

Molecular docking and ADMET profiling of selected *Moringa oleifera* phytochemicals against key therapeutic targets in type 2 diabetes mellitus

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Abstract: This study investigated the potential of selected *Moringa oleifera* phytochemicals as inhibitors of key therapeutic targets associated with type 2 diabetes mellitus using molecular docking and computational pharmacokinetic profiling. The structures of the phytochemicals (quercetin, kaempferol, chlorogenic acid, and niazirin) were retrieved from PubChem, while the target protein structures [α -glucosidase (AGL; PDB ID: 2QMJ), dipeptidyl peptidase-4 (PDB ID: DPP-4), and protein tyrosine phosphatase 1B (PDB ID: PTP1B)] were obtained from the RCSB Protein Data Bank. Molecular docking was performed using Molegro Virtual Docker, and protein-ligand interactions were visualized using BIOVIA Discovery Studio Visualizer. Drug-likeness and absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were assessed using SwissADME and pkCSM, respectively. Against α -glucosidase, quercetin exhibited the most favorable MolDock and rerank scores (-119.159 and -107.397 kcal/mol, respectively). Against DPP-4, kaempferol produced the most favorable MolDock score (-70.531 kcal/mol), whereas quercetin produced the best rerank score (-65.059 kcal/mol). Against protein tyrosine phosphatase 1B (PTP1B), kaempferol recorded the most favorable MolDock score (-78.440 kcal/mol), while chlorogenic acid recorded the best rerank score (-74.938 kcal/mol). Interaction analysis revealed hydrogen bonding, hydrophobic contacts, and electrostatic interactions. Quercetin, kaempferol, and niazirin satisfied Lipinski's rule of five without violations, whereas chlorogenic acid had one violation. Predicted human intestinal absorption values were 77.21%, 74.29%, 36.38%, and 58.33%, respectively. Overall, quercetin and kaempferol demonstrated promising computational profiles, supporting further experimental investigation of their potential relevance to type 2 diabetes mellitus management.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia arising primarily from insulin resistance and progressive impairment of pancreatic β -cell function [1]. It represents the most prevalent form of diabetes and constitutes a major global public health challenge. The World Health

Organization [2] reported a substantial increase in the global number of people living with diabetes, with the burden rising more rapidly in low- and middle-income countries than in high-income countries. Poorly controlled T2DM can result in serious complications, including cardiovascular disease, kidney failure, neuropathy, and visual impairment [3-5]. These consequences underscore the need for effective strategies for diabetes prevention and management, as well as continued research into potential therapeutic agents. Several molecular targets involved in glucose regulation and insulin signalling have attracted considerable interest in antidiabetic drug discovery. Among these, α -glucosidase (AGL), dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B) represent complementary targets. α -glucosidase participates in the final stages of carbohydrate digestion, and its inhibition can delay glucose absorption and reduce postprandial hyperglycemia. DPP-4 degrades incretin hormones, including glucagon-like peptide-1, which contributes to glucose-dependent insulin secretion; therefore, DPP-4 inhibition can help maintain incretin activity. PTP1B negatively regulates insulin signalling and has consequently been investigated as a potential target for improving insulin sensitivity [6-8]. Investigating compounds against these targets provides an opportunity to explore different molecular pathways relevant to T2DM management.

Natural products remain important sources of structurally diverse compounds for drug discovery. *Moringa oleifera* Lam. (*M. oleifera*), a member of the family Moringaceae, is widely recognized for its nutritional value and diverse phytochemical composition, which includes flavonoids, phenolic acids, and nitrile glycosides [9, 10]. Its potential relevance to glucose regulation has been investigated in experimental and computational studies. A systematic review of animal and human studies on *M. oleifera* reported encouraging findings in some investigations while highlighting limitations in the available evidence [9]. Similarly, another review evaluated the plant's potential effects in diabetes mellitus through a review and meta-analysis of the available evidence [10]. These reviews indicate that the plant warrants further investigation. Among the phytochemicals associated with *M. oleifera*, quercetin and kaempferol have received particular attention because of their reported biological activities and potential relevance to glucose regulation. Flavonoid and non-flavonoid constituents of *M. oleifera* have been reviewed and evidence discussed, from *in vitro*, *in vivo*, and *in silico* investigations of antidiabetic and insulin-resistance-related activities [11]. However, the biological effects reported for individual phytochemicals do not necessarily establish their ability to inhibit specific therapeutic targets. Moreover, findings obtained using plant extracts cannot automatically be attributed to individual constituents, given the chemical complexity of extracts and the possible contributions of multiple compounds [12-14]. Investigating individual phytochemicals against defined molecular targets may provide useful insights into their possible mechanisms of action.

Computational approaches offer a practical means of prioritizing compounds for further investigation. Molecular docking predicts plausible ligand-binding poses and estimates interactions between small molecules and target proteins, thereby facilitating preliminary comparisons of candidate compounds [15]. Visualization of protein-ligand complexes can further assist in identifying potential hydrogen bonds, hydrophobic contacts, and other non-covalent interactions. Nevertheless, docking scores are dependent on the scoring function employed and should not be interpreted as direct measurements of binding affinity, enzyme inhibition, or therapeutic efficacy [16, 17]. Complementary computational methods, including drug-likeness assessment and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction, can provide additional information for preliminary compound prioritization [18-21]. Despite existing investigations into the antidiabetic potential of *M. oleifera* and its constituents, further comparative assessment of selected individual phytochemicals across multiple diabetes-associated molecular targets, together with their predicted drug-likeness and ADMET properties, remains a useful research direction. In particular, evaluating quercetin, kaempferol, chlorogenic acid, and niazirin within a common computational framework may help clarify their relative predicted binding profiles against α -

glucosidase, DPP-4, and PTP1B [22, 23]. Integrating molecular docking, protein-ligand interaction analysis, and pharmacokinetic prediction also allows binding-related findings to be considered alongside preliminary properties relevant to compound development. This integrated assessment is intended to support the rational prioritization of phytochemicals for subsequent experimental investigation rather than to establish their inhibitory activity. Therefore, this study evaluates the predicted interactions of quercetin, kaempferol, chlorogenic acid, and niazirin from *M. oleifera* with α -glucosidase, DPP-4, and PTP1B using molecular docking. The predicted protein-ligand interactions are examined using molecular visualization, while drug-likeness and ADMET properties are assessed using SwissADME and pkCSM, respectively. By comparing the four compounds across the three targets and integrating their docking results with predicted pharmacokinetic and toxicity characteristics, this study seeks to identify candidates with promising computational profiles for further investigation. The findings are expected to contribute to the molecular characterization of *M. oleifera* phytochemicals and provide a basis for subsequent enzyme inhibition assays, molecular dynamics simulations, and pharmacokinetic and toxicity studies.

Materials and methods

Computational resources and software: Computational analyses were performed on a DESKTOP-P11ENUB computer equipped with an Intel® Celeron® N4000 processor (1.10 GHz), 4 GB RAM, and a 64-bit Windows 10 operating system. ChemDraw 22.2.0 (64-bit) was used for chemical structure drawing, BIOVIA Discovery Studio 2021 for protein preparation and interaction visualization, and Molegro Virtual Docker (MVD) for molecular docking. SwissADME and pkCSM were employed for drug-likeness and ADMET predictions [24, 25].

Ligand and protein preparation: Four phytochemicals from *M. oleifera* (quercetin, kaempferol, chlorogenic acid, and niazirin) were investigated against α -glucosidase (maltase-glucoamylase), dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B), which are implicated in T2DM. The chemical structures and canonical Simplified Molecular Input Line Entry System (SMILES) representations of the phytochemicals and reference drugs were obtained from PubChem [26]. The two-dimensional structures were drawn or inspected using ChemDraw (**Figure 1**), converted into three-dimensional structures, and energy-minimized using Chem3D software before docking to obtain suitable starting geometries [25, 27].

The experimentally determined three-dimensional structures of the target proteins were retrieved from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB; <https://www.rcsb.org>), which provides macromolecular structures for structural and computational investigations [28]. Protein preparation was performed using BIOVIA Discovery Studio 2021 and involved structural inspection, addition of hydrogen atoms, assignment of appropriate protonation states, and removal of water molecules where appropriate. Relevant structural components, including bound ions or cofactors, were assessed before the prepared proteins were used as docking receptors. The corresponding PDB accession codes were recorded.

Molecular docking and interaction analysis: Molecular docking was performed using MVD, which implements the MolDock search algorithm and scoring function to predict protein-ligand binding poses [29]. The phytochemicals and reference drugs were docked into the designated binding sites of the three target proteins, 2QMJ, 2ONC, and 2HNP. Binding cavities were defined using the selected binding-site coordinates or cavity-detection procedure. The docking search space for each protein was defined by specifying the binding site coordinates, a radius of 15 Å, and the corresponding cavity volume and surface area. For protein 2QMJ, the binding-site center was defined by the coordinates ($x = -24.17$), ($y = 6.53$), and ($z = -30.60$), with a cavity volume of 108.032 and a surface area of 350.72. For protein 2ONC, the coordinates were ($x = -53.72$), ($y = -12.73$), and ($z = 22.44$), with a cavity volume of 7298.56 and a surface area of 7059.20. For protein 2HNP, the binding-site coordinates were ($x = -47.32$), ($y = 18.35$), and ($z = 2.58$), with a cavity volume of 860.16 and a surface area of

340.48. This expresses the binding-site cavity volume and surface area in cubic ångströms ($\text{\AA}^3$) and square ångströms ($\text{\AA}^2$), respectively. We conducted ten independent docking runs for each docking procedure to explore possible ligand-binding poses and improve the reliability of the predicted binding conformations. Predicted poses were ranked using MolDock and rerank scores. More negative scores generally indicate more favorable predicted interactions within the scoring framework [25, 27].

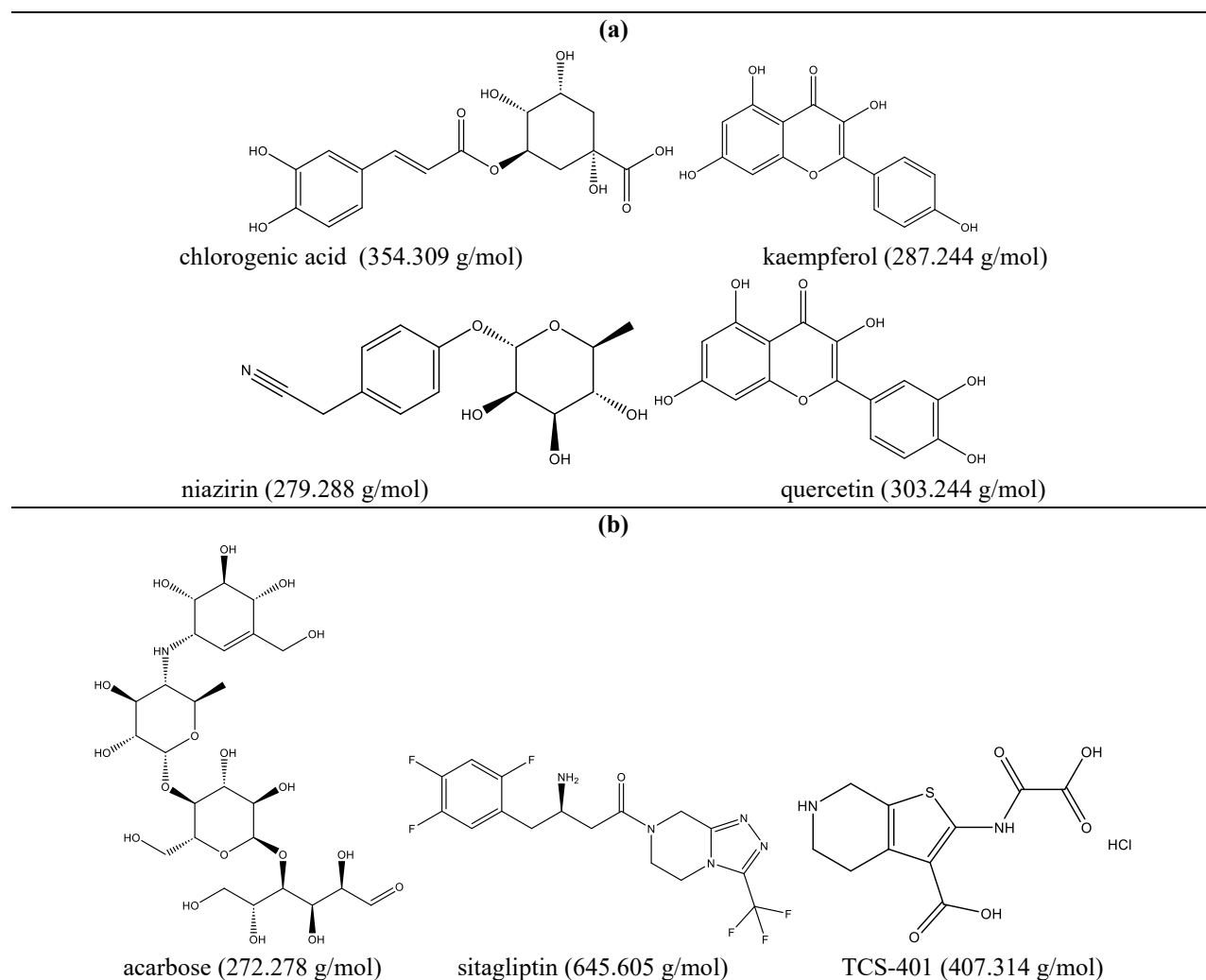


Figure 1: 2D structures of **(a)** phytochemicals and **(b)** reference drugs

Docking validation was performed by redocking the native ligands into their respective binding sites. The predicted and experimental poses were compared using root-mean-square deviation (RMSD), with values ≤ 2.0 Å considered indicative of acceptable pose reproduction [25]. Ligand-protein interactions were visualized using BIOVIA Discovery Studio. Hydrogen bonds, hydrophobic interactions, π -related interactions, and other relevant non-covalent contacts were examined, and interacting residues and distances were recorded where available. These analyses supported the comparative interpretation of predicted binding.

Drug-Likeness and ADMET prediction: Drug-likeness and predicted pharmacokinetic properties were assessed using SwissADME (<https://www.swissadme.ch>) [30], while ADMET endpoints were predicted using pkCSM (<https://biosig.lab.uq.edu.au/pkcsm/prediction>) [31]. Canonical SMILES representations were submitted to the respective platforms. Evaluated properties included molecular weight, lipophilicity, hydrogen-bond donors and acceptors, topological polar surface area, rotatable bonds, compliance with Lipinski's Rule of Five, and predicted

gastrointestinal absorption, where available. The resulting ADMET predictions were compared to identify potentially favorable or unfavorable properties for further investigation. These computational assessments were treated as preliminary screening results requiring experimental validation [25, 32].

Results and discussion

Molecular docking results: The docking scores of the selected phytochemicals and the reference drug acarbose with the target enzyme α -glucosidase (maltase-glucoamylase) are shown in **Table 1**. The docking results were evaluated using the MolDock score, Re-rank score, hydrogen bond score, and protein-ligand interactions to predict the binding affinity and stability of each ligand within the enzyme's active site. The MolDock score provides an initial estimate of the binding affinity between the ligand and the receptor, with more negative values indicating stronger predicted binding. The Re-rank score is a secondary scoring function that re-evaluates the docked poses using a more detailed energy calculation and is often considered a more reliable indicator of binding stability [29]. The hydrogen bond score and interaction profile were also considered because hydrogen bonds and other non-covalent interactions contribute significantly to the stability of the ligand-protein complex.

Table 1: Molecular docking scores of the selected phytochemicals and the reference drug (acarbose) with α -glucosidase (maltase-glucoamylase), PDB ID:2QMJ

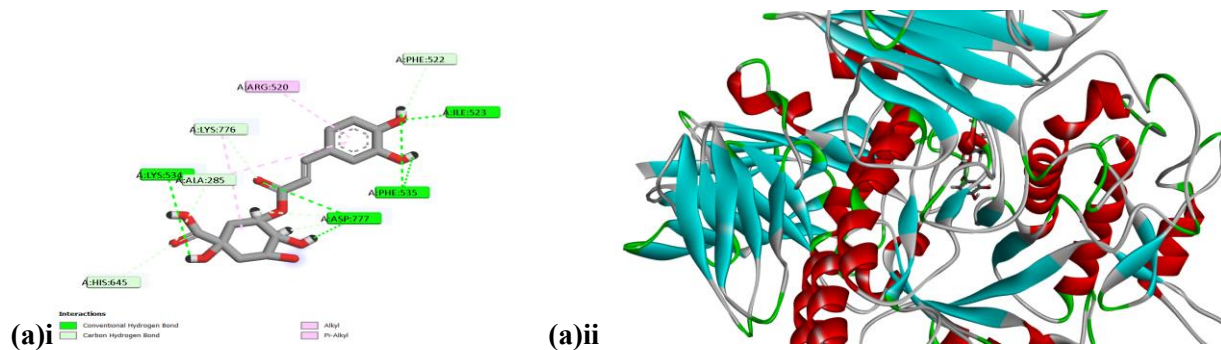
Compound	MolDock Score	Re-rank Score	Hydrogen Bond
Acarbose	-100.073	-83.0985	-8.47209
Chlorogenic acid	-68.0775	-64.2188	-11.2609
Kaempferol	-124.739	-109.593	-10.1881
Niazirin	-102.518	-89.3998	-9.91743
Quercetin	-122.01	-107.387	-8.78424

The docking results showed favorable interactions between the selected *M. oleifera* phytochemicals and α -glucosidase (2QMJ). The docking results indicate that all tested compounds exhibited favorable binding toward the target, as reflected by their strongly negative MolDock and re-rank scores. Among them, kaempferol showed the best overall affinity (MolDock: -124.739; re-rank: -109.593), followed closely by quercetin (-122.01; -107.387), suggesting stable interaction with the active site. Niazirin also demonstrated strong binding (-102.518; -89.3998), comparable to the reference compound acarbose (-100.073; -83.0985). Chlorogenic acid showed comparatively weaker docking performance (-68.0775; -64.2188), though it still retained a substantial interaction profile. The hydrogen bond values further support these findings, with all ligands forming notable polar interactions, particularly chlorogenic acid (-11.2609) and kaempferol (-10.1881). The findings suggest that binding affinity is influenced not only by hydrogen bonding but also by hydrophobic interactions, van der Waals forces, and electrostatic interactions (**Figure 2**), which are incorporated into the overall docking scores. Overall, quercetin demonstrated the strongest predicted binding affinity, followed by kaempferol. The results suggest that these compounds may have potential inhibitory activity against α -glucosidase and could be investigated for their contribution to the antidiabetic potential of *M. oleifera*.

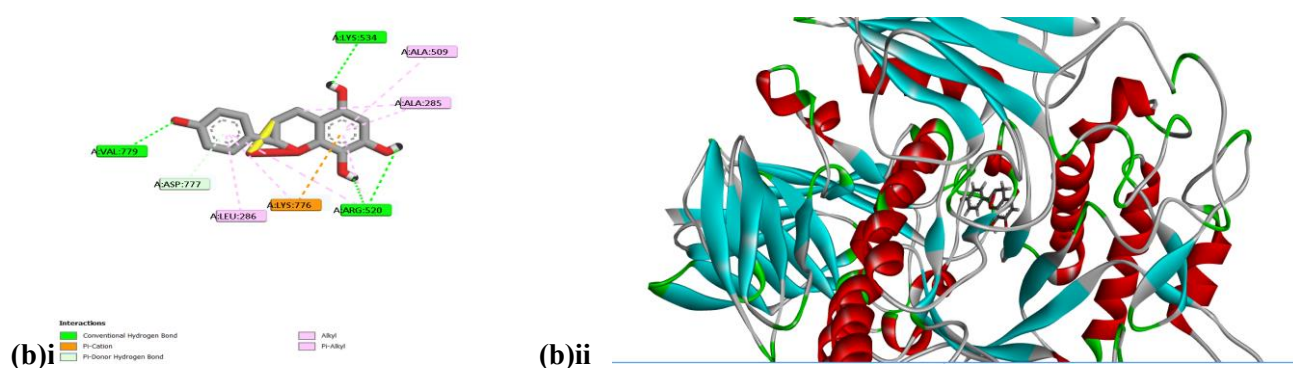
The 2D visualization (**Figure 2(i)**) showed that all the selected *M. oleifera* phytochemicals interacted favorably with the active site of the α -glucosidase (PDB ID: 2QMJ). These interactions contribute to the stability of the protein-ligand complex and suggest their potential inhibitory activity against the enzyme. The interactions observed included hydrogen bonding, hydrophobic, and electrostatic interactions, indicating that the compounds were able to establish stable contacts with the target enzyme. Among the compounds, quercetin showed extensive interactions with the target protein, which is consistent with its favorable docking score and suggests strong

binding within the enzyme's active site. Kaempferol, chlorogenic acid, and niazirin also demonstrated favorable protein-ligand interactions. Overall, the visualization results support the docking findings and suggest that the selected phytochemicals can bind effectively to α -glucosidase. These interactions may contribute to their potential inhibitory activity on 2QMJ.

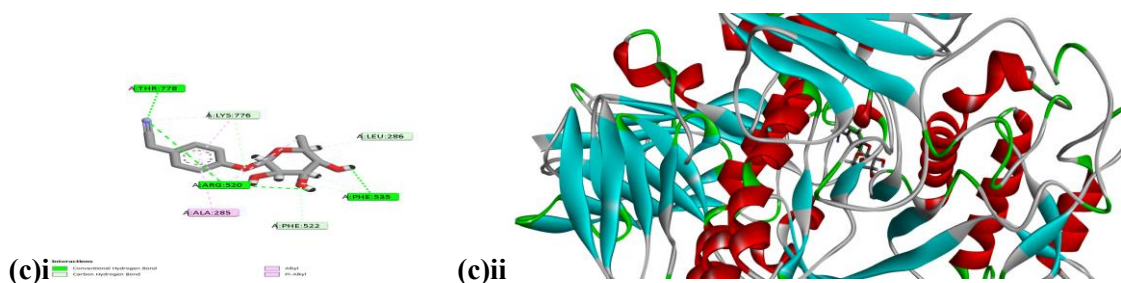
(a) 2QMJ docked with chlorogenic acid



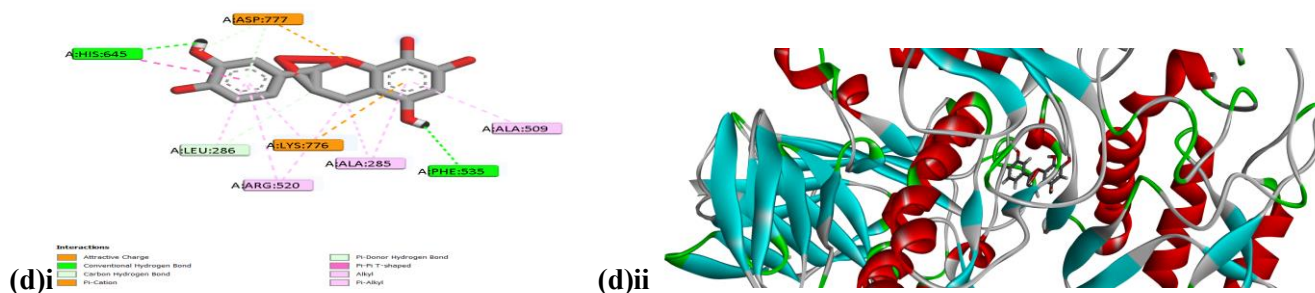
(b) 2QMJ docked with kaempferol



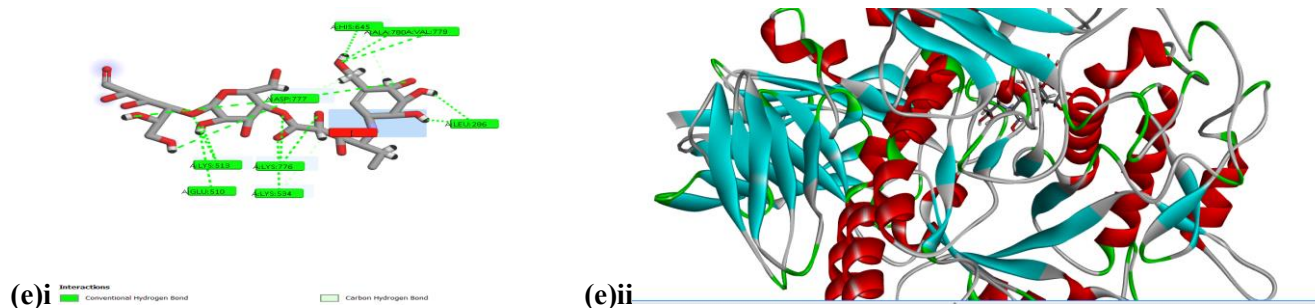
(c) 2QMJ docked with niazirin



(d) 2QMJ docked with quercetin



(e) 2QMJ docked with acarbose

**Figure 2:** (i) 2D and (ii) 3D interactions of (a) chlorogenic acid, (b) kaempferol, (c) niazirin, (d) quercetin, and (e) acarbose with the N-terminal subunit of human maltase-glucoamylase (MGAM)-2QMJ**Table 2:** 2D Binding modes of the selected phytochemicals with α -glucosidase (PDB ID 2QMJ)

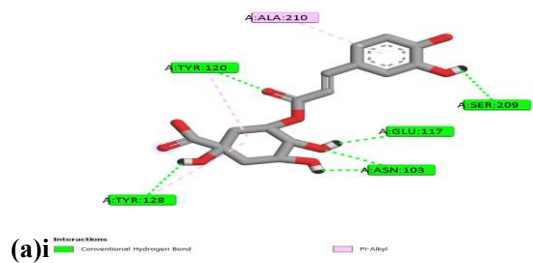
Compound	Hydrogen bonds	Hydrophobic interactions	Electrostatic interactions
Acarbose	HIS 645, ALA 780, VAL 779 ASP 777, LEU 286, LYS 513 LYS 776, GLU 510, LYS 534	-	-
Chlorogenic acid	LYS 534, ASP 777 PHE 535, ILE 523	ALA 285, LYS 776	PHE 522
Kaempferol	LYS 534, ARG520 VAL779	ASP 777	ALA 509,ALA285 LEU 286 pi-pi stack LYS776 ALA285
Niazirin	THR778, ARG 285 PHE 535	LYS 776, LEU 286	ALA285
Quercetin	HIS 645, PHE 535	ARG 520, ALA 285 ALA 509	ASP 777, LYS 776

Table 3: Molecular docking scores of the selected phytochemicals and the reference drug sitagliptin with DPP-4 (PDB ID: 2ONC)

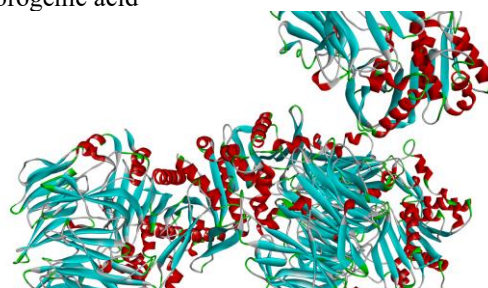
Compound	MolDock Score	Re-rank Score	Hydrogen Bond
Sitagliptin	-49.1825	-51.2499	-15.7567
Chlorogenic acid	-41.047	-46.2392	-9.74233
Kaempferol	-76.2119	-66.2886	-7.74531
Niazirin	-62.8021	-60.8208	-3.66984
Quercetin	-63.9239	-56.4592	-9.40425

The molecular docking results displayed in **Table 3** revealed differences in the predicted binding of the selected *M. oleifera* phytochemicals and sitagliptin to DPP-4 (PDB ID: 2ONC). Kaempferol exhibited the most favorable MolDock (-76.2119) and re-rank (-66.2886) scores, outperforming sitagliptin (-49.1825 and -51.2499, respectively). Niazirin and quercetin also recorded more favorable scores than sitagliptin, suggesting potentially favorable interactions within the DPP-4 binding pocket. However, their relative ranking differed between the two scoring functions, highlighting the importance of considering both measures [32]. In contrast, chlorogenic acid showed the least favorable docking scores (MolDock: -41.0470; re-rank: -46.2392). The hydrogen-bond scores varied among the compounds, with chlorogenic acid and quercetin exhibiting more negative values than kaempferol and niazirin. Overall, kaempferol emerged as the most promising candidate based on the docking scores, followed by niazirin and quercetin.

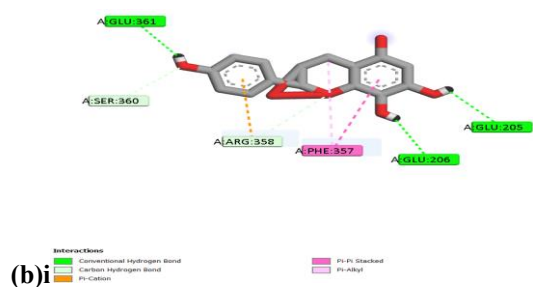
(a) 2ONC docked with chlorogenic acid



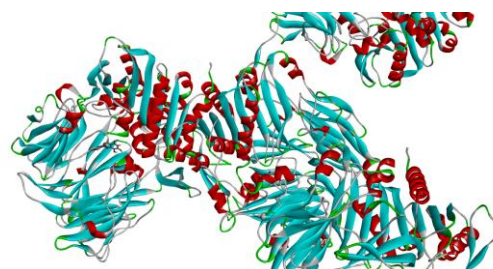
(a)ii



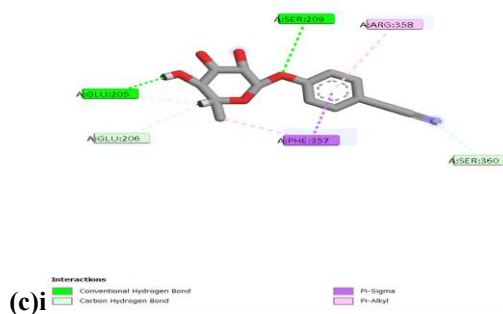
(b) 2ONC docked with kaempferol



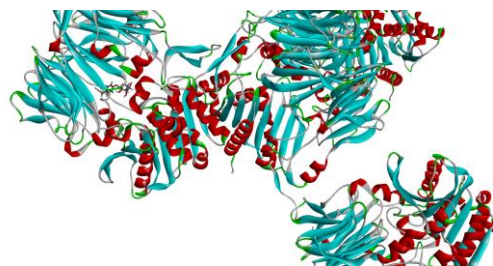
(b)ii



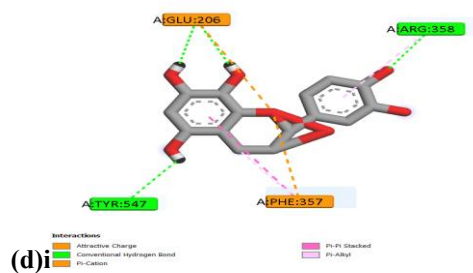
(c) 2ONC docked with niazirin



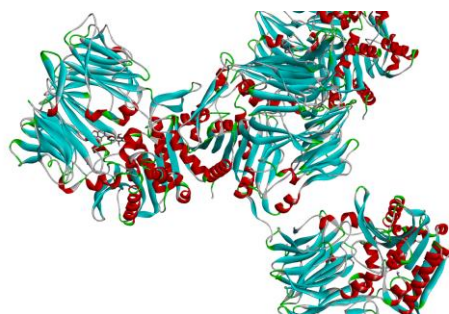
(c)ii



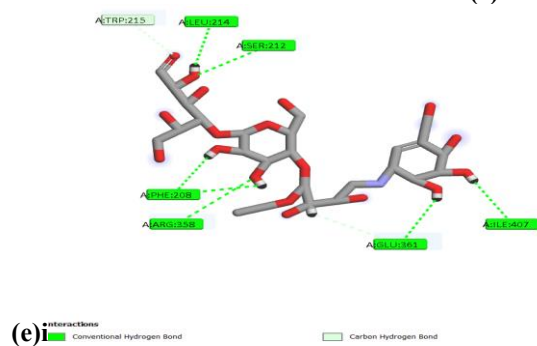
(d) 2ONC docked with quercetin



(d)ii



(e) 2ONC docked with sitagliptin



(e)ii

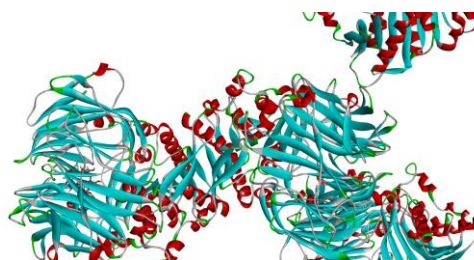


Figure 3: (i) 2D and (ii) 3D interaction of (a) chlorogenic acid (b) kaempferol (c) niazirin (d) quercetin and (e) sitagliptin with the human dipeptidyl peptidase-4 (DPP-4) -2ONC

Table 4: Protein-ligand interactions of the selected phytochemicals and the reference drug sitagliptin with DPP-4 (PDB ID: 2ONC)

Compound	Hydrogen bond	Hydrophobic interaction	Electrostatic
Sitagliptin	LEU 214, SER 212, PHE 208 ARG 358, GLU 361, ILE 407	TRP 215	-
Chlorogenic acid	TYR 120, TYR 128, ASN 103 GLU 117, SER 209	ALA 210	
Kaempferol	GLU 361, GLU 206, GLU 205	ARG 358, SER350	PHE 357 pi-pi stacked
Niazirin	GLU 205, SER 209	GLU 206, SER 360	PHE357 pi-sigma
Quercetin	ARG 358, TYR 547		GLU 206, PHE 357 pi-cation

Table 4 shows the protein-ligand interaction profiles of the selected phytochemicals and the reference drug sitagliptin with the target enzyme DPP-4. The results revealed differences in the binding modes of the selected *M. oleifera* phytochemicals and sitagliptin within the DPP-4 active site. This is also displayed in 2D and 3D in **Figure 3**. Sitagliptin formed hydrogen-bond interactions with LEU214, SER212 and PHE208, alongside hydrophobic interactions involving ARG358, GLU361 and ILE407, and an additional interaction with TRP215. Kaempferol interacted through hydrogen bonds with GLU361, GLU206 and GLU205, hydrophobic contacts with ARG358 and SER350, and π - π stacking with PHE357, indicating multiple potential contributions to ligand stabilization. Niazirin formed hydrogen bonds with GLU205 and SER209, hydrophobic interactions with GLU206 and SER360, and a π -sigma interaction with PHE357. Quercetin interacted through hydrogen bonds with ARG358 and TYR547 and a π -cation interaction involving PHE357. Chlorogenic acid formed hydrogen bonds with TYR120, TYR128, ASN103, GLU117, and SER209, alongside a hydrophobic contact with ALA210. These interactions suggest that the phytochemicals may adopt distinct binding orientations within DPP-4. Notably, kaempferol's hydrogen-bond and aromatic interactions are consistent with its more favorable docking scores. However, residue contacts alone do not establish inhibitory potency; further structural validation and experimental enzyme inhibition studies are required [33].

Table 5: Molecular docking scores of the selected phytochemicals and the reference drug TSC-401 with PTP 1B (PDB ID: 2HNP)

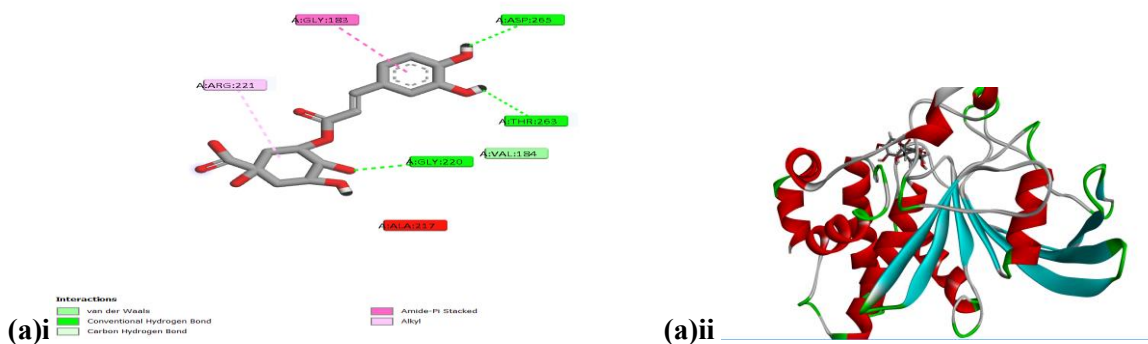
Compound	MolDock Score	Re-rank Score	Hydrogen Bond
TSC-401	-92.8091	-74.8939	-3.1733
Chlorogenic acid	-65.6301	-74.9437	-9.32723
Kaempferol	-90.371	-74.8846	-8.28332
Niazirin	-71.2063	-76.2323	-8.91888
Quercetin	-80.467	-70.9205	-8.37172

As shown in **Table 5**, the molecular docking results revealed differences in the predicted binding of the selected *M. oleifera* phytochemicals and the reference inhibitor TCS-401 to protein tyrosine phosphatase 1B (PTP1B; PDB ID: 2HNP). TCS-401 recorded the most favorable MolDock score (-92.8091), closely followed by kaempferol (-90.3710), suggesting potentially favorable binding poses for both compounds. However, chlorogenic acid exhibited the most favorable re-rank score (-74.9437), followed closely by TCS-401 (-74.8939), indicating that the secondary scoring function produced a slightly different ranking. Niazirin recorded the most favorable hydrogen-bond score (-8.91888) among the phytochemicals, followed by quercetin (-8.37172) and kaempferol (-8.28332). These results suggest that the compounds may interact differently with the PTP1B binding site, with kaempferol showing the strongest initial docking score and niazirin exhibiting the most favorable

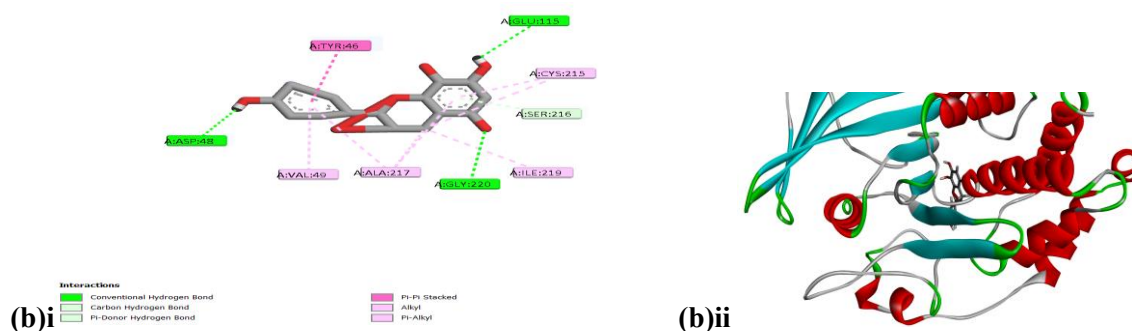
hydrogen-bond score among the phytochemicals. Such differences highlight the importance of considering multiple scoring functions when interpreting docking results [32, 34]. Nevertheless, these scores are computational predictions and do not establish inhibitory potency or superiority to TCS-401. Further binding-interaction analysis, molecular dynamics simulations, and experimental PTP1B inhibition assays are required to validate the findings [35, 36].

As shown in **Table 6**, the protein-ligand interaction profiles revealed differences in the binding modes of the selected *M. oleifera* phytochemicals and the reference inhibitor TCS-401 within the PTP1B binding site (**Figure 4**). TCS-401 formed hydrogen bonds with ARG221 and SER216, alongside hydrophobic interactions involving CYS215, ALA217, and TYR46. Kaempferol formed hydrogen bonds with GLY220, ASP48, and GLU115; hydrophobic interactions with VAL49, ALA217, CYS215, and ILE219; and a π - π stacking interaction with TYR46, suggesting multiple contributions to ligand stabilization. Chlorogenic acid formed hydrogen bonds with ASP265, THR263, and GLY220, a hydrophobic interaction with ARG221, and an amide- π stacking interaction involving GLY183. Niazirin exhibited several hydrogen-bond interactions with GLN266, GLY183, ARG221, PRO180, and ASP181, together with a π -alkyl interaction involving CYS215. Quercetin formed hydrogen bonds with GLY220 and ASP48, a hydrophobic interaction with VAL49, π -alkyl interactions involving ALA217 and ILE219, and π -cation interactions involving TYR46 and CYS215. Overall, the interaction profiles suggest that the phytochemicals engage different residues within the PTP1B binding pocket through combinations of hydrogen bonding, hydrophobic contacts, and aromatic interactions. These observations provide structural context for the docking scores presented in **Table 5**.

(a) 2HNP docked with chlorogenic acid



(b) 2HNP docked with kaempferol



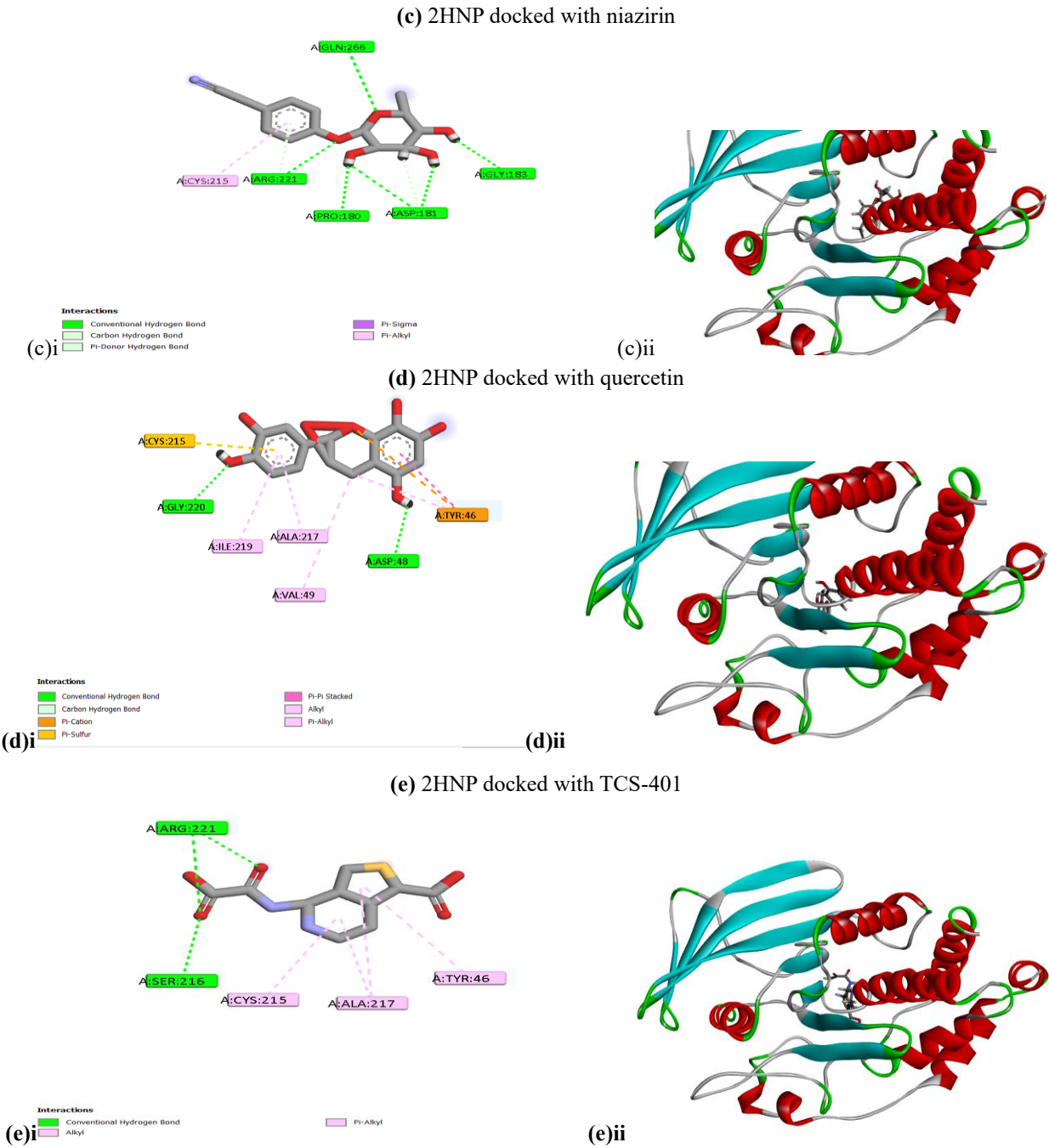


Figure 4: (i) 2D and (ii) 3D interaction of (a) chlorogenic acid (b) kaempferol (c) niazirin (d) and (e) TCS-401 with the human protein tyrosine phosphatase 1B (PTP 1B)- 2HNP

Table 6: Molecular docking scores of the selected phytochemicals and the reference drug TSC-401 with PTP 1B (PDB ID 2HNP)

Compound	Hydrogen bond	Hydrophobic interactions	Electrostatic interaction
TSC-401	ARG 221, SER 216	CYS 215, ALA 217, TYR 46	-
Chlorogenic acid	ASP 265, THR 263, GLY 220	ARG221	GLY 183 (amide-pi stacked)
Kaempferol	GLY 220, ASP 48, GLU 115	VAL 49, ALA 217, CYS 215, ILE 219	TYR 46 (pi-pi stacked)
Niazirin	GLN 266, GLY 183, ARG 221, PRO 180, ASP 181		CYS 215 pi-alkyl
Quercetin	GLY 220, ASP 48,	VAL 49	ALA 217, ILE 219 (pi-alkyl) TYR 46, CYS 215 (pi- cation)

Lipinski Rule of Five (RO5): The Lipinski Rule of Five (RO5) is a set of guidelines used in drug discovery to evaluate whether a chemical compound is likely to be an orally active drug in humans. It predicts oral drug absorption, helps identify compounds with good bioavailability, assists in selecting promising drug candidates during drug discovery, and reduces the likelihood of failure in later stages of drug development. **Table 7** shows the predicted drug-likeness of the phytochemicals used in this study.

Table 7: Predicted drug-likeness properties of the selected phytochemicals based on Lipinski's rule of five, consensus LogP, topological polar surface area (TPSA), and synthetic accessibility

Compound	Molecular mass	HBA	HBD	TPSA	Lipinski# violation	LogP	Synthetic accessibility	Bioavailability score
Chlorogenic acid	354.31	9	6	164.75	1	-0.71	4.16	0.11
Kaempferol	286.24	6	4	111.13	0	1.12	3.14	0.55
Niazirin	279.29	6	3	102.94	0	-0.17	4.03	0.55
Quercetin	302.24	7	5	131.36	0	0.79	3.23	0.55

HBA: hydrogen bond acceptor, HBD: hydrogen bond donor, TPSA: topological polar surface area

The drug-likeness evaluation showed that all four phytochemicals possessed generally favorable physicochemical properties with some drawbacks. Quercetin, kaempferol, and niazirin complied fully with Lipinski's Rule of Five, with no violations, indicating a higher probability of favorable passive absorption and oral bioavailability. Chlorogenic acid exhibited one Lipinski violation due to its high topological polar surface area (TPSA) and hydrogen-bonding capacity, which may reduce membrane permeability and oral absorption. All compounds had molecular weights below 500 Da, satisfying the Lipinski criterion for molecular weight. Their Consensus LogP values were below 5, indicating acceptable lipophilicity and a suitable balance between water and lipid solubility. Quercetin, kaempferol, and niazirin predicted a bioavailability score of 0.55, suggesting good oral bioavailability, whereas chlorogenic acid exhibited a lower bioavailability score (0.11). Overall, the drug-likeness analysis indicates that the selected *M. oleifera* phytochemicals possess favorable characteristics for oral drug development, with quercetin and kaempferol demonstrating the most promising drug-like properties warranting further investigations.

In **Table 8**, the ADMET analysis demonstrated that the selected phytochemicals possessed generally favorable pharmacokinetic and safety profiles. Quercetin and kaempferol exhibited high human intestinal absorption (74.21% and 74.29%, respectively), indicating good potential for oral absorption, whereas chlorogenic acid and niazirin showed moderate absorption. All compounds displayed negative LogBB and LogPS values, suggesting poor penetration across the blood-brain barrier and limited distribution into the central nervous system, which is desirable for antidiabetic agents that act on peripheral targets. Furthermore, none of the phytochemicals were predicted to be substrates or inhibitors of CYP2D6 and CYP3A4, indicating a low likelihood of drug-drug interactions mediated by these major metabolizing enzymes. The predicted total clearance values suggested acceptable elimination profiles, while all compounds were negative for AMES toxicity and skin sensitization, indicating low mutagenic potential and a favorable preliminary safety profile. Overall, the ADMET results suggest that the selected *M. oleifera* phytochemicals possess suitable pharmacokinetic characteristics and safety profiles, supporting their potential as candidates for further investigation as antidiabetic agents.

The current findings are based exclusively on in silico predictions and do not establish actual enzyme inhibitory activity, therapeutic efficacy, or safety. Favorable docking scores alone cannot confirm binding stability or biological activity. Thus, further investigations, including molecular dynamics simulations to assess the persistence of predicted interactions, in vitro enzyme inhibition assays to determine inhibitory activity and

potency, and experimental pharmacokinetic and toxicity evaluations, are necessary to validate these predictions. Subsequent in vivo studies, subject to supportive preliminary findings, would help establish their biological relevance and potential for further drug development.

Table 8: In silico ADMET predictions of the selected compounds

Compound	HIA %	BBB LogBB	CNS LogP S	CYP2D6		CYP3A4		ROS	TCE	AMES	SK
				S	I	S	I				
Chlorogenic acid	36.38	-1.407	-3.856	NO	NO	NO	NO	NO	0.307	NO	NO
Kaempferol	74.29	-0.939	-2.228	NO	NO	NO	NO	NO	0.477	NO	NO
Niazirin	58.33	-0.65	-3.016	NO	NO	NO	NO	NO	1.165	NO	NO
Quercetin	77.21	-1.098	-3.065	NO	NO	NO	NO	NO	0.407	NO	NO

HIA: human intestinal absorption, BBB: blood-brain barrier, CNS: central nervous system, LogBB: the logarithmic ratio of brain to plasma drug concentration, LogPS: blood-brain permeability-surface area product, CYP2D6: cytochrome P450 isoform, CYP3A4: cytochrome P450 isoform, S: substrate, I: inhibitor, TCE: total clearance, SK: skin sensitivity

Conclusion: This study provides computational evidence that selected phytochemicals from *M. oleifera*, particularly quercetin and kaempferol, may be promising candidates for further investigation against key enzyme targets associated with type 2 diabetes mellitus. Their favorable molecular docking scores and predicted protein-ligand interactions suggest potential binding affinity within the investigated enzyme binding sites. Among the compounds evaluated, quercetin demonstrated an encouraging overall computational profile, combining favorable docking performance with compliance with Lipinski's rule of five, relatively high predicted human intestinal absorption, and a favorable preliminary ADMET profile. Kaempferol and niazirin exhibited promising predicted drug-like properties, whereas chlorogenic acid showed comparatively less favorable drug-likeness characteristics, including one Lipinski rule violation and lower predicted intestinal absorption. These findings suggest that *M. oleifera* phytochemicals, particularly quercetin and kaempferol, warrant further investigation as potential lead compounds for antidiabetic drug discovery.

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