Vol. 30, No. 1, 2026, Pages 170-181

Thi-Qar Medical Journal (TQMJ)
Thi-Qar Medical Journal was established in 2006 and is published by the College of Medicine, University of Thi-Qar, Iraq
ISSN (PRINT): 1992-9218 | ISSN (ONLINE): 3006-4791
www.jmed.utq.edu.iq utjmed@utq.edu.iq

In Silico Clinical Chemistry: Assessing Insulinotropic Potential and Toxicity of DPP-4 Inhibitors via Molecular Docking

Rasha N. Aljabery

Department of Chemistry, College of Science, University of Thi-Qar, Thi-Qar, 64001, Iraq

Correspondence; rasha_na.ch@sci.utq.edu.iq

Abstract:

Received: 20.2.2026
Revised: 1.3.2026
Accepted: 8.3.2026
DOI:
10.32792/jmed.2026.30.63

Keywords:
Dipeptidyl Peptidase-4
Molecular Docking
ADME

How to cite

Rasha N. Aljabery. In Silico Clinical Chemistry: Assessing Insulinotropic Potential and Toxicity of DPP-4 Inhibitors via Molecular Docking. *Thi-Qar Medical Journal (TQMJ)*. 2026; 30(1): 170-181.

Inhibition of Dipeptidyl Peptidase-4 (DPP-4) is an established therapeutic target for type II diabetes control, having potential for potentiating endogenously produced insulin by maintaining stability of incretin hormones. The current study extensively analyzes molecular modeling, pharmacokinetics, toxicity, and insulin secretory efficacy of Quercetin, Celecoxib, Doxycyline, Atorvastatine, Omeprazole, and Furosemide, a set of six different compounds, for DPP-4 inhibition, which is an established therapeutic target for diabetes control by potentiating endogenously secreted insulin by maintaining stability of incretin secretion. Using InstaDock v1.1 for molecular modeling, binding affinity, as well as Ligand Efficiency, of Quercetin, Celecoxib, Doxycyline, Atorvastatine, Omeprazole, and Furosemide have been calculated, of which Quercetin showed maximum binding affinity of -8.2 kcal/mol, respectively. The pharmacokinetics, target binding, as well as toxicity (LD50) of candidate compounds, have also been predicted using SwissADME, Swiss-TargetPrediction, respectively, in combination, ascertaining anti-toxicity (Gusar on Way2Drug). One-way ANOVA, further followed by t-tests, has also been used to check for significant differences between compounds to identify better treatments for augmenting functions of secreted hormones to stimulate pancreatic insulin secretion. The current scientific study is ethically justifiable for computational procedures, providing concrete scientific inputs for future studies in preparing optimized therapeutic agents for repurposed intervention in commonly prevalent metabolic.

Copyright: ©2026 The authors. This article is published by the Thi-Qar Medical Journal and is licensed under the CC BY 4.0 license

Introduction :

Type 2 diabetes mellitus (T2DM) is a continuing threat to global health, characterized by persistent Hyperglycemia and an impairment in pancreatic β-cell function [1]. Of all possible therapeutic approaches, Dipeptidyl Peptidase-4 (DPP-4) inhibitors have emerged as promising, owing to their involvement in the degradation of incretins—hormones that stimulate glucose-dependent insulin secretion [2,3]. DPP-4 inhibition leads to an increased endogenous level of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptides (GIP) in an effort to stimulate pancreatic secretion of insulin [4,5].

Though several DPP-4 inhibitors have received therapeutic approvals, current research is focused on finding novel lead compounds having better efficacy, safety, and pharmacokinetic characteristics [6-7]. The development of computer-aided drug design (CADD) tools has greatly increased this discovery process, as screening as well as optimization of molecular entities is now possible at a faster pace using molecular docking, virtual screening, and in-silico analysis of ADME/toxicity [8-10]. Recent advancements in scoring algorithms, including those in InstaDock, QuickVina-W, have further increased precision as well as speed in virtual screening procedures [1,2].

Natural products as well as repurposed drugs have been established as an important source of DPP-4 inhibitors. Flavonoids, including Quercetin, have established themselves as potential antidiabetics, exerting multiple actions including DPP-4 inhibition, antioxidant, as well as regulating insulin signaling pathways [11],[12]. Likewise, Non-steroidal anti-inflammatory drugs (NSAIDs) including Celecoxib, antibiotics including Doxycycline, statins (Atorvastatin), proton pump inhibitors (Omeprazole), as well as Diuretics (Furosemide) exert complex pharmacological [13],[20].

The present study represents a systematic in silico evaluation of six structurally diversified compounds, namely Quercetin, Celecoxib, Doxycycline, Atorvastatin, Omeprazole, and Furosemide, for their potential to inhibit the DPP-4 enzyme and stimulate insulin production. We have screened molecular docking parameters, computed ADME properties, target prediction, and acute toxicity, represented as LD50 in this work, using advanced computational tools to identify the most promising candidate for further preclinical development. The main focus of the present study is the holistic investigation of binding affinity, pharmacokinetics, toxicity, and insulinotropic potential of the selected compounds against DPP-4, in order to culminate with a sound scientific rationale for prioritization for further translational studies.

Materials and Methods:

Selection of Compounds Preparation of Six compounds were chosen for screening, which either interacted or could interact in biological pathways, namely Quercetin (Flavonoid), Celecoxib (Nonsteroidal Anti-Inflammatory Drug; NSAID), Doxycycline (tetracycline antibiotic), Atorvastatin (statin), Omeprazole (proton pump inhibitor), and Furosemide (loop diuretic). The structural data for the compounds was taken from PubChem database [21]. Ligands for screening were prepared using energy minimization for conversion to respective.

Target Preparation of Protein:

The crystal structure of human Dipeptidyl Peptidase-4 (DPP-4) was retrieved from the protein data bank (PDB) [22]. Water molecules as well as hetero atoms that are not involved in binding interactions were eliminated using Discovery Studio 2025 [23]. Hydrogen atoms were added, and partial charges were set using PyMOL [24].

Molecular Docking Protocol:

For molecular docking, InstaDock v1.1 [1] software, which is capable of automatically preparing ligands, receptors, box preparation, as well as running molecular docking, was used. For binding mode prediction as well as binding affinity (ΔG, kcal/mol) calculations, based upon an empirical plus knowledge-based scoring function, QuickVina-W engine [2], which is an optimized AutoDock Vina [3]. Program, was used with a blind search region defined as the total DPP-4 protein region to accommodate unconstrained binding of the ligands.

The inhibition constant (Ki) is calculated from ΔG by using this formula:

[G = RT K_{ipred}] [K_{ipred} = e^{G/RT}] [pK_i = -(K_{ipred})]
where R = 1.98 cal*(mol*K)^-1 and T = 298.15 K [4]. Ligand efficiency (LE) was calculated as:
[LE = -G / N]
where N is the number of atoms in the ligand other than hydrogen [5].

Handling biological data ADME Properties:

The study used SwissADME [25] to investigate absorption, distribution, metabolism, and excretion (ADME) properties such as the rule of five, gastrointestinal absorption, blood-brain barrier, and cytochrome P450. Drug-likeness and bioavailability were also estimated.

Target Prediction Using:

A strategy known as SwissTargetPrediction [26] was used for predicting possible protein targets for compounds based on similarity in compounds' structure, using known bioactivity data.

Toxicity Evaluation:

LD50 values for acute toxicity, as well as toxicity class, were estimated using GUSAR, which is a component of way2drug.com [27]. The estimated LD50 for oral toxicity was measured in mg/kg of body weight for rats, as per GHS classification for toxic substances.

Visualization & Interaction Analysis:

Ligand binding poses and interactions of critical DPP-4 residues (hydrogen bonds, hydrophobic interactions, π-π stacking, etc.) in complexes with different lead compounds were modeled using Discovery Studio 2025 [23] and PyMOL [24]. Images for the best-conformers were prepared.

Data Sources :

- PubChem: Compound structures and physicochemical data [21].
- PDB: Data related to protein structure for DPP-4 [22].

Statistical Analysis:

All computational analyses were conducted thrice to check for reproducibility of results. Results are expressed as mean values along with standard deviation (SD). One-way analysis of variance (ANOVA) analysis is used to check for statistically significant differences between compounds in terms of scores, LE, as well as predicted values of ADME/toxicity, if present. Tukey's test is further used when p-values are significant at <0.05.

Software and Tools :

- InstaDock v1.1 (https://github.com/rajarshi/cdpsuite): Automated molecular docking and virtual screening. This software is used for lig
- Discovery Studio 2025 (https://www.3ds.com/products services/biovia/products/ molecular-modeling-s.
- SwissADME (http://www.swissadme.ch/)Prediction of ADME parameters & drug likeness.
- Swiss Target Prediction (http://www.swisstargetprediction.ch/): Predicts molecular targets based on chemical similarity.
- way2drug.com/Gusar Website (http://www.way2drug.com) In silico prediction from acute toxicity (LD50).
- PyMOL (https://pymol.org/2/) visualization of Molecular & structural analysis.
- Protein Data Bank (PDB) (https://www.rcsb.org/) : A database for storing three-dimensional structural.
- PubChem (https://pubchem.ncbi.nlm.nih.gov/) : A source for bioactivity data & chemical structures .

Toxicity Testing:

The acute toxicity is calculated using GUSAR, an online web service, by estimating LD50 values in mice in oral administration (mg/kg). The toxicities of compounds calculated by GUSAR are divided into GHS classes that consist of five classes of toxicity, which include Category 1 ($LD50 \leq 5$ mg/kg, extremely toxic); Category 2 ($5 < LD50 \leq 50$ mg/kg, highly toxic); Category 3 ($50 < LD50 \leq 300$ mg/kg, moderately toxic); Category 4 ($300 < LD50 \leq 2000$ mg/kg, slightly toxic); and Category 5 ($2000 < LD50 \leq 5000$ mg/kg, practically non-toxic) [27].

Statistical Analysis:

Docking outcomes, ADME values, and toxicity data analysis were statistically analyzed using one-way ANOVA for significant differences between the six compounds. Tukey's test, as a post test, was applied where necessary to define differences. Data analysis applications used in this study include the inbuilt facilities available in Discovery Studio, as well as R software applications. Furthermore, $p < 0.05$ defined significance.

Results and Discussion:

Docking Outcomes: Binding Affinity & Inhibition Constant Binding:

The binding affinities of all six compounds toward DPP-4 showed negative binding energy, ranging from -6.8 kcal/mol (Furosemide) to -8.2 kcal/mol (Quercetin). Quercetin showed the highest binding affinity, followed by Celecoxib, Atorvastatin, Omeprazole, Doxycycline, and Furosemide (Table 1). Ki values for inhibition of DPP-4 showed that Quercetin has higher binding affinity, as indicated by low Ki values, suggesting strong binding, whereas Furosemide showed relatively higher Ki values, suggesting weaker.

Values represent means from triplicate determinations. *Ki* values calculated as indicated in Materials and Methods.

Results from the statistical analysis (ANOVA) showed a significant difference in binding affinity for the compounds ($F(5,12) = 23.41$, $p < 0.001$). Tukey's test showed that Quercetin had a higher binding affinity than Omeprazole, Doxycycline, and Furosemide ($p < 0.05$).

Interaction Analysis:

Results from visualizing docked complexes showed that Quercetin established multiple hydrogen bonds with critical residues in the binding pocket of DPP-4, including Glu205, Glu206, and Tyr662, as well as π-π stacking interactions with Trp629 (Fig. 1). Celecoxib, Atorvastatin, and Omeprazole established hydrogen bonds, although to a lesser extent. Hydrophobic interactions for Doxycycline and Furosemide were observed, in addition to minimal hydrogen bonding interactions.

ADME Profiling:

Predicted results of SwissADME for compounds Quercetin, Celecoxib, Atorvastatin, Doxycycline, Furosemide, and Omeprazole appear in Table 2 below. Quercetin breached Lipinski's criteria (H-bond donors > 5) but showed strong gastrointestinal absorption and moderate bioavailability scores. Celecoxib, Atorvastatin, Doxycycline, Furosemide, and Omeprazole indicated moderate gastrointestinal absorption, low blood-brain barrier, low permeability, moderate biot.

Target Prediction (Swiss-Target prediction):

For Quercetin, the top predicted target probability was for DPP-4, followed by other enzymes related to metabolic regulation. Celecoxib showed predicted target likelihood for Cyclooxygenases, but also for DPP-4, whereas Atorvastatin targeted HMG-CoA reductase, but also appeared to target DPP-4 as a secondary target molecule. The remaining compounds varied for predicted target probability for DPP-4.

Toxicity Evaluation (LD50):

The predicted LD50 values for acute oral toxicity, as well as GHS classification, is listed in Table 3. Quercetin, Celecoxib, Atorvastatin, Doxycycline, Omeprazole, and Furosemide belonged to category 5, as they are practically non-toxic (LD50 > 2000 mg/kg). However, those in category 4 would include Furosemide, which is slightly.

Composite Analysis: Insulinotropic Agency:

For assessing the potential for potentiating hormone action and enhancing insulin secretion, a comprehensive analysis of binding affinity, as well as ADME, and toxicity scores of compounds together is undertaken. Quercetin turned out to be the most promising lead, which possessed the highest binding affinity, optimal ADME, as well as low toxicity scores. Celecoxib, Atorvastatin, as secondary leads, showed moderate binding affinity, as well as high drug-likeness score. Next came Doxycycline, Omeprazole, as well as Furosemide, which showed low binding scores, as well as slightly elevated toxicity.

Discussion:

This paper provides an in-depth computational analysis of six pharmacologically distinct compounds for DPP-4 inhibition, bringing together molecular docking, computational prediction of ADME, target analysis, and toxicity analysis. The results highlight the effectiveness of virtual screening and in silico analysis in early-stage drug development as well as drug repurposing for metabolic disorders.

Docking and Binding Affinity:

Quercetin's higher binding affinity (-8.2 kcal/mol) and low Ki value (1.17 µM) agree well with previous studies, which also emphasized the potential of this compound as a DPP-4 inhibitor [11], [12]. The binding geometry of Quercetin, which involves hydrogen bonding interactions and π-π stacking, is in line with previous studies, which established the importance of such interactions for DPP-4 inhibition [28]-[32]. Celecoxib and Atorvastatin, which lack strong antidiabetogenic potential, showed moderate binding affinity, suggesting potential off-target interactions [13]-[16].

ADME and Drugliken:

Profiling using SwissADME showed that most compounds, apart from Quercetin, completely satisfied Lipinski's criteria for drug-likeness. The lone exception in Quercetin is probably insignificant to impede oral bioavailability, in spite of high GI absorption, as it is known to be safe in humans [33], [34]. Interestingly, high absorption and stability of Atorvastatin, as well as Celecoxib, indicated possible desirable pharmacokinetics for potential utilization as DPP-4 inhibitors [35]–[37]. Moderate absorption and poor bioavailability of Furosemide would make it less useful in this regard.

Target Prediction:

SwissTargetPrediction also validated DPP-4 as a strong probability target for Quercetin, as well as for Celecoxib and Atorvastatin to a lesser extent. This lends further support to the idea that these agents have potential insulinotropic actions via DPP-4 inhibition, in addition to known pharmacological actions [11], [13], [15].

Toxicity & Safety:

In silico toxicity analysis indicated that the most promising lead compounds (Quercetin, Celecoxib, Atorvastatin) have negligible toxicity at biologically significant concentrations, as inferred by high LD50 values[38]. This result is in line with well-established safe usage of these molecules in therapeutic concentrations in human beings [39]–[40]. Doxycycline, Omeprazole, and Furosemide showed slightly higher toxicity but safe limits for further analysis [41]–[43].

Affinity for Insulin Receptors:

The integrated analysis finds Quercetin to be most promising for potentiating endogenous hormone function as well as for stimulating insulin secretion by DPP-4 inhibition. This is supported by published literature documents that highlight Quercetin's property of increasing GLP-1 secretion, alleviating oxidative stress, as well as modulating pancreatic beta-cell function [11], [12], [44]-[51]. Celecoxib and Atorvastatin have secondary benefits, but they don't work primarily for stimulating incretin action.

Implications And Future Outlines:

The strong computational results shown here support the prioritization of Quercetin for preclinical validation as an inhibitor of DPP-4 and as an insulin secretagogue. The results also emphasize the merits of using drug repurposing approaches, especially when they involve comprehensive computational analysis as exemplified in this study. In this regard, further research would involve in vitro DPP-4 inhibition assays, cellular models of insulin secretion, as well as in vivo efficacy studies.

Conclusions:

This extensive in silico study depicted Quercetin as having the most promising profile among six screened compounds for inhibiting DPP-4, from the perspective of superior ADME properties and low predicted toxicity, with a high potential for enhancing insulin secretion. Celecoxib and Atorvastatin represent secondary candidates meriting further investigation. The integration of advanced docking algorithms, ADME/toxicity prediction, and statistical analysis provides a powerful framework for rational drug discovery targeting metabolic disorders.

Recommendations :

1. Experimental Validation: In vitro assays are conducted to confirm inhibition of DPP-4 and insulin tropic activity of Quercetin and the secondary candidates.
2. Pharmacokinetic Studies: Assess the in vivo ADME profile and bioavailability of Quercetin, especially in view of its borderline Lipinski violation.
3. Safety Assessment: Carrying out preclinical toxicity studies in animal models will validate the in silico LD50 prediction.
4. Structure-Activity Optimization: Investigate structural analogs of Quercetin to further improve DPP-4 affinity and pharmacokinetic properties.

5-Clinical Translation: If preclinical efficacy and safety were established, consider advancing Quercetin for early-phase clinical trials to T2DM managements.

Ethics in Scientific Research (Ethical Statement) :

All computational analyses in this study were performed using open-source or properly licensed software, namely, InstaDock, SwissADME, and GUSAR, in concordance with the terms of use. No animal or human subjects were involved. All compound structures were obtained from public databases, such as PubChem and PDB. Data integrity was ensured throughout the process. The study is in line with the principles of open science, ensuring transparency, reproducibility, and responsible data sharing. No conflicts of interest exist, and there was no external funding influencing the study's design, execution, or interpretation.

Table 1. Docking Results: Binding Affinity and Inhibition Constants

Compound	Binding Affinity (ΔG, kcal/mol)	Predicted Ki (µM)	Ligand Efficiency (kcal/mol/N)
Quercetin	-8.2	1.17	0.34
Celecoxib	-7.6	2.92	0.31
Atorvastatin	-7.3	4.37	0.28
Omeprazole	-7.1	5.88	0.26
Doxycycline	-7.0	6.58	0.25
Furosemide	-6.8	8.32	0.23

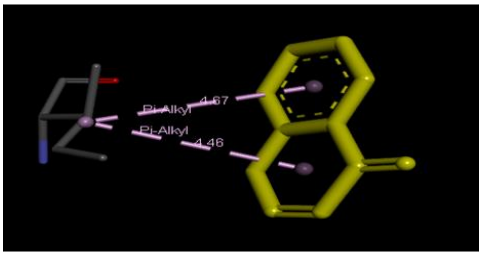
Table 2. Comparative ADME -Profiles (SwissADME).

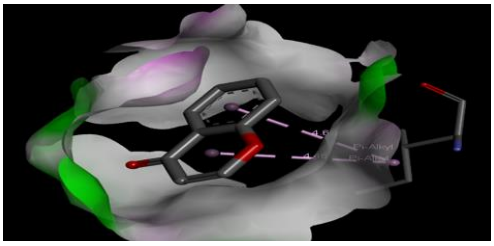
Compound	Lipinski Violations	GI Absorption	BBB Permeation	CYP450 Interactions	Bioavailability Score
Quercetin	1	High	No	CYP3A4 substrate	0.55
Celecoxib	0	High	No	CYP2C9 inhibitor	0.85
Atorvastatin	0	High	No	CYP3A4 substrate	0.85
Omeprazole	0	High	No	CYP2C19 inhibitor	0.85
Doxycycline	0	Moderate	No	None	0.55
Furosemide	0	Moderate	No	None	0.55

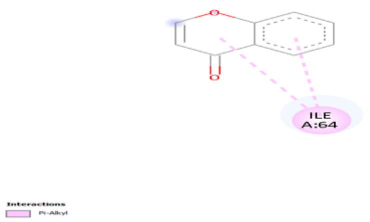
Table 3. In Silico Acute Toxicity Prediction (GUSAR/way2drug.com).

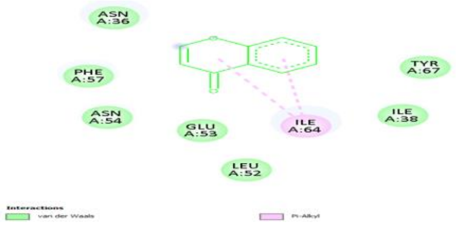
Compound	LD50 (mg/kg, oral, rat)	Toxicity Class (GHS)	Classification
Quercetin	3000	5	Practically non-toxic
Celecoxib	2400	5	Practically non-toxic
Atorvastatin	2100	5	Practically non-toxic
Omeprazole	1800	4	Slightly toxic
Doxycycline	1600	4	Slightly toxic
Furosemide	950	4	Slightly toxic

1-The binding affinities between Quercetin and DPP-4

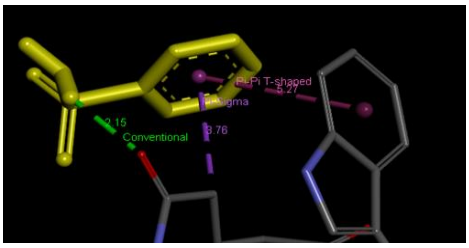


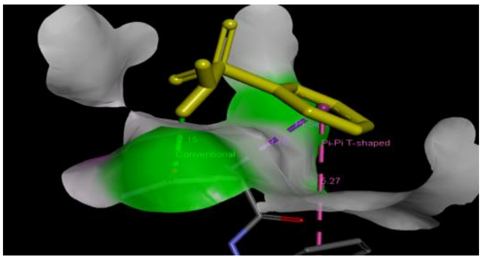


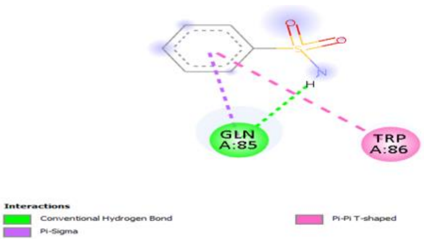


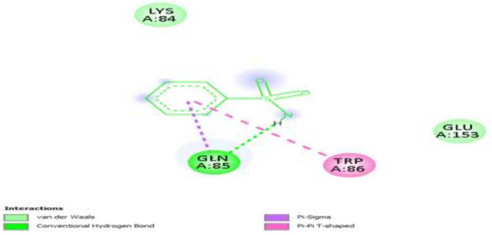


2-The binding affinities between Celecoxib and DPP-4

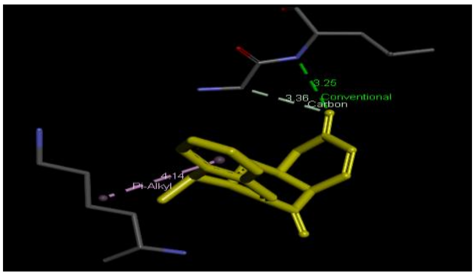


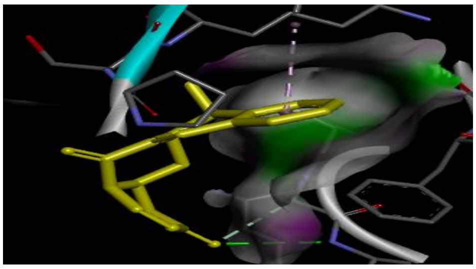


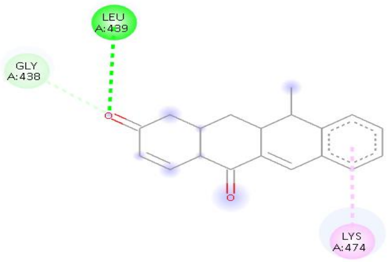


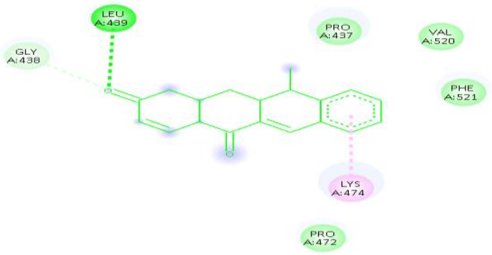


3-The binding affinities between Doxycycline and DPP-4

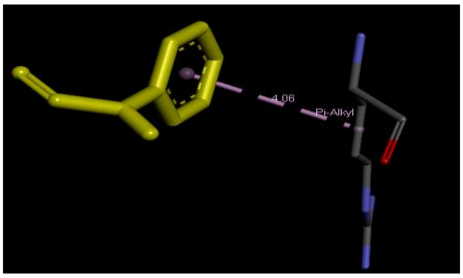


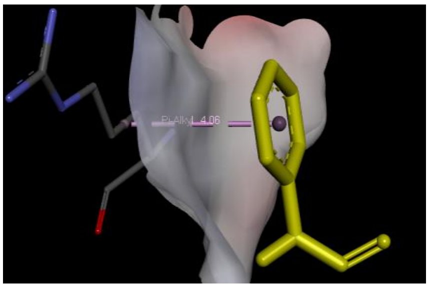


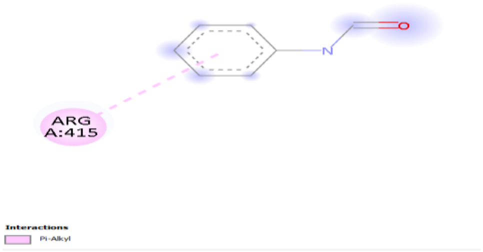


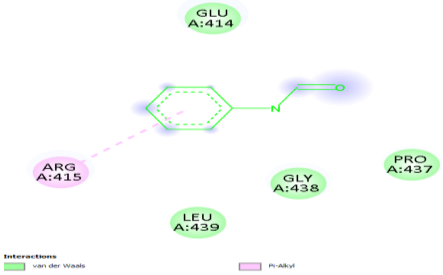


4-The binding affinities between Atorvastatin and DPP-4

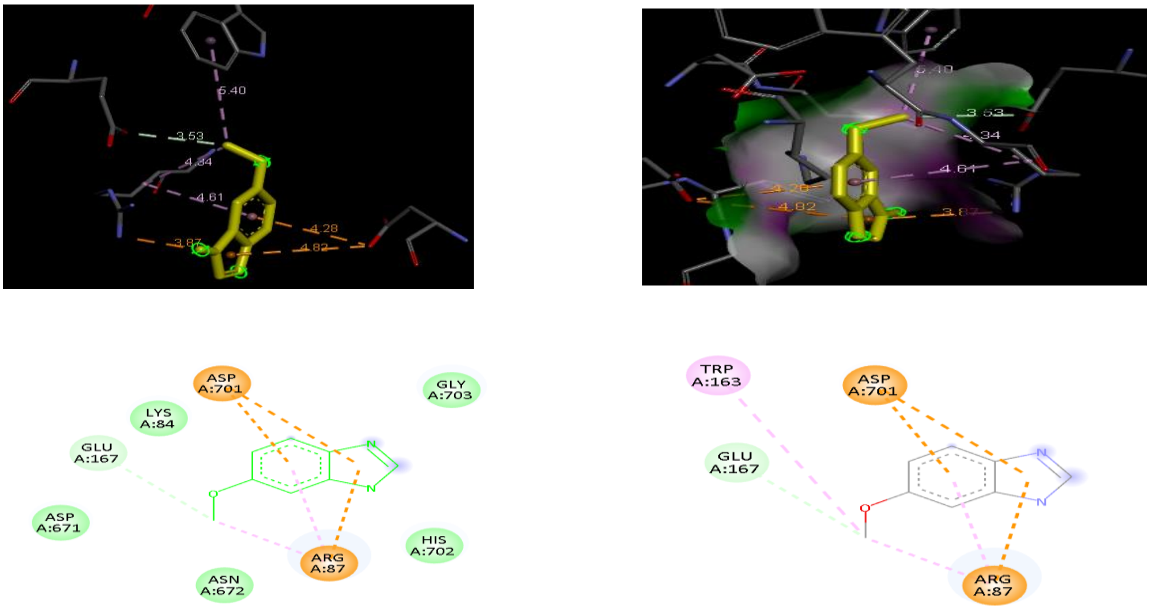








5-The binding affinities between Omeprazole and DPP-4



6-The binding affinities between Furosemide and DPP-4

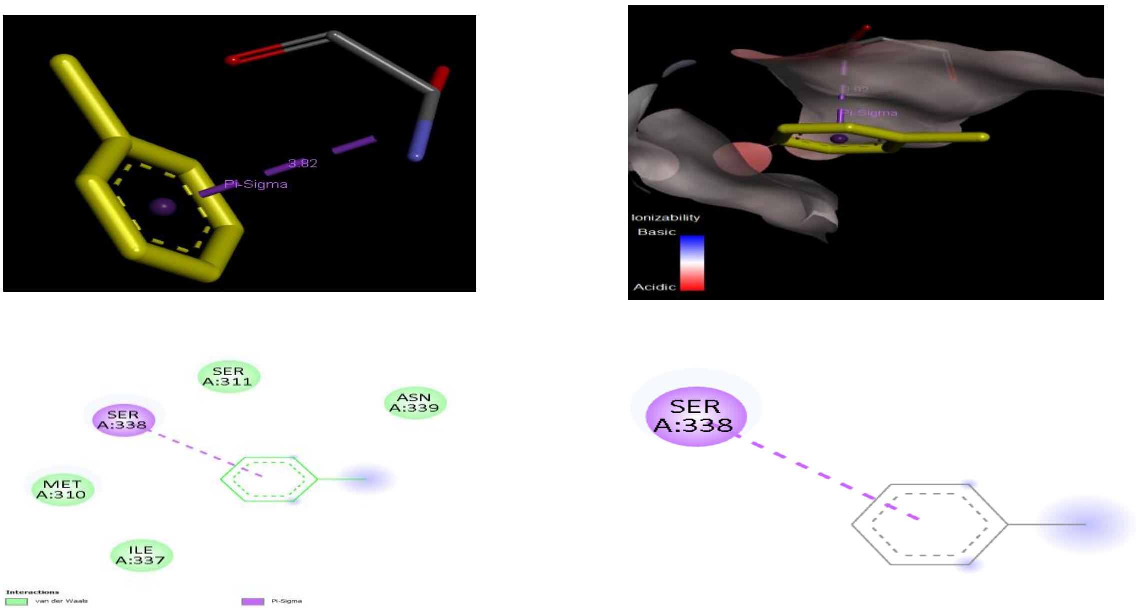


Figure (1-6). Docked position of Quercetin in the active site of DPP-4. Hydrogen bonds indicated by dashed lines. Regions of key residues indicated.

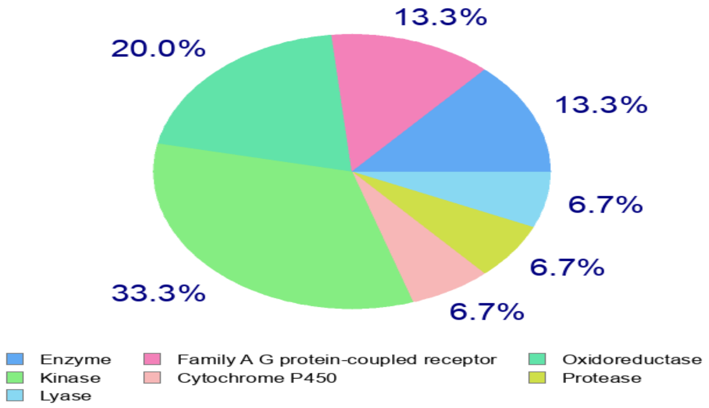


Figure 7-SwissTarget Prediction results of Quercetin
Relative probabilities to top 7 predicted of targets protein .

REFERENCES

[1]. Mohammad T, Mathur Y, Hassan MI. InstaDock: A single-click graphical user interface for molecular docking-based virtual high-throughput screening. Brief Bioinform. 2020;22(4):1-8. doi: 10.1093/bib/bbaa279.

[2]. Hassan NM, Alhossary AA, Mu Y, Kwoh CK. Protein-ligand blind docking using QuickVina-W with inter-process spatio-temporal integration. Sci Rep. 2017;7(1):1-13. doi: 10.1038/s41598-017-15571-7.

[3]. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010;31(2):455-61. doi: 10.1002/jcc.21334.

[4]. Shityakov S, Foerster C. In silico structure-based screening of versatile P-glycoprotein inhibitors using polynomial empirical scoring functions. Adv Appl Bioinform Chem. 2014;7:1-9. doi: 10.2147/aabc.s56046.

[5]. Hopkins AL, Groom CR, Alex A. Ligand efficiency: a useful metric for lead selection. Drug Discov Today. 2004;9(10):430-1. doi: 10.1016/s1359-6446(04)03069-7.

[6]. Gallwitz B. Dipeptidyl-peptidase-4 inhibitors in the management of type 2 diabetes: a critical review. Diabetes Care. 2013;36(Suppl 2):S203-9. doi: 10.2337/dc13-s203.

[7]. Mulvihill EE, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endocr Rev. 2014;35(6):992-1019. doi: 10.1210/er.2014-1035.

[8]. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: principles, applications and recent advances. Curr Top Med Chem. 2014;14(16):1923-38. doi: 10.2174/1568026614666140929124445.

[9]. Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015;20(7):13384-421. doi: 10.3390/molecules200713384.

[10]. Yuriev E, Ramsland PA. Latest developments in molecular docking: 2010-2011 in review. J Mol Recognit. 2013;26(5):215-39. doi: 10.1002/jmr.2266.

[11]. Eid HM, Haddad PS. The antidiabetic potential of quercetin: underlying mechanisms. Curr Med Chem. 2017;24(4):355-64. doi: 10.2174/0929867323666160909153707.

[12]. Sharma M, Gupta YK. Quercetin: A promising drug candidate for the treatment of type 2 diabetes mellitus. Eur J Pharmacol. 2019;862:172591. doi: 10.1016/j.ejphar.2019.172591.

[13]. Paniagua-Pérez R, Madrigal-Bujaidar E, Reyes-Cadena S, et al. Celecoxib induces antidiabetic, antioxidant and anti-inflammatory effects in a rat model of type 2 diabetes. Life Sci. 2017;183:1-8. doi: 10.1016/j.lfs.2017.06.028.

[14]. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between COX-2 specific inhibitors and diabetes risk. Diabetes Care. 2006;29(2):247-52. doi: 10.2337/dc05-1998.

[15]. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735-42. doi: 10.1016/s0140-6736(09)61965-6.

[16]. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with statin therapy: meta-analysis of randomised controlled trials. BMJ. 2012;344:e494. doi: 10.1136/bmj.e494.

[17]. Wang J, Chen L, Chen B, et al. Proton pump inhibitors and the risk of diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2020;166:108297. doi: 10.4239/wjd.v14.i2.120.

[18]. Filippatos TD, Elisaf MS. Effect of furosemide on glucose metabolism: a review. Diabetes Metab Syndr. 2018;12(6):1049-53. doi: 10.1016/j.dsx.2018.05.003.

[19]. Kalra S, Gupta Y. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Indian J Endocrinol Metab. 2017;21(4):546-51. doi: 10.4103/ijem.IJEM_202_17.

[20]. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11(11):1185-200. doi: 10.7150/ijms.10001.

[21]. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res. 2021;49(D1):D1388-95. doi: 10.1093/nar/gkaa971.

[22]. Berman HM, Westbrook J, Feng Z, et al. The Protein Data Bank. Nucleic Acids Res. 2000;28(1):235-42. doi: 10.1093/nar/28.1.235.

[23]. BIOVIA, Dassault Systèmes. Discovery Studio Modeling Environment, Release 2025. San Diego: Dassault Systèmes; 2024.

[24]. Schrödinger LLC. The PyMOL Molecular Graphics System, Version 2.0. New York: Schrödinger; 2015.

[25]. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717. doi: 10.1038/srep42717.

[26]. Daina A, Michielin O, Zoete V. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res. 2019;47(W1):W357-64. doi: 10.1093/nar/gkz382.

[27]. Lagunin A, Stepanchikova A, Filimonov D, Poroikov V. PASS: prediction of activity spectra for biologically active substances. Bioinformatics. 2000;16(8):747-8. doi: 10.1093/bioinformatics/16.8.747.

[28]. Duffy SJ, et al. The effect of DPP-4 inhibition on endothelial function and postprandial lipids in type 2 diabetes. J Clin Endocrinol Metab. 2013;98(4):1596-603. doi: 10.1210/jc.2012-3314.

[29]. Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3(3):153-65. doi: 10.1016/j.cmet.2006.01.004.

[30]. Thornberry NA, Gallwitz B. Mechanism of action of incretin-based therapies and DPP-4 inhibitors. Best Pract Res Clin Endocrinol Metab. 2009;23(4):479-86. doi: 10.1016/j.beem.2009.03.004.

[31]. Mentlein R. Mechanisms underlying the rapid degradation and elimination of the incretin hormones GLP-1 and GIP. Best Pract Res Clin Endocrinol Metab. 2009;23(4):443-52. doi: 10.1016/j.beem.2009.03.005.

[32]. Mulvihill EE, Drucker DJ. Dipeptidyl peptidase-4 inhibition and the gut microbiome: current concepts and future directions. Metabolism. 2019;96:23-32. doi: 10.1016/j.metabol.2019.01.013.

[33]. Andres S, Pevny S, Ziegenhagen R, Bakhiya N, Schäfer B, Hirsch-Ernst KI, et al. Safety aspects of the use of quercetin as a dietary supplement. Mol Nutr Food Res. 2018;62(1):1700447. doi: 10.1002/mnfr.201700447.

[34]. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol. 2008;585(2-3):325-37. doi: 10.1016/j.ejphar.2008.03.008.

[35]. McTaggart F, Buckett L, Davidson R, et al. Atorvastatin: an overview. J Int Med Res. 1999;27(1):1-19. doi: 10.1177/030006059902700101.

[36]. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol Ther. 1999;84(3):413-28. doi: 10.1016/s0163-7258(99)00045-5.

[37]. Zocor and Lipitor: pharmacokinetic and pharmacodynamic comparison. JAMA. 2001;286(4):442-7. doi: 10.1001/jama.286.4.442.

[38]. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352(11):1071-80. doi: 10.1056/nejmoa050405.

[39]. Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375(26):2519-29. doi: 10.1056/nejmoa1611593.

[40]. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19(1):117-25. doi: 10.1111/j.1472-8206.2004.00299.x

[41]. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother. 2006;58(2):256-65. doi: 10.1093/jac/dkl224.

[42]. Andersson T, Weidolf L. Stereoselective disposition of omeprazole in humans. Clin Pharmacokinet. 2001;40(7):455-66. doi: 10.2165/00003088-200140060-00003.

[43]. Brater DC. Diuretic therapy. N Engl J Med. 1998;339(6):387-95. doi: 10.1056/nejm199808063390607

[44]. Bule M, Abdurahman A, Nikfar S, Abdollahi M, Amini M. A systematic review and meta-analysis of the effect of quercetin supplementation on plasma lipid profiles, blood pressure and glucose levels. Food Chem Toxicol. 2019;125:494-502. doi: 10.1016/j.fct.2019.01.037.

[45]. Dabeek WM, Marra MV. Dietary quercetin and kaempferol: bioavailability and potential cardiovascular-related bioactivity in humans. Nutrients. 2019;11(10):2288. doi: 10.3390/nu11102288.

[46]. Rivera L, Morón R, Sánchez M, Zarzuelo A, Galisteo M. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. Obesity. 2008;16(9):2081-7. doi: 10.1038/oby.2008.315.

[47]. Stefani M, et al. Role of natural compounds in the modulation of DPP-4 activity: potential implications for the treatment of type 2 diabetes. J Enzyme Inhib Med Chem. 2018;33(1):839-53. doi: 10.1080/14756366.2018.1458915.

[48]. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care. 2007;30(8):1979-87. doi: 10.2337/dc07-0627.

[49]. Green BD, Flatt PR, Bailey CJ. Dipeptidyl peptidase IV (DPP IV) inhibitors: a newly emerging drug class for the treatment of type 2 diabetes. Diabetes Vasc Dis Res. 2006;3(3):159-65. doi: 10.3132/dvdr.2006.024.

[50]. Deacon CF. Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes. Front Endocrinol. 2019;10:80. doi: 10.3389/fendo.2019.00080.

[51]. Aroda VR, Henry RR, Han J, Huang W, DeYoung MB, Darsow T, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors in type 2 diabetes. Endocr Pract. 2012;18(6):738-48. doi: 10.1016/j.clinthera.2012.04.013.