Alsharif and H Khan. SwissADME studies and density functional theory (DFT) approaches of methyl-substituted curcumin derivatives. *Computational Biology and Chemistry* 2024; **112**, 108153.

[14] H Natsir, NH Hasan, NU Permatasari, W Rauf, Anita, P Taba and RA Arfah. Novel anti-cancer agents: Potential of protease enzymes from *Vibrio alginolyticus* as a breast cancer therapy for MCF-7 cells. *Trends in Sciences* 2025; **22(10)**, 10450.

[15] A Marbán-González, V Ramírez-Cid, A Cristóbal-Ramírez and JL Medina-Franco. Exploiting PubChem and other public databases for virtual screening in 2025: What are the latest trends? *Expert Opinion on Drug Discovery* 2025; **20(11)**, 1387-1403.

[16] L Fu, L Zhao, F Li, F Wen, P Zhang, X Yang and Y Wang. Pharmacological mechanism of quercetin in the treatment of colorectal cancer by network pharmacology and molecular simulation. *Journal of Biomolecular Structure and Dynamics* 2024; **42(13)**, 7065-7076.

[17] M Hu, H Yan, H Li, Y Feng, W Sun, Y Ren, L Ma, W Zeng, F Huang, Z Jiang and H Dong. Use of network pharmacology and molecular docking to explore the mechanism of action of *Curcuma* in the treatment of osteosarcoma. *Scientific Reports* 2023; **13(1)**, 9569.

[18] Q Huang, R Liu, J Liu, Q Huang, S Liu and Y Jiang. Integrated network pharmacology analysis and experimental validation to reveal the mechanism of anti-insulin resistance effects of *Moringa oleifera* seeds. *Drug Design, Development and Therapy* 2020; **14**, 4069-4084.

[19] VS Patil, SH Deshpande, DR Harish, AS Patil, R Virge, S Nandy and S Roy. Gene set enrichment analysis, network pharmacology and *in silico* docking approach to understand the molecular mechanism of traditional medicines for the treatment of diabetes mellitus. *Journal of Proteins and Proteomics* 2020; **11(4)**, 297-310.

[20] S Zarougui, M Er-Rajy, A Faris, H Imtara, ME Fadili, AA Qurtam, FA Nasr, M Al-Zharani and M Elhallaoui. 3D computer modeling of inhibitors targeting the MCF-7 breast cancer cell line. *Frontiers in Chemistry* 2024; **12**, 1384832.

[21] SE Rhabori, M Alaqarbeh, AE Aissouq, M Bouachrine, S Chtita and F Khalil. Design, 3D-QSAR, molecular docking, ADMET, molecular dynamics, and MM-PBSA simulations for new anti-breast cancer agents. *Chemical Physics Impact* 2024; **8**, 100455.

[22] K Kavitha, JV Jothikanth, KP Kaniga, KS Manoj, RP Revathi, ER Esakiprasanth, MS Mohan, SNL Gowri, JR Jubilee, SM Srinithi and KH Lokesh. Synthesis, molecular docking, *in silico* drug-likeness, and *in vitro* cytotoxicity study on MCF-7 cell line of quinazolin-4-one scaffold. *Journal of Young Pharmacists* 2024; **16(4)**, 725-734.

[23] P Banerjee, E Kemmler, M Dunkel and R Preissner. ProTox 3.0: A webserver for the prediction of toxicity of chemicals. *Nucleic Acids Research* 2024; **52(W1)**, W513-W520.

[24] P Banerjee, O Ulker, I Ozkan and OC Ulker. The investigation of the toxicity of organophosphorus flame retardants (OPFRs) by using *in silico* toxicity prediction platform ProTox-3.0. *Toxicology Mechanisms and Methods* 2025; **35(1)**, 32-42.

[25] R Gašparová. *In silico* studies of biological activity and toxicity of naturally occurring buchenavianines. *Chemistry Proceedings* 2025; **18(1)**, 99.

[26] H Mude, PA Maroju, A Balapure, R Ganesan and JR Dutta. Water-soluble caffeic acid-dopamine acid-base complex exhibits enhanced bactericidal, antioxidant, and anticancer properties. *Food Chemistry* 2022; **374**, 131830.

[27] K Chen, X Chen, L Liang and X Xu. Gallic acid-aided cross-linking of myofibrillar protein fabricated soluble aggregates for enhanced thermal stability and a tunable colloidal state. *Journal of Agricultural and Food Chemistry* 2020; **68(41)**, 11535-11544.

[28] B Cheng, W Wang, X Niu, Y Ren, T Liu, H Cao, S Wang, Y Tu, J Chen, S Liu, X Yang and J Chen. Discovery of novel and highly potent resorcinol dibenzyl ether-based PD-1/PD-L1 inhibitors with improved drug-like and pharmacokinetic properties for cancer treatment. *Journal of Medicinal Chemistry* 2020; **63(24)**, 15946-15959.

[29] NF Shamsudin, QU Ahmed, S Mahmood, SAA Shah, MN Sarian, MMAK Khattak, A Khatib, ASMS Sabere, YM Yusoff and J Latip. Flavonoids as antidiabetic and anti-inflammatory agents: A review on structure–activity relationship-based studies and meta-analysis. *International Journal of Molecular Sciences* 2022; **23(20)**, 12605.

[30] A Selka, FJN Moutombi, M Cormier and M Touaibia. Phenethyl esters and amide of ferulic acid, hydroferulic acid, homovanillic acid, and vanillic acid: Synthesis, free radical scavenging activity, and molecular modeling as potential cholinesterase inhibitors. *Molbank* 2020; **2020(3)**, M1151.

[31] YZ Zheng, G Deng, R Guo, ZM Fu and DF Chen. Effects of different ester chains on the antioxidant activity of caffeic acid. *Bioorganic Chemistry* 2020; **105**, 104341.

[32] R Majeed and AK Mahmood. Phytochemical and antioxidant analysis of ginger (*Zingiber officinale*) Ethanol Extract. *Advancements in Life Sciences* 2025; **12(2)**, 331-339.

[33] DA Omoboyowa, G Singh, JO Fatoki and OE Oyeneyin. Computational investigation of phytochemicals from *Abrus precatorius* seeds as modulators of peroxisome proliferator-activated receptor gamma (PPARγ). *Journal of Biomolecular Structure and Dynamics* 2023; **41(12)**, 5568-5582.

[34] SC Yavuz. Synthesis of new two 1,2-disubstituted benzimidazole compounds: Their *in vitro* anticancer and *in silico* molecular docking studies. *BMC Chemistry* 2024; **18(1)**, 146.

[35] S Nallapaty, N Malothu, SK Konidala, AR Areti and C Guntupalli. HR-LCMS metabolite profiling and *in silico* evaluation of the antidiabetic activity of methanolic leaf extract of *Chrozophora rottleri* (Geiseler) A. Juss. ex Spreng. *Indian Journal of Pharmaceutical Education and Research* 2024; **58(4)**, 1277-1286.

[36] AI Alqosaibi. Small molecule 6"-O-malonylglycitin inhibits ERK2 activity and promotes cytotoxicity in colon adenocarcinoma cells paving for the colon cancer treatment. *Advancements in Life Sciences* 2025; **12(4)**, 753-761.

[37] AH Umar, SA Widuri, YC Sulistyaningsih and D Ratnadewi. Integrating metabolomic analysis, network pharmacology, and molecular docking to underlying pharmacological mechanism and ethnobotanical rationalization for diabetes mellitus: Study on medicinal plant *Fibraurea tinctoria* Lour. *Phytochemical Analysis* 2025; **36(4)**, 912-933.