Universal Library of Chemistry **Research Article**

Volume 1, Issue 1

Open Access | PP: 01-11

DOI: https://doi.org/10.70315/uloap.ulche.2025.0101001

Moringa Oleifera Bioactive Compounds as a Novel DPP-IV Inhibitor: An In-Silico Study

Kolawole T. Mesileya[1], Precious C. Onyeka[1], Mark-Solomon C. Ogologo[1], Michael A.Aderiye[2], Prosper S. Olorunda[1], Ayeni E. Ayomide[1], Michail O. Avwojekpaye[3], Olamide O. Omokoye[4], Damilola S. Bodun[5]

[1]College of Pharmacy, Afe Babalola University, Ado Ekiti, Ekiti State, Nigeria.
[2]Department of Physiology Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria.
[3]College of Engineering, Afe Babalola University, Ado Ekiti, Ekiti State, Nigeria.
[4]Department of Chemistry, University of Ilorin, Ilorin, Kwara State, Nigeria.
[5]Department of Biochemistry, Adekunle Ajasin University, Akungba-Akoko, Ondo state, Nigeria.

Abstract

Background: *Diabetes mellitus is a global health crisis affecting over 422 million people and causing 1.5 million annual deaths, particularly in low- and middle-income countries. Dipeptidyl peptidase IV (DPP-IV) inhibitors effectively manage blood glucose by enhancing insulin secretion and extending glucagon-like peptide-1 (GLP-1) activity. Moringa oleifera, a traditional medicinal plant, has gained attention as a source of natural DPP-IV inhibitors with antidiabetic potential.*

Results: *This study evaluated the antidiabetic potential of Moringa oleifera phytochemicals using molecular docking, drug-likeness prediction, toxicity assessment, and Density Functional Theory (DFT) analysis. The top five compounds Chlorogenic acid, Rhamnetin, Quercetin, Ellagic acid, and Apigenin demonstrated strong binding affinities to DPP-IV, with docking scores ranging from -8.342 kcal/mol to -6.796 kcal/mol, surpassing the standard drug Alogliptin (-4.097 kcal/mol). DFT analysis revealed favorable electronic properties, including low band gap energies and strong electron-accepting capabilities, highlighting their chemical stability and reactivity. ADMET predictions confirmed minimal cytotoxicity and favorable drug-likeness profiles for the compounds.*

Conclusion: *This study identifies Moringa oleifera phytochemicals as promising natural DPP-IV inhibitors with superior binding affinities and favorable drug profiles compared to standard drugs. These findings provide a basis for further in vitro and in vivo studies to validate their therapeutic efficacy and develop them into effective antidiabetic agents.*

Keywords: *DPP-IV, ADMET, Diabetes, Moringa Oleifera, In-Silico, DFT.*

INTRODUCTION

Diabetes mellitus is a long-term disorder affecting how proteins, fats, and carbohydrates are metabolized. A defining hallmark of diabetes mellitus is an impaired or insufficient insulin secretory response, which results in impaired utilization of carbohydrates (glucose) and subsequent hyperglycemia (Kuma *et al*., 2020). As the most prevalent endocrine illness, diabetes mellitus (DM) is commonly referred to as "sugar." Long-term high blood sugar levels are one of its defining characteristics, along with abnormalities in the metabolism of fat, protein, and carbohydrates caused by deficiencies in either insulin activity or secretion (Alam *et al*., 2020). Nearly 422 million people worldwide have diabetes, and the disease is directly responsible for 1.5 million fatalities annually, according to the World Health Organization. Over time, diabetes causes significant morbidity and mortality due to several complications such as retinopathy, neuropathy, nephropathy, heart attack, stroke, and peripheral vascular disease (Bhuyan and Ganguly, 2023). One of the most prevalent forms of diabetes, particularly in adults, is type 2. The body is unable to produce enough insulin or develops insulin resistance due to impaired or lacking incretin action (Holst and Deacon, 2004). Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are the two most important hormones responsible for the maximum percentage release of insulin by the pancreas after meal intake; they can also suppress glucagon secretion (Drucker, 2023). The consumption of fats, carbohydrates, and proteins

Citation: Kolawole T. Mesileya, Precious C. Onyeka, et al., "Moringa Oleifera Bioactive Compounds as a Novel DPP-IV Inhibitor: An In-Silico Study", Universal Library of Chemistry, 2025; 1(1): 01-11. DOI: https://doi.org/10.70315/uloap.ulche.2025.0101001.

stimulates the release of these hormones, GLP-1 and GIP, into the blood. GIP, a peptide with approximately 42 amino acid residues, is primarily produced by the K cells of the duodenum, whereas GLP-1, a peptide with approximately 30 amino acids, is mainly produced by the L cells of the lower section of the small intestine (Bhuyan and Ganguly, 2023). The enzyme dipeptidyl peptidase-4 (DPP-4; CD26; EC 3.4.14.5) is found in various human organs, including the liver, pancreas, and adipose tissue. DPP-4 is a versatile serine peptidase that cleaves the N-terminal of dipeptide substrates containing proline or alanine amino acid residues at their penultimate position (Tomovic *et al*., 2020). As a result, it quickly degrades GLP-1 and GIP hormones once they are released. Inactivation of both GIP and GLP-1 hormones can interfere with insulin secretion stimulation, resulting in hyperglycemia. By suppressing DPP-4, the half-life of GLP-1 and GIP can be extended, increasing pancreatic insulin secretion while decreasing glucagon production and improving hyperglycemia regulation (Bhuyan and Ganguly, 2023). Consequently, inhibiting the DPP-4 enzyme is a critical therapeutic target for the treatment of type 2 diabetes. Moringa oleifera is a small tree native to the Sub-Himalayan regions of Northwest India that has now spread to many areas including Africa, Arabia, Southeast Asia, the Pacific Islands, and South America. Traditionally, in addition to being a common food in these regions, Moringa is widely known and utilized for its health benefits. It has earned the nickname "the miracle tree" among ordinary people due to its outstanding healing properties for a variety of ailments and certain chronic conditions. Several studies have been conducted to isolate bioactive components from various parts of the plant due to its numerous applications (Guevara *et al*., 1999). According to some scientific studies, specific components of *M. oleifera* preparations exhibit a wide range of pharmacological activities, including antimicrobial, anti-inflammatory, and antidiabetic properties. Muhammad *et al*. (2016) studied the anti-diabetic effects of *M. oleifera* seeds, roots, and stem bark extracts in diabetic mice and discovered that aqueous, ethanolic, and methanolic extracts from these plant parts provided good glycemic control in diabetic animals. To explore the potential of *M. oleifera* phytochemicals as inhibitors of DPP-4, a computer-aided molecular modeling approach was employed that includes molecular docking, MM/GBSA calculations, ADMETox screening, and DFT to screen a library of *M. oleifera* phytochemicals and identify those compounds with inhibitory properties against DPP-4.

METHODS AND MATERIALS

Retrieval of Receptor

The three-dimensional (3D) X-ray crystallographic structure of DPP-IV co-crystallized with the selective inhibitor 1,3-thiazolidin-3-yl[(2S,4S)-4-{4-[2-(trifluoromethyl)quinolin-4-yl]piperazin-1-yl}pyrrolidin-2-yl]methanone, resolved at 2.10 Å with accession ID 3VJM, was retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/home.do). Using Maestro, the PDB data was processed, and the protein preparation wizard was used to process the proteins. As part of the preparation, constrained energy minimization, the inclusion of missing side chains, the removal of water and unconventional ligands, and adjustments to hydrogen placement were all required.

Preparation of Compounds from M. Oleifera

M. oleifera has been reported to contain one hundred and six (106) active compounds, which were gathered from published literature (Adusei *et al*., 2022; Abd Rani *et al*., 2018; Anzano *et al*., 2021; and Fidrianny *et al*., 2021). To identify these compounds, we searched PubChem (https://pubchem.ncbi.nlm.nih.gov) for their chemical names or structures. Following that, the compounds were downloaded in SDF format by selecting the SDF file format from the "Download" option on the PubChem compound information page. Similar methods were used to obtain alogliptin, the standard drug. The LigPrep tool was then used to prepare each compound using the OPLS_2005 force field once they had been imported into the Schrödinger workspace. Furthermore, the 3VJM co-ligand (1,3-thiazolidin-3-yl[(2S,4S)-4-{4-[2-(trifluoromethyl)quinolin-4-yl]piperazin-1-yl}pyrrolidin-2-yl]methanone) was also looked up and downloaded in SDF format from PubChem via the same procedure. As a reference, this ligand was prepared in the same way as the standard drug, alogliptin.

Receptor Grid Generation

The grid generation job was configured, and a receptor structure was specified using the receptor grid panel. The receptor grid shows the region of the receptor where the ligand and protein interact. The created protein grid was placed on the binding site (Glide Grid) using the Receptor Grid Generation tool. The binding domain of protein 3VJM was generated by choosing the co-crystallized ligand to define the coordinates. All amino acid residues at the active site were automatically synthesized as a cubic grid box. The three-dimensional coordinates of the generated grid were (x = 51.67 Å, y = 63.91 Å, z = 35.05 Å) for 3VJM.

Molecular Docking

Docking was performed on Maestro 13.4 (Schrödinger 2022) using the Glide tool (Friesner *et al*., 2004). Using three hierarchical docking filtering methodologies, alogliptin (the standard drug), co-crystallized ligand, and one hundred six (106) compounds from *M. oleifera* were virtually screened. The large number of ligands was quickly screened using high-throughput virtual screening (HTVS) docking precision, which has considerably more limited conformational sampling than existing precision filters. Thus, using HTVS docking, the 106 compounds were screened against DPP-IV. The standard precision (SP) filtering technology was utilized to conduct additional screening on the top twenty hit compounds. Using the extra precision (XP) scoring algorithm, five (5) hits that had docking affinities greater than those of the reference drug (alogliptin) were screened further. The docking protocol was validated through a redocking procedure to ensure the accuracy of the docking parameters.

ADME/Tox Screening

The pharmacokinetic profile, drug-likeness, and toxicity of the hit compounds were evaluated along with their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties using the AdmetSar web server, Pro-Tox II web server, and QikProp module within Schrödinger's Maestro interface.

MM/GBSA

The docked protein-ligand complex binding free energy was calculated by the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) continuum solvent model. The OPLS3 force field and the VSGB solvent model were combined with rotamer search methods from Prime. The binding free energy was calculated using the following equation:

$$\Delta G^{bind} = G^{complex}X - (G^{protein} + G^{Ligand}) \quad (1)$$

where ΔG^{bind} is the protein-ligand complex's binding free energy, $G^{complex}$ is the complex's free energy, and $G^{protein}$ and G^{ligand}, respectively, are the free energies of the protein and the ligand.

Density Functional Theory (DFT)

Quantum chemical analyses and density functional theory (DFT) were utilized to evaluate the molecular characteristics of an *M. oleifera* compounds to forecast the biological activities of the top-ranked compounds. The most stable conformer was chosen following a conformer distribution calculation using the computational chemistry program Spartan 10 to perform DFT analysis in a vacuum. EHOMO and ELUMO, two thermodynamic parameters, were computed from this analysis. The global reactivity descriptors and other features were then derived using these values. For instance, the difference between ELUMO and EHOMO was used to calculate the energy band gap.

$$Eg = E_{LUMO} - E_{HOMO} \quad (2)$$

While Koopman's theory connects the Ionization energy (I) and Electron Affinity (A) to EHOMO

and ELUMO (Koopmans, 1993).

$$I = -E_{HOMO} \quad (3)$$

$$A = -E_{LUMO} \quad (4)$$

$$x = \frac{I+A}{2} \quad (5)$$

$$\eta = \frac{I-A}{2} \quad (6)$$

$$\delta = \frac{1}{\eta} \quad (7)$$

RESULTS/DISCUSSION

Docking/MMGBSA

The docking scores and MM/GBSA screening outcomes for the hit compounds are represented graphically in figure 1 and table 1, respectively. To assess the potential inhibitory effects of the chosen *M. oleifera* ligands, the target protein's DPP IV binding pocket was docked with enhanced precision (XP). Along with looking at the structural interactions of the top compounds, the important amino-acid interactions at the DPP IV binding site were discovered.

Table 1. The binding affinity (kcal/mol) and MMGBSA of the top-ranked M. Oleifera phytochemical constituents and standard drug against DPP-IV.

s/n	Compound name	PubChem Cid	Docking score(kcal/mol)	MMGBSA (ΔG bind)
1	Chlorogenic acid	1794427	-8.342	-41.58
2	Rhamnetin	5281691	-7.757	-37.82
3	Quercetin	5280343	-7.714	-36.21
4	Ellagic acid	5281855	-7.25	-41.06
5	Apigenin	5280443	-6.796	-31.02
6	Alogliptin(standard)	11450633	-4.097	-34.39
7	Co-crystallized Ligand	57525787	-3.781	-36.55

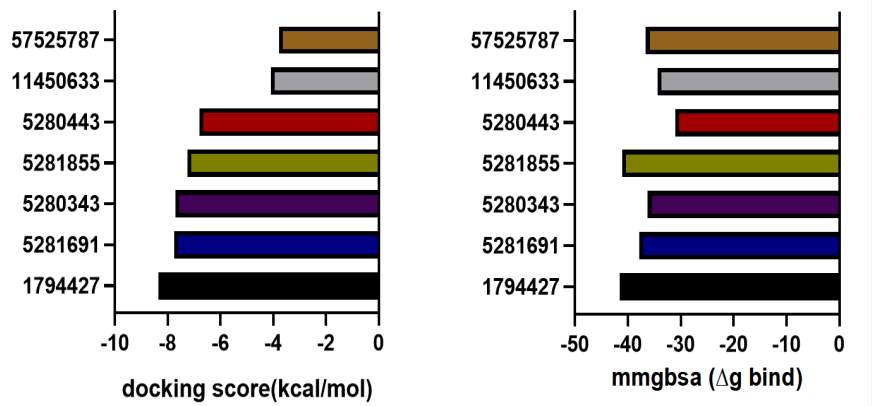


Figure 1. Graphical representation of the docking score and MMGBSA (ΔG bind) binding energy for the top compounds and standards.

Table 1 and figure 1, presents the docking scores of the top five ligands derived from Moringa oleifera against DPP-IV, alongside a standard drug and the co-crystallized ligand. Chlorogenic acid exhibited the highest docking score (-8.342 kcal/mol), followed by rhamnetin (-7.757 kcal/mol), quercetin (-7.714 kcal/mol), ellagic acid (-7.25 kcal/mol), and apigenin (-6.796 kcal/mol). Notably, chlorogenic acid demonstrated a significantly better binding affinity compared to the standard drug, alogliptin (-4.097 kcal/mol), and the co-crystallized ligand (-3.781 kcal/mol). To validate the docking results, the binding free energies of the protein-ligand complexes were calculated using the MM/GBSA method within the Schrödinger suite. MM/GBSA is a reliable post-docking approach for evaluating the structural stability and binding energy of docked complexes (Omoboyowa *et al*., 2022) and has been widely recognized for its accuracy in identifying binding interactions (Tripathi *et al*., 2013). As shown in Table 1, chlorogenic acid not only had the highest docking score but also demonstrated the most favorable binding energy (-41.58 kcal/mol), surpassing both the reference drug alogliptin (-34.39 kcal/mol) and the co-crystallized ligand (-36.55 kcal/mol). This result highlights its stronger interaction and potential stability within the target binding site. To further explore the inhibitory potential of the selected ligands, extra precision (XP) docking was employed to refine the interactions within the DPP-IV binding pocket. Structural relationships among the leading compounds, the standard drug, and the co-crystallized ligand were analyzed, with a focus on key amino acid interactions in the DPP-IV binding region.

Table 2 and Figure 2 show that five hydrogen bonds were formed by chlorogenic acid with GLN553, CYS551, TYR585, LYS554, and ARG125 without pi-pi stacking. Quercetin produced three hydrogen bonds with TYR585, CYS551, GLN553, and pi-pi stacking with TYR547, while rhamnetin interacted with TYR547, CYS551, GLN553, and LYS554. Alogliptin formed one hydrogen bond with the amino acid ARG125 without pi-pi stacking, and ellagic acid formed one hydrogen bond with the amino acids TYR547 with pi-pi stacking involving TYR547. Additionally, the co-crystallized ligand formed one hydrogen bond with the amino acids HIP740 and pi-pi stacking with TYR547.

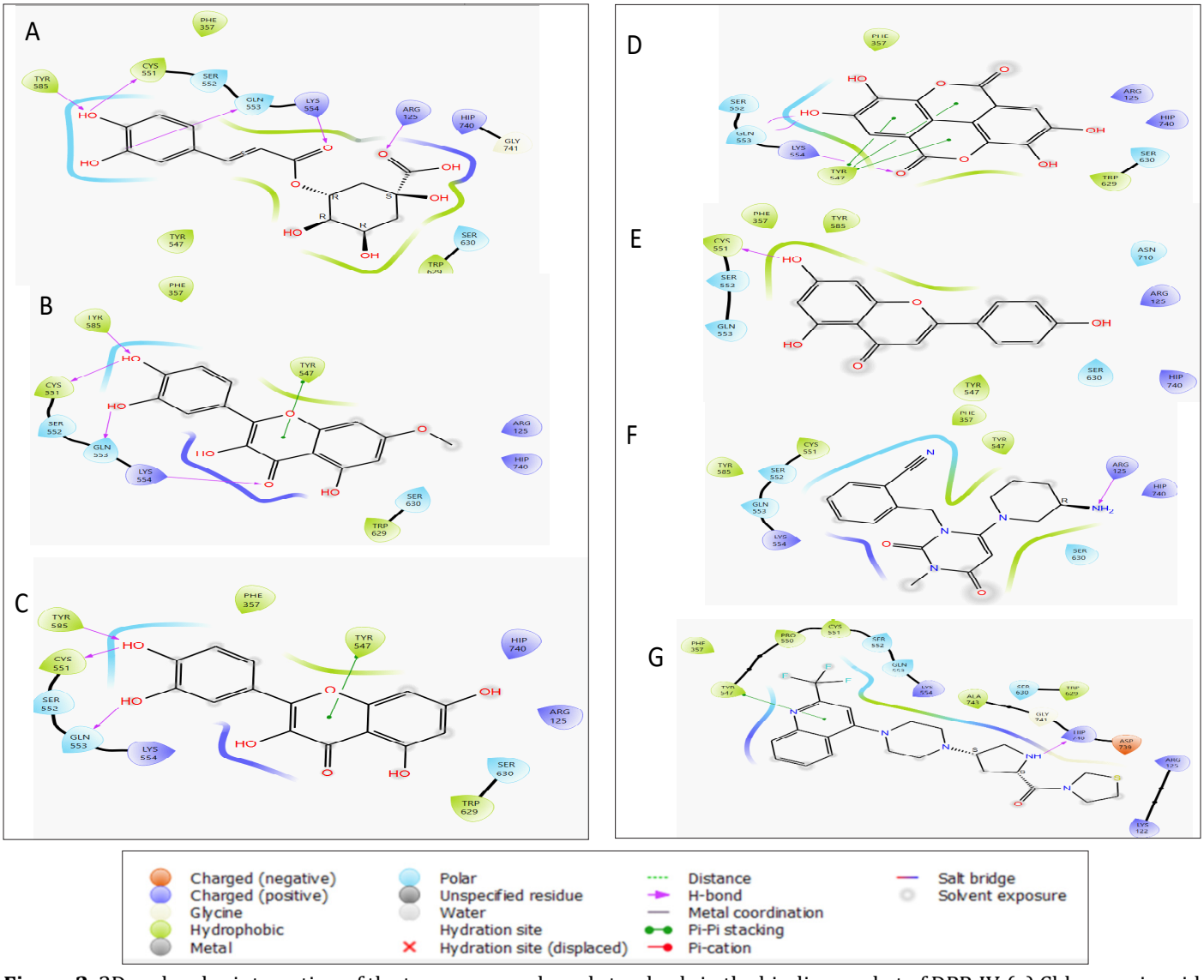


Figure 2. 2D molecular interaction of the top compounds and standards in the binding pocket of DPP-IV. (a) Chlorogenic acid (b) Rhamnetin (c) Quercetin (d) Ellagic acid (e) Apigenin (f) Alogliptin(standard drug) (G) Co-crystallized Ligand.

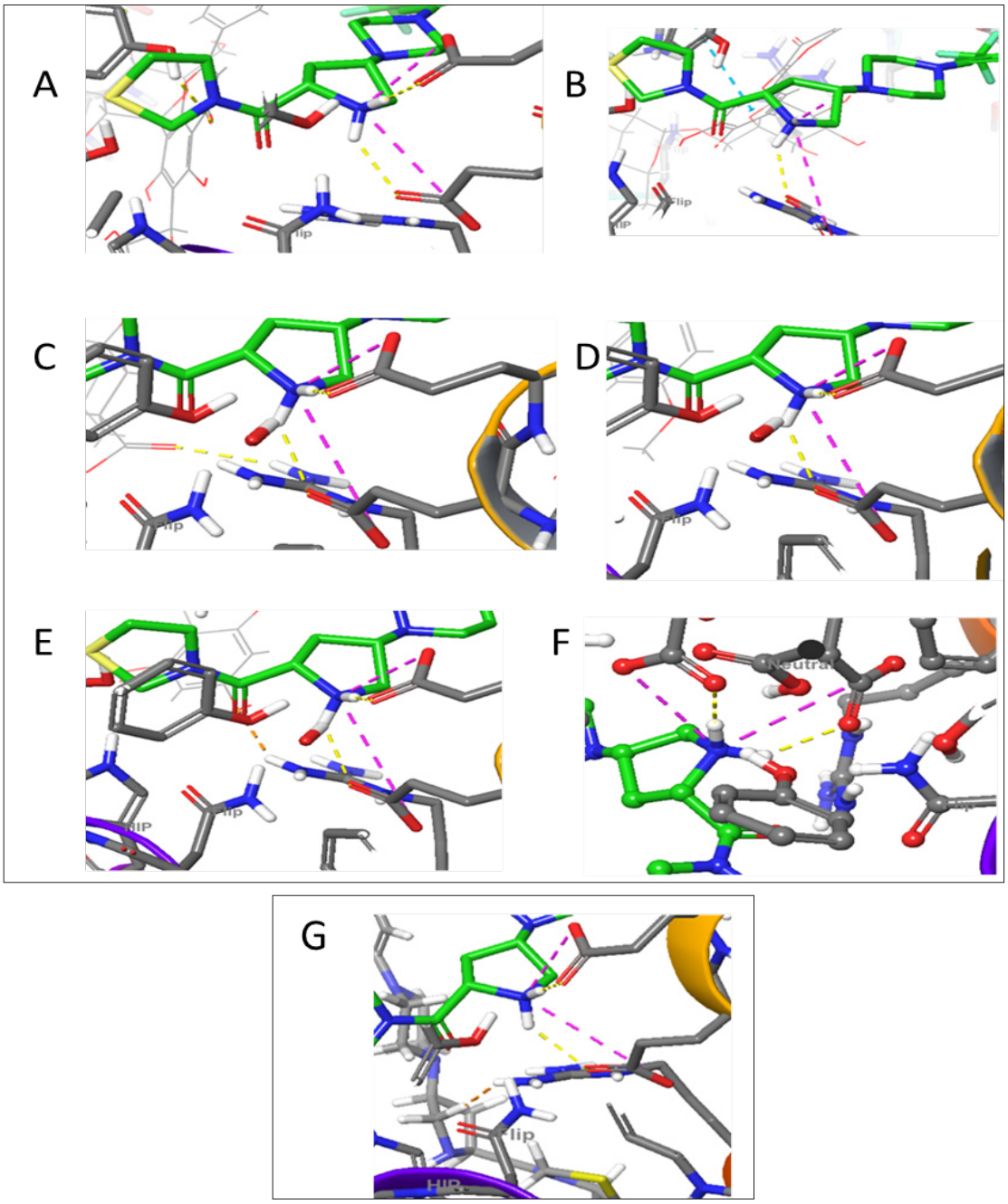


Figure 3. 3D molecular interaction of the top compounds and standards in the binding pocket of DPP-IV (a) Chlorogenic acid (b) Rhamnetin (c) Quercetin (d) Ellagic acid (e) Apigenin (f) Alogliptin(standard drug) (G) Co-crystallized Ligand.

Table 2. Molecular contact profiling of the top *M. Oleifera* phytochemicals and reference ligands.

COMPOUND NAME	H-BOND INTERACTION	HYDROPHOBIC AMINO ACID	OTHER INTERACTION
Chlorogenic acid	GLN553, CYS551, TYR585, LYS554, ARG125	TRP629, TYR547, TYR585, PHE357, CYS551	NONE
Rhamnetin	TYR585, CYS551, GLN553, LYS554,	TRP629, TYR547, TYR585, PHE357, CYS551,	PI-PI STACKING: TYR547
Quercetin	TYR585, CYS551, GLN553	TRP629, TYR547, PHE357, TYR585, CYS551,	PI-PI STACKING: TYR547
Ellagic acid	TYR547	PHE357, TYR547, TRP629	PI-PI STACKING: TYR547
Apigenin	CYS551	PHE357, TYR585, CYS551, TYR547	NONE
Alogliptin	ARG125	TYR546, CYS551, PHE357, TYR585,	NONE
Co-crystallized Ligand.	HIP740	PHE357, PRO550, CYS551, TYR547, ALA743, TRP629	PI-PI STARKING: TYR547

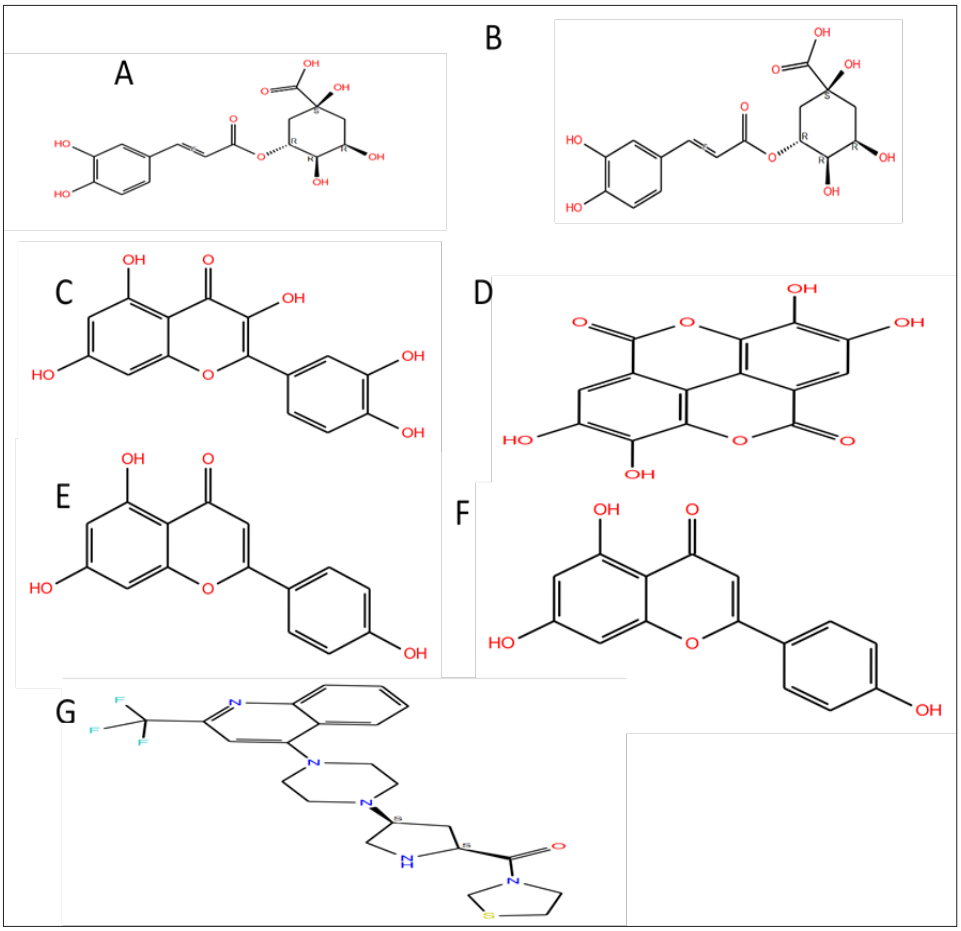


Figure 4. Molecular Structure of hit compounds (M. oleifera) (a) Chlorogenic acid (b) Rhamnetin (c) Quercetin (d) Ellagic acid (e) Apigenin (f) Alogliptin(standard drug) (G) Co-crystallized Ligand. Structures were sourced from PubChem (https://pubchem.ncbi.nlm.nih.gov).

Table 3. Drug-likeness, predicted oral bio-availability, pharmacokinetic properties, predicted toxicity profile, and predicted Cytochrome P450 metabolizing enzymes inhibitory potentials of the top ligands from *M. Oleifera* and reference ligands

Compound name	Chlorogenic acid	Rhamnetin	Quercetin	Ellagic acid	Apigenin	Alogliptin	Co-crystallized Ligand.
MW g/mol	354.31	316.26	302.24	302.19	270.24	339.39	465.53
BBB permeant	NO	NO	NO	NO	NO	NO	YES
GI absorption	LOW	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH
PGP Substrate	NO	NO	NO	NO	NO	NO	YES
CYP1A2 inhibitor	NO	YES	YES	YES	YES	NO	NO
CYP2C19 inhibitor	NO	NO	NO	NO	NO	NO	NO
CYP2C9 inhibitor	NO	NO	NO	NO	NO	NO	NO
CYP2D6 inhibitor	NO	YES	YES	NO	YES	NO	YES
CYP3A4 inhibitor	NO	YES	YES	NO	YES	NO	YES
Bioavailability Score	0.11	0.55	0.55	0.55	0.55	0.55	0.55
Hepatotoxicity	inactive	inactive	Inactive	Inactive	inactive	Inactive	Inactive
Carcinogenicity	inactive	active	active	active	Inactive	Inactive	Inactive
Immunotoxicity	Active	inactive	Inactive	Inactive	inactive	Inactive	active
Mutagenicity	Inactive	active	active	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	inactive	inactive	Inactive	Inactive	inactive	Inactive	Inactive
LD50:mg/kg	5000	5000	159	2200	2500	1000	100
Toxicity class	5	5	3	4	5	4	3
Rule of five (5)	1	0	0	0	0	0	0

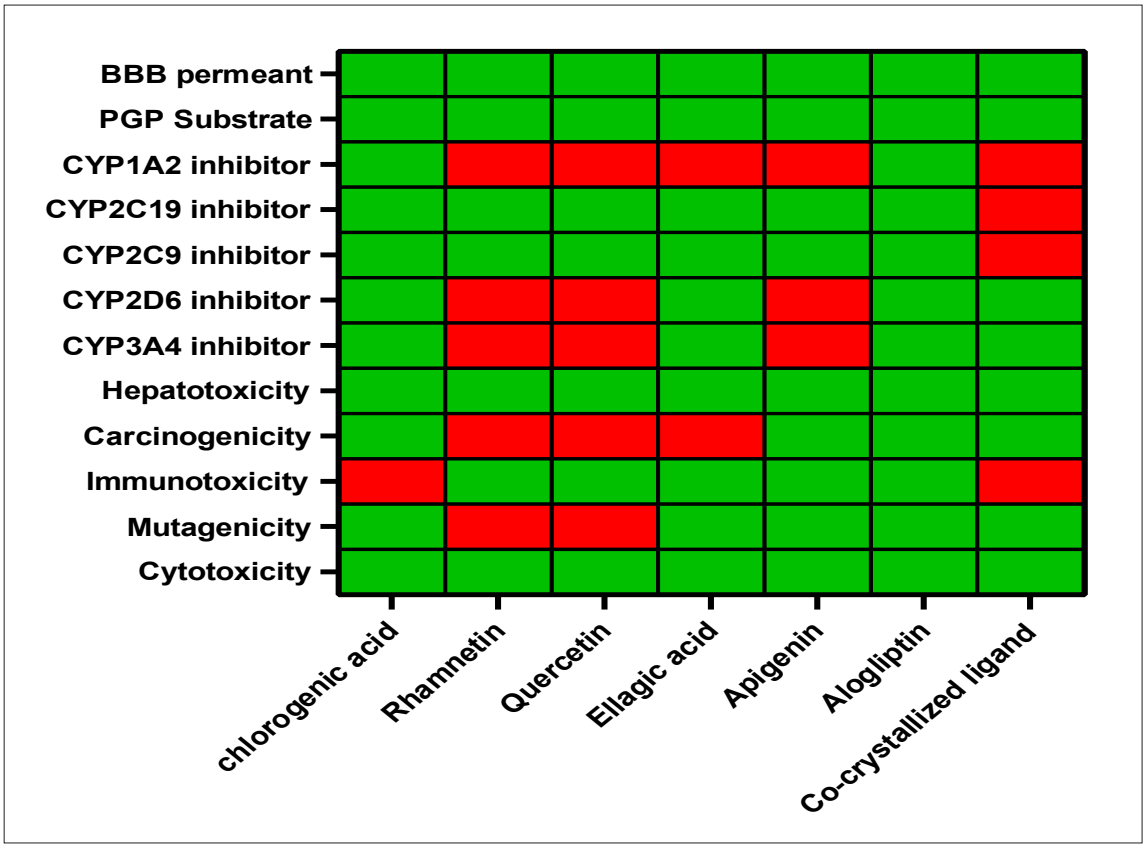


Figure 5. The Heat Map of The ADMET Parameter of Selected *M. oleifera* phytochemical constituent and standard drug

Pharmacokinetic Screening:

The evaluation of blood-brain barrier (BBB) permeability is an essential pharmacokinetic screening test that serves two purposes: assessing the central nervous system (CNS) bioavailability of potential drugs and preventing harmful substances from entering the brain. The development of innovative drug candidates has proven to be a time- and cost-saving method, even though computer-aided assessments of BBB permeability may not always be accurate. Medicinal substances that inhibit particular CYP isoforms, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, which are involved in the metabolism of numerous medications, can cause drug-drug interactions (DDIs). Chlorogenic acid, the top compound in Table 3, exhibited no inhibitory effect on these CYP isoforms, suggesting that it is unlikely to affect the metabolism of other pharmaceutical compounds. Drug-drug interactions (DDIs) may occur because P-glycoprotein substrate drugs often share characteristics with CYP3A4 substrate drugs. The excretion of P-glycoprotein substrates in bile and urine decreases their bioavailability and increases P-gp clearance (Finch and Pillans, 2014). All of the compounds studied, as shown in Table 3, are P-gp substrates according to the in silico research performed for this study. The term "bioavailability" in pharmacology describes the degree and rate of absorption and conversion of a bioactive molecule into a usable state (Kim *et al*., 2014). Low oral bioavailability is a frequent obstacle in drug discovery since it can cause a molecule to show high performance in in vitro and in vivo investigations but fail in clinical trials due to low oral bioavailability (Erhirhie *et al*., 2018). Rath *et al*. (2002) found that a bioavailability score above 0.5 implies high oral bioavailability, while a score below 0.5 indicates low oral bioavailability. Every compound shown in Table 3 has a bioavailability score of 0.55, indicating good oral bioavailability, except for chlorogenic acid. Acute oral toxicity is a crucial endpoint in drug development, and in silico techniques are increasingly being used as efficient substitutes for labor-intensive experimental procedures (Li *et al*., 2014). LD50 (mg/kg body weight), the dose at which 50% of subjects succumb to exposure to a drug, is the standard unit of measurement for toxic doses (Erhirhie *et al*., 2018). Based on their chemical similarity to known hazardous compounds and the presence of dangerous fragments, test chemicals are divided into six toxicity categories according to the acute oral toxicity model (Banerjee *et al*., 2018). Chlorogenic acid and rhamnetin, which includes apigenin, are all classified as belonging to class 5, as shown in Table 3, with LD50 values of 5000 mg/kg and 2500 mg/kg, respectively. With LD50 values of 2200 mg/kg and 1000 mg/kg, respectively, ellagic acid and the standard drug (alogliptin) both fall within class 4. With an LD50 value of 159 mg/kg, quercetin belongs to class 3.

Table 4. Structures of the ligands in Optimized, HOMO and LUMO FORM.

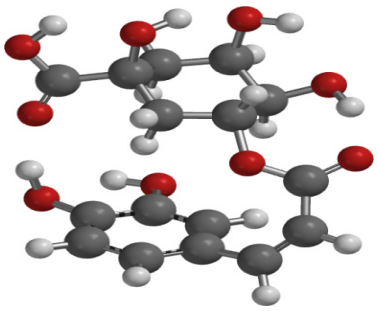
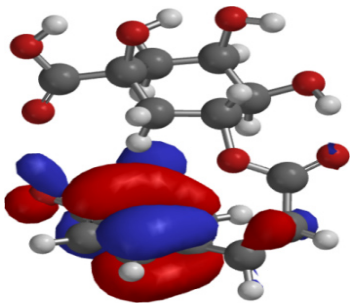
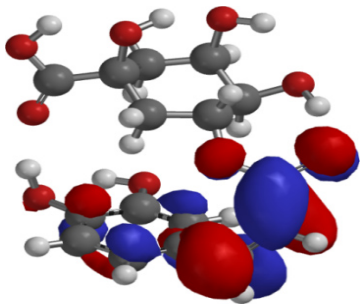
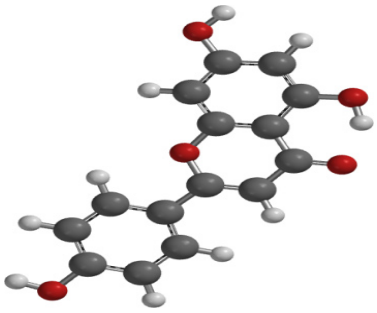
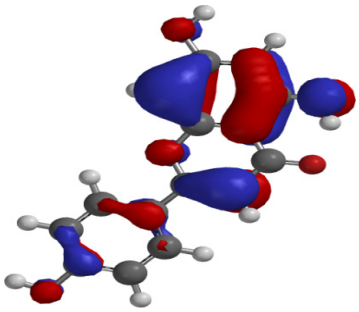
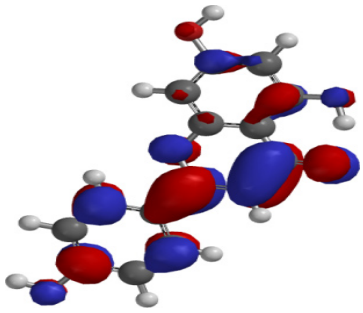
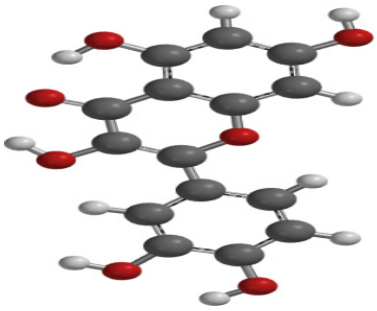
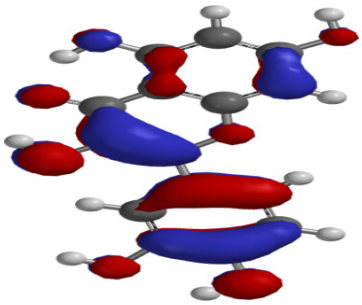
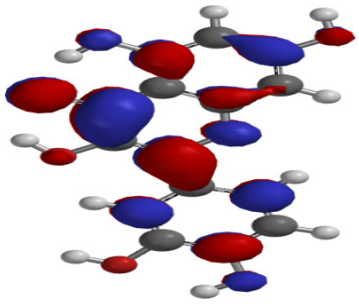
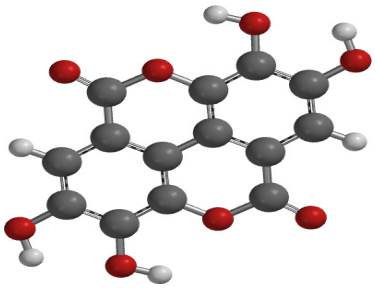
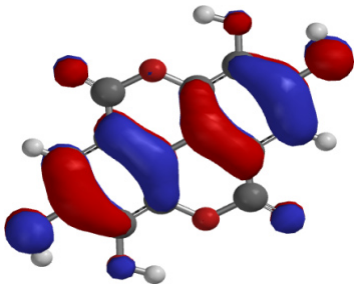
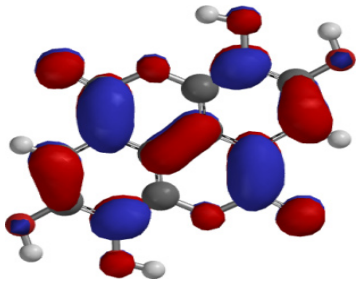
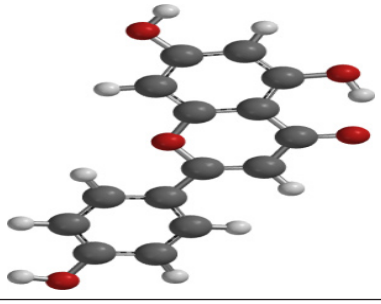
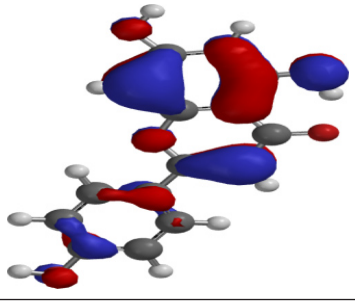
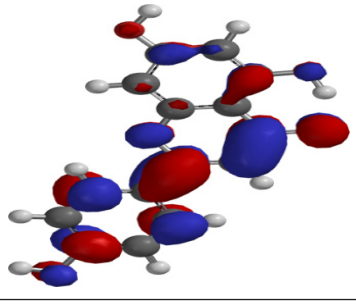
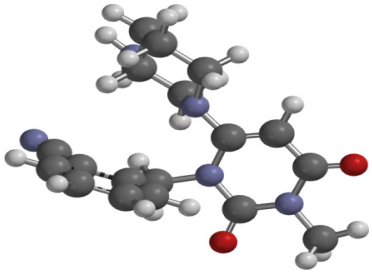
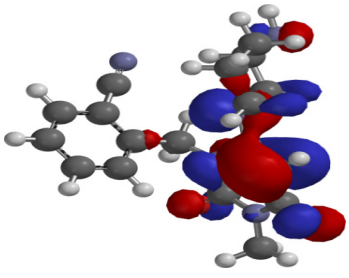
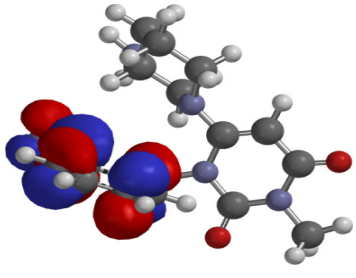
Compound name	Optimized Structure	EHOMO	ELOMO
Chlorogenic acid			
Rhamnetin			
Quercetin			
Ellagic acid			
Apigenin			
Alogliptin			

Table 5. The Calculated Thermodynamic Quantities (Enthalpy and Free Energy) Via DFT

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	E_g (eV)	I((eV)	A(eV)	η (eV)	δ (eV^{-1})	χ (eV)	ω(eV)
Chlorogenic acid	-6.07	-1.78	4.29	6.07	1.78	2.145	0.4662	3.925	3.591055
Rhamnetin	-5.91	-1.73	4.18	5.91	1.73	2.09	0.478469	3.82	3.491005
Quercetin	-5.48	-1.84	3.64	5.48	1.84	1.82	0.549451	3.66	3.68011
Ellagic acid	-6.03	-2.04	3.99	6.03	2.04	1.995	0.501253	4.035	4.080508
Apigenin	-5.91	-1.73	4.18	5.91	1.73	2.09	0.478469	3.82	3.491005
Alogliptin(standard)	-6.25	-1.61	4.64	6.25	1.61	2.32	0.431034	3.93	3.328642

Density Functional Theory

Frontier Molecular Orbitals (FMOs)

The energies of the Frontier Molecular Orbitals (FMOs) provide critical insights into the chemical reactivity and interaction potential of molecules. The energy of the Lowest Unoccupied Molecular Orbital (LUMO) indicates a molecule's ability to accept electrons, while the energy of the Highest Occupied Molecular Orbital (HOMO) reflects its electron-donating capacity. Together, the HOMO and LUMO energies play a pivotal role in determining a molecule's optical, electrical, and chemical properties. A lower LUMO energy correlates with a higher likelihood of accepting electrons, enhancing a molecule's reactivity, whereas a higher HOMO energy signifies a greater tendency to donate electrons (Olugbogi *et al*., 2023). In this study, the ELUMO values of the compounds ranged from -1.61 eV to -2.04 eV, demonstrating their electron-accepting capabilities. Among them, ellagic acid exhibited the strongest electron-accepting behavior, as indicated by its ELUMO value. The band gap energy (Eg), defined as the energy difference between EHOMO and ELUMO, significantly influences a molecule's thermochemical reactivity. The band gap provides valuable information about chemical stability and reactivity: molecules with larger band gaps are more stable and less reactive, while those with smaller band gaps are more reactive but less stable. In this study, the band gap energies varied, reflecting differences in the stability and reactivity of the compounds. The optimized HOMO and LUMO structures of the compounds, along with their electronic affinities, are presented in Tables 4 and 5. The electronic affinities of the predicted inhibitors ranged from -1.61 eV to -2.04 eV, supporting their potential as electron acceptors. Additionally, the thermodynamic properties (enthalpy and free energy) computed using Density Functional Theory (DFT) are detailed in Table 5. The compounds' reactivity was further evaluated using global reactivity descriptors (GRDs), including chemical hardness (η), softness (δ), electronegativity (χ), and chemical potential (μ). Chemical hardness reflects a molecule's resistance to electron cloud deformation. Hard molecules, characterized by larger band gaps, are less polarizable and more stable than soft molecules with smaller band gaps. Alogliptin exhibited the highest hardness (2.32 eV), confirming its chemical stability, while quercetin displayed the lowest hardness (1.82 eV), indicative of higher reactivity. Electronegativity, a measure of a molecule's ability to attract electrons during chemical reactions, was highest for ellagic acid (4.035 eV). This aligns with its strong electron-accepting behavior. Alogliptin, with an ionization energy of -6.25 eV, exhibited the highest propensity for electron loss, suggesting its potential for anion formation.

CONCLUSION

Diabetes mellitus remains a significant global health challenge, with its rising prevalence and associated mortality underscoring the urgent need for effective therapeutic interventions. Dipeptidyl peptidase IV (DPP-IV) inhibitors play a pivotal role in diabetes management by enhancing insulin sensitivity and prolonging the half-life of glucagon-like peptide-1 (GLP-1), thereby promoting insulin action and glycemic control. This study has identified phytochemicals from Moringa oleifera, including chlorogenic acid, rhamnetin, quercetin, ellagic acid, and apigenin as potential DPP-IV inhibitors with promising antidiabetic properties. These findings suggest that these compounds may serve as natural alternatives or complementary agents in diabetes treatment. However, further research is essential to validate these computational findings. This includes the isolation and purification of these compounds for in vitro assays to evaluate their inhibitory activity against DPP-IV, followed by in vivo studies to assess their pharmacokinetics, safety, and therapeutic efficacy. Such comprehensive investigations are critical to fully elucidate the medicinal potential of these compounds and advance their development as effective antidiabetic agents.

List of Abbreviations

DPP-IV: Dipeptidyl-peptidase

GLP-1: Glucagon-like peptide-1

MM-GBSA: Molecular mechanics generalized born surface area;

PDB: Protein database;

CYP: Cytochrome;

ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity.

BBB-: Blood Brain Barrier permeability negative.

HBA: Hydrogen Bond Acceptor

HBD: Hydrogen Bond Donor

TPSA: Topological Polar Surface Area

MW: Molecular Weight

Log Kp: Human Skin Permeability coefficient

REFERENCES

1. Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A Review on Diabetes Mellitus: Type1 & Type2. *World Journal of Pharmacy and Pharmaceutical Sciences*, *9*(10), 838-850
2. DOI:10.20959/wjpps202010-17336
3. Alam, U., Asghar, O., Azmi, S., & Malik, R. A. (2014). General aspects of diabetes mellitus. *Handbook of clinical neurology*, *126*, 211-222. DOI:10.1016/B978-0-444-53480-4.00015-1
4. Bhuyan, P., & Ganguly, M. (2023). In silico Assessment of Dipeptidyl Peptidase 4 (DPP-4) Inhibiting Potential of a few Bioactive Compounds Present in Black Rice Bran for Effective Management of Postprandial Hyperglycemia. DOI:10.21203/rs.3.rs-2407380/v1
5. Holst, J. J., & Deacon, C. F. (2004). Glucagon-like peptide 1 and inhibitors of dipeptidyl peptidase IV in the treatment of type 2 diabetes mellitus. *Current opinion in pharmacology*, *4*(6), 589-596. DOI:10.1016/j.coph.2004.08.005
6. Bhuyan, P., & Ganguly, M. (2023). In silico Assessment of Dipeptidyl Peptidase 4 (DPP-4) Inhibiting Potential of a few Bioactive Compounds Present in Black Rice Bran for Effective Management of Postprandial Hyperglycemia. DOI:10.21203/rs.3.rs-2407380/v1
7. Drucker, D. J. (2006). The biology of incretin hormones. *Cell metabolism*, *3*(3), 153-165. DOI:10.1016/j.cmet.2006.01.004
8. Tomovic, K., Ilic, B. S., Smelcerovic, Z., Miljkovic, M., Yancheva, D., Kojic, M., ... & Smelcerovic, A. (2020). Benzimidazole-based dual dipeptidyl peptidase-4 and xanthine oxidase inhibitors. *Chemico-Biological Interactions*, *315*, 108873. DOI:10.1016/j.cbi.2019.108873
9. Guevara, A. P., Vargas, C., Sakurai, H., Fujiwara, Y., Hashimoto, K., Maoka, T., ... & Nishino, H. (1999). An antitumor promoter from *Moringa oleifera* Lam. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *440*(2), 181-188. DOI:10.1016/S1383-5718(99)00025-X
10. Muhammad, H. I., Asmawi, M. Z., & Khan, N. A. K. (2016). A review of promising phytochemical, nutritional, and glycemic control studies on *Moringa oleifera* Lam. in tropical and subtropical regions. *Asian Pacific Journal of Tropical Biomedicine*, *6*(10), 896-902. DOI:10.1016/j.apjtb.2016.08.006
11. Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B. A., Thiessen, P. A., Yu, B., Zaslavsky, L., Zhang, J., & Bolton, E. E. (2023). PubChem 2023 update. Nucleic Acids Res., 51(D1), D1373–D1380. https://doi.org/10.1093/nar/gkac956
12. Adusei, S., Azupio, S., Emmanuel, T. M., MacCarthy, C., & Akomeng, N. (2022). Phytochemistry, nutritional composition and pharmacological potential of *Moringa oleifera*: A comprehensive review. *International Journal of plant-based pharmaceuticals*, *2*(2), 228-238. DOI:10.29228/ijpbp.5
13. Abd Rani, N. Z., Husain, K., & Kumolosasi, E. (2018). Moringa genus: a review of phytochemistry and pharmacology. *Frontiers in pharmacology*, *9*, 108. DOI;10.3389/fphar.2018.00108
14. Anzano, A., Ammar, M., Papaianni, M., Grauso, L., Sabbah, M., Capparelli, R., & Lanzotti, V. (2021). *Moringa oleifera* lam.: A phytochemical and pharmacological overview. *Horticulturae*, *7*(10), 409. DOI:10.3390/horticulturae7100409
15. Fidrianny, I., Kanapa, I., & Singgih, M. (2021). Phytochemistry and pharmacology of moringa tree: an overview. *Biointerface Res Appl Chem*, *11*(3), 10776-10789. DOI:10.33263/BRIAC113.1077610789
16. Friesner, R. A., Banks, J. L., Murphy, R. B., Halgren, T. A., Klicic, J. J., Mainz, D. T., ... & Shenkin, P. S. (2004). Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *Journal of medicinal chemistry*, *47*(7), 1739-1749.DOI:10.1021/jm0306430
17. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci. Rep. (2017) 7:42717.
18. Banerjee, Priyanka, et al. "ProTox-II: A Webserver for the Prediction of Toxicity of Chemicals." Nucleic Acids Research, vol. 46, no. Web Server issue, 2018, p. W257, https://doi.org/10.1093/nar/gky318. Accessed 25 Aug. 2024.
19. Koopmans, T. (1933). Ordering of wave functions and eigenenergies to the individual electrons of an atom. *Physica*, *1*, 104-113. DOI:10.1016/S0031-8914(34)90011-2
20. Omoboyowa, D. A., Iqbal, M. N., Balogun, T. A., Bodun, D. S., Fatoki, J. O., & Oyeneyin, O. E. (2022). Inhibitory potential of phytochemicals from Chromolaena odorata L. against apoptosis signal-regulatory kinase 1: A computational model against colorectal cancer. *Computational Toxicology*, *23*, 100235. DOI:10.1016/j.comtox.2022.100235
21. Tripathi, S. K., Muttineni, R., & Singh, S. K. (2013). Extra precision docking, free energy calculation, and molecular

dynamics simulation studies of CDK2 inhibitors. *Journal of theoretical biology*, *334*, 87-100. DOI:10.1016/j.jtbi.2013.05.014

22. Finch, A., & Pillans, P. (2014). P-glycoprotein and its role in drug-drug interactions. *Aust Prescr*, *37*(4), 137-139. DOI:10.18773/austprescr.2014.050
23. Kim, M. T., Sedykh, A., Chakravarti, S. K., Saiakhov, R. D., & Zhu, H. (2014). Critical evaluation of human oral bioavailability for pharmaceutical drugs by using various cheminformatics approaches. *Pharmaceutical research*, *31*, 1002-1014. DOI:10.1007/s11095-013-1222-1
24. Erhirhie, E. O., Ihekwereme, C. P., & Ilodigwe, E. E. (2018). Advances in acute toxicity testing: strengths, weaknesses and regulatory acceptance. *Interdisciplinary toxicology*, *11*(1), 5-12. DOI: 10.2478/intox-2018-0001
25. Rath, B., Qais, F. A., Patro, R., Mohapatra, S., & Sharma, T. (2021). Design, synthesis, and molecular modeling studies of novel mesalamine-linked coumarin for treatment of inflammatory bowel disease. *Bioorganic & Medicinal Chemistry Letters*, *41*, 128029. DOI:10.1016/j.bmcl.2021.128029
26. Li, Xiao, Lei Chen, Feixiong Cheng, Zengrui Wu, Hanping Bian, Congying Xu, Weihua Li, Guixia Liu, Xu Shen, and Yun Tang. "In silico prediction of chemical acute oral toxicity using multi-classification methods." *Journal of chemical information and modeling* 54, no. 4 (2014): 1061-1069. DOI: 10.1021/ci5000467
27. Banerjee, P., Eckert, A. O., Schrey, A. K., & Preissner, R. (2018). ProTox-II: a web server for the prediction of toxicity of chemicals. *Nucleic acids research*, *46*(W1), W257-W263. DOI:10.1093/nar/gky318
28. Olugbogi , E. A. O. (2023, April 1). *COMPUTER-BASED SCREENING OF THE ANTICANCER PROPERTY OF SELECTED PANAX GINSENG PHYTO-LIGANDS*. Ijpsr. Retrieved April 5, 2023, from https://ijpsr.com/bft-article/computer-based-screening-of-the-anticancer-property-of-selected-panax-ginseng-phyto-ligands DOI:10.13040/IJPSR.0975-8232.14(3).1714-27