RESEARCH ARTICLE

Potential inhibitors of Dipeptidyl Peptidase IV dependent from Moroccan *phytocompound*: molecular docking, molecular dynamics simulations, and MM-PBSA analyses

[version 1; peer review: 2 approved with reservations]

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Abstract

Type 2 Diabetes Mellitus (T2DM) is the most prevalent form of diabetes and is characterized by beta-cell dysfunction and reduced insulin sensitivity. Dipeptidyl peptidase IV (DPP-IV) has emerged as a pivotal target in the development of antihyperglycemic drugs aimed at improving glycemic control.

Methods

This study aimed to identify potential natural DPP-IV inhibitors through virtual screening of the Moroccan Phytochemical Database (MPDB), using structure-based molecular docking techniques. Phytochemicals were evaluated for their interaction and binding affinity with DPP-IV, and top candidates were selected based on docking scores. Lead compounds were further subjected to molecular dynamics (MD) simulations to examine the stability of their binding within the DPP-IV active site, alongside silico Absorption, Distribution, Metabolism, and Excretion (ADME) analyses to assess their pharmacokinetic profiles.

Results

The findings revealed that Quercitrin and Hesperidin showed greater affinity and stability in interactions with the target enzyme DPP-IV compared to the reference compound Sitagliptin. ADME calculations showed that such phytocompounds showed good pharmacokinetic properties. MD simulations for 150 ns validated that Quercitrin and

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Hesperidin showed sustained stability and good binding energy in the active site of the target enzyme compared to Sitagliptin.

Conclusion

Overall, quercitrin and hesperidin, isolated from Moroccan plants Argania spinosa and Anabasis aretioides, respectively, translate into potential natural DPP-IV inhibitors with antihyperglycemic activities. Their potential therapeutic application towards the control of postprandial blood glucose in the case of individuals suffering from T2DM is reinforced, and the compounds represent a natural option whose pharmacokinetic profile is acceptable.

Keywords
DPP-IV, Sitagliptin, Virtual Screening, Moroccan Phytochemical Database, Molecular Dynamics Simulation, Phytochemicals.

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Introduction

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and insufficient insulin secretion from pancreatic beta cells, which together impair the maintenance of normal blood glucose levels. Diagnosis is typically based on elevated plasma glucose measurements, with risk factors including obesity and excess body fat (Bouyahya *et al.*, 2021; Kelly & Ismail, 2015). Dysregulation in insulin synthesis, release, and detection can cause diabetes and its consequences, including retinopathy, nephropathy, neuropathy, cardiovascular disease, and infertility. (Galicia-Garcia *et al.*, 2020).

The Moroccan government has a comprehensive diabetes prevention and management policy to combat rising diabetes rates. To reduce diabetes-related mortality, this technique includes risk assessment, early screening, and lifestyle adjustment. Similar approaches are seen worldwide, reflecting T2DM's significant incidence. (Bouyahya *et al.*, 2021; Pengpid & Peltzer, 2022).

Existing antidiabetic medications, including Exenatide (a GLP-1 receptor agonist), gliptins (DPP-IV inhibitors), and gliflozins (SGLT2 inhibitors) use different mechanisms to control glucose levels. Among these, DPP-IV inhibition is particularly effective as it prolongs incretin activity, thus promoting insulin secretion in response to glucose elevations (Bohannon, 2009; Paul *et al.*, 2021). DPP-IV, a serine protease encoded by a 70-kb gene on chromosome 2, is critical in glucose metabolism due to its role in degrading incretin hormones such as GLP-1 and GIP, which are involved in regulating insulin biosynthesis. DPP-IV inhibitors, by extending the activity of these hormones, represent an attractive target for antihyperglycemic therapy (Deacon, 2019; Seino *et al.*, 2010). However, common adverse effects associated with synthetic DPP-IV inhibitors, such as hypersensitivity reactions and respiratory infections, highlight the need for alternative therapies with improved safety profiles (Yang *et al.*, 2020).

Natural products, long used for medicinal purposes, provide a promising source of novel therapeutic agents with fewer adverse effects. Identifying natural DPP-IV inhibitors is therefore essential for advancing effective and safer T2DM therapies. The rich biodiversity of Morocco, that offers approximately 5,200 vascular plant species (including 900 endemics), is noted for its exceptional medicinal flora, as over 600 species traditionally used in healthcare (Barkaoui *et al.*, 2017). Of the various classes of phytochemicals, compounds such as flavonoids, phenols, alkaloids, terpenoids, and polypeptides have shown DPP-IV inhibitory potential (Paul *et al.*, 2021).

As illustrated in Figure 1, we use a computational technique based on virtual screening in this investigation to find potential DPP-IV inhibitors. We evaluate the binding affinities of Moroccan phytochemicals that obtained from the Moroccan Phytochemical Database (MPDB) using a crystal structure of DPP-IV from the Protein Data Bank (PDB). The highest-ranking phytochemicals were determined based on binding affinity and root-mean-square deviation (RMSD) and were further validated by molecular dynamic simulations.

Material and methods

1. Protein preparation

The X-ray crystal structure of human DPP-IV in complex with inhibitor sitagliptin was downloaded from the RCSB PDB (ID: 1X70) at a 2.10 Å resolution (https://www.rcsb.org). Remodeling of missing residues of chain A of DPP-IV was done by protein preparation SWISS MODEL (https://swissmodel.expasy.org/) and then unnecessary ligands and water molecules were removed by PyMOL (version 3.1.3) (https://pymol.org/).

2. Phytochemicals preparation

A total of 545 phytochemicals were downloaded from the Moroccan Phytochemical Database (MPDB) (Lamiae *et al.*, 2023). The three-dimensional structures of these phytochemicals were initially obtained in SDF format. Subsequently, these structures were converted into PDB and PDBQT formats utilizing Open Babel software.

3. Actif site identification

To identify the active site, an analysis was performed based on the co-crystallized structure (PDB ID: 1X70) (Kim *et al.*, 2005). The comparison of interaction between DPP-IV and sitagliptin enables us to determine the mechanism of inhibition

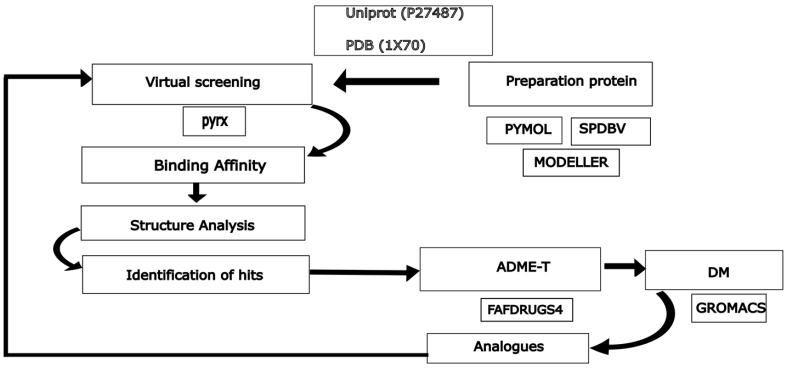

Figure 1. Workflow sums up the methodology prosecuted.

and hence demonstrates that sitagliptin is a prospective inhibitor as a drug in type 2 diabetes. The interaction analysis between DPP-IV and the inhibitor was performed using Ligplot+ (version 2.2) (https://www.ebi.ac.uk/thornton-srv/software/LigPlus/). The amino acid residues involved in the active site of the 1X70 protein were Asn710, Arg125, Tyr662, Glu205, Glu206, Arg358, Ser209, and Ser630.

4. Docking validation

Before starting the virtual screening of phytocompounds, we performed molecular docking between the previously prepared three-dimensional structure of DPP-IV and sitagliptin (PubChem ID: 4369359). This procedure aimed to calculate the binding energy and validate the docking approach by comparing the docking results with the co-crystallized structure (PDB ID: 1X70).

5. Virtual screening

We docked the protein target against Moroccan phytocompounds using the software PyRx version 0.8, based on the incorporation of the free docking tool AutoDock Vina. The docking grid box was defined carefully to cover the active site residues previously identified so that important interactions may be captured. Grid coordinates were set at X = 13.5427, Y = 26.4458, Z = 55.8465, and the box dimensions were set as X = 25.0000, Y = 25.0000, Z = 25.0000 Å, offering enough room for the flexibility of the ligands and precise pose prediction. All the ligands were energy-minimized before docking to optimize their conformations, and the docking procedure used default settings to estimate the binding affinities based on the Vina scores.

6. Structure analysis

We selected the best-docked conformers for interaction analysis, using the LigPlot+ program to identify the binding network and examine the precise chemical interactions between the phytochemicals and the DPP-IV active site.

7. Drug-likeness evaluation

We used the FAF-Drugs4 program to test the drug-likeness of the top phytochemicals from our structural analysis. FAF-Drugs filter compounds based on properties such as molecular weight, hydrogen bond donors/acceptors, and logP values, according to Lipinski's Rule of Five (Lipinski *et al.*, 1997). This guarantees that the selected phytochemicals have advantageous pharmacokinetic characteristics, making them potential therapeutic candidates.

8. Molecular dynamic simulation

The application of molecular dynamics allows proteins-ligand conformation alterations, flexibility, and stability to be explored under physiological settings (Ghahremanian *et al.*, 2022). We runed a 150 ns molecular dynamic simulation among Quercitrin, Sitagliptin, and probable DPP-IV targets. The atoms and molecules were allowed to interact over a pre-determined time, giving an overview of the progress of a dynamic system using GROMACS simulation (version 2023) (https://www.gromacs.org/) and following the GROMACS tutorial (http://www.mdtutorials.com/gmx/) (version 2018). In order to create the DPP-IV topology with pdb2gmx, we relied on ProDRG to create the topology of the ligands quercetin and sitagliptin. We performed system solvation using the SPC216 water model by enclosing them in cubical boxes (2.0 nm^3). The system was then neutralized by adding sodium (Na+) and chloride (Cl-) ions, and energy minimization was carried out to remove steric clashes and relax the system using 50,000 steps of steepest descent with a maximum step size of 0.01 nm, maintaining a tolerance of 1000 kJ mol/nm. Subsequently, the system was equilibrated at 300 K and 1 bar for 100 ps, with the protein-heavy atoms restrained using the position restraints and employing LINCS constraints for all bonds. The position constraint procedure was used for receptors and ligands of each system for 50 ps using isothermal-NVT (Number of atoms, Volume, Temperature) and isobaric-NPT (Number of atoms, Pressure, Temperature) ensembles. After the entire system was subjected to a 150 ns MD simulation, we computed the trajectory files containing the Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), Radius of Gyration (Rg), analysis of the number of hydrogen bonds (H-bonds), solvent-accessible surface area (SASA), and MMPBSA for further analysis (Ahamad *et al.*, 2023; Gogoi & Saikia, 2022). The energy charts and graphs have been defined and illustrated with the XMGrace visualization tool.

Results and discussion

1. Docking validation

The self-docking of Sitagliptin, the bound ligand in the 1X70 crystal structure of DPP-IV, was conducted using optimized docking parameters. The ensuing root mean square deviation (RMSD) among the docked and co-crystallized poses was 0.127 Å, indicating high alignment and reliable docking accuracy. The docking score for Sitagliptin was calculated to be -8.7 kcal/mol, reflecting a strong binding affinity within the active site of DPP-IV. These results validate the accuracy of the docking protocol used in this study.

As shown in Figure 2, the docked pose (green) closely overlaps with the co-crystallized ligand (red), further confirming the robustness of the docking methodology.

2. Virtual screening

Virtual screening is a computational method used to evaluate a large set of compounds against a specific protein target to identify potential lead molecules. In this study, we screened 545 natural compounds from the Moroccan Phytochemical Database against DPP-IV using AutoDock Vina within the PyRx platform. Following docking, 12 compounds were selected based on favorable docking scores, hydrogen-bond interactions, and hydrophobic bonding networks within the DPP-IV active site. These compounds exhibited strong predicted binding affinities, with docking scores ranging from -10.5 kcal/mol to -9.0 kcal/mol, as summarized in Table 1. Each compound displayed an RMSD of 0.0, indicating consistent binding modes within the DPP-IV active site.

For comparison, Sitagliptin, a well-established DPP-IV inhibitor used for its antihyperglycemic effects, was docked using the same protocol. It achieved a docking score of -8.3 kcal/mol

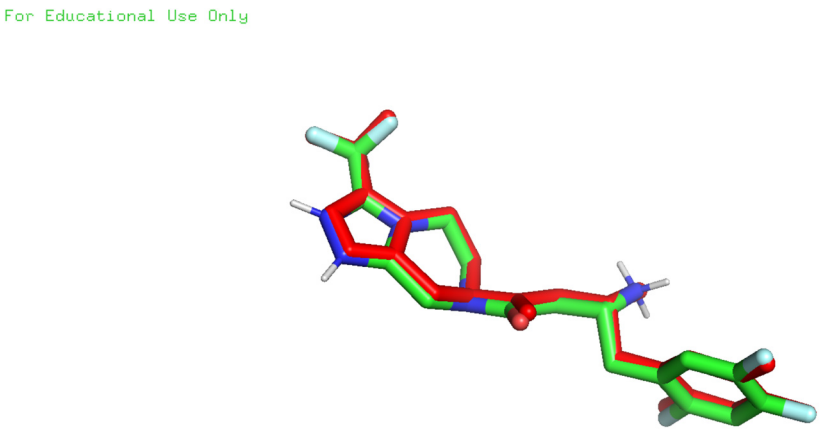

Figure 2. Validation of docking protocol, the docked pose of a co-crystal ligand is shown in green, and the co-crystal ligand is shown in red.

Table 1. Binding affinities of selected hits toward DPP-IV.

Ligand	Compound	Plants	h-bond interaction	Affinity (kcal/mol)
MNPDB00052	Alpha-amyrin	Inula crithmoides	Arg 253	-9.5
MNPDB00092	Citriquinochroman	Ceratonia Siliqua	Arg 61, Trp 157, Lys 463	-10.3
MNPDB00201	3,5-dicaffeoylquinic acid	Inula viscosa	Lys 589, Thr 350, Asp 588, Ser 376, Glu 347, 3Arg 382, Trp 353, 2Gly 355	-9
MNPDB00206	Apigenin 7- O-rutinoside	Adenocarpus anagyrifolius	Tyr 631, Arg 358, Pro 359, Arg 356	-9.5
MNPDB00213	Chrysoeriol 7-O-glucoside, Thermopsoside	Adenocarpus anagyrifolius	2 Arg 40, Leu 504, Arg 560, 2 Met 509	-9.1
MNPDB00216	Cupressuflavone	Tetraclinis articulata	Tyr 457, Arg 356, Arg 382, 2 Ile 407, His 363	-9.4
MNPDB00297	Quercitrin	Argania spinosa	2 Ser 630, Arg 125, His 740, 2 Glu 206, Asp 708	-9.2
MNPDB00349	Apigenin 7-allosyl (1→2) glucoside	Lavandula stoechas	Glu 347, Ser 376, Trp 353, Arg 382, Ser 349, Asp 588, Thr 351	-9.4
MNPDB00351	Apigetrin	Chrysanthemum viscidehirtum	Leu 504, 2 Arg 40, 2 Met 509	-9
MNPDB00443	Hesperidin	Artemisia dracunculus	2Tyr662, 2Arg125, Glu205,2 Glu206, 2Ser209, Ile405,2 Arg669	-10.5
MNPDB00503	Transtaganolide B	Thapsia transtagana	Ser 630, His 740	-9
MNPDB00515	Withanolide J	Withania adpressa Coss.	His 126, 2 Glu 205	-9.5

(Table 2). The stronger predicted binding affinities of the selected phytochemicals relative to Sitagliptin underscore their potential as potent DPP-IV inhibitors. Unlike Sitagliptin, which formed hydrogen bonds with Arg-358, Tyr-547, and Arg-125 (as depicted in Figure 3), Quercitrin and Hesperidin established distinct interactions with key catalytic residues. These distinct interaction patterns do not necessarily indicate reduced

Table 2. Drug references and their binding affinities toward DPP-IV.

ligand	Binding Affinity	h-bond interaction
Sitagliptin	-8,7	Arg 358, Tyr 547, Arg 125

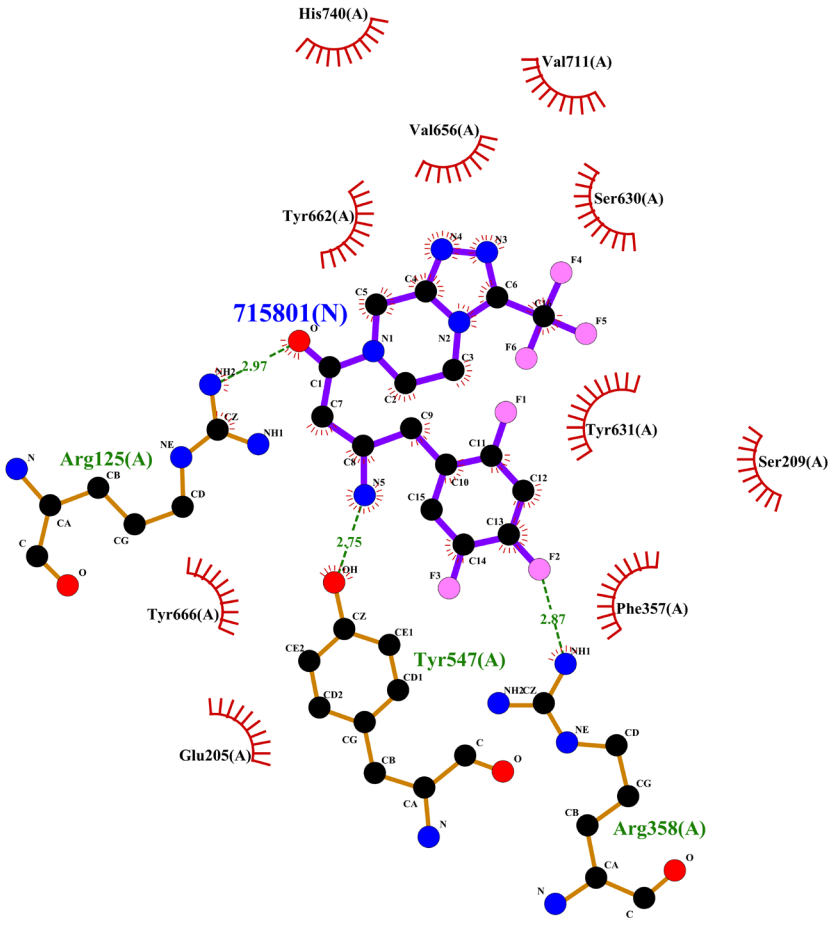

Figure 3. The 2D interaction of dipeptidyl peptidase IV (DPP-IV) with Sitagliptin.

inhibitory potential but rather suggest alternative binding mechanisms that may still interfere with DPP-IV activity. Notably, Glu205 and Glu206 are critical residues for substrate alignment and peptide cleavage, and their interactions with the proposed compounds could contribute to effective inhibition.

Quercitrin (MNPDB00297) and Hesperidin (MNPDB00443), sourced from two endemic Moroccan species (*Argania spinosa* and *Anabasis aretioides*, respectively), emerged as the top candidates (Hebi & Eddouks, 2019). Quercitrin formed hydrogen bonds with Ser630 and His740, located in the enzyme's catalytic α/β-hydrolase region (Oefner *et al.*, 2003). Additionally, it interacted with Glu206 via salt bridges with its amino group and formed hydrogen bonds between its carbonyl oxygen and Arg125. Figure 4 illustrates the 2D and 3D interaction diagrams of quercitrin bound to DPP-IV, revealing these interactions.

Furthermore, Hesperidin generated hydrogen bonds with Glu205 and Glu206, Making salt bridges with the N-terminal amino group of DPP-IV, a typical property of peptide alignment before cleavage (Rasmussen *et al.*, 2003). Hesperidin also interacted with Asn710, Arg125, Ser209, Tyr662, and Arg358, and made a vast array of interactions around the active site. These interactions are depicted in Figure 5, showing 2D and 3D interaction diagrams of Hesperidin bound to DPP-IV.

Our findings support that these phytochemicals bind to DPP-IV efficiently, which may improve GLP-1 and GIP activity and half-life. This mechanism offers the potential for reducing blood glucose levels through DPP-IV inhibition, opening a viable path for the development of natural antidiabetic agents.

3. ADME prediction properties of compounds

The potential of the screened phytocompounds as drug candidates was evaluated based on their physicochemical properties and compliance with Lipinski's Rule of Five (Yang *et al.*, 2020). As summarized in Table 3, Quercitrin and Hesperidin closely aligned with most criteria for drug-likeness. The selected compounds were then subjected to ADME analysis for their pharmacokinetic characteristics using the FAF-Drugs website, which revealed molecules devoid of hazardous patterns. The results demonstrated that Hesperidin violated 3 rules: HBD-HBA, the LogP, and MV which may reduce its likelihood

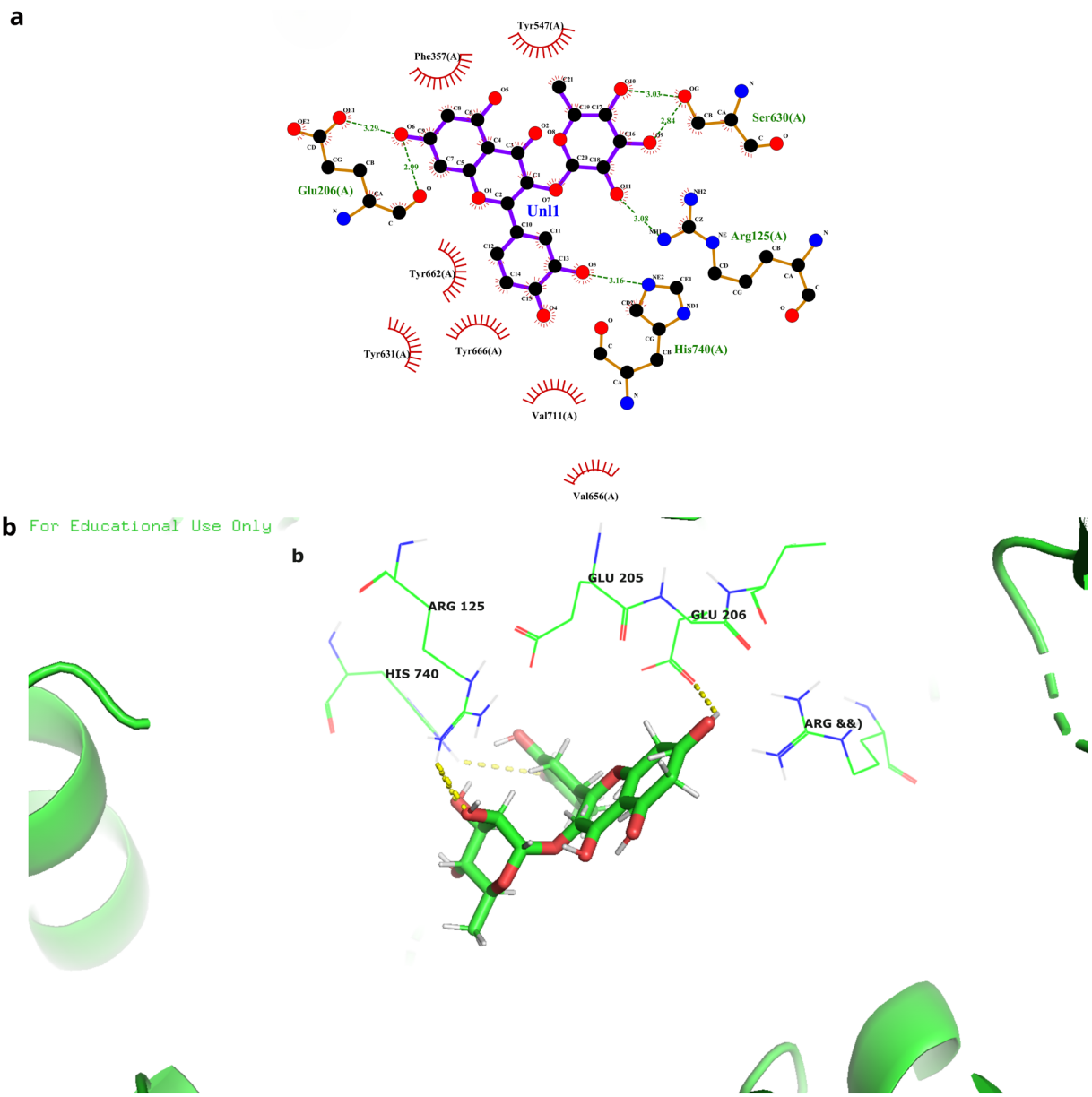

Figure 4. The 2D (**a**) and 3D (**b**) interaction of dipeptidyl peptidase IV (DPP-IV) with Quercitrin.

of being a successful orally active drug. for Quercitrin violated 1 rule: HBD-HBA, while satisfying the other three criteria. Although, this suggests a higher probability for these two compounds to become successful orally active drugs, keep in mind that Lipinski's Rule of Five is a guiding principle, and that there are certain exceptions. While some that fit the criteria may not be effective medications, others may not, even if they don't perfectly follow the standards.

4. Molecular dynamic simulation

Molecular dynamics (MD) simulation, based on Newton's equations of motion, is a powerful tool used to explore atomic-level intermolecular interactions and the dynamic behavior of macromolecules (Shah *et al.*, 2021). We employed MD simulation to investigate the stability of the DPP-IV protein in complex with the phytochemicals Quercitrin and Hesperidin, as well as the reference drug Sitagliptin. The simulations were run for

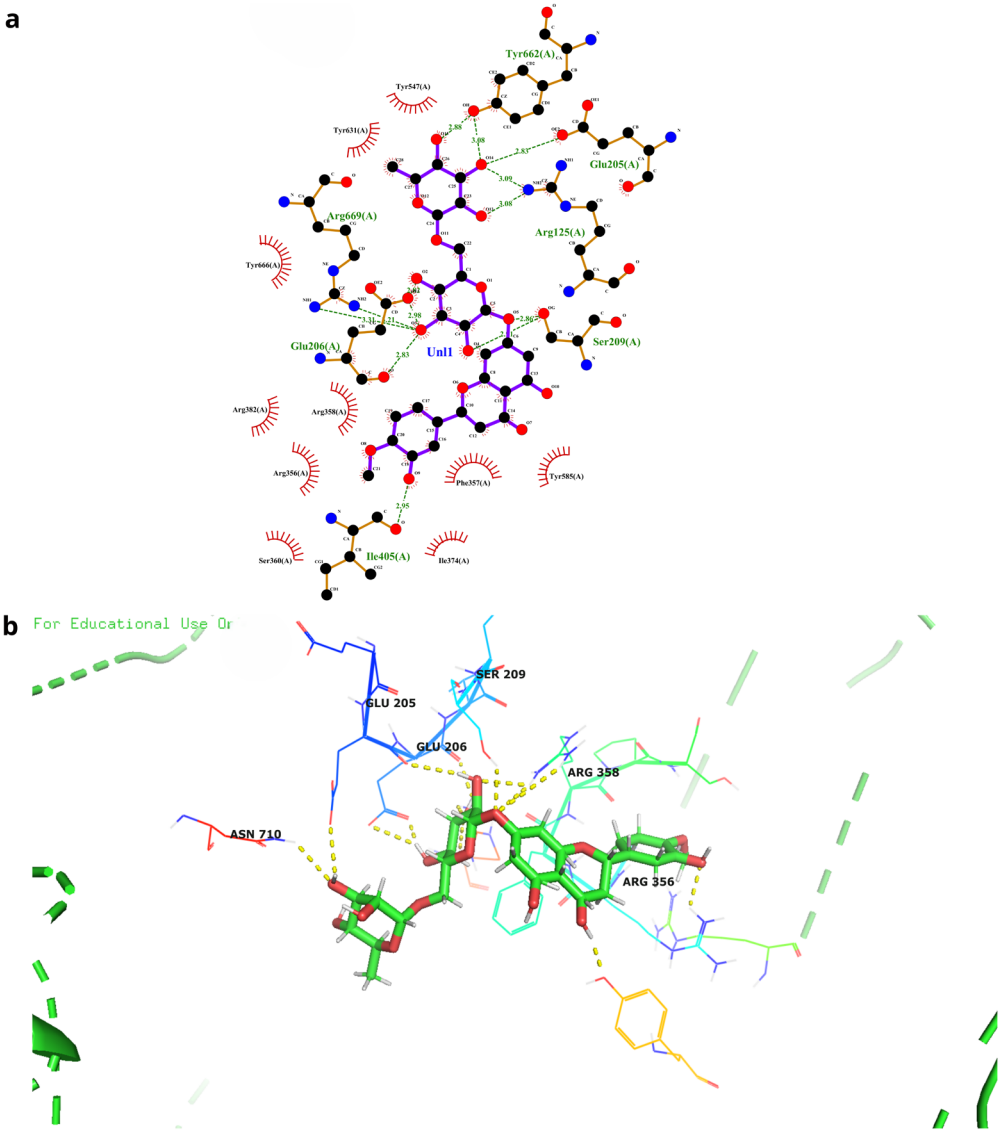

Figure 5. The 2D (**a**) and 3D (**b**) interaction of dipeptidyl peptidase IV (DPP-IV) with Hesperidin.

Table 3. ADME properties of phytocompounds.

Ligand	MV	Log P	HBD-HBA	SolubilityForecastIndex	Oral_ Bioavailability_ VEBER	result
MNPDB00297	448,38	0,86	16	Good Solubility	Good	Accepted
MNPDB00443	610.56	-1,02	23	Good Solubility	Good	Accepted

150 ns, during which we examined root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), hydrogen bonding (H-bonds), solvent-accessible surface area (SASA), and G-MMPBSA to evaluate the stability and dynamic actions of these complexes.

The RMSD calculates the conformational stability of a protein-ligand complex over time (Kufareva & Abagyan, 2011). As shown in Figure 6a, both the Hesperidin and Quercitrin complexes stabilized in around 20 ns, reaching equilibrium around 0.6 nm. This reveals that both phytocompounds achieve

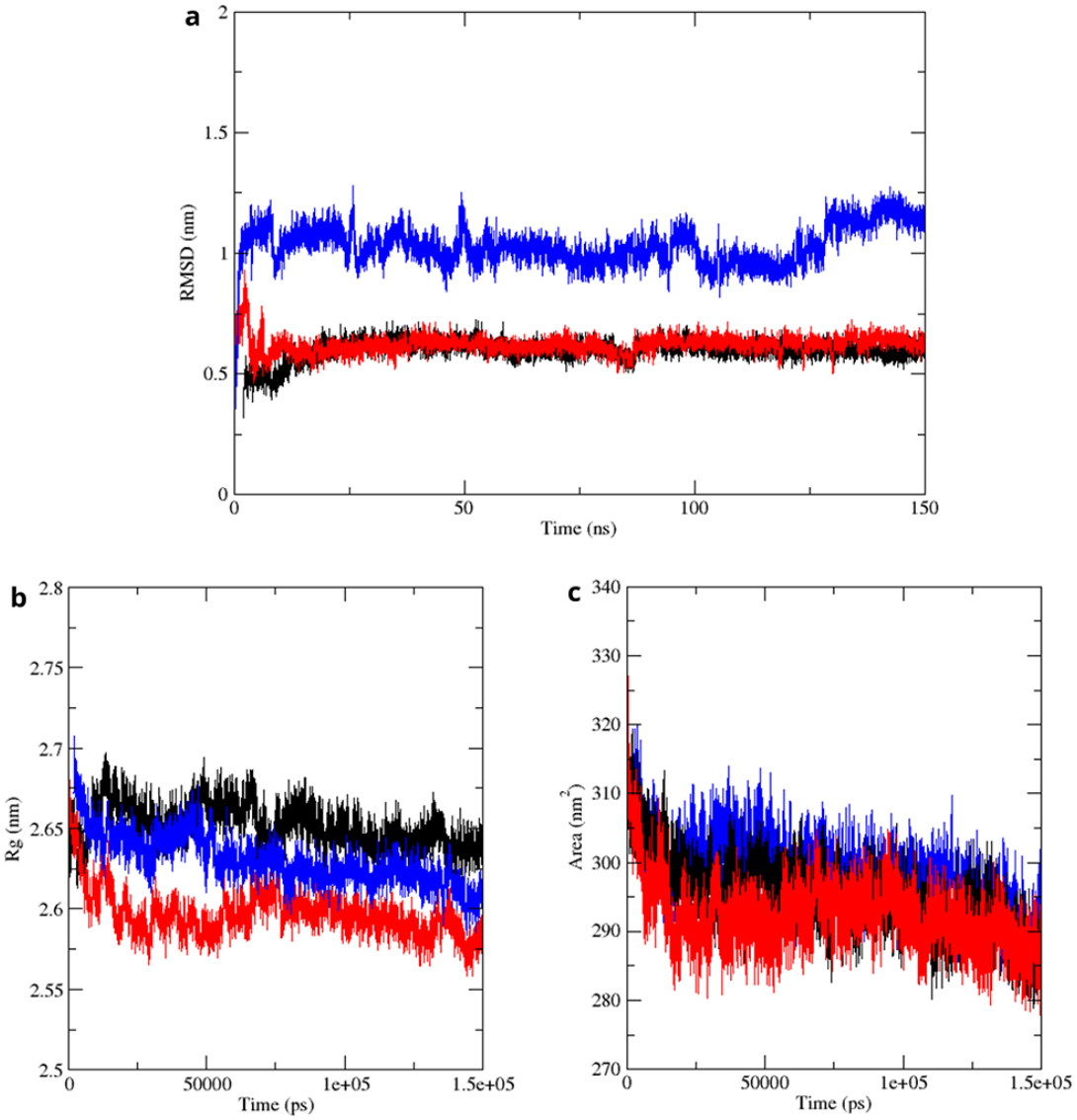

Figure 6. (**a**) RMSD of DPP-IV complexes, (**b**) Radius of gyration plot of Three DPP-IV complexes, and (**c**) Solvent-accessible surface area (SASA) plot of different DPP-IV complexes with color-coded panels. The receptor binds to Sitagliptin is represented in bleu Quercitrin in Black color, and Hesperidin in red color.

stable binding at the active site of DPP-IV following early optimizations of conformation. The Sitagliptin complex, however, displayed more visible oscillations, between 1.0 and 1.4 nm throughout the 150 ns simulation time, indicating reduced stability in binding. The peak in RMSD observed in both Quercitrin and Hesperidin is a result of structural rearrangements occurring in the binding site, showing a need to optimize more and achieve a proper conformation.

Rg (Radius of Gyration) Analysis is a measure of a protein-ligand complex's compactness (Zhao *et al.*, 2021). As we see in Figure 6b, Sitagliptin shows a Rg that is constant around ~2.65 nm, showing a moderate level of compactness and stability, as we would expect considering its potency as a DPP-IV inhibitor. Quercitrin shows slightly higher Rg values (~2.65–2.7 nm), showing less compact and possibly more dynamic receptor structure, likely as a result of weaker binding interactions. Hesperidin induces lowest Rg (~2.55–2.6 nm), showing a most compact and stable receptor-ligand complex, which might correspond to stronger binding and higher stabilization of the receptor. These results show that binding by a ligand significantly impacts a receptor's compactness, with Hesperidin

showing the highest stabilizing impact, followed by Sitagliptin, and with Quercitrin showing the lowest impact.

SASA (Solvent-Accessible Surface Area) quantifies the extent of protein exposure to solvent, which affects protein stability and folding (Nagasundaram *et al.*, 2016). As shown in Figure 6c, SASA analysis showed that the Hesperidin complex had the lowest solvent-exposed surface area (~280–290 nm²) demonstrating the most compact structure with minimal solvent exposure, suggesting strong ligand-induced stabilization, followed by Quercitrin (~290–300 nm²) indicating modest compactness and Sitagliptin (~300–310 nm²) suggesting a less compact and more solvent-exposed structure. The reduced SASA of the Hesperidin complex further supports its stronger binding interactions, likely through better packing within the DPP-IV active site.

RMSF assesses the flexibility of individual amino acid residues during the simulation, providing information on dynamic stability (Shah *et al.*, 2021). Figure 7a shows that while all three complexes exhibited similar fluctuations at the N-terminal and C-terminal regions, the Sitagliptin complex displayed significantly higher RMSF values in the active site, particularly around key residues such as Arg125, Glu205, and Glu206. In contrast, Quercitrin and Hesperidin demonstrated lower RMSF values, with Quercitrin stabilizing Arg125 at 0.13 nm and Hesperidin at 0.16 nm, compared to 0.26 nm for Sitagliptin (Figure 7b). The lower RMSF values for Quercitrin and Hesperidin at residues Glu205 and Glu206 (Figure 7c and 7d) indicate more stable interactions at these catalytic sites, with hydrogen bonding contributing to their stability.

Hydrogen bonds play a critical role in maintaining the stability of protein-ligand complexes. As shown in Figure 8, Quercitrin and Hesperidin each formed an average of five hydrogen bonds with DPP-IV, significantly more than the two hydrogen bonds formed by Sitagliptin. This higher number of H-bonds in the phytochemical complexes suggests stronger and more stable interactions with the protein, contributing to their higher binding affinity.

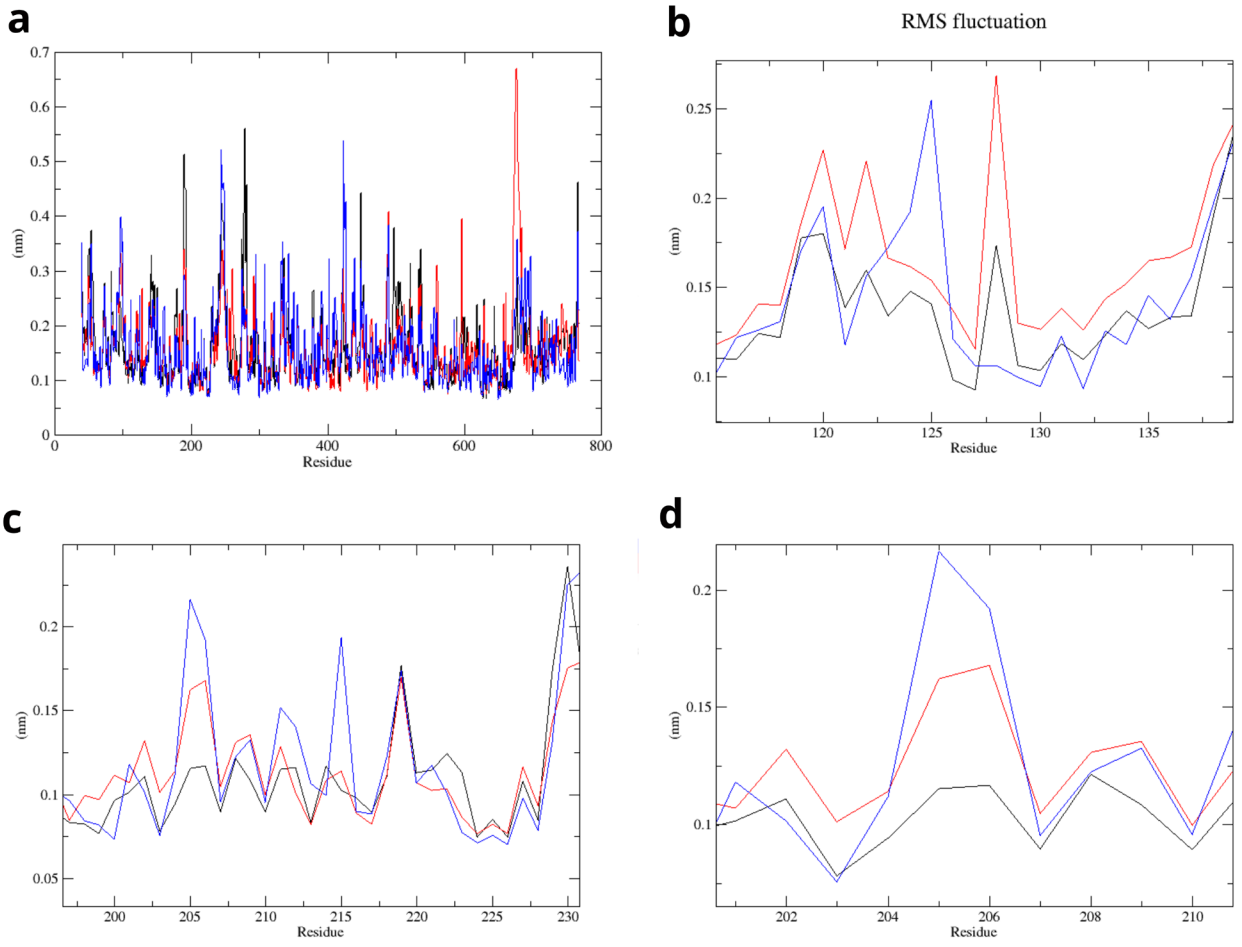

Figure 7. (**a**) 150 ns simulation of Root Mean Square Fluctuation (RMSF) of DPP-IV complexes to Quercitrin, Hesperidin and Sitagliptin. (**b**) fluctuation of Arg125 residue of DPP-IV (**c**) fluctuation of Glu 205 residue of DPP-IV (**d**) fluctuation of Glu206 residue of DPP-IV. The receptor binds to Sitagliptin is represented in bleu Quercitrin in Black color, and Hesperidin in red color.

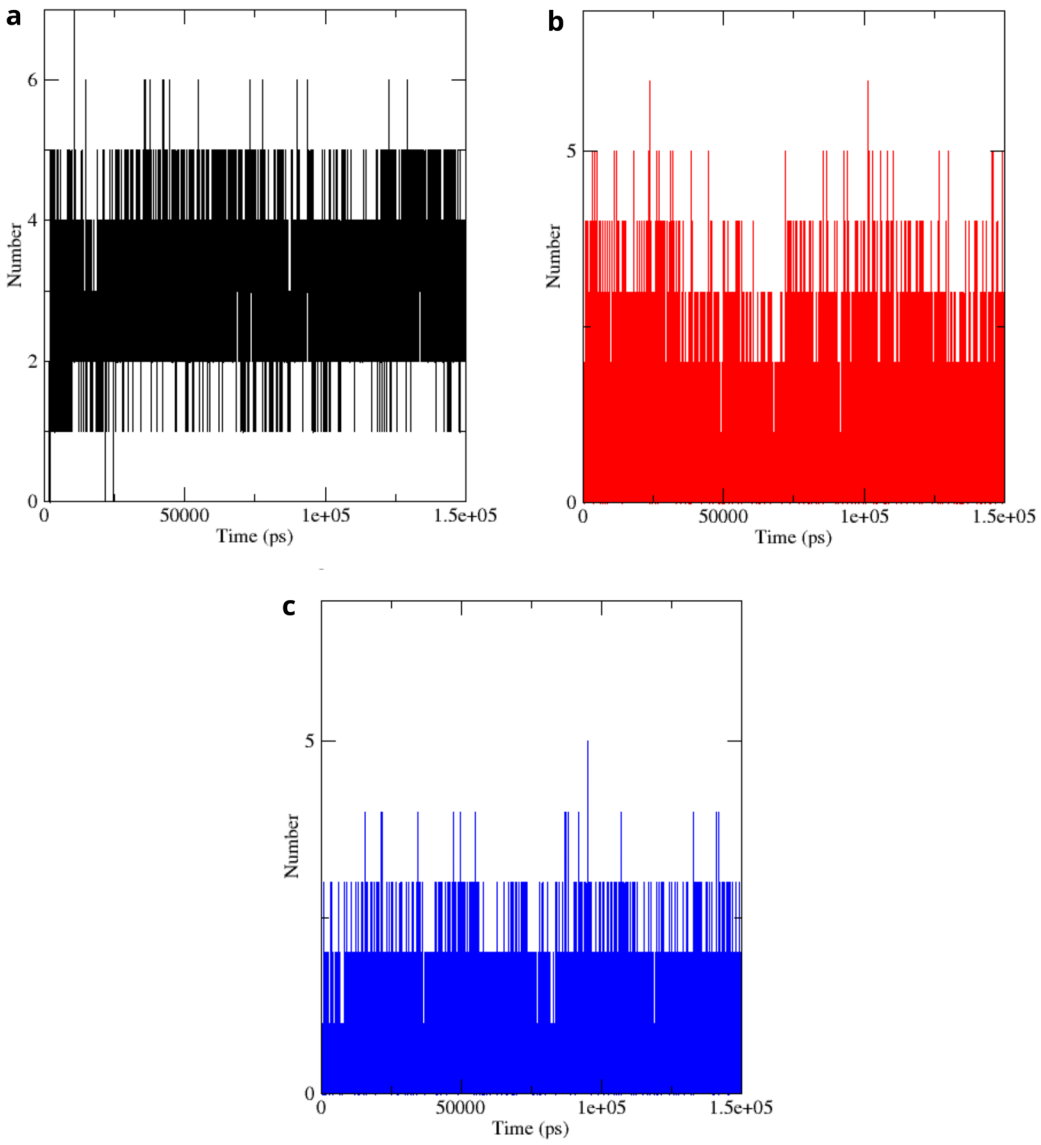

Figure 8. The 2D diagram of 150 ns simulation observed the hydrogen bond for DPPIV- Quercitrin (**a**), DPPIV-Hesperidin (**b**), and DPPIV-Sitagliptin (**C**). The receptor binds to Sitagliptin is represented in bleu Quercitrin in Black color, and Hesperidin in red color.

Overall, the MD simulation results indicate that both Quercitrin and Hesperidin form stable complexes with DPP-IV, characterized by favorable RMSD, RMSF, Rg, SASA, and H-bond interactions. These findings suggest that Quercitrin and Hesperidin exhibit stronger and more stable binding to DPP-IV compared to Sitagliptin, making them promising candidates for DPP-IV inhibition and potential antidiabetic therapy.

Free binding energy

The binding energy analysis of phytochemical interactions with Dipeptidyl Peptidase IV (DPP-IV) revealed that Quercitrin exhibited the strongest binding affinity, with a free binding energy of -203.419 kJ/mol, as presented in Table 4. Both Quercitrin and Hesperidin demonstrated robust interactions with DPP-IV, outperforming the reference drug Sitagliptin, which displayed a lower binding energy of -166.573 kJ/mol. While Quercitrin and Hesperidin had less favorable electrostatic energies compared to Sitagliptin, which recorded the most favorable electrostatic energy at -116.434 kJ/mol, their superior overall binding affinities were driven by other interaction forces. Sitagliptin also exhibited the highest polar solvation energy (196.201 kJ/mol), which significantly exceeded that of Quercitrin (63.810 kJ/mol) and Hesperidin (72.297 kJ/mol). This indicates that Sitagliptin incurs higher energetic costs

Table 4. The mean and standard deviation values of the binding energies for the complexes were computed using the g_mmpbsa method.

Compound name	Binding energy	Electrostatic energy	Polar solvation energy	van der Waal energy	SASA energy
Sitagliptin	-166,573kj/mol	-116,434kJ/mol	196,201 kJ/mol	-212,501kj/mol	-19,499kJ/mol
Quercitrin MNPDB00297	-203,419kJ/mol	-5,322kJ/mol	63,813kJ/mol	-242,411kJ/mol	-19,053kJ/mol
Hesperidin MNPDB00443	-176,454kJ/mol	-8,049kj/mol	72,297kj/mol	-237,168kJ/mol	-18,320kj/mol

in desolvation during binding, contributing to its lower binding affinity compared to the phytochemicals. Van der Waals interactions were most favorable for Quercitrin, with an energy of -242.411 kJ/mol, indicating strong nonpolar interactions with DPP-IV. In comparison, Sitagliptin showed less favorable van der Waals energy, further explaining its reduced binding affinity.

Furthermore, the solvent-accessible surface area (SASA) energy varied slightly between the two phytochemical complexes. Hesperidin reveals a favorable SASA energy of -19.053 kJ/mol, possibly suggesting solvent exposure or minor conformational changes during binding. Sitagliptin, Nevertheless, had less favorable SASA energy, additionally indicates weaker overall binding stability. Quercitrin and Hesperidin, with their stronger van der Waals interactions and good overall binding energies, show promise candidates for further investigation as potential DPP-IV inhibitors. Their binding profiles suggest advantages over Sitagliptin, warranting additional research to explore their therapeutic potential in managing diabetes.

5. Analogs

In this section, we identified analogs of the selected phytochemicals, Quercitrin and Hesperidin, which possess similar physicochemical and biological properties (Pavlović *et al.*, 2022). A total of 600 analogs of Quercitrin were downloaded as 2D structures from Mcule (https://mcule.com/). These structures were then converted into 3D format using Frog, a tool within the FAFDrugs4 platform (https://fafdrugs4.rpbs.univ-paris-diderot.fr/), and subsequently converted from SDF to PDB and PDBQT formats using Open Babel to prepare them for molecular docking.

The molecular docking of these analogs was performed using PyRx software, which allows for flexible docking at the target protein's active site. This flexibility enables a more accurate assessment of binding potential. The selection of the optimal analogues was guided by achieving an RMSD value of 0, demonstrating high binding affinity, and ensuring that the Tanimoto coefficient approaches 1. As presented in Table 5 and Table 6, the top-ranked compounds exhibited significant binding affinities to DPP-IV, highlighting their potential as promising antidiabetic agents.

Table 5. Molecular docking-based virtual screening for Quercitrin analog.

Ligand	Binding Affinity	Tanimoto coefficient
MCULE-1472799470-0	-10.0	0,775
MCULE-2600117901-0	-10.0	0,904
MCULE-3225447479-0	-11.1	0,917
MCULE-3603671410-0	-10.2	0,775
MCULE-4196792859-0	-10.1	0,773
MCULE-4199935049-0	-10.0	0,896
MCULE-5366593054-0	-10.0	0,914
MCULE-5512229078-0	-10.3	0,844
MCULE-5570472394-0	-10.4	0,921
MCULE-6538344932-0	-10.2	0,873
MCULE-8798161238-0	-10.1	0,974
MCULE-8805656232-0	-10.2	0,818
MCULE-9016479238-0	-10.7	0,878
MCULE-9205786266-0	-10.0	0,920
MCULE-9241900907-0	-10.1	0,856
MCULE-9290513099-0	-10.2	0,921

These analogs displayed promising interactions, comparable to or better than the parent compounds, Quercitrin and Hesperidin, suggesting their suitability for further investigation as DPP-IV inhibitors.

Conclusion

In this study, we performed a hierarchical virtual screening of 545 phytochemicals from the Moroccan Phytochemical Database to identify potential DPP-IV inhibitors. Quercitrin and Hesperidin emerged as the top candidates, demonstrating strong binding affinities of -9.2 kcal/mol and -10.5 kcal/mol,

Table 6. Molecular docking-based virtual screening for Hesperidin analog.

Ligand	Binding affinity	Tanimoto coefficient
MCULE-1309363202-0	-10.1	0,794
MCULE-1472799470-0	-10.2	0,806
MCULE-2306135710-0	-10.2	1,000
MCULE-3131534165-0	-10.2	0,806
MCULE-3279420850-0	-10.3	0,965
MCULE-3523854272-0	-10.9	0,814
MCULE-4012809924-0	-10.1	0,991
MCULE-4058220272-0	-10.1	0,976
MCULE-4650430122-0	-10.7	0,965
MCULE-5452697247-0	-10.2	0,965
MCULE-5690233048-0	-10.4	1,000
MCULE-7514536669-0	-10.2	0,991
MCULE-7699014860-0	-10.3	0,991
MCULE-7833385381-0	-10.1	0,900
MCULE-8159571365-0	-10.3	0,982
MCULE-8798216862-0	-10.3	0,965
MCULE-9298480560-0	-10.2	0,976
MCULE-9896770923-0	-10.3	0,923

respectively, outperforming the reference drug Sitagliptin. Further validation through molecular dynamics (MD) simulations confirmed the stability of these compounds in the DPP-IV active site, engaging key residues such as Asn710, Arg125, Glu205, and Ser630. The ADME analysis indicated that despite minor deviations from Lipinski's Rule of Five, Quercitrin and Hesperidin have promising pharmacokinetic properties.

Additionally, the investigation of Quercitrin analogs, sourced from Mcule and screened through molecular docking, revealed several analogs with comparable or superior binding affinities. These analogs further enhance the therapeutic potential of Quercitrin as a lead compound in the development of new DPP-IV inhibitors. Based on these, computational study we aim to follow up with experimental validation, including *in vitro* enzymatic inhibition assays and other relevant biological tests, in future phases of the project. These experiments will serve to confirm the results obtained *in silico* and provide further insights into the activity and mechanism of the identified compounds.

Ethical considerations

Ethical approval and informed consent were not required as this study involved only *in silico* data obtained from publicly available databases.

Data availability

All data underlying the results are available as part of the article and no additional source data is required.

Acknowledgments

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References

Ahamad S, Hema K, Gupta D: **Identification of Novel Tau-Tubulin Kinase 2 Inhibitors Using Computational Approaches.** *ACS Omega.* 2023; **8**(14): 13026–13037.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Barkaoui M, Katiri A, Boubaker H, *et al.*: **Ethnobotanical survey of medicinal plants used in the traditional treatment of diabetes in Chtouka Ait Baha and Tiznit (Western Anti-Atlas), Morocco.** *J Ethnopharmacol.* 2017; **198**: 338–350.
PubMed Abstract | **Publisher Full Text**

Bouyahya A, El Omari N, Elmenyiy N, *et al.*: **Moroccan antidiabetic medicinal plants: ethnobotanical studies, phytochemical bioactive compounds, preclinical investigations, toxicological validations and clinical evidences; challenges, guidance and perspectives for future management of diabetes worldwide.** *Trends Food Sci Technol.* 2021; **115**: 147–254.
Publisher Full Text

Bohannon N: **Overview of the gliptin class (Dipeptidyl Peptidase-4 inhibitors) in clinical practice.** *Postgrad Med.* 2009; **121**(1): 40–45.
PubMed Abstract | **Publisher Full Text**

Deacon CF: **Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes.** *Front Endocrinol (Lausanne).* 2019; **10**: 80.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Galicia-Garcia U, Benito-Vicente A, Jebari S, *et al.*: **Pathophysiology of type 2 diabetes mellitus.** *Int J Mol Sci.* 2020; **21**(17): 6275.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Gogoi B, Saikia SP: **Virtual screening and network pharmacology-based study to explore the pharmacological mechanism of *Clerodendrum* species for anticancer treatment.** *Evid Based Complement Alternat Med.* Edited by M. Bourhia, 2022; **2022**: 3106363.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Ghahremanian S, Rashidi MM, Raeisi K, *et al.*: **Molecular dynamics simulation approach for discovering potential inhibitors against SARS-CoV-2: a structural review.** *J Mol Liq.* 2022; **354**: 118901.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Hebi M, Eddouks M: **Leaf aqueous extract of *Argania Spiniosa* exhibits antihyperglycemic effect in diabetic rats.** *Cardiovasc Hematol Agents Med Chem.* 2019; **17**(1): 64–71.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Kelly SJ, Ismail M: **Stress and type 2 diabetes: a review of how stress contributes to the development of type 2 diabetes.** *Annu Rev Public Health.* 2015; **36**(1): **441–462.**
PubMed Abstract | **Publisher Full Text**

Kim D, Wang L, Beconi M, *et al.*: **(2*R*)-4-Oxo-4-[3-(Trifluoromethyl)-5,6-dihy**

dro[1,2,4]triazolo[4,3- *a*]pyrazin- 7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine: a potent, orally active Dipeptidyl Peptidase IV inhibitor for the treatment of type 2 diabetes. *J Med Chem.* 2005; **48**(1): 141–151.
PubMed Abstract | **Publisher Full Text**

Kufareva I, Abagyan R: **Methods of protein structure comparison**. In: A.J.W. Orry and R. Abagyan (eds.) *Homology Modeling.* Totowa, NJ: Humana Press (Methods in Molecular Biology): 2011; 231–257.
Publisher Full Text

Lamiae E, Salwa Z, Fairouz M, *et al.*: **Data insights from a Moroccan Phytochemical Database (MPDB) derived from aromatic & medicinal plants.** *Bioinformation.* 2023; **19**(12): 1217–1224.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Lipinski CA, Lombardo F, Dominy BW, *et al.*: **Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings.** *Adv Drug Deliv Rev.* 1997; **23**(1–3): 3–25.
Publisher Full Text

Nagasundaram N, Doss GPC, Chakraborty C, *et al.*: **Mechanism of artemisinin resistance for malaria PfATP6 L263 mutations and discovering potential antimalarials: an integrated computational approach.** *Sci Rep.* 2016; **6**(1): 30106.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Oefner C, D'Arcy A, Sweeney AM, *et al.*: **High-resolution structure of human apo dipeptidyl peptidase IV/CD26 and its complex with 1-[({2-[(5-iodopyridin-2-yl)amino]-ethyl}amino)-acetyl]-2-cyano-(*S*)-pyrrolidine.** *Acta Crystallogr D Biol Crystallogr.* 2003; **59**(7): 1206–1212.
Publisher Full Text

Paul RK, Nath V, Kumar V: **Structure based virtual screening of natural compounds and molecular dynamics simulation: Butirosin as Dipeptidyl Peptidase (DPP-IV) inhibitor.** *Biocatal Agric Biotechnol.* 2021; **35**: 102042.
Publisher Full Text

Pavlović N, Milošević N, Đanić M, *et al.*: **Antimetastatic potential of quercetin analogues with improved pharmacokinetic profile: a pharmacoinformatic preliminary study.** *Anticancer Agents Med Chem.* 2022; **22**(7): 1407–1413.
PubMed Abstract | **Publisher Full Text**

Pengpid S, Peltzer K: **Prevalence and correlates of undiagnosed, diagnosed, and total type 2 diabetes among adults in Morocco, 2017.** *Sci Rep.* 2022; **12**(1): 16092.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Rasmussen HB, Branner S, Wiberg FC, *et al.*: **Crystal structure of human Dipeptidyl Peptidase IV/CD26 in complex with a substrate analog.** *Nat Struct Biol.* 2003; **10**(1): 19–25.
PubMed Abstract | **Publisher Full Text**

Seino Y, Fukushima M, Yabe D: **GIP and GLP-1, the two incretin hormones: similarities and differences.** *J Diabetes Investig.* 2010; **1**(1–2): 8–23.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Shah BM, Modi P, Trivedi P: **Pharmacophore- based virtual screening, 3D- QSAR, molecular docking approach for identification of potential Dipeptidyl Peptidase IV inhibitors.** *J Biomol Struct Dyn.* 2021; **39**(6): 2021–2043.
PubMed Abstract | **Publisher Full Text**

Yang Y, Shi CY, Xie J, *et al.*: **Identification of potential Dipeptidyl Peptidase (DPP)-IV inhibitors among *Moringa oleifera* phytochemicals by virtual screening, molecular docking analysis, ADME/T-based prediction, and In Vitro analyses.** *Molecules.* 2020; **25**(1): 189.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Zhao L, Zhang M, Pan F, *et al.*: ***In silico* analysis of novel Dipeptidyl Peptidase-IV inhibitory peptides released from *Macadamia integrifolia* Antimicrobial Protein 2 (MiAMP2) and the possible pathways involved in diabetes protection.** *Curr Res Food Sci.* 2021; **4**: 603–611.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

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Version 1

Reviewer Report 10 March 2026

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- The novelty of the study is not clearly highlighted. The authors should clarify how this work differs from previously reported DPP-IV inhibitor studies.
- The introduction section should include more recent references related to natural DPP-IV inhibitors and computational drug discovery.
- The description of the Moroccan Phytochemical Database and compound selection process needs to be explained more clearly.
- The protein preparation procedure is insufficiently described. Details regarding missing residue modeling and structure validation should be provided.
- The authors should specify how protonation states of the protein were assigned before docking.
- Docking protocol validation using only sitagliptin is not sufficient. Additional known DPP-IV inhibitors should be used for validation.
- The reported RMSD value for docking validation appears unusually low and should be clarified.
- The docking grid box parameters require justification, and a figure showing the docking site would improve clarity.
- The comparison of docking scores with sitagliptin should be interpreted cautiously.
- Ligand efficiency or other normalization metrics should be calculated when comparing ligands of different sizes.
- The ADME analysis is limited and should include additional pharmacokinetic parameters.
- The interpretation of Lipinski rule violations should be reconsidered, particularly for hesperidin.
- The molecular dynamics simulation methodology lacks important details such as force field, time step, and simulation parameters.
- The use of PRODRG for ligand topology generation should be justified or replaced with a more reliable method.
- RMSD results for the sitagliptin complex appear unusually high and should be verified.

- The RMSF analysis requires deeper interpretation related to key catalytic residues.
- Hydrogen bond analysis should include occupancy percentage or statistical evaluation.
- The radius of gyration analysis needs better discussion regarding protein structural stability.
- SASA results should be interpreted more clearly in relation to ligand binding.
- The MM-PBSA calculation protocol should be described in detail.
- The number of frames used for MM-PBSA analysis should be specified.
- The analog screening methodology using Mcule compounds should be explained more clearly.
- Toxicity prediction and safety assessment of the selected compounds are missing.
- The conclusions appear overstated considering the purely computational nature of the study.
- The manuscript requires careful language editing to correct grammatical and formatting issues.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Computational Biology; Bioinformatics, Drug Resistance; Computer-aided drug design.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 28 February 2026

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Chandra Sekhar Tripathy
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The article is well written and described.
1. Kindly check the grammatical errors throughout the manuscript.
2. In material and method section, there spelling error- “3. Actif site identification”.
3. Give citation for the tools used in 5. Virtual screening, 7. Drug-likeness evaluation section of material and method.
4. In molecular dynamics section of material and method in 8. Molecular dynamic simulation; It is stated that, “we relied on ProDRG to create the topology of the ligands quercetin and sitagliptin”. Here the clearance required for the mentioning of “quercetin” before mentioning the optimal docking scores as results. Here also mention the full form of MMPBSA and its requirement. XMGrace visualization tool, give citation.

5. Authors still not clarified regarding, whether the study is continued with crystal structure of DPP-IV, with PDB id 1X70 or with the Remodelled structure of DPP-IV was done
by protein preparation SWISS MODEL.
6. If modelling of the DPP-IV, has been done, then there is no proof of validation of it.
7. In result section, in 4. Molecular dynamic simulation part, in figure 6, 7, and 8 the trajectories of three compounds Sitagliptin is represented in bleu Quercitrin in Black color, and Hesperidin in red color with respect to DPP-IV is shown, but there is no trajectory of DPP-IV self. Kindly give the 150 ns trajectory of DPP-IV in all conformations.

Kindly do the needful
Resubmit after required corrections.

Major revision required.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: BIOINFORMATICS, COMPUTATIONAL DRUG DESIGN

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.