

Integrating network pharmacology, molecular docking, and molecular dynamics to explore the antidiabetic mechanism of *Physalis angulata* L.

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Abstract

Diabetes mellitus is a chronic metabolic disorder that continues to rise globally, leading to severe health complications and economic burdens. Despite the availability of synthetic antidiabetic drugs, their side effects, limited efficacy, and long-term complications have driven interest in natural products as potential alternatives. *Physalis angulata* L. has been traditionally used for its anti-inflammatory, antioxidant, and hypoglycemic properties, but its molecular mechanisms in diabetes management remain unclear. This study employed network pharmacology (NP), molecular docking, and molecular dynamics (MD) simulations to systematically explore the bioactive compounds in *Physalis angulata* L. and their interactions with key diabetic targets. NP was utilized to predict compound-target interactions, followed by Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses to identify metabolic pathways involved in diabetes regulation. The predicted protein–protein interaction (PPI) networks were visualized using Cytoscape, revealing key targets linked to glucose metabolism and insulin sensitivity. To validate these predictions, molecular docking was performed to assess the binding affinity and stability of *Physalis angulata* L. metabolites with diabetic target proteins. The top-ranked compounds were further analyzed through MD simulations during a 50 ns simulation period, with root-mean-square deviation (RMSD) and root-mean-square fluctuation (RMSF) analysis confirming their structural stability within the receptor binding sites. Binding free energy calculations using MM-PBSA provided additional validation of ligand-receptor interactions. The results identified quercetin and myricetin as the most promising multi-target antidiabetic compounds, exhibiting strong and stable interactions with multiple key diabetic receptors. This study highlights the potential of *Physalis angulata* L. as a natural source for diabetes treatment, demonstrating the effectiveness of computational approaches in identifying bioactive compounds with multi-target therapeutic potential.

Keywords

diabetes mellitus therapy, *Physalis angulata* L., network pharmacology (NP), molecular docking studies, molecular dynamics (MD) simulations

Introduction

Diabetes mellitus remains one of the most pressing global health concerns, with its prevalence rising at an alarming rate. According to the International Diabetes Federation (IDF) 2021 report, approximately 537 million adults were living with diabetes worldwide, with projections estimating an increase to 643 million by 2030 and 783 million by 2045 (Kumar et al. 2023). Type 2 diabetes (T2D), which accounts for over 90% of cases, is primarily linked to sedentary lifestyles, unhealthy diets, and genetic predispositions. The disease is associated with serious complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy, making it a major cause of morbidity and mortality (Galicia-Garcia et al. 2020). Current antidiabetic drugs, such as insulin analogs, metformin, sulfonylureas, and SGLT-2 inhibitors, help regulate blood glucose levels but often come with undesirable side effects such as hypoglycemia, gastrointestinal distress, and long-term metabolic imbalances (Kieffer and Robertson 2020; Dahlén et al. 2022). The limited efficacy of conventional treatments in preventing diabetes-related complications has driven the search for alternative therapeutic approaches (Taloní et al. 2023). Natural products, particularly those derived from medicinal plants, have gained attention for their potential multi-target effects, which could offer a safer and more effective strategy for diabetes management.

Medicinal plants have long been valued for their therapeutic properties, including their antioxidant, anti-inflammatory, and hypoglycemic activities, which make them promising candidates for diabetes treatment (Formaggio et al. 2013; Ejiofor et al. 2023). The secondary metabolites found in these plants often exhibit multi-target mechanisms, interacting with various enzymes and receptors involved in glucose metabolism and insulin regulation. However, the identification of specific bioactive compounds, their protein targets, and molecular mechanisms remains a significant challenge (Shehadeh et al. 2021). To address this, network pharmacology (NP) approaches are widely used to study the complex interactions between phytochemicals, protein targets, and metabolic pathways. Unlike traditional single-target drug discovery, NP provides a holistic and systems-level perspective, allowing researchers to identify active compounds and predict their biological effects (Lee et al. 2019; Lu et al. 2019). By integrating systems biology, cheminformatics, and computational modeling, NP serves as a powerful tool for discovering novel therapeutic agents with potential applications in diabetes management.

One of the medicinal plants with significant ethnopharmacological value is *Physalis angulata* L., which belongs to the Solanaceae family and is commonly referred to as cutleaf groundcherry. This plant has been traditionally used in various regions for its antibacterial, anti-inflammatory, and antidiabetic properties (Magalhaes et al. 2006; Carniel et al. 2017). Studies have shown that *Physalis angulata* L. contains flavonoids, withanolides, steroids, and alkaloids that are known to exhibit potent biological activities. These bioactive compounds have been linked to

the modulation of glucose metabolism, enhancing insulin sensitivity, and protecting pancreatic β -cells from oxidative stress (Meng et al. 2019; de Oliveira et al. 2020). While experimental evidence suggests the antidiabetic potential of *Physalis angulata* L., the exact molecular mechanisms underlying its therapeutic effects remain unclear. Therefore, a computational approach is necessary to systematically explore the pharmacological targets and pathways influenced by its metabolites (Hananto et al. 2021; Iwansyah et al. 2022). This approach will help elucidate the plant's mechanisms of action, supporting its potential role in diabetes treatment.

To validate the findings obtained from NP, molecular docking is employed to analyze the binding affinity and stability of selected *Physalis angulata* L. metabolites with key diabetic targets. This method enables researchers to identify the most promising lead compounds based on their ability to form stable interactions with proteins involved in glucose metabolism and insulin signaling. Molecular docking simulations provide valuable insights into ligand-receptor interactions, allowing for a comparative evaluation of different phytochemicals (Hikmawati et al. 2022). Following docking analysis, molecular dynamics (MD) simulations are conducted to assess the structural stability and conformational changes of the ligand-receptor complexes over time. MD simulations further refine docking predictions by simulating the real-time behavior of molecules in a dynamic environment (Abbas et al. 2022). By integrating NP, molecular docking, and MD simulations, this study aims to elucidate the mechanistic basis of *Physalis angulata* L. metabolites in diabetes treatment, offering a computationally driven approach for discovering natural multi-target antidiabetic agents.

Materials and methods

Secondary metabolites of *Physalis angulata* L.

The secondary metabolites analyzed in this study were sourced from the KNApSACk Family Database (<http://www.knapsackfamily.com/>) and Dr. Duke's Phytochemical and Ethnobotanical Database (<https://phytochem.nal.usda.gov/>) (Nakamura et al. 2013). These databases were chosen for their comprehensive coverage of bioactive compounds and ethnopharmacological data relevant to *Physalis angulata* L. Chemical structures of the metabolites were validated using the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>), ensuring accuracy for subsequent computational analyses (Kim et al. 2023). Molecular structures were downloaded in Structure Data File (SDF) format and converted into 3D representations using Marvin Sketch software, which also facilitated structural optimization and visualization (ChemAxon 2022). The validated metabolites provided a basis for exploring their biological activities and interactions with diabetic target receptors. These preparations ensured that all selected compounds were accurately represented and suitable for in silico studies.

Prediction of biological activity and protein targets

The biological activities and protein targets of *Physalis angulata* L. metabolites were predicted using Way2Drug PASS Online (<http://way2drug.com/passonline/>) and Swiss Target Prediction (<http://www.swisstargetprediction.ch/>) (Lohidashan et al. 2018). Way2Drug PASS Online predicted potential antidiabetic activities by analyzing structural features of the metabolites, while Swiss Target Prediction identified protein targets based on molecular fingerprints and similarity to known bioactive compounds (Yao et al. 2024). All predictions were restricted to Homo sapiens proteins to ensure clinical relevance. The analysis specifically focused on proteins associated with diabetes-related pathways. A probability score threshold of 0.7 was used to filter high-confidence targets. These tools provided valuable insights into the pharmacological potential of the metabolites for diabetes management.

Pathway and interaction network analysis

Pathway analysis was conducted to understand the role of *Physalis angulata* L. metabolites in diabetes-related pathways. Protein-protein interactions were analyzed using the STRING database (<https://string-db.org/>), which integrates experimental data, co-expression studies, and literature mining to predict protein associations (Szklarczyk et al. 2023). Additional information on diabetes-specific pathways was obtained from GeneCards (<https://www.genecards.org/>) and the KEGG Pathway Database (<https://www.genome.jp/kegg/pathway.html>) (Safran et al. 2022). The interaction between metabolites and proteins was further examined using the STITCH database (<http://stitch.embl.de/>), which maps chemical-protein associations (Szklarczyk et al. 2016). The constructed interaction networks were visualized using Cytoscape v.3.8.2, allowing for a clear representation of the metabolites' influence on diabetes-related signaling pathways (Shannon et al. 2003). Node sizes indicated protein importance, while edge thickness represented interaction confidence scores, providing a detailed pharmacological map.

Prediction of ADME and toxicity

The Absorption, Distribution, Metabolism, and Excretion (ADME) profiles of *Physalis angulata* L. metabolites were

evaluated using Molsoft and SwissADME tools (<http://www.swissadme.ch/>) (Daina et al. 2017). Thresholds for oral bioavailability (OB) and drug-likeness (DL) were set at 30% and 0.18, respectively, to filter compounds with favorable pharmacokinetic properties. OB, which measures how efficiently a drug enters systemic circulation after oral administration, and DL, which evaluates molecular features for drug-likeness, were critical for compound selection. Toxicity profiles were assessed using ProTox-3.0 (https://tox.charite.de/protox3/index.php?site=compound_input), focusing on parameters such as hepatotoxicity, carcinogenicity, and mutagenicity (Banerjee et al. 2018). Metabolites with high toxicity were excluded from further studies. These predictions ensured the selection of compounds with optimal safety and efficacy profiles, making them suitable candidates for diabetes treatment.

Molecular docking studies

Molecular docking simulations were conducted to evaluate the binding interactions between *Physalis angulata* L. metabolites and key antidiabetic target receptors, including aldose reductase (3RX2) (Zheng et al. 2012), alpha amylase (3BAJ) (Maurus et al. 2008), alpha glucosidase (3W37) (Tagami et al. 2013), dipeptidyl peptidase-4 (DPP4) (4FFW) (Tang et al. 2013), glucagon-like peptide-1 (GLP-1) (7S15) (Griffith et al. 2022), peroxisome proliferator-activated receptor gamma (PPAR-Gamma) (2P4Y) (Einstein et al. 2008), sodium-glucose co-transporter 2 (SGLT-2) (7VS1) (Arole et al. 2023), AMP-activated protein kinase (AMPK) (5KQ5) (Cameron et al. 2016), and glucose transporter type 4 (GLUT4) (7WSM) (Yuan et al. 2022) (Table 1). The crystal structures of the receptors were obtained from the RCSB Protein Data Bank and pre-processed using PyMOL v.3.0, where water molecules and heteroatoms were removed, and polar hydrogens and charges were added (Delano 2002). Metabolite structures were optimized using Marvin Sketch and converted to PDBQT format in AutoDock Tools 1.5.7. Docking simulations were performed using AutoDock 4.2 with the Lamarckian genetic algorithm (LGA) to identify the most stable ligand-receptor conformations, considering binding energy, hydrogen bonding, and hydrophobic interactions (Forli et al. 2012). Visualization of docking results with PyMOL v.3.0 and Discovery Studio Visualizer v.2024 Client highlighted key residues that contributed to complex stabilization (BIOVIA 2017).

Table 1. Molecular docking parameters for various diabetes-related target receptors.

Target Receptor	PDB ID	Grid Center (Å)	Grid Box (Å)	Spacing (Å)
Aldose reductase	3RX2	−10.289 × 9.723 × 17.593	64 × 60 × 60	0.375
Alpha amylase	3BAJ	8.652 × 15.386 × 40.189	64 × 60 × 60	0.375
Alpha glucosidase	3W37	25.392 × −46.636 × −60.453	64 × 60 × 60	0.375
DPP4	4FFW	20.845 × −9.87 × 53.615	64 × 60 × 60	0.375
GLP-1	7S15	68.778 × 70.15 × 60.516	64 × 60 × 60	0.375
PPAR-Gamma	2P4Y	14.162 × 6.579 × 12.34	64 × 60 × 60	0.375
SGLT-2	7VS1	39.007 × 51.962 × 45.448	64 × 60 × 60	0.375
AMPK	5KQ5	15.489 × 23.365 × 30.825	64 × 60 × 60	0.375
GLUT4	7WSM	99.206 × 102.793 × 106.287	64 × 60 × 60	0.375

Lower binding energy values indicated strong interactions, reinforcing the potential of *Physalis angulata* L. metabolites as multi-target antidiabetic agents. This analysis provided critical insights into the molecular basis of their antidiabetic activity.

Molecular dynamics simulations

The three-dimensional structures of the target diabetic receptors in complex with *Physalis angulata* L. metabolites were prepared for molecular dynamics simulations. The receptor-ligand complexes were pre-processed using PyMOL v.3.0, where water molecules and heteroatoms were removed, and polar hydrogens were added. Ligands were positioned within the active binding site using the docking results obtained from AutoDock 4.2. The prepared complexes were then subjected to molecular dynamics (MD) simulations using GROMACS v.2020.3, employing the Amber99sb-ildn force field (Van Der Spoel et al. 2005; Abraham et al. 2015). The complexes were placed in a triclinic simulation box with dimensions extending 11 Å from the receptor-ligand complex in each direction. The systems were solvated with a TIP3P water model, and sodium (Na^+) and chloride (Cl^-) ions were added to achieve a 0.150 M NaCl ionic concentration and to neutralize the system's net charge. Energy minimization was conducted using the steepest descent algorithm for 50,000 steps, ensuring system stability. The systems were equilibrated under NVT (constant volume and temperature) conditions for 1 ns at 300 K using the Berendsen thermostat with position restraints applied to the receptor's heavy atoms at $1000 \text{ kJ mol}^{-1} \text{ nm}^{-2}$. This was followed by NPT (constant pressure and temperature) equilibration for 1 ns at 1 bar, using the Berendsen barostat with similar position restraints (Lin et al. 2017). A final equilibration step of 1 ns was performed without position restraints, employing the Parrinello-Rahman barostat and the Verlet thermostat to maintain pressure and temperature at 1 bar and 300 K, respectively (Ke et al. 2022). The production run, conducted under equilibrated conditions, lasted for 50 ns with periodic boundary conditions. An integration time step of 2 fs was used, and data, including energy values and compressed coordinates, were saved every 100 ps. The MD simulations provided insight into the structural stability and dynamics of the receptor-ligand complexes, forming the basis for subsequent binding energy calculations.

Statistical molecular dynamics analysis

The root-mean-square deviation (RMSD) was analyzed to evaluate the structural stability of the receptor-ligand complexes during the MD simulations. RMSD calculations were performed using the GROMACS analysis toolkit, focusing on the backbone atoms of the receptor and all atoms of the ligand. The RMSD plots were

generated to track conformational changes and stability over the 50 ns simulation period. The RMSD values were monitored from the initial equilibration phase to the production run, with the first 10 ns of the simulation excluded to ensure the system reached equilibrium. Stable RMSD values indicated minimal conformational fluctuations, reflecting a well-stabilized interaction between the ligand and receptor. Visualizations of RMSD data were created using pyMOL v.3.0 and VMD v.1.9.4a51, allowing a detailed examination of the structural integrity and dynamic behavior of the complexes (Prall 2001). These analyses confirmed the stability of *Physalis angulata* L. metabolites when bound to their respective antidiabetic targets, supporting their potential pharmacological relevance. In addition to RMSD, root-mean-square fluctuation (RMSF) analysis was carried out to evaluate the flexibility of individual residues in the receptor throughout the MD simulation. The RMSF plots revealed that most residues exhibited low fluctuations, particularly those involved in ligand binding, indicating restricted mobility due to stable interactions. Higher RMSF values were mainly observed in the loop regions and terminal ends of the receptor, which are known to be inherently flexible.

Molecular mechanics Poisson-Boltzmann surface area (MM-PBSA)

The MM-PBSA approach was employed to calculate the binding free energies of the receptor-ligand complexes, providing quantitative insights into their interaction strengths (Kumari et al. 2014; Wang et al. 2018). Calculations were performed using the *g_mmpbsa* tool in GROMACS v.2020.3, which included three energy components: vacuum potential energy, polar solvation energy, and non-polar solvation energy. The polar solvation energy was computed by solving the Poisson-Boltzmann equation with dielectric constants set to 2 for the solute and 80 for the solvent and an ionic strength of 150 mM. Non-polar solvation energy was approximated using surface area-dependent terms with parameters $\gamma = 0.0226778 \text{ kJ mol}^{-1} \text{ Å}^{-2}$ and $b = 3.84982 \text{ kJ mol}^{-1}$. For each receptor-ligand complex, 100 frames were extracted from the final 50 ns of the MD simulation to ensure representative sampling of equilibrated states. Binding energy contributions from van der Waals, electrostatic, polar solvation, and non-polar solvation components were calculated. The *MmPbSaStat.py* script was used to compute average binding energies, while *MmPbSaDecomp.py* was utilized to identify key residue contributions. Results indicated that the binding free energy was predominantly influenced by van der Waals and electrostatic interactions, while polar solvation energy partially offset these favorable contributions. These analyses provided critical insights into the molecular mechanisms underlying the antidiabetic potential of *Physalis angulata* L. metabolites.

Results and discussion

Prediction of metabolites contained in *Physalis angulata* L.

The analysis of plant metabolites was conducted using the KNApSACk and Dr. Duke's Phytochemical and Ethnobotanical databases, revealing various active compounds with unique characteristics. Based on the data in Table 2, several key metabolites were identified, including quercetin, myricetin, physagulin, withanolide, and physalin. Each compound exhibits distinct molecular weights (Mw), as well as varying synthetic accessibility and bioavailability, which indicate its potential biological activity. KNApSACk is a comprehensive database that contains information on the relationships between metabolites, biological activities, and plant species (Afendi et al. 2012). Dr. Duke's phytochemical and ethnobotanical database offers advantages such as free accessibility and supporting references that correlate with ethnomedicinal data of high significance (Jayabal et al. 2023). The presence of these metabolites in plants suggests their significant pharmacological potential. Many of these compounds have been widely used in traditional medicine for treating various diseases, including cancer, inflammation, and microbial infections. Their structural diversity contributes to their ability to interact with different biological targets in the human body. The chemical compound components used in this study are derived from various parts of the *Physalis angulata* L. plant, including the leaves, stems, roots, and fruits, as all parts have been reported to contain diverse bioactive secondary metabolites. These metabolites serve as essential candidates for further pharmacological research, particularly in drug discovery and therapeutic development. Future investigations should focus on isolating these compounds to better understand their bioactivity and safety profiles.

Several important metabolites have been identified within the dataset, each with distinctive chemical properties and biological potential. Flavonoids, such as quercetin (C₁₅H₁₀O₇) and myricetin (C₁₅H₁₀O₈), are known for their strong antioxidant and anti-inflammatory activities. These compounds have been widely studied for their role in preventing oxidative stress-related diseases, including cardiovascular disorders and neurodegenerative conditions (Griffiths et al. 2016; Marín et al. 2018). Another significant class of compounds includes withanolides, such as withangulatin A, B, and C, which have demonstrated anti-inflammatory and anticancer properties (Sun et al. 2010). Additionally, physalin derivatives, including physalin B, D, F, G, I, and K, exhibit potential immunomodulatory and cytotoxic activities. Physagulin compounds, including physagulin A, B, C, D, E, F, G, H, and J, have structurally complex frameworks that contribute to their diverse pharmacological actions (Garcia et al. 2006; Pinto et al. 2016). The variation in chemical structures suggests that these compounds may have different mechanisms of action, making them promising candidates for pharmaceu-

tical applications. The molecular composition of these metabolites influences their bioavailability, metabolism, and potential therapeutic effects. These findings highlight the importance of further research into the pharmacokinetics and pharmacodynamics of these natural compounds.

Biological activity prediction of identified metabolites in *Physalis angulata* L.

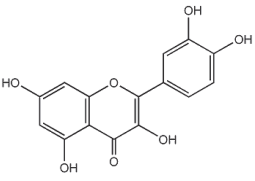
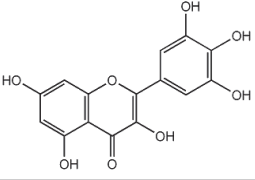
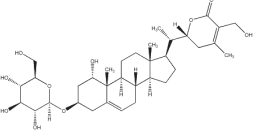
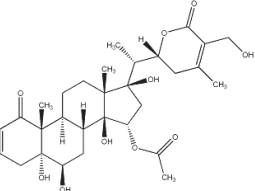
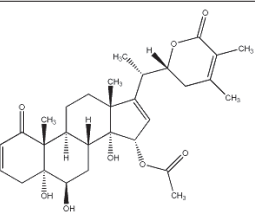
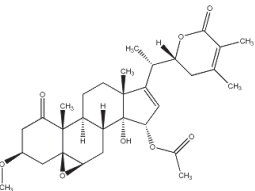
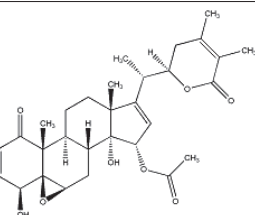
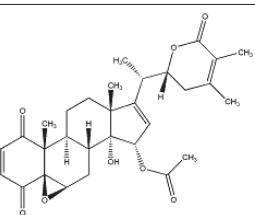
The data in Table 3 present the predicted biological activities of several key plant metabolites based on their Pa values (probability of activity). Quercetin and myricetin stand out as strong alpha glucosidase inhibitors, with Pa values of 0.858 and 0.904, respectively, indicating a high likelihood of effectiveness in suppressing carbohydrate breakdown. Additionally, quercetin exhibits moderate inhibitory activity against mannosyl-glycoprotein endo-beta-N-acetylglucosaminidase (Pa = 0.575), glucan endo-1,3-beta-D-glucosidase (Pa = 0.516), and antidiabetic activity (Pa = 0.528). Myricetin shows a similar profile but with slightly higher Pa values in glucan endo-1,3-beta-D-glucosidase inhibition (Pa = 0.612) and antidiabetic activity (Pa = 0.584). These findings suggest that both flavonoids play a significant role in regulating glucose metabolism, which aligns with their known antidiabetic and antioxidant properties. The presence of multiple enzyme inhibitory activities for quercetin and myricetin indicates broad pharmacological potential, particularly in metabolic disorders.

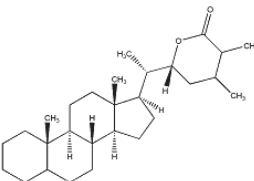
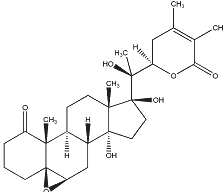
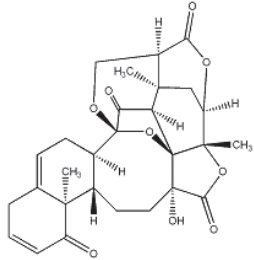
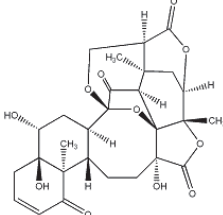
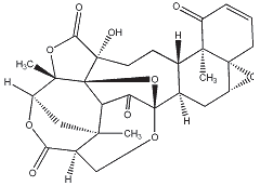
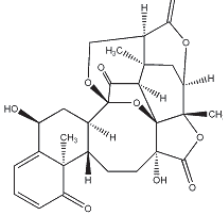
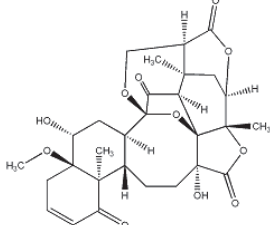
Other compounds, such as physagulin D and L, exhibit moderate activity as glucan endo-1,3-beta-D-glucosidase inhibitors, both with Pa values of 0.698, indicating potential but weaker enzyme inhibition compared to flavonoids. Meanwhile, withanolides and withangulatin show notable antidiabetic activity, with Pa values ranging from 0.596 to 0.718, suggesting that these compounds may contribute to glucose regulation through different mechanisms. Dihydrowithanolide E (Pa = 0.703) and withangulatin D (Pa = 0.718) have the highest predicted antidiabetic activities among steroidal lactones, making them potential candidates for further study. Others withangulatin, such as B, C, and E, exhibit lower but still relevant antidiabetic activity (Pa = 0.596 to 0.624). The varying Pa values among withanolides and physagulin derivatives indicate structural differences influencing their biological effects. These predictions suggest that while flavonoids demonstrate the highest probability of enzyme inhibition, withanolides and physagulin compounds still hold significant pharmacological value. The presence of these bioactive compounds in medicinal plants further supports their potential role in metabolic health applications.

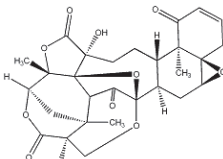
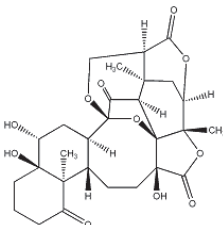
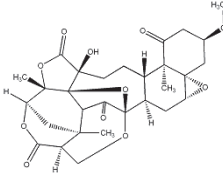
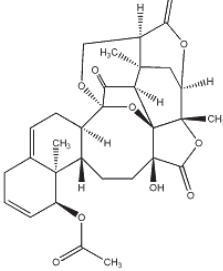
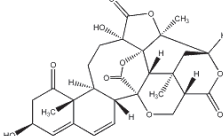
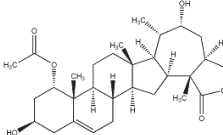
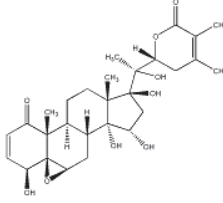
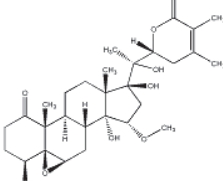
Interaction network analysis between *Physalis angulata* L. metabolites and target proteins

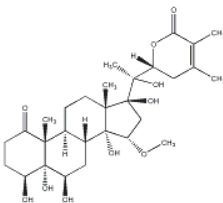
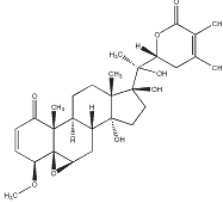
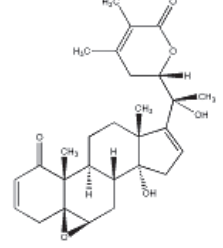
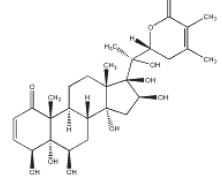
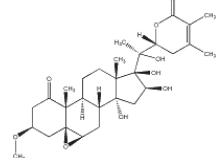
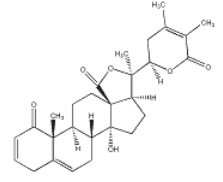
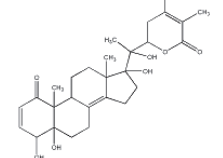
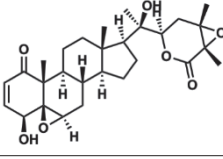
The interaction network between identified plant metabolites and their target proteins was constructed using STITCH, with visualization based on a confidence view.

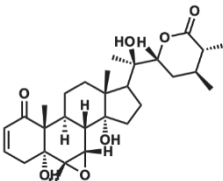
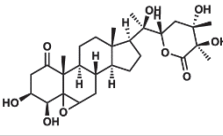
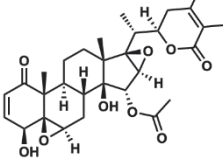
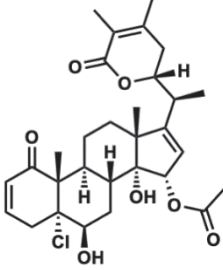
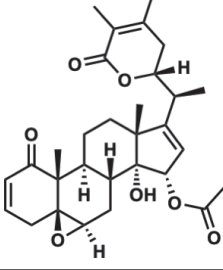
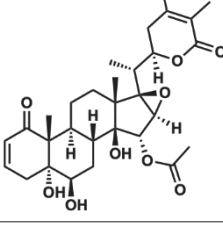
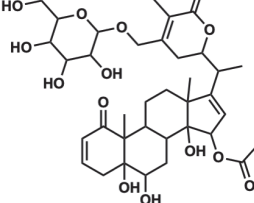
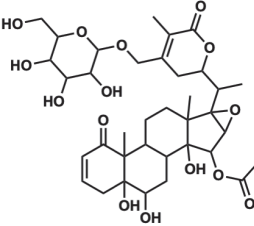
Table 2. Bioactive metabolites in *Physalis angulata* L. and their molecular characteristics.

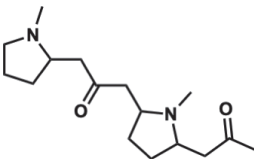
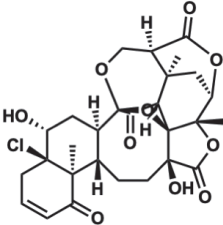
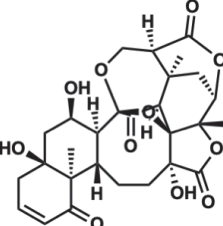
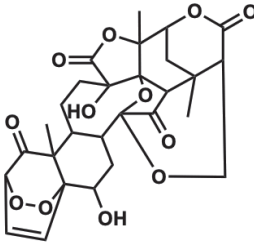
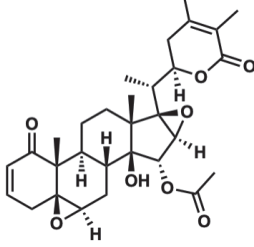
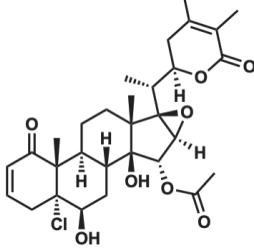
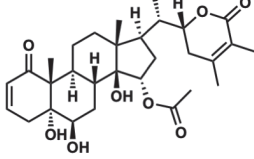
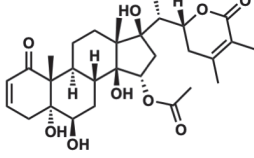
C_ID	CAS ID	Active Compound	Molecular Formula	MW	Synthetic Accessibility	Bioavailability Score	2D Structure
C00004631	117-39-5	Quercetin	C ₁₅ H ₁₀ O ₇	302.04	3.23	0.55	
C00001071	529-44-2	Myricetin	C ₁₅ H ₁₀ O ₈	318.03	3.27	0.55	
C00031019	146713-92-0	Physagulin D	C ₃₄ H ₅₂ O ₁₀	620.35	7.78	0.17	
C00031020	914774-49-5	Physagulin L	C ₃₀ H ₄₂ O ₁₀	562.27	6.83	0.55	
C00031021	914774-50-8	Physagulin M	C ₃₀ H ₄₀ O ₉	544.26	6.72	0.55	
C00031022	914774-51-9	Physagulin N	C ₃₁ H ₄₂ O ₈	542.28	7.30	0.55	
C00032510	120824-03-5	Withangulatin A	C ₃₀ H ₃₈ O ₈	526.25	7.18	0.55	
C00032511	1039021-31-2	Withangulatin I	C ₃₀ H ₃₆ O ₈	524.24	7.00	0.55	

C_ID	CAS ID	Active Compound	Molecular Formula	MW	Synthetic Accessibility	Bioavailability Score	2D Structure
C00032512	40326-62-3	Withanolide	C ₂₈ H ₄₆ O ₂	414.34	5.42	0.55	
C00039032	38253-76-8	Dihydrowithanolide E	C ₂₈ H ₄₀ O ₇	488.27	6.88	0.55	
C00039999	23133-56-4	Physalin B	C ₂₈ H ₃₀ O ₉	510.18	7.01	0.55	
C00040000	54980-22-2	Physalin D	C ₂₈ H ₃₂ O ₁₁	544.19	7.21	0.17	
C00040001	57423-71-9	Physalin F	C ₂₈ H ₃₀ O ₁₀	526.18	7.29	0.55	
C00040002	69913-56-0	Physalin G	C ₂₈ H ₃₀ O ₁₀	526.18	7.29	0.55	
C00040003	70293-99-1	Physalin I	C ₂₉ H ₃₄ O ₁₁	558.21	7.33	0.17	

C_ID	CAS ID	Active Compound	Molecular Formula	MW	Synthetic Accessibility	Bioavailability Score	2D Structure
C00040005	57517-46-1	Physalin J	C ₂₈ H ₃₀ O ₁₀	526.18	—	—	
C00040006	73051-80-6	Physalin T	C ₂₈ H ₃₄ O ₁₁	546.21	7.12	0.17	
C00040007	877823-77-3	Physalin U	C ₂₉ H ₃₄ O ₁₁	558.21	7.38	0.17	
C00040008	904892-55-3	Physalin V	C ₃₀ H ₃₄ O ₁₀	554.21	7.37	0.55	
C00040009	944718-72-3	Physalin W	C ₂₈ H ₃₀ O ₁₀	526.18	7.18	0.55	
C00040013	904892-54-2	Physanolide A	C ₃₀ H ₄₄ O ₆	500.31	6.56	0.55	
C00040653	946074-78-8	Withangulatin B	C ₂₈ H ₃₈ O ₉	518.25	7.09	0.55	
C00040654	946074-79-9	Withangulatin C	C ₂₉ H ₄₂ O ₉	534.28	7.19	0.55	

C_ID	CAS ID	Active Compound	Molecular Formula	MW	Synthetic Accessibility	Bioavailability Score	2D Structure
C00040655	946074-80-2	Withangulatin D	C ₂₉ H ₄₄ O ₁₀	552.29	6.85	0.17	
C00040656	946074-81-3	Withangulatin E	C ₂₉ H ₄₂ O ₈	518.28	7.16	0.55	
C00040657	946074-82-4	Withangulatin F	C ₂₈ H ₃₈ O ₆	470.26	6.79	0.55	
C00040658	946074-83-5	Withangulatin G	C ₂₈ H ₄₀ O ₁₀	536.26	6.74	0.17	
C00040659	946074-84-6	Withangulatin H	C ₂₉ H ₄₂ O	534.28	7.16	0.55	
C00040660	57423-72-0	Withaphysalin A	C ₂₈ H ₃₄ O	466.23	6.66	0.55	
C00040661	74799-65-8	Withaphysanolide	C ₂₈ H ₃₈ O ₇	486.26	6.28	0.55	
C0054835	107221-66-9	24,25-Epoxywithanolide D, 5,6	C ₂₈ H ₃₈ O ₇	486.26	6.91	0.55	

C_ID	CAS ID	Active Compound	Molecular Formula	MW	Synthetic Accessibility	Bioavailability Score	2D Structure
C00056416	107221-65-8	14-Hydroxyxocarpanolide	C ₂₈ H ₄₀ O ₇	488.27	6.45	0.55	
C00057016	131749-58-1	Physangulide	C ₂₈ H ₄₂ O ₉	522.28	6.68	0.55	
C00057038	136997-67-6	Physagulin C	C ₃₀ H ₃₈ O ₉	542.25	7.21	0.55	
C00057072	146713-97-5	Physagulin B	C ₃₀ H ₃₉ ClO ₇	546.23	6.74	0.55	
C00057073	146713-98-6	Physagulin A	C ₃₀ H ₃₈ O ₇	510.26	7.07	0.55	
C00057085	148054-12-0	Physagulin F	C ₃₀ H ₄₀ O ₉	544.26	6.76	0.55	
C00057086	148054-13-1	Physagulin E	C ₃₆ H ₅₀ O ₁₄	706.32	8.07	0.17	
C00057087	148076-22-6	Physagulin G	C ₃₆ H ₅₀ O ₁₅	722.31	8.07	0.17	

C_ID	CAS ID	Active Compound	Molecular Formula	MW	Synthetic Accessibility	Bioavailability Score	2D Structure
C00057088	148139-97-3	Phygrine	C ₁₆ H ₂₈ N ₂ O ₂	280.21	3.08	0.55	
C00057504	70241-09-7	Physalin H	C ₂₈ H ₃₁ ClO ₁₀	562.16	7.21	0.55	
C00057505	70241-10-0	Physalin E	C ₂₈ H ₃₂ O ₁₁	544.19	7.21	0.17	
C00057540	76045-35-7	Physalin K	C ₂₈ H ₃₀ O ₁₂	558.17	8.27	0.17	
C00057555	791084-72-5	Physagulin H	C ₃₀ H ₃₈ O ₈	526.25	7.12	0.55	
C00057556	791084-73-6	Physagulin I	C ₃₀ H ₃₉ ClO ₈	562.23	6.79	0.55	
C00057557	791084-74-7	Physagulin J	C ₃₀ H ₄₂ O ₈	530.28	6.73	0.55	
C00057558	791084-75-8	Physagulin K	C ₃₀ H ₄₂ O ₉	546.28	6.81	0.55	

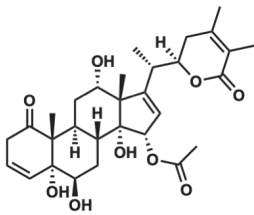
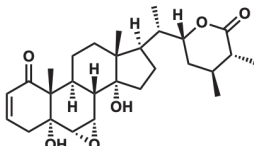
C_ID	CAS ID	Active Compound	Molecular Formula	MW	Synthetic Accessibility	Bioavailability Score	2D Structure
C00057689	952671-88-4	Physagulin O	C30H40O9	544.26	6.94	0.55	
C00057779	114332-66-0	Vamonolide	C28H40O6	472.28	6.39	0.55	

Table 3. Predicted biological activities of identified *Physalis angulata* L. metabolites.

Active Compound	Pa Value	Biological Activity
Quercetin	0.858	Alpha glucosidase inhibitor
	0.575	Mannosyl-glycoprotein endo-beta-N-acetylglucosaminidase inhibitor
	0.528	Antidiabetic
	0.516	Glucan endo-1,3-beta-D-glucosidase inhibitor
Myricetin	0.904	Alpha glucosidase inhibitor
	0.612	Glucan endo-1,3-beta-D-glucosidase inhibitor
	0.593	Mannosyl-glycoprotein endo-beta-N-acetylglucosaminidase inhibitor
	0.584	Antidiabetic
	0.505	Oligo-1,6-glucosidase inhibitor
	0.518	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor
Physagulin D	0.698	Glucan endo-1,3-beta-D-glucosidase inhibitor
Physagulin L	0.698	Glucan endo-1,3-beta-D-glucosidase inhibitor
Withanolide	0.596	Glucan endo-1,3-beta-D-glucosidase inhibitor
Dihydrowithanolide E	0.703	Antidiabetic
Withangulatin B	0.624	Antidiabetic
Withangulatin C	0.596	Antidiabetic
Withangulatin D	0.718	Antidiabetic
Withangulatin E	0.597	Antidiabetic

The thickness of the edges in the network representation indicates different levels of interaction confidence, which are determined based on binding affinity, inhibition constants (K_i), EC_{50} , or IC_{50} values. A medium confidence level (>0.400) was set as the threshold, indicating significant interactions between metabolites and their target proteins. STITCH integrates data from various sources, including genomic content predictions, experimental results, co-expression patterns, text mining, and known protein-protein interactions, making it a widely used tool in network pharmacology (NP) research (Kuhn et al. 2008). The network reveals the presence of intracellular target proteins, which suggests the activation of intracellular signaling pathways upon metabolite binding. The thicker the interaction line, the stronger the bond between the metabolite and its respective target protein, signifying a greater likelihood of biological activity. The identification of these interactions highlights the potential pharmacological relevance of quercetin, myricetin, physagulin, withanolide, and withangulatin, which interact with key regulatory proteins involved in metabolic and signaling pathways.

Based on the interaction analysis, quercetin and myricetin target multiple proteins, including NMUR2, ADRA2A, ADRA2C, ACHE, AKR1B1, CA7, CA12, and NOX4, among others, indicating broad pharmacological potential (Table 4). Physagulin D interacts with STAT3, PRKCA, JUN, and BCL2L1, suggesting possible involvement in cell signaling and apoptosis regulation. Withanolides and withangulatin interact with an extensive list of metabolic, immune-related, and signaling proteins. These include VDR, HMGCR, JAK2, MAPK14, and AKT1, supporting their role in anti-inflammatory and antidiabetic pathways. Some metabolites, such as physagulin L and dihydrowithanolide E, did not have associated target proteins in the dataset, indicating a need for further exploration of their biological interactions. The NP approach, visualized through Cytoscape v.3.8.2, provides a clear representation of how these plant metabolites influence biological pathways, potentially affecting key physiological processes. The identification of these protein interactions emphasizes the importance of these natural compounds in drug discovery, particularly in metabolic disorders and inflammatory conditions.

Table 4. Predicted target proteins of identified *Physalis angulata* L. metabolites.

PubChem ID	Active Compound	Target Genes
44259099	Quercetin	NMUR2, ADRA2A, ADRA2C, ACHE, AKR1B1, CA7, CA12, CA4, NOX4, CA2, NQO2, RPS6KA3, XDH, CD38, PTGS2, PDE5A, TNF, IL2, ADORA1, ALOX5, TERT
44259460	Myricetin	NMUR2, ADRA2A, ADRA2C, ACHE, AKR1B1, NQO2, CA7, CA12, CA4, NOX4, PTGS2, CA2, RPS6KA3, XDH, CD28, PDE5A, TNF, IL2, ADORA1, ALOX5, TERT
10100412	Physagulin D	TTL, PRKCA, JUN, STAT3, PTPN1, PRKCE, PRKCH, PPM1B, PPP1CC, PPP2CA, RORC, ATP1A1, IARS, IL2, PRKCB, PDE4D, BCL2L1, F2, PDCD4, PLA2G2A, PLA2G1B, GLI1, PRKCD, PRKCQ, TERT, HSD11B2
16082070	Physagulin L	–
53477765	Withanolide	CDC25A, VDR, PTPN1, HMGCR, HSD11B1, SIRT2, OPRK1, CYP19A1, ACHE, UGT2B7, CA1, CA9, HSD17B3, OPRM1, PDE10A, TRPV1, TSPO, CDC25B, JAK2, ALK, LIMK2, TRPM8, TNKS, PDGFRB, KDR, IDH1, GCGR, MAPK14, CA2, HRH3, GRIA2, TAAR1, CASR, FKBP1A, OPRD1, CYP11B2, P2RX7, PTGDR2, TARC1, TARC3, MDM2, PRKCA, AVPR1A, QPCT, FLT1, CYP11B1, PRKCQ, GPR55, NPY5R, KCNA3, SMO, SSTR4, CES1, SLC6A15, F2R, AKT1, IMPDH2, VCAM1, HRH1, KCNH2, GRIA4, HRH4, BRD4, BRD2, BRD3, ADORA1, NR1I2, GRM2, PPM1B, PPP1CC, CCR4, AVPR2, SLC9A1, EP300
131751517	Dihydrowithanolide E	–
16757497	Withangulatin B	PRKCA, TERT, AR, ATP2A1, PDE4D, PTGS2, PTPN1, PRKCE, JUN, PRKCD, PDCD4, IARS, NR3C2, VAV1, F2RL1, NOS2, CYP19A1, SLC5A2, SLC5A1, ADK, GLI1, TTL, CXCR1, TRPV4, GSTM1, ADORA1, PRKCG, PRKCB, PRKCH, PRKCQ, SIRT2, LGALS3, LGALS1, ADORA3, CDC25B, IRAK4, PLA2G2A, POLB, ADORA2A, CCR1, JAK1, JAK2, F3, TK2, SLC29A1, IMPDH2, PYGL, MAP2K1, F2, PDE10A, IL1B, PGR, UPP1, FNTA FNTB
16757390	Withangulatin C	JUN, PRKCA, PDCD4, IARS, AR, TTL, PRKCD, PTPN1, PTGS2, ATP2A1, PDE4D, PRKCE, TRPV4, CXCR1, CDC25B, F2RL1, PRKCB, KCNA3, ADK, CDK4, MAPK8, MAPK14, MAPK10, MAPK3, SLC5A2, MAPK9, ADORA2A, LGALS3, LGALS1, TERT, CXCR2, FNTA FNTB, PGGT1B FNTA, ADORA3, SLC29A1, SORD, SLC5A1, GABRA5, ACVRL1, HSD11B1, SYK, PDE10A, CCNA2, CDK2, MAPK1, CDK6, CRHR1, MAP2K1, MAP3K14, PDE6A, CTSK, CTSS
Not Found	Withangulatin D	PRKCA, JUN, PDCD4, IARS, AR, TTL, ATP2A1, PDE3D, PRKCD, PTPN1, VAV1, PRKCE, PTGS2, F2RL1, ADK, KCNA3, SLC5A2, CXCR1, SLC5A1, TRPV4, LGALS3, LGALS1, ADORA2A, PRKCB, IRAK4, PRKCQ, SLC5A11, SLC5A4, F3, SLC2A1, CHEK1, ABCB1, EIF4A1, MAP2K1, SLC28A2, ADORA3, PRKCG, PRKCH, PDE10A, MAPK14, TOP1, IMPDH2, FNTA FNTB, SLC29A1, NTRK1, TERT, CTSD, TK2, CXCR2, GSTM1, UPP1
102471220	Withangulatin E	JUN, PRKCA, PTPN1, PTGS2, PDE4D, TERT, AR, PRKCE, PRKCD, ATP2A1, FNTA FNTB, PGGT1B, FNTA, F2RL1, CXCR1, KCNA3, IARS, ABCB1, PRKCQ, TTL, PRKCB, GSTM1, PRKCG, PRKCH, PDCD4, GLI1, HSD11B1, VAV1, P2RX3, TRPV4, F2, CDC25B, BACE2, MAPK1, SIRT2, CRHR1, SYK, MAPK14, MAPK8, MAP3K14, MMP3, MMP1, MMP7, SORD, SRC, HMGCR, MAP2K1, ADAM17, MMP14, IRAK4, JAK1, JAK2, LRRK2, IMPDH2, CHEK1, NR3C2, FLT4, CCNA2, CDK2, VHL, ELOC, ELOB VHL, ADORA1, ADY1, KCNJ1, KCNH2, NTRK1, PCSK7, ACHE, LGALS3, P2RX7, AXL, LGALS1, TYRO3, ADORA3, CXCR2, PDE11A, PDE10A, NR3C1, F10, ACVRL1, CALM1, DUSP3, CASP8, SLC5A1, FKBP1A, MTOR, AURKA, CDK4, POLB, CDK6, CTSD, ADK

ADMET analysis of identified plant metabolites in *Physalis angulata* L.

The pharmacokinetic properties and toxicity predictions of the identified plant metabolites were evaluated through ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis using the SwissADME tool. Table 5 presents standard pharmacokinetic parameters, including gastrointestinal (GI) absorption, blood-brain barrier (BBB) penetration, P-glycoprotein (P-gp) substrate status, cytochrome enzyme inhibition (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), skin permeation (Log Kp), and toxicity profiles (hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity). The ADMET analysis provides essential insights into the pharmacological potential of these compounds and their suitability for drug development. Among the analyzed metabolites, quercetin exhibits high GI absorption, suggesting strong bioavailability, whereas other compounds – including myricetin, physagulin derivatives, and withanolides

– demonstrate low GI absorption, which may limit their oral bioavailability. None of the compounds exhibit BBB penetration, implying they are unlikely to cross into the central nervous system (CNS), which may reduce the risk of neurological side effects (Haywood et al. 2019). The P-gp substrate analysis indicates that physagulin D, L, and some withangulatin derivatives are substrates for P-glycoprotein, suggesting that they may be actively transported out of cells, potentially affecting drug retention and absorption.

The cytochrome P450 (CYP) enzyme inhibition profile highlights the potential metabolic interactions of these metabolites. Quercetin and myricetin inhibit CYP1A2 and CYP3A4, indicating they may interfere with the metabolism of drugs processed by these enzymes, which could result in drug-drug interactions. Other compounds, such as physagulin derivatives, withanolides, and withangulatin, do not inhibit major CYP enzymes, suggesting a lower likelihood of metabolic interference. The toxicity analysis provides further insights into the safety of these compounds (Pang et al. 2022). Quercetin and myricetin

Table 5. ADMET analysis of identified metabolites based on pharmacokinetic and toxicity predictions.

Standard Parameters	Quercetin	Myricetin	Physagulin D	Physagulin L	Withanolide
GI absorption	High	Low	Low	Low	Low
BBB	No	No	No	No	No
P-gp substrate	No	No	Yes	Yes	No
CYP1A2 inhibitor	Yes	Yes	No	No	No
CYP2C19 inhibitor	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No
CYP2D6 inhibitor	Yes	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	No	No	No
Log Kp (Skin Permeation; cm/s)	-7.05	-7.40	-7.86	-9.11	-2.08
Toxicity					
Hepatotoxicity	No	No	No	No	No
Carcinogenicity	Yes	Yes	No	No	No
Immunotoxicity	No	No	Yes	Yes	Yes
Mutagenicity	Yes	Yes	No	No	No
Cytotoxicity	No	No	Yes	Yes	Yes
	Dihydrowithanolide E	Withangulatin B	Withangulatin C	Withangulatin D	Withangulatin E
GI absorption	Low	Low	Low	Low	High
BBB	No	No	No	No	No
P-gp substrate	No	Yes	Yes	No	Yes
CYP1A2 inhibitor	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No
CYP2C9 inhibitor	Yes	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No
Log Kp (Skin Permeation; cm/s)	-2.08	-9.70	-9.43	-10.25	-8.62
Toxicity					
Hepatotoxicity	No	No	No	No	No
Carcinogenicity	No	No	No	No	No
Immunotoxicity	Yes	Yes	Yes	Yes	Yes
Mutagenicity	No	No	No	No	No
Cytotoxicity	Yes	Yes	Yes	No	Yes

exhibit carcinogenic and mutagenic properties, which raise concerns regarding their long-term use in therapeutic applications. However, they do not show hepatotoxicity, immunotoxicity, or cytotoxicity, making them potentially safe for short-term use. Physagulin derivatives, withanolides, and withangulatin, on the other hand, show immunotoxicity and cytotoxicity, which may contribute to their pharmacological effects; however, these findings also necessitate further evaluation of their therapeutic index. The Log Kp (skin permeation) values indicate that most of these compounds have low skin permeability, except for a specific withanolide compound and dihydrowithanolide E, suggesting potential applications in topical formulations. These findings highlight the complex pharmacokinetic and toxicity profiles of plant-derived metabolites and emphasize the importance of further research to optimize their drug-like properties for therapeutic applications.

Interaction network analysis for Myricetin and Quercetin

The interaction networks for myricetin and quercetin, visualized through STITCH and Cytoscape v.3.8.2, high-

light their connections with critical proteins involved in inflammation, oxidative stress, and metabolic regulation (Figs 1, 2). Both compounds interact strongly with PTGS2 (prostaglandin-endoperoxide synthase 2), a key enzyme in the inflammatory pathway, and AKR1B1 (aldo-keto reductase family 1 member B1), which is associated with diabetic complications. Additionally, interactions with NOX4 (NADPH oxidase 4) emphasize their potential as antioxidants, reducing reactive oxygen species (ROS) in oxidative stress-related conditions (Chen et al. 2017). These central hubs in the networks underscore the therapeutic potential of both compounds in inflammatory and metabolic disorders. The confidence of interactions, indicated by the thickness of edges, reflects the robustness of these binding affinities. While there are similarities between the networks, such as overlapping targets, distinct secondary interactions reveal unique pharmacological profiles for each compound. The visualization provides a systems-level understanding of how these flavonoids influence complex biological pathways. This reinforces their potential as multi-target therapeutic agents with applications in chronic inflammatory diseases and oxidative stress disorders.

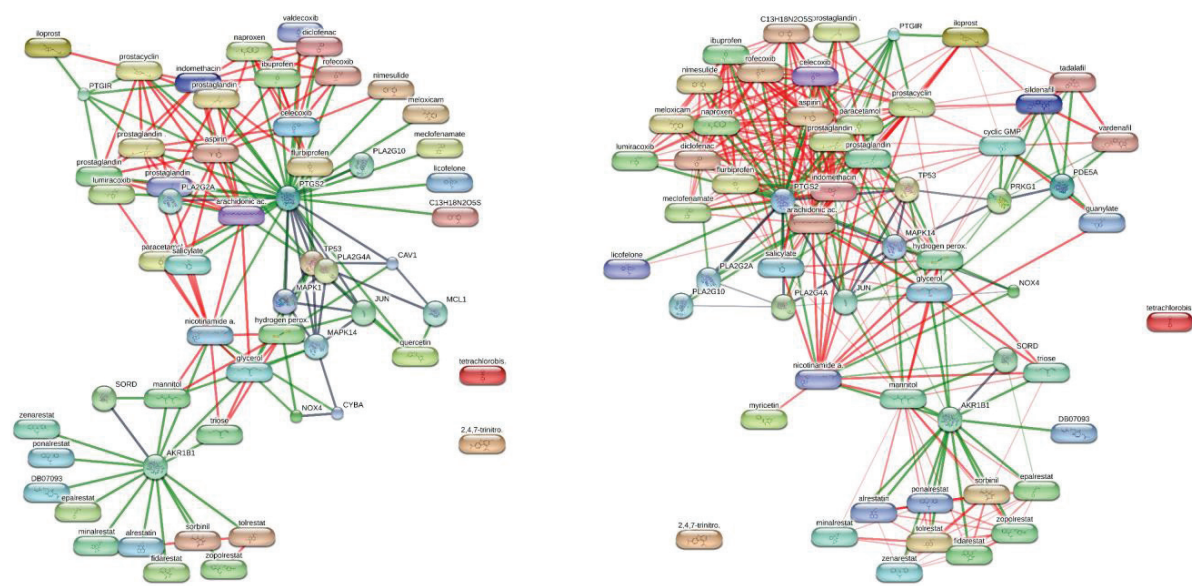


Figure 1. Interaction network analysis for myricetin and quercetin using STITCH.

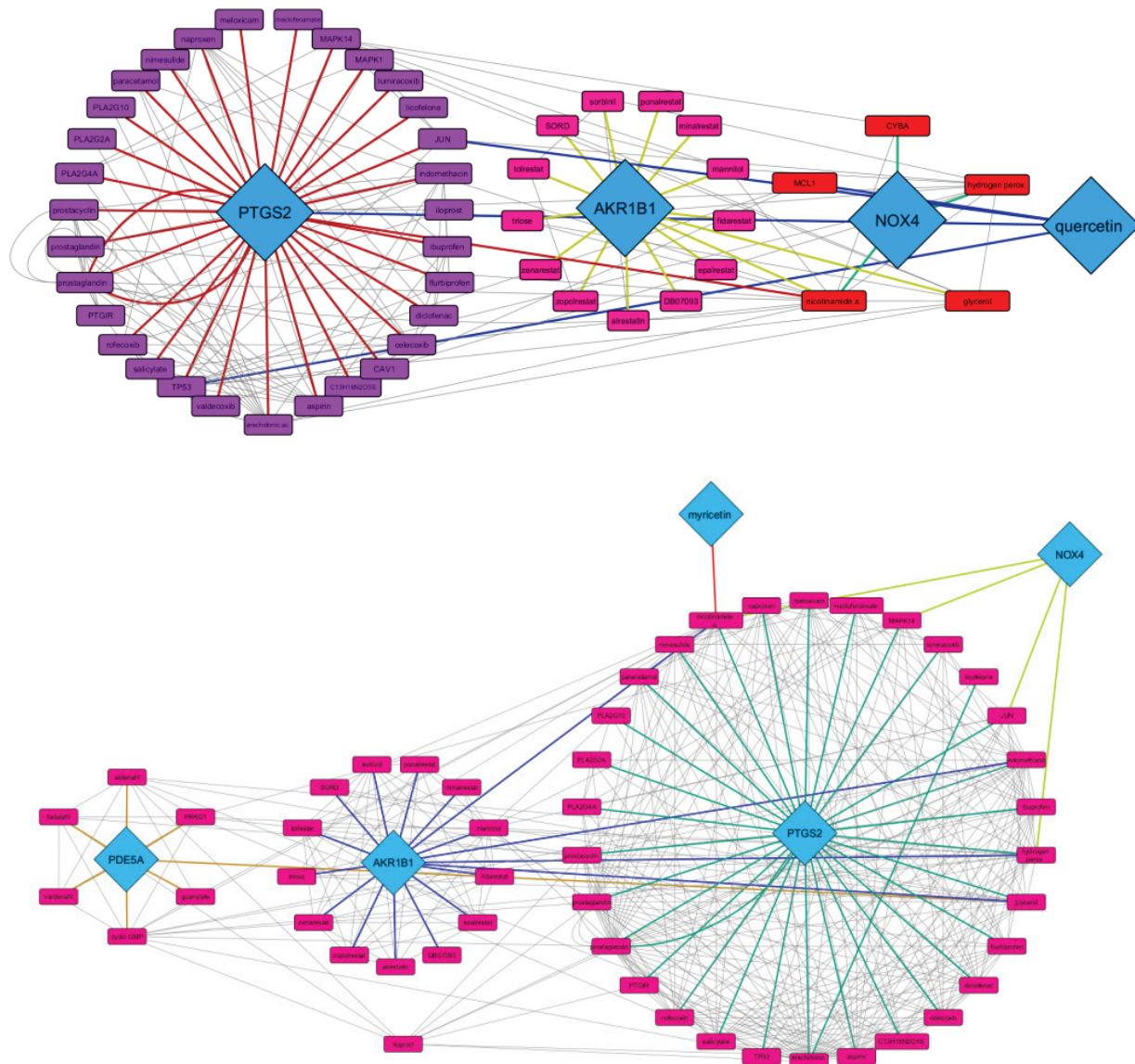


Figure 2. Interaction network analysis for myricetin and quercetin using Cytoscape v.3.8.2.

The interaction network for myricetin reveals strong connections to PTGS2, linking it to prostaglandins and cyclooxygenase inhibitors, demonstrating its robust anti-inflammatory potential. Its interaction with AKR1B1 and related enzymes, such as SORD and alrestatin, suggests a role in modulating glucose metabolism and addressing diabetic complications. The association with NOX4 indicates its potential to mitigate oxidative damage by reducing ROS, making it a promising candidate for antioxidant therapies. Furthermore, the network highlights myricetin's ability to influence lipid inflammatory mediators, such as arachidonic acid and PLA2G2A, emphasizing its involvement in metabolic regulation. Its connections to various enzymatic and metabolic pathways underscore its comprehensive role in maintaining cellular homeostasis (Liu et al. 2014). These characteristics position myricetin as a potential therapeutic agent for managing chronic inflammation, diabetes, and metabolic dysregulation. The confidence levels of its interactions suggest a well-defined mechanism of action, supporting further exploration of its pharmacological effects. The network visualization reinforces the therapeutic relevance of myricetin, particularly in pathways central to inflammation and oxidative stress.

The interaction network for quercetin highlights its broad pharmacological activity, with notable connections to PTGS2, AKR1B1, and NOX4, similar to myricetin. However, quercetin also interacts uniquely with JUN (a transcription factor) and MAPK14 (a mitogen-activated protein kinase), which are central to cellular stress and immune response pathways. These additional interactions suggest quercetin's ability to regulate gene expression and signal transduction, extending its influence beyond inflammation to include stress response mechanisms (Groeger et al. 2017). Like myricetin, quercetin shows strong antioxidant properties by targeting NOX4, reducing ROS, and protecting cells from oxidative damage. Its connections to AKR1B1 indicate its potential in modulating glucose metabolism, further supporting its relevance in managing diabetic complications. The network also shows interactions with inflammatory mediators such as PLA2G4A and prostaglandins, reinforcing its anti-inflammatory effects. These features position quercetin as a versatile therapeutic compound with applications in chronic inflammation, metabolic disorders, and oxidative stress-related conditions. The robust confidence in its interactions highlights the strength of its potential as a multi-target therapeutic agent, with significant promise for drug development and clinical applications.

Molecular docking studies

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia due to insulin resistance, impaired insulin secretion, or both. Various molecular targets have been explored for diabetes management. This study selected key enzymes and receptors involved in glucose metabolism, insulin regulation, and diabetic complications (Dilworth et al. 2021). Aldose reductase was chosen because it

plays a critical role in the polyol pathway, which contributes to oxidative stress and diabetic complications such as neuropathy and retinopathy (Singh et al. 2021). Alpha amylase and alpha glucosidase were included as they regulate carbohydrate digestion, and their inhibition can help reduce postprandial glucose spikes (Gong et al. 2020). Sodium-glucose cotransporter 2 (SGLT-2) and peroxisome proliferator-activated receptor gamma (PPAR-gamma) were selected due to their involvement in renal glucose reabsorption and insulin sensitivity, respectively (Kim et al. 2017). Dipeptidyl peptidase-4 (DPP4) and glucagon-like peptide-1 (GLP-1) were included because they regulate incretin hormones, affecting insulin secretion (Deacon 2019). Moreover, AMP-activated protein kinase (AMPK) and glucose transporter type 4 (GLUT4) were chosen due to their role in energy homeostasis and glucose uptake in peripheral tissues (Lee et al. 2012). These targets represent multifaceted approaches to diabetes management, making them suitable for evaluating the therapeutic potential of quercetin and myricetin from *Physalis angulata* L.

Molecular docking analysis revealed that quercetin and myricetin from *Physalis angulata* L. exhibit strong binding affinities to key antidiabetic targets (Tables 6, 7). Both compounds showed notable interactions with aldose reductase, an enzyme involved in diabetic complications such as neuropathy and retinopathy. Quercetin demonstrated a binding energy of -8.33 kcal/mol with an inhibition constant of 782.33 nM, interacting with TYR48, VAL297, and TRP20 through hydrogen bonding and hydrophobic interactions. Myricetin exhibited a stronger binding energy of -9.19 kcal/mol with an inhibition constant of 181.97 nM, interacting with LYS21, ILE260, and TYR209. These interactions suggest that both compounds may effectively inhibit aldose reductase and reduce excessive sorbitol accumulation. The involvement of hydrophobic residues such as CYS298 and LEU300 contributes to the stabilization of the ligand-enzyme complex. In contrast, metformin, a widely used antidiabetic drug, exhibited a significantly weaker binding affinity for aldose reductase, with a binding energy of -3.71 kcal/mol and an inhibition constant of 1.91 mM (Table 8). This suggests that quercetin and myricetin have superior potential in targeting aldose reductase compared to metformin.

In addition to aldose reductase inhibition, quercetin and myricetin also interact with alpha amylase and alpha glucosidase, key enzymes in carbohydrate metabolism. Quercetin showed a binding energy of -6.71 kcal/mol against alpha amylase and -4.36 kcal/mol against alpha glucosidase, while myricetin exhibited -7.21 kcal/mol against alpha amylase and -3.75 kcal/mol against alpha glucosidase, respectively. The inhibition constants were 12.05 μ M for quercetin and 5.16 μ M for myricetin against alpha amylase, while against alpha glucosidase, they were 639.45 μ M and 1.77 mM, respectively. Comparatively, metformin exhibited a binding energy of -7.78 kcal/mol against alpha amylase and -5.06 kcal/mol against alpha glucosidase. The inhibition constant of 2.00 μ M for alpha amylase suggests that metformin is a stronger inhibitor than quercetin and

Table 6. Interaction energy analysis of quercetin from *Physoalis angulata* L. for antidiabetic applications.

Target Receptor	Binding Free Energy (kcal/mol)	Inhibition Constant	Amino Acid Residue Interactions	Interaction Category	Interaction Type
Aldose reductase	−8.33	782.33 nM (nanomolar)	A:TYR48	Hydrogen Bond	Conventional Hydrogen Bond
			A:VAL297	Hydrogen Bond	Conventional Hydrogen Bond
			A:TRP20	Hydrophobic	Pi-Pi Stacked
			A:TRP20	Hydrophobic	Pi-Pi Stacked
			A:TRP219	Hydrophobic	Pi-Pi Stacked
			A:TRP219	Hydrophobic	Pi-Pi Stacked
			A:TRP219	Hydrophobic	Pi-Pi Stacked
			A:TRP111	Hydrophobic	Pi-Pi T-shaped
			A:TYR209	Hydrophobic	Pi-Pi T-shaped
			A:CYS298	Hydrophobic	Pi-Alkyl
			A:LEU300	Hydrophobic	Pi-Alkyl
			A:CYS298	Hydrophobic	Pi-Alkyl
			A:LEU300	Hydrophobic	Pi-Alkyl
			A:CYS298	Hydrophobic	Pi-Alkyl
Alpha amylase	−6.71	12.05 uM (micromolar)	A:HIS305	Hydrogen Bond	Conventional Hydrogen Bond
			A:THR163	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLN63	Hydrogen Bond	Conventional Hydrogen Bond
			A:TRP59	Hydrogen Bond	Conventional Hydrogen Bond
			A:HIS305	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP300	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLN63	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:LEU165	Hydrophobic	Pi-AlkylBond
Alpha glucosidase	−4.36	639.45 uM (micromolar)	A:ALA817	Hydrogen Bond	Conventional Hydrogen Bond
			A:THR825	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU905	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER789	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU818	Electrostatic	Pi-Anion
			A:GLU818	Electrostatic	Pi-Anion
			A:THR825	Hydrophobic	Pi-Sigma
			A:PHE816	Hydrophobic	Pi-Pi T-shaped
			A:ALA788	Hydrophobic	Pi-Alkyl
DPP4	−6.70	12.34 uM (micromolar)	A:LYS903	Hydrophobic	Pi-Alkyl
			A:TYR663	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG670	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG670	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG670	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU203	Hydrogen Bond	Conventional Hydrogen Bond
			A:TYR548	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU204	Hydrogen Bond	Conventional Hydrogen Bond
			A:PHE206	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU204	Hydrogen Bond	Conventional Hydrogen Bond
GLP-1	−6.93	8.31 uM (micromolar)	A:ARG123	Electrostatic	Pi-Cation
			A:PHE355	Hydrophobic	Pi-Pi T-shaped
			R:GLN221	Hydrogen Bond	Conventional Hydrogen Bond
			R:THR207	Hydrogen Bond	Conventional Hydrogen Bond
			R:SER31	Hydrogen Bond	Conventional Hydrogen Bond
			R:TRP203	Hydrogen Bond	Conventional Hydrogen Bond
			R:LEU217	Hydrogen Bond	Conventional Hydrogen Bond
			R:LEU201	Hydrogen Bond	Conventional Hydrogen Bond
			R:LYS202	Hydrogen Bond	Conventional Hydrogen Bond
			R:TRP203	Hydrogen Bond	Carbon Hydrogen Bond
PPAR-Gamma	−6.94	8.17 uM (micromolar)	R:LEU32	Hydrophobic	Pi-Sigma
			R:LEU217	Hydrophobic	Pi-Alkyl
			R:LEU217	Hydrophobic	Pi-Alkyl
			A:ARG288	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER289	Hydrogen Bond	Conventional Hydrogen Bond

Target Receptor	Binding Free Energy (kcal/mol)	Inhibition Constant	Amino Acid Residue Interactions	Interaction Category	Interaction Type
PPAR-Gamma			A:ARG288	Hydrogen Bond	Conventional Hydrogen Bond
			A:LEU228	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU295	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG288	Hydrophobic	Pi-Sigma
			A:ARG288	Hydrophobic	Amide-Pi Stacked
			A:ARG288	Hydrophobic	Pi-Alkyl
			A:ALA292	Hydrophobic	Pi-Alkyl
			A:MET329	Hydrophobic	Pi-Alkyl
			A:ALA292	Hydrophobic	Pi-Alkyl
SGLT-2	-7.85	1.78 μ M (micromolar)	A:ILE326	Hydrophobic	Pi-Alkyl
			A:PHE98	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU99	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER287	Hydrogen Bond	Conventional Hydrogen Bond
			A:LEU84	Hydrophobic	Pi-Sigma
			A:TYR290	Hydrophobic	Pi-Pi Stacked
AMPK	-6.82	9.98 μ M (micromolar)	A:ALA102	Hydrophobic	Pi-Alkyl
			A:ASN203	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN203	Hydrogen Bond	Conventional Hydrogen Bond
			A:ALA205	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER226	Hydrogen Bond	Conventional Hydrogen Bond
			A:ALA227	Hydrogen Bond	Conventional Hydrogen Bond
			A:PRO229	Hydrogen Bond	Carbon Hydrogen Bond
			A:SER314	Hydrogen Bond	Carbon Hydrogen Bond
			A:ILE312	Hydrophobic	Pi-Sigma
			A:ILE204	Hydrophobic	Pi-Alkyl
			A:VAL225	Hydrophobic	Pi-Alkyl
			A:ILE312	Hydrophobic	Pi-Alkyl
			A:ALA227	Hydrophobic	Pi-Alkyl
			A:ARG299	Hydrophobic	Pi-Alkyl
			A:ILE204	Hydrophobic	Pi-Alkyl
GLUT4	-6.65	13.45 μ M (micromolar)	A:ALA205	Hydrophobic	Pi-Alkyl
			A:VAL225	Hydrophobic	Pi-Alkyl
			A:ASN431	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU396	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU396	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN304	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN427	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN427	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN427	Hydrogen Bond	Pi-Donor Hydrogen Bond

myricetin in this regard. However, for alpha glucosidase, the inhibition constant of 194.33 μ M suggests that quercetin and myricetin might still have therapeutic relevance in carbohydrate digestion inhibition. These findings highlight that while metformin remains effective, quercetin and myricetin may provide additional benefits when combined.

Quercetin and myricetin also exhibit strong interactions with SGLT-2 and PPAR-gamma, key regulators of glucose homeostasis and insulin sensitivity. Quercetin has a binding energy of -7.85 kcal/mol with SGLT-2 and -6.94 kcal/mol with PPAR-gamma, while myricetin exhibits -7.98 kcal/mol with SGLT-2 and -7.01 kcal/mol with PPAR-gamma, respectively. Their inhibition constants suggest that myricetin binds slightly more effectively, with 1.41 μ M for SGLT-2 and 7.27 μ M for PPAR-gamma, compared to 1.78 μ M and 8.17 μ M for quercetin. In contrast, metformin exhibits significantly weaker binding with SGLT-2 (-4.13 kcal/

mol) and PPAR-gamma (-4.22 kcal/mol), with inhibition constants of 938.29 μ M and 807.02 μ M, respectively. These results indicate that quercetin and myricetin may have significantly greater potential in modulating these targets compared to metformin. The stronger binding affinities of the flavonoids suggest that they may serve as effective SGLT-2 inhibitors, promoting glucose excretion through urine, and as PPAR-gamma modulators, improving insulin sensitivity. These findings support the potential of quercetin and myricetin as multitarget antidiabetic agents.

Both compounds also interact with DPP4 and GLP-1, which regulate insulin secretion and glucose metabolism. Quercetin demonstrated a binding energy of -6.70 kcal/mol with DPP4 and -6.93 kcal/mol with GLP-1, while myricetin showed -6.57 kcal/mol with DPP4 and -6.28 kcal/mol with GLP-1, respectively. These interactions involve TYR663, ARG670, and GLU204, stabilizing the ligand-protein com-

Table 7. Interaction energy analysis of myricetin from *Physalis angulata* L. for antidiabetic applications.

Target Receptor	Binding Free Energy (kcal/mol)	Inhibition Constant	Amino Acid Residue Interactions	Interaction Category	Interaction Type
Aldose reductase	−9.19	181.97 nM (nanomolar)	A:LYS21	Hydrogen Bond	Conventional Hydrogen Bond
			A:ILE260	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP43	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLN183	Hydrogen Bond	Conventional Hydrogen Bond
			A:TYR209	Hydrogen Bond	Conventional Hydrogen Bond
			A:PRO211	Hydrogen Bond	Carbon Hydrogen Bond
			A:TYR48	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:TYR48	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:SER210	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:TYR209	Hydrophobic	Pi-Pi Stacked
			A:TYR209	Hydrophobic	Pi-Pi Stacked
			A:TRP20	Hydrophobic	Pi-Pi T-shaped
			A:TYR48	Hydrophobic	Pi-Pi T-shaped
			A:CYS298	Hydrophobic	Pi-Alkyl
			A:LYS262	Hydrophobic	Pi-Alkyl
Alpha amylase	−7.21	5.16 uM (micromolar)	A:GLN63	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP197	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP197	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP300	Hydrogen Bond	Conventional Hydrogen Bond
			A:TYR62	Hydrogen Bond	Conventional Hydrogen Bond
			A:TRP59	Hydrophobic	Pi-Pi Stacked
			A:TRP59	Hydrophobic	Pi-Pi Stacked
			A:TRP59	Hydrophobic	Pi-Pi Stacked
			A:TYR62	Hydrophobic	Pi-Pi Stacked
Alpha glucosidase	−3.75	1.77 mM (millimolar)	A:LEU165	Hydrophobic	Pi-Alkyl
			A:ILE821	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN823	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU818	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU905	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU905	Electrostatic	Pi-Anion
DPP4	−6.57	15.41 uM (micromolar)	A:THR825	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:ARG356	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG670	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU204	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU204	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU203	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG356	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG356	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:ARG356	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:ARG356	Hydrophobic	Pi-Alkyl
GLP-1	−6.28	24.88 uM (micromolar)	A:ARG356	Hydrophobic	Pi-Alkyl
			R:GLN221	Hydrogen Bond	Conventional Hydrogen Bond
			R:LEU201	Hydrogen Bond	Conventional Hydrogen Bond
			R:LEU201	Hydrogen Bond	Conventional Hydrogen Bond
			R:SER206	Hydrogen Bond	Conventional Hydrogen Bond
			R:THR207	Hydrogen Bond	Conventional Hydrogen Bond
			R:SER31	Hydrogen Bond	Conventional Hydrogen Bond
			R:LEU32	Hydrophobic	Pi-Sigma
			R:LEU32	Hydrophobic	Pi-Alkyl
PPAR-Gamma	−7.01	7.27 uM (micromolar)	R:LEU217	Hydrophobic	Pi-Alkyl
			A:ARG288	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER289	Hydrogen Bond	Conventional Hydrogen Bond
			A:CYS285	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER289	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG288	Hydrogen Bond	Conventional Hydrogen Bond
PPAR-Gamma	−7.01	7.27 uM (micromolar)	A:GLU295	Hydrogen Bond	Conventional Hydrogen Bond

Target Receptor	Binding Free Energy (kcal/mol)	Inhibition Constant	Amino Acid Residue Interactions	Interaction Category	Interaction Type
PPAR-Gamma			A:LEU228	Hydrogen Bond	Conventional Hydrogen Bond
			A:ARG288	Hydrophobic	Pi-Sigma
			A:ARG288	Hydrophobic	Pi-Alkyl
			A:ALA292	Hydrophobic	Pi-Alkyl
			A:MET329	Hydrophobic	Pi-Alkyl
			A:LEU333	Hydrophobic	Pi-Alkyl
			A:ALA292	Hydrophobic	Pi-Alkyl
			A:ILE326	Hydrophobic	Pi-Alkyl
SGLT-2	-7.98	1.41 uM (micromolar)	A:ASN75	Hydrogen Bond	Conventional Hydrogen Bond
			A:LYS321	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER287	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER287	Hydrogen Bond	Conventional Hydrogen Bond
			A:PHE98	Hydrogen Bond	Conventional Hydrogen Bond
			A:THR153	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP158	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN75	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:TYR290	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:TYR290	Hydrophobic	Pi-Pi Stacked
			A:TYR290	Hydrophobic	Pi-Pi Stacked
			A:LYS154	Hydrophobic	Pi-Alkyl
			A:VAL157	Hydrophobic	Pi-Alkyl
			A:ALA102	Hydrophobic	Pi-Alkyl
AMPK	-6.53	16.38 uM (micromolar)	A:ASN203	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN203	Hydrogen Bond	Conventional Hydrogen Bond
			A:ALA205	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER226	Hydrogen Bond	Conventional Hydrogen Bond
			A:PRO229	Hydrogen Bond	Carbon Hydrogen Bond
			A:SER314	Hydrogen Bond	Carbon Hydrogen Bond
			A:ILE312	Hydrophobic	Pi-Sigma
			A:ILE204	Hydrophobic	Pi-Alkyl
			A:VAL225	Hydrophobic	Pi-Alkyl
			A:ILE312	Hydrophobic	Pi-Alkyl
			A:ALA227	Hydrophobic	Pi-Alkyl
			A:ARG299	Hydrophobic	Pi-Alkyl
			A:ILE204	Hydrophobic	Pi-Alkyl
			A:ALA205	Hydrophobic	Pi-Alkyl
			A:VAL225	Hydrophobic	Pi-Alkyl
GLUT4	-6.26	25.81 uM (micromolar)	A:ASN304	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN431	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN427	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASN427	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLY424	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER153	Hydrogen Bond	Conventional Hydrogen Bond
			A:SER153	Hydrogen Bond	Pi-Donor Hydrogen Bond
			A:ILE42	Hydrophobic	Pi-Sigma
			A:TRP428	Hydrophobic	Pi-Pi Stacked
			A:TRP428	Hydrophobic	Pi-Pi Stacked
			A:TRP428	Hydrophobic	Pi-Pi Stacked
			A:TRP428	Hydrophobic	Pi-Pi Stacked
			A:PHE38	Hydrophobic	Pi-Pi T-shaped

plex through hydrogen bonding. DPP4 inhibitors prevent incretin degradation, increasing GLP-1 levels and enhancing glucose-dependent insulin secretion. Comparatively, metformin exhibited a binding energy of -5.99 kcal/mol against DPP4 and -3.90 kcal/mol against GLP-1, with inhibition constants of 40.98 μ M and 1.38 mM, respectively.

These findings suggest that while metformin has some activity against these targets, quercetin and myricetin exhibit stronger binding affinities and may be more effective in regulating incretin-based insulin secretion. This supports their potential role as natural DPP4 inhibitors, possibly complementing existing pharmacological treatments.

Table 8. Interaction energy analysis of metformin as a comparator for antidiabetic applications.

Target Receptor	Binding Free Energy (kcal/mol)	Inhibition Constant	Amino Acid Residue Interactions	Interaction Category	Interaction Type
Aldose reductase	−3.71	1.91 mM (millimolar)	A:ASP43	Hydrogen Bond	Salt Bridge
			A:ASP43	Electrostatic	Attractive Charge
			A:ASP43	Hydrogen Bond	Salt Bridge
			A:ASP43	Electrostatic	Attractive Charge
			A:SER210	Hydrogen Bond	Conventional Hydrogen Bond
			A:TYR48	Hydrogen Bond	Conventional Hydrogen Bond
			A:TYR48	Hydrogen Bond	Conventional Hydrogen Bond
			A:TRP20	Hydrogen Bond	Carbon Hydrogen Bond
			A:SER210	Hydrogen Bond	Carbon Hydrogen Bond
Alpha amylase	−7.78	2.00 uM (micromolar)	A:SER214	Hydrogen Bond	Carbon Hydrogen Bond
			A:GLU233	Hydrogen Bond	Salt Bridge
			A:GLU233	Electrostatic	Attractive Charge
			A:ASP197	Electrostatic	Attractive Charge
			A:ASP300	Electrostatic	Attractive Charge
			A:ASP300	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP300	Hydrogen Bond	Conventional Hydrogen Bond
Alpha glucosidase	−5.06	194.33 uM (micromolar)	A:GLU233	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP300	Hydrogen Bond	Carbon Hydrogen Bond
			A:GLU818	Hydrogen Bond	Salt Bridge
			A:GLU818	Electrostatic	Attractive Charge
DPP4	−5.99	40.98 uM (micromolar)	A:SER819	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU818	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU204	Hydrogen Bond	Salt Bridge
			A:GLU204	Electrostatic	Attractive Charge
GLP-1	−3.90	1.38 mM (millimolar)	A:GLU203	Electrostatic	Attractive Charge
			A:GLU203	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU203	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU203	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU203	Hydrogen Bond	Conventional Hydrogen Bond
			A:TYR548	Hydrogen Bond	Carbon Hydrogen Bond
PPAR-Gamma	−4.22	807.02 uM (micromolar)	A:TYR548	Hydrogen Bond	Carbon Hydrogen Bond
			R:GLU138	Electrostatic	Attractive Charge
			R:LEU32	Hydrogen Bond	Conventional Hydrogen Bond
			R:THR207	Hydrogen Bond	Conventional Hydrogen Bond
			R:THR207	Hydrogen Bond	Conventional Hydrogen Bond
SGLT-2	−4.13	938.29 uM (micromolar)	A:GLU295	Hydrogen Bond	Conventional Hydrogen Bond
			A:LEU228	Hydrogen Bond	Conventional Hydrogen Bond
			A:MET329	Hydrogen Bond	Conventional Hydrogen Bond
			A:LEU228	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU295	Hydrogen Bond	Carbon Hydrogen Bond
AMPK	−5.31	127.34 uM (micromolar)	A:ASP158	Hydrogen Bond	Salt Bridge
			A:ASP158	Electrostatic	Attractive Charge
			A:TYR290	Hydrogen Bond	Conventional Hydrogen Bond
			A:THR153	Hydrogen Bond	Conventional Hydrogen Bond
			A:LYS154	Hydrogen Bond	Conventional Hydrogen Bond
			A:LYS154	Hydrogen Bond	Conventional Hydrogen Bond
			A:ASP158	Hydrogen Bond	Conventional Hydrogen Bond
			A:THR153	Hydrogen Bond	Carbon Hydrogen Bond
GLUT4	−3.94	1.29 mM (millimolar)	A:ASP317	Electrostatic	Attractive Charge
			A:ASP317	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLY199	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLN197	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLY199	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU396	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU396	Electrostatic	Salt Bridge
			A:GLN177	Hydrogen Bond	Attractive Charge
			A:GLN177	Hydrogen Bond	Conventional Hydrogen Bond
			A:THR337	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU396	Hydrogen Bond	Conventional Hydrogen Bond
			A:GLU396	Hydrogen Bond	Carbon Hydrogen Bond

Lastly, quercetin and myricetin interact with AMPK and GLUT4, which regulate energy homeostasis and glucose uptake. Quercetin exhibited a binding energy of -6.82 kcal/mol with AMPK and -6.65 kcal/mol with GLUT4, while myricetin had -6.53 kcal/mol with AMPK and -6.26 kcal/mol with GLUT4, respectively. These interactions involve ASN203, SER226, and ILE312, contributing to stable ligand binding. AMPK activation improves insulin sensitivity and lipid metabolism, similar to metformin's mechanism of action. In contrast, metformin exhibited a weaker binding energy of -5.31 kcal/mol for AMPK and -3.94 kcal/mol for GLUT4, with inhibition constants of 127.34 μ M and 1.29 mM, respectively. This indicates that quercetin and myricetin have stronger binding affinities for AMPK and GLUT4 compared to metformin, suggesting their potential in improving glucose uptake and insulin sensitivity. The findings further reinforce the potential of quercetin and myricetin as multitarget antidiabetic agents capable of addressing multiple pathways involved in diabetes pathophysiology.

Molecular dynamics simulations

Molecular dynamics (MD) simulations are essential tools for evaluating the structural stability of ligand-protein interactions. In this study, myricetin and quercetin were analyzed for their binding behavior with several key antidiabetic targets. The analyses focused on root mean square deviation (RMSD) and root mean square fluctuation (RMSF) values to assess the global and local structural dynamics of the protein-ligand complexes (Figs 3, 4). Targets included aldose reductase, alpha amylase, alpha glucosidase, DPP4, GLP-1 receptor, PPAR-gamma, SGLT-2, AMPK, and GLUT4. Both myricetin and quercetin are known for their antidiabetic properties through various mechanisms such as enzyme inhibition and insulin sensitivity enhancement. RMSD measures the overall stability of the complex over time, while RMSF reflects flexibility at the residue level. These two parameters provide a comprehensive view of how stable and strong the binding interactions are. The goal of the simulations was to evaluate how well these flavonoids interact with the target proteins and whether they maintain stable complexes during the simulation period. This information is critical for predicting pharmacological efficacy and potential multitarget activity. Furthermore, the combined analysis of RMSD and RMSF offers valuable insight into the structural behavior of these compounds *in silico*.

Based on the RMSD results, both myricetin and quercetin demonstrated stable binding with most targets throughout the 50 ns simulation. The aldose reductase complex stabilized after 10 ns, with quercetin showing a lower RMSD (0.20 nm) compared to myricetin (0.25 nm), indicating more stable binding. Alpha amylase and alpha glucosidase complexes also showed strong stability, with RMSD values ranging between 0.15 and 0.20 nm. Quercetin consistently displayed lower RMSD values than myricetin across most targets, implying stronger binding.

DPP4 complexes stabilized at 0.22 nm for myricetin and 0.20 nm for quercetin, further supporting this trend. The GLP-1 receptor showed higher RMSD values due to its dynamic nature, with myricetin at 0.70 nm and quercetin at 0.75 nm. PPAR-gamma maintained a stable RMSD of 0.30 nm for both flavonoids. SGLT-2 complexes were also stable, with RMSD values of 0.30 nm for myricetin and 0.25 nm for quercetin. AMPK showed consistent stability at 0.25 nm for both compounds. Lastly, GLUT4 complexes demonstrated stable behavior, with RMSD values of 0.28 nm for myricetin and 0.24 nm for quercetin, again indicating stronger interaction for quercetin.

RMSF analysis was used to evaluate the local flexibility of amino acid residues within each protein during ligand binding. Generally, RMSF values remained low (< 0.25 nm) across most active site regions, suggesting that the ligands did not destabilize their respective proteins. For aldose reductase, alpha amylase, and alpha glucosidase, residue fluctuations were minimal, especially within binding pockets. Quercetin slightly reduced residue flexibility compared to myricetin in these regions, aligning with the lower RMSD values. DPP4 and PPAR-gamma complexes also showed low fluctuations at the ligand-binding sites, with minor variations in loop and terminal regions. The GLP-1 receptor, as expected, exhibited higher flexibility (> 0.30 nm) in its extracellular loops, reflecting its inherent structural dynamics. However, the key residues within the binding pocket remained stable with both ligands. In SGLT-2 and GLUT4, fluctuations were observed to be more prominent in extracellular regions, while transmembrane helices and ligand-binding residues remained rigid. AMPK residues showed strong structural integrity, particularly in catalytic domains, supporting its role in energy metabolism. Overall, quercetin consistently dampened residue-level flexibility across targets, indicating stronger and more stable interactions.

Across both RMSD and RMSF analyses, quercetin generally demonstrated superior performance compared to myricetin in terms of stability and binding tightness. Lower RMSD values suggest that quercetin formed more stable complexes with the protein targets. This may be attributed to its planar structure, which facilitates stronger hydrogen bonding and π - π stacking interactions. In RMSF data, quercetin also contributed to greater rigidity within active site residues, minimizing structural fluctuations. These effects were particularly noticeable in key targets such as aldose reductase, GLUT4, and SGLT-2. While myricetin also demonstrated good stability, its complexes showed slightly higher structural deviations and residue fluctuations. The GLP-1 receptor remained stable with both ligands, although the higher RMSD values reflected its natural dynamic behavior. The consistent performance of quercetin suggests a higher affinity and a potentially longer residence time at binding sites. Both compounds preserved their overall complex structure during the simulation, indicating promising drug-like behavior. These comparative insights highlight quercetin as a stronger candidate for further pharmacological exploration.

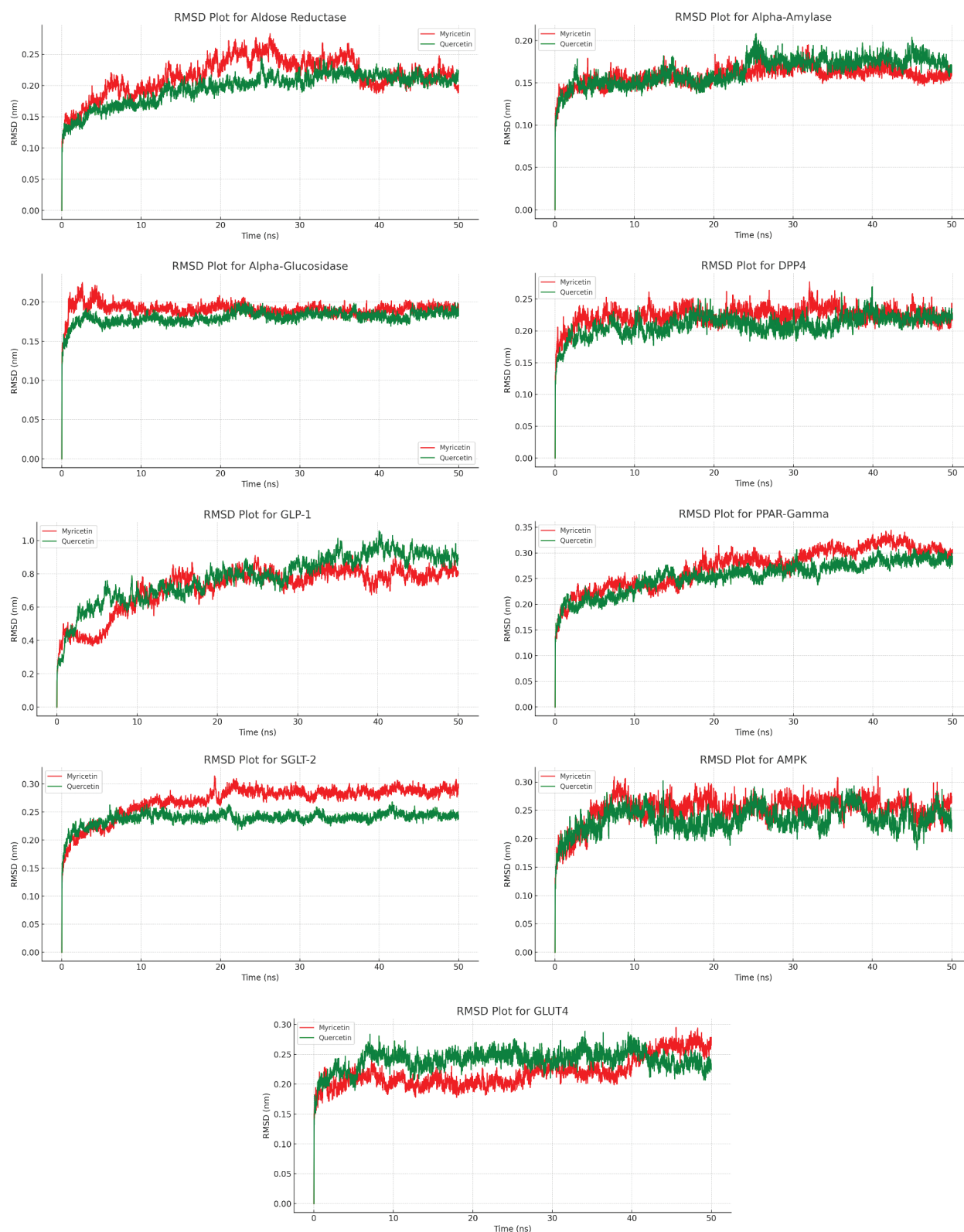


Figure 3. RMSD analysis of myricetin and quercetin interactions with key antidiabetic targets.

The stability and low residue fluctuation observed in these simulations suggest that both myricetin and quercetin have strong potential as multitarget antidiabetic agents. Their ability to interact stably with key enzymes and transporters indicates effectiveness in modulating various pathways involved in glucose metabolism. Inhi-

bition of alpha amylase and alpha glucosidase may reduce postprandial glucose levels, while DPP4 and GLP-1 interactions support insulin secretion enhancement. Activation of PPAR-gamma and AMPK promotes insulin sensitivity and lipid metabolism regulation. Furthermore, stable interactions with SGLT-2 and GLUT4 suggest their

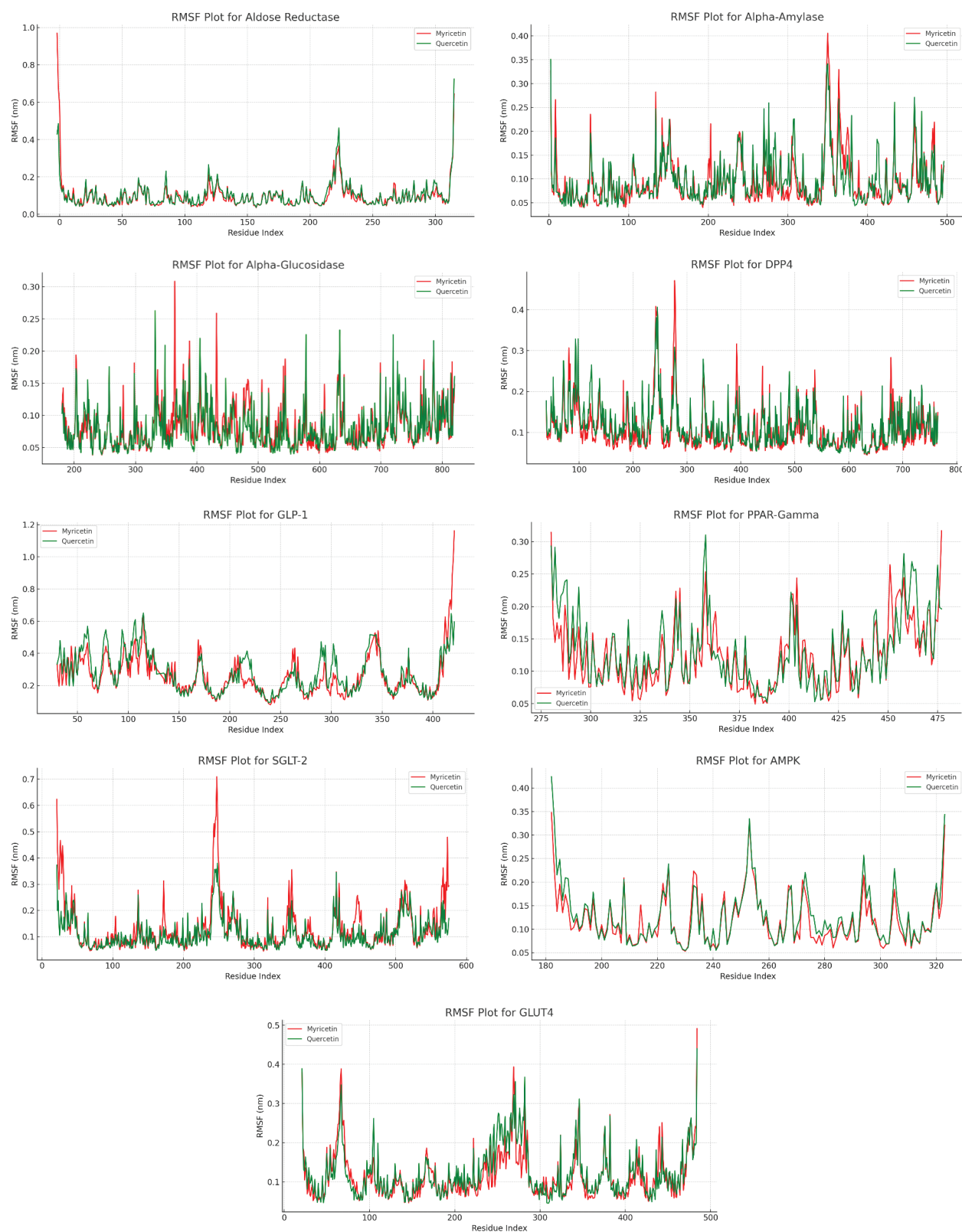


Figure 4. RMSF analysis of myricetin and quercetin across multiple diabetes-related protein targets.

potential in improving renal glucose handling and peripheral glucose uptake. Quercetin, in particular, demonstrated superior stability and rigidity, strengthening its candidacy for drug development. The low RMSD and RMSF values across diverse targets confirm the compounds' structural compatibility and adaptability. These findings

support the use of natural flavonoids as a basis for designing multitarget therapeutics for type 2 diabetes. The study also validates MD simulation as a reliable method for pre-clinical evaluation of ligand-target interactions. In addition, myricetin and quercetin exhibit promising profiles for development as broad-spectrum antidiabetic agents.

Effect of interactions on binding affinity

The binding free energy values for quercetin, calculated using the MM/PBSA method, reveal strong interactions with multiple antidiabetic receptors, emphasizing its potential as a multi-target therapeutic agent. Among the targets, quercetin exhibits the strongest binding energy with GLP-1 (-84.693 kJ/mol) and SGLT-2 (-84.237 kJ/mol), highlighting its ability to modulate glucose transport and enhance insulin secretion. Additionally, quercetin shows a binding energy of -80.340 kJ/mol with PPAR- γ , indicating its role in improving insulin sensitivity and regulating lipid metabolism. The interaction with aldose reductase (-72.714 kJ/mol) suggests its potential to inhibit this enzyme, which is crucial for managing diabetic complications like neuropathy and retinopathy. Quercetin's strong van der Waals interactions contribute significantly to the total binding energy, as seen in its interaction with aldose reductase (-151.316 kJ/mol). Electrostatic interactions also play an important role, as seen in its binding to DPP4 (-82.500 kJ/mol), which regulates glucose metabolism. However, the polar solvation energy partially offsets these favorable interactions, particularly for GLP-1, where the solvation energy is 150.545 kJ/mol, indicating significant solvent effects. Despite this, the overall negative binding energy indicates the formation of stable complexes. Notably, quercetin also binds strongly to GLUT4 (-78.277 kJ/mol), suggesting its potential to enhance glucose uptake into peripheral tissues. Overall, quercetin's ability to form energetically favorable and stable complexes with multiple targets reinforces its pharmacological relevance in diabetes management.

The MM/PBSA analysis for myricetin demonstrates its strong and consistent binding to key antidiabetic targets, with the highest binding energy observed for GLP-1 (-92.952 kJ/mol). This suggests that myricetin may effectively modulate insulin secretion and glucose regulation via GLP-1 signaling pathways. Interestingly, myricetin shows the strongest binding to aldose reductase (-89.211 kJ/mol) among all targets, surpassing quercetin's affinity for the same receptor. This indicates a higher inhibitory potential against aldose reductase, making it more effective in preventing diabetic complications involving oxidative stress. The interaction with PPAR- γ (-82.797 kJ/mol) further supports myricetin's role in enhancing insulin sensitivity and lipid metabolism. Electrostatic contributions are significantly higher in myricetin's interactions – for instance, -102.043 kJ/mol with aldose reductase – compared to -30.709 kJ/mol for quercetin. This suggests a greater reliance on polar interactions by myricetin, which may influence selectivity and receptor affinity. However, myricetin also experiences higher polar solvation penalties, such as 213.978 kJ/mol for aldose reductase, partially counterbalancing its favorable binding energies. In the case of SGLT-2, myricetin's binding energy is -64.709 kJ/mol, still indicating a significant inhibitory potential for glucose reabsorption. Myricetin also exhibits strong interactions with GLUT4 (-87.574 kJ/mol), suggesting

potent glucose uptake activation. These results emphasize myricetin's superior binding affinity for several critical receptors compared to quercetin, reinforcing its potential as a multi-target antidiabetic agent.

A comparative analysis of the binding free energy values between quercetin and myricetin reveals distinct interaction profiles, with myricetin generally exhibiting stronger binding affinities across most receptors. For example, myricetin binds more strongly to aldose reductase (-89.211 kJ/mol) compared to quercetin (-72.714 kJ/mol), suggesting greater efficacy in mitigating diabetic complications. However, quercetin shows better interaction with α glucosidase (-34.584 kJ/mol), while myricetin exhibits a highly positive binding energy (704.179 kJ/mol) for the same receptor, indicating a weak or even unfavorable interaction. Both compounds exhibit strong binding to GLP-1 and PPAR- γ , with myricetin displaying slightly better affinities (-92.952 and -82.797 kJ/mol, respectively) than quercetin (-84.693 and -80.340 kJ/mol, respectively). Electrostatic interactions are more prominent in myricetin's binding – particularly with aldose reductase (-102.043 kJ/mol) – compared to quercetin's lower electrostatic contribution (-30.709 kJ/mol). Interestingly, quercetin binds more strongly to SGLT-2 (-84.237 kJ/mol) than myricetin (-64.709 kJ/mol), suggesting complementary roles in renal glucose regulation. Both compounds demonstrate stable interactions with AMPK, another key metabolic regulator, with binding energies of -75.227 kJ/mol for quercetin and -69.149 kJ/mol for myricetin. For GLUT4, myricetin again shows stronger binding (-87.574 kJ/mol) compared to quercetin (-78.277 kJ/mol), reinforcing its effect on glucose uptake. These findings suggest that quercetin and myricetin could play complementary or synergistic roles in targeting multiple aspects of glucose metabolism. Their unique interaction profiles highlight the potential for combination therapy or structural optimization of flavonoid-based antidiabetic drugs.

The detailed energy breakdown in Tables 9, 10 highlights the dominance of van der Waals and electrostatic interactions in stabilizing the ligand-receptor complexes for both flavonoids. For example, the van der Waals energy for aldose reductase binding is -185.446 kJ/mol for myricetin and -151.316 kJ/mol for quercetin, underscoring the significance of hydrophobic interactions. Similarly, electrostatic energy is substantially higher for myricetin in multiple complexes, suggesting a stronger polar binding nature. However, polar solvation energy often offsets these favorable contributions, particularly in myricetin's interactions – for example, the 213.978 kJ/mol penalty for aldose reductase. Quercetin, by contrast, tends to exhibit more balanced solvation profiles, resulting in a more favorable net binding in targets like SGLT-2 and α glucosidase. The SASA energy (solvent-accessible surface area) also plays a stabilizing role, with negative values contributing to complex formation. For instance, SASA energies are consistently favorable across both ligands, such as -15.484 kJ/mol for quercetin-aldose reductase and -16.266 kJ/mol for myricetin-GLUT4. These com-

Table 9. Binding free energy (MM/PBSA) between the quercetin ligand and the target diabetic receptor.

Target Receptor	Van der Waal Energy (kJ/mol)	Electrostatic Energy (kJ/mol)	Polar Solvation Energy (kJ/mol)	SASA Energy (kJ/mol)	Binding Energy (kJ/mol)
Aldose reductase	-151.316	-30.709	124.795	-15.484	-72.714
Alpha amylase	-0.000	0.001	46.435	0.627	47.062
Alpha glucosidase	-65.696	-57.316	98.675	-10.248	-34.584
DPP4	-89.698	-82.500	132.301	-10.740	-50.636
GLP-1	-145.206	-73.980	150.545	-16.053	-84.693
PPAR-Gamma	-160.082	-38.994	134.918	-16.182	-80.340
SGLT-2	-155.046	-64.975	151.253	-15.469	-84.237
AMPK	-133.877	-50.230	122.474	-13.594	-75.227
GLUT4	-133.361	-110.165	181.719	-16.470	-78.277

Table 10. Binding free energy (MM/PBSA) between the myricetin ligand and the target diabetic receptor.

Target Receptor	Van der Waal Energy (kJ/mol)	Electrostatic Energy (kJ/mol)	Polar Solvation Energy (kJ/mol)	SASA Energy (kJ/mol)	Binding Energy (kJ/mol)
Aldose reductase	-185.446	-102.043	213.978	-15.700	-89.211
Alpha amylase	-118.684	-132.779	184.865	-14.211	-80.809
Alpha glucosidase	-12.279	-17.069	736.056	-2.529	704.179
DPP4	-94.457	-48.360	109.301	-10.383	-43.899
GLP-1	-161.655	-37.945	122.452	-15.804	-92.952
PPAR-Gamma	-162.326	-22.671	118.716	-16.516	-82.797
SGLT-2	-151.093	-97.779	199.637	-15.474	-64.709
AMPK	-122.922	-39.344	105.966	-12.849	-69.149
GLUT4	-167.737	-37.340	133.769	-16.266	-87.574

ponents contribute to the overall stability and drug-likeness of the ligands. The combination of strong non-covalent interactions and solvent compatibility enhances the pharmacodynamic profile of both compounds. Together, the energetic profiles validate quercetin and myricetin as promising candidates for further development as natural antidiabetic therapies.

Conclusion

This study demonstrates the potential of *Physalis angulata* L. metabolites, especially quercetin and myricetin, as multi-target antidiabetic agents. Molecular docking and MM/PBSA analyses revealed strong binding affinities with key diabetic targets, including aldose reductase, GLP-1 receptor, PPAR-gamma, SGLT-2, AMPK, and GLUT4. Myricetin showed superior binding to aldose reductase (-89.211 kJ/mol) and GLP-1 (-92.952 kJ/mol), supporting its role in preventing complications and enhancing insulin secretion. Quercetin exhibited stronger interactions with SGLT-2 (-84.237 kJ/mol) and PPAR-gamma (-80.340 kJ/mol), indicating its potential in glucose transport and lipid regulation. RMSD and RMSF analyses from molecular dynamics simulations confirmed that both ligands maintained stable and consistent interactions across multiple targets. Myricetin demonstrated stronger electrostatic contributions, while quercetin had better solvation stability and residue rigidity. Both compounds also interacted favorably with AMPK and GLUT4, reinforcing their effects on energy balance and glucose uptake. These findings highlight the complementarity of both flavonoids in

modulating various pathways related to diabetes. The use of computational methods efficiently revealed their multitarget potential and pharmacological relevance. Overall, quercetin and myricetin represent strong candidates for further development as natural antidiabetic therapies.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

SPF: Conceptualization, Methodology, Data curation, Resources, Writing – original draft, Funding acquisition. NFK: Project administration, Supervision, Validation, Writing – review & editing. TMF: Methodology, Software, Writing – original draft,

Visualization. IKA: Project administration, Supervision, Validation, Writing – review & editing.

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Data availability

All of the data that support the findings of this study are available in the main text.

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