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Comparative computer-based docking analysis of quercetin targeting protein tyrosine phosphatase 1B as a potential antidiabetic agent

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Abstract

Protein tyrosine phosphatase 1B (PTP1B) is a key negative regulator of insulin signaling and represents an attractive therapeutic target for type 2 diabetes. In this study, the binding potential of quercetin, a natural flavonoid, toward PTP1B was evaluated using molecular docking. A precisely defined grid box encompassing the catalytic pocket ensured accurate exploration of ligand conformations. Docking simulations using Auto Dock Vina identified a top-ranked binding pose with a binding affinity of −7.2 kcal/mol, supported by RMSD values of 0 Å, indicating a highly stable and well-converged orientation. Quercetin formed multiple hydrogen bonds with essential residues (ARG112, GLN123, THR154, SER151, ARG156), along with hydrophobic interactions involving ILE149 and VAL113. A significant π–cation interaction with HIS175 further contributed to ligand stabilization within the catalytic site. These interactions collectively highlight quercetin's strong binding complementarity and support its potential as a PTP1B inhibitor. The findings align with previous reports demonstrating quercetin's role in improving insulin sensitivity. Overall, the computational results suggest that quercetin may serve as a promising natural inhibitor of PTP1B; however, further experimental validation is necessary to confirm its therapeutic relevance.

Keywords: Quercetin; Protein Tyrosine Phosphatase 1b; Molecular Docking; Diabetes Mellitus; PYRX

1. Introduction

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonol and one of the six subclasses of flavonoids. It is moderately soluble in alcohol and lipids, insoluble in cold water, and poorly soluble in hot water [1]. Quercetin is the most abundant flavonoid in nature, widely distributed throughout the plant kingdom, and is recognized as one of the most important plant-derived antioxidants [2,3]. It is present in a variety of foods, including *Morus alba (Moraceae), Camellia sinensis (Theaceae), Allium fistulosum (Amaryllidaceae), Centella asiatica (Apiaceae), Moringa oleifera (Moringaceae), Hypericum perforatum (Hypericaceae), Brassica oleracea varieties (Brassicaceae), Apium graveolens (Apiaceae), Coriandrum sativum (Apiaceae), Allium cepa (Liliaceae), Lactuca sativa (Asteraceae), Prunus domestica and Prunus avium (Rosaceae), Vaccinium oxycoccus (Ericaceae), Solanum lycopersicum (Solanaceae), Vitis vinifera (Vitaceae), Ginkgo biloba (Ginkgoaceae), and Sambucus canadensis (Adoxacea*e). It may also occur as glycones or carbohydrate conjugates [4-7].

Quercetin exhibits diverse pharmacological activities, including anti-inflammatory, anticancer, anti-allergic, cardiovascular-protective, antiviral, anti-tumor, antidiabetic, antihypertensive, immunomodulatory, and gastroprotective effects [7–9]. The most common derivatives of quercetin include ethers and glycosides, such as quercetin 3-O-glycoside, quercetin 3-sulfate, quercetin 3-glucuronide, and quercetin 3′-methyl ether. Despite its broad pharmacological potential, the clinical application of quercetin is limited by extensive first-pass metabolism, poor water

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solubility, and consequently low bioavailability [7]. Quercetin, a widely occurring dietary flavanol, has shown significant antidiabetic potential in previous studies, though its structural interactions with PTP1B remain underexplored.

Diabetes mellitus is a chronic metabolic disorder resulting from either insufficient insulin production by the pancreas or the body's inability to effectively utilize produced insulin [8]. It represents a major global health challenge, affecting individuals across all age groups [1]. According to the International Diabetes Federation, approximately 589 million adults currently live with diabetes worldwide, and this number is projected to rise to 853 million by 2050 [9]. Insulin is a key hormone that facilitates glucose uptake and storage in tissues such as the liver, adipose tissue, and skeletal muscle [10]. Deficiencies in insulin secretion or action led to the various manifestations of diabetes mellitus, whose etiology is complex and influenced by both genetic and environmental factors [11].

Protein tyrosine phosphatases (PTPs) play a critical role in the regulation of insulin receptor signaling by removing phosphate groups from tyrosine residues within the receptor's regulatory domain, resulting in receptor inactivation [12]. Protein tyrosine phosphorylation is mediated by protein tyrosine kinases (PTKs), whereas dephosphorylation is carried out by PTPs. Among PTPs, Protein Tyrosine Phosphatase 1B (PTP1B) was the first member to be purified and characterized and has been extensively studied for its role in insulin resistance and diabetes [13].

In modern drug discovery, computational techniques—including bioinformatics tools and molecular databases—are widely employed to identify potential therapeutic candidates based on efficacy and safety profiles and to facilitate their advancement toward clinical evaluation [14,15]. Among these approaches, molecular docking is one of the most widely used methods in structure-based drug design. It predicts the binding affinity and orientation of small molecules to specific target sites, thereby aiding in the identification of compounds capable of modulating target protein functions [16,17]. Docking studies are particularly valuable for predicting receptor–ligand interactions, where the receptor is typically a protein or nucleic acid, and the ligand is a small molecule or peptide.

Given the pharmacological relevance of quercetin and the therapeutic importance of PTP1B in diabetes, the present study aims to investigate the potential of quercetin as a PTP1B inhibitor through in silico molecular docking analysis, focusing on binding affinity, catalytic pocket interactions, and structural orientation within the active site.

2. Materials and Methods

2.1. Protein Preparation

The 3D crystal structure of PTP1B (PDB ID: 1Q1M) was downloaded from the RCSB PDB. Water molecules, heteroatoms, and non-essential ligands were removed in Discovery Studio. Hydrogen atoms were added, and the structure was subjected to energy minimization using the CHARMM force field [18,21,22].

2.2. Ligand Preparation

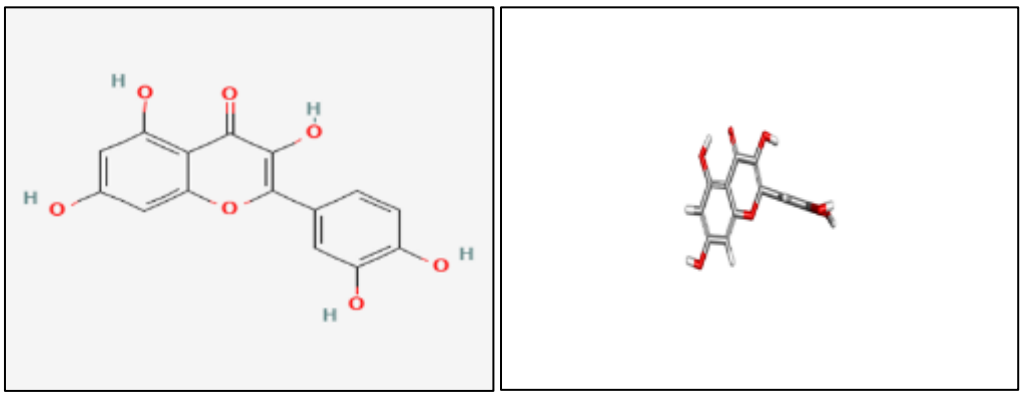

Figure 1 (a) 2D structure of Quercetin; (b) 3D structure of Quercetin

Quercetin (PubChem CID: 5280343) was retrieved in SDF format and converted to a 3D conformer using Open Babel (Figure 1). Energy minimization was performed using the UFF force field, and the ligand was saved as PDBQT for docking [18,19,21].

2.3. Docking Grid Box Preparation

A three-dimensional grid box was generated to define the docking search space around the active site region (Figure 2). The grid box was centered at X = 368.935, Y = 297.736, and Z = 325.507, ensuring accurate targeting of the catalytic pocket. The dimensions of the search box were set to 53.571 Å (X), 62.796 Å (Y), and 42.066 Å (Z) to fully cover the binding pocket and surrounding functional residues [19,20,23]. This configuration ensured sufficient conformational freedom for the ligand during docking and efficient exploration of all potential orientations and interactions.

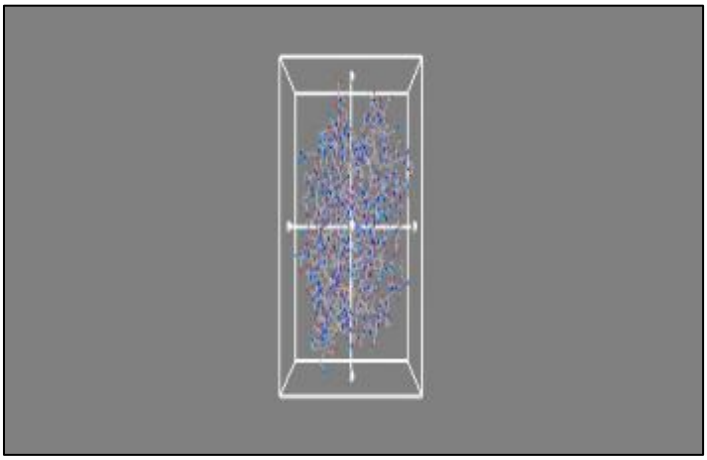

Figure 2 3D representation of the docking grid box (white) encompassing the active site of the protein, used for molecular docking simulations with the ligand

2.4. Active Site Identification

The catalytic binding pocket of PTP1B was identified using Discovery Studio, guided by previously reported active-site residues, including ARG112, GLN123, ARG156, THR154, SER151, and HIS175 [20,21,24]. This information was used to accurately define the functional region of the protein for subsequent docking simulations, ensuring that the ligand would be positioned within the biologically relevant catalytic site

2.5. Molecular Docking

Molecular docking simulations were performed using AutoDock Vina implemented in PyRx version 0.9.8. Prior to docking, both the protein and ligand structures were prepared and converted to PDBQT format to ensure compatibility with the docking algorithm. The docking grid box was positioned to encompass the active-site cavity of the target protein. Docking parameters were set with an exhaustiveness of 8, generating a total of 9 binding poses for each ligand [19,21,23,25]. The scoring of ligand–protein interactions was performed using the default Vina scoring function. This protocol allowed comprehensive sampling of ligand conformations and reliable prediction of binding affinities within the active site.

2.6. Interaction Analysis

The ligand–protein complexes were analyzed based on the top-ranked docking pose, selected according to the lowest binding energy and RMSD values. Detailed interaction analysis was performed using Discovery Studio, examining both two-dimensional (2D) and three-dimensional (3D) representations of the complexes. Key interactions evaluated included hydrogen bonding, hydrophobic and van der Waals contacts, electrostatic interactions, and the ionizability of residues within the binding pocket [18,21,22,26]. This comprehensive analysis allowed identification of the critical residues involved in stabilizing the ligand within the active site and provided insights into the molecular determinants of binding specificity and affinity.

3. Results

3.1. Docking Grid Validation

The defined grid box successfully encompassed the complete active site region, ensuring comprehensive coverage of the catalytic pocket (Figure 2). The chosen grid center coordinates (X = 368.935, Y = 297.736, Z = 325.507) accurately aligned with the functional residues responsible for ligand recognition. The optimized dimensions (53.571 × 62.796 ×

42.066 Å) provided adequate spatial volume for the ligand to explore multiple conformations without positional restriction (Table 1) [19,20].

Table 1 Auto Dock Vina search space parameters showing the grid center coordinates and box dimensions (Å) used for defining the docking region around the active site of the target protein

Centre	X=368935
	Y=297736
	Z=325507
Dimension (Anstrom)	X:535713
	Y:627966
	Z:420662

3.2. Docking Scores

The docking analysis performed using Auto Dock Vina (via PYRX) generated multiple binding poses for the ligand within the active site of the target protein (Table 2). The top-ranked pose exhibited a binding affinity of −7.2 kcal/mol, with RMSD/LB = 0 Å and RMSD/UB = 0 Å, indicating a highly stable and well-defined conformation [18,19,21,22]. The zero RMSD values suggest that the predicted pose shows no deviation from the reference orientation, reflecting strong reliability and convergence of the docking algorithm.

Table 2 Docking affinity and RMSD

Pose	Binding Affinity (kcal/mol)	RMSD (UB)	RMSD (LB)
1	−7.2	0	0
2	−7.0	29.93	28.43
3	−6.7	31.03	29.33
4	−6.6	29.64	28.87
5	−6.6	31.95	28.46
6	−6.5	31.06	29.72
7	−6.5	29.43	28.59
8	−6.4	31.05	28.28
9	−6.3	31.07	29.35

The −7.2 kcal/mol pose was selected as the final binding conformation

Table 3 Summary of ligand–protein interaction types, involved amino acid residues, and their functional roles in stabilizing binding within the active pocket

Interaction Type	Residues Involved	Description
Hydrogen Bonds	Ser151, Thr154, Gln123, Gln127, Arg156	Stabilize ligand orientation in the pocket
Polar/Electrostatic Contacts	Arg112, His175	Provide charged/polar stabilization
Hydrophobic Interactions	Val113, Ile149	Promote van der Waals packing
π–Interactions (if any)	PHE-like residues not prominent in figure	Minor aromatic stabilization
Pocket Type	Semi-hydrophobic cavity	Compatible for planar flavonoid binding

The remaining docking modes displayed binding energies ranging from −7.0 to −6.3 kcal/mol, accompanied by significantly higher RMSD values (>28 Å) [18,19]. These higher RMSD conformations represent alternative, less favorable orientations that deviate substantially from the primary pose and therefore lack biological relevance. As such, only the top-ranked pose (−7.2 kcal/mol, RMSD 0 Å) was considered for subsequent structural interpretation and interaction analysis.

3.3. Protein–Ligand Interactions

The binding mode of quercetin within the active site of PTP1B (Table 3) revealed a network of stabilizing interactions that collectively support its inhibitory potential. Quercetin established several hydrogen-bond interactions with key active-site residues, including ARG112, GLN123, THR154, SER151, and ARG156, indicating strong anchoring within the catalytic pocket. In addition to these polar contacts, the ligand was further stabilized through hydrophobic and van der Waals interactions involving ILE149 and VAL113, which contributed to the overall binding complementarity of the pocket.

Moreover, a notable π–cation interaction was observed between quercetin and HIS175, enhancing the affinity and structural stability of the ligand–protein complex [26,27]. Collectively, these non-covalent interactions confirm that quercetin fits snugly into the catalytic region of PTP1B, supporting its potential role as a promising inhibitor of this enzyme.

3.4. Visualization

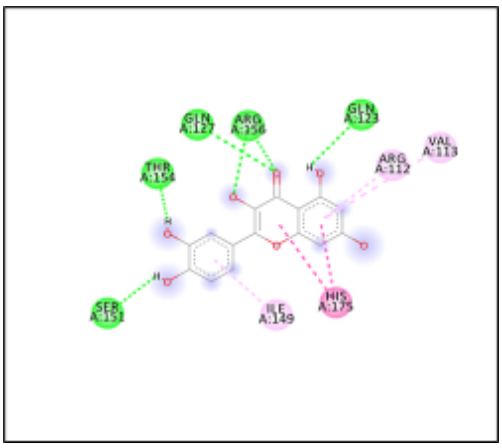

Figure 3 2D interaction diagram of quercetin within the active pocket of PTP1B. Hydrogen bonds with Ser151, Thr154, Gln123, Gln127, and Arg156 are shown in green dashed lines. Polar and electrostatic interactions with Arg112 and His175 are displayed in pink. Hydrophobic residues Val113 and Ile149 contribute to ligand stabilization

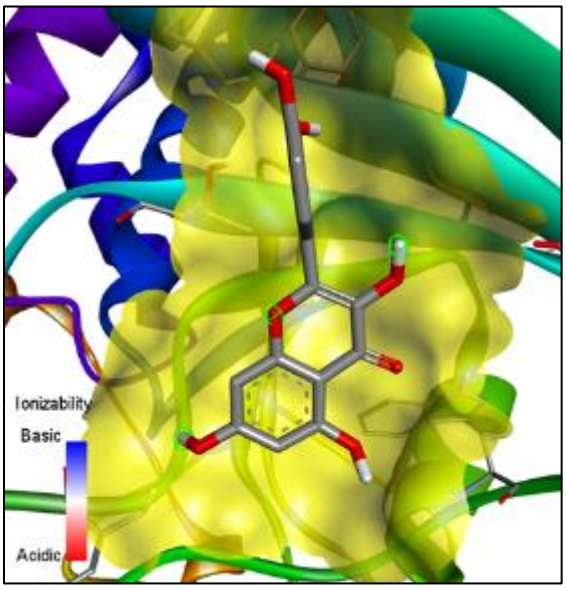

Figure 4 3D surface representation of the PTP1B binding pocket showing quercetin occupying a semi-hydrophobic cleft. Yellow surface indicates pocket boundary, while the surrounding secondary structures are shown in cartoon representation. The ligand fits tightly within the ionizable surface, supporting strong binding compatibility

2D interaction diagram and 3D pocket mapping (yellow surface) confirmed tight binding orientation inside the active site (Figure 3; Figure 4). Electrostatic mapping showed quercetin occupying the moderately basic region of the pocket, facilitating strong hydrogen bonding and polar interactions [18,21,26].

4. Discussion

The docking results indicate that quercetin exhibits a notable binding affinity (−7.2 kcal/mol) toward PTP1B, suggesting a moderate-to-strong inhibitory potential relative to other natural flavonoids reported in previous studies [18-20]. The top-ranked binding pose demonstrated multiple hydrogen-bond interactions with key catalytic residues, including ARG112, THR154, and GLN123, which collectively contribute to a stable and well-anchored orientation within the active site. These interactions are likely to facilitate effective suppression of PTP1B phosphatase activity, thereby modulating its downstream signaling pathways.

The interaction with HIS175 is particularly significant, as this residue plays a central role in the enzymatic activity of PTP1B. Additionally, hydrophobic and van der Waals interactions with residues such as ILE149 and VAL113 further reinforce ligand stabilization, ensuring that quercetin fits snugly into the catalytic pocket. The comprehensive network of non-covalent interactions observed in the docking analysis supports a high degree of complementarity between quercetin and the active site [18,20,22,26].

These computational findings are in agreement with prior experimental studies reporting quercetin's ability to enhance insulin sensitivity, promote glucose uptake, and positively influence metabolic pathways associated with type 2 diabetes. Collectively, the data suggest that quercetin has the potential to act as a natural PTP1B inhibitor, offering promising implications for antidiabetic therapeutic strategies. Nevertheless, to fully establish its pharmacological relevance, further wet-lab validation—including enzyme inhibition assays, cellular studies, and in vivo investigations—is recommended [28-32].

5. Conclusion

This study demonstrates that quercetin effectively binds to the active site of PTP1B with a favorable binding affinity and a stable network of molecular interactions. The molecular docking results highlight quercetin's potential role as a natural PTP1B inhibitor, indicating its promise in the management of insulin resistance and type 2 diabetes. These findings provide a computational foundation for future experimental validation and the potential development of quercetin-based therapeutic interventions. Further biochemical and pharmacological studies are necessary to confirm these predictions and to explore its efficacy and safety in biological systems.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflict of interests.

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