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In silico analysis of quercetin and its derivatives as potential TRPC6-targeted treatments for diabetic neuropathy

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ABSTRACT

Background: Diabetic neuropathy is a condition that arises as a complication of diabetes mellitus and often causes pain in patient. Quercetin and its derivatives have antinociceptive activity, making them potential agents for relieving the pain associated with diabetic neuropathy.

Objective: This study aims to analyze the interactions between quercetin and its eight derivatives with canonical transient receptor potential channels 6 (TRPC6) as protein target.

Method: The TRPC6 structure (PDB ID: 6UZ8) was prepared and validated with redocked to native ligand R0D using Autodock 4.2.6, with the established grid box and grid center settings. The test compounds were then optimized and docked using the same grid box and grid center settings as in the validation process, followed by visualization and analysis of the docking results.

Results: The compound with the best affinity for TRPC6 was tamarixetin, with a binding energy value of -3.27 kcal/mol, close to the binding energy value of the native ligand, which was -4.22 kcal/mol. The amino acid residues interacting with tamarixetin at the active site were 702-Asn, 705-Tyr, 706-Val, and 709-Gly. This indicates that tamarixetin and the native ligand bind to the same active site amino acids, resulting in a similar affinity to the native ligand in inhibiting TRPC6.

Conclusion: A total of ten quercetin derivatives were predicted to have TRPC6 antagonistic activity against diabetic neuropathy, with tamarixetin exhibiting the highest affinity compared to the other quercetin derivatives.

Keywords: diabetic neuropathy, TRPC6, docking, quercetin

Introduction

Diabetic neuropathy is a common complication of diabetes mellitus (DM), affecting 60-70% of the 371 million people with diabetes worldwide [1][2]. Among the key proteins involved in diabetic neuropathy are the canonical transient receptor potential channels (TRPC). TRPC channels consist of seven isoforms (C1-C7), which are grouped into three subfamilies: TRPC1/4/5, TRPC3/6/7, and TRPC2. These channels play a crucial role in cellular signaling by facilitating the entry of Ca^{2+} and Na^{+}, thereby promoting cell depolarization in response to extracellular signals transmitted by GPCR agonists [3].

Research has highlighted the impact of TRPC6 expression on neuropathic pain in diabetic rats [4]. TRPC6, a non-selective cation channel, is six times more permeable to Ca^{2+} than Na^{+} [3]. Its activity is regulated by phosphorylation events and phosphoinositides, and it is activated by diacylglycerol. TRPC6 is expressed in various tissues, including the kidney, smooth muscle, placenta, and brain. It works synergistically with other channels, such as TRPV4 and TRPC1, to modulate mechanical hyperalgesia and nociceptor sensitization. Importantly, TRPC6 inhibitors have demonstrated

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strong analgesic effects, potentially by suppressing microglial activation and reducing pro-inflammatory cytokine levels through the p38 signaling pathway, making TRPC6 inhibition a potential therapeutic target for neuropathic pain [5].

Current first-line therapies for diabetic neuropathy include pregabalin and gabapentin [6], but the development of new treatments has been hindered by side effects and inconsistent efficacy. As a result, patients often require a combination of anti-diabetic drugs and symptom management strategies [7].

Quercetin, a flavonoid found in plants such as *Ginkgo biloba* and *Hypericum perforatum*, has shown promise as an antinociceptive agent in diabetic neuropathy [8]. Quercetin has multiple derivatives, including rutin, quercitrin, and isorhamnetin [9]. The structure of quercetin contains a carbonyl ketone group in its molecule, and the oxygen atom on the first carbon is basic and can form salts with strong acids. Its molecular structure includes four active groups: the dihydroxy group between ring A, the o-dihydroxy B group, C ring C2, the double bond of C3, and 4-carbonyl. The phenolic hydroxyl group and the double bond in quercetin and its derivatives exhibit strong antioxidant activity [10].

The potential of quercetin and its derivatives as therapeutic agents for diabetic neuropathy can be explored using in silico approaches, such as molecular docking. This technique predicts the interaction between small molecules and protein targets before conducting laboratory experiments [11]. Docking analysis helps identify and evaluate the interactions between ligands and protein molecules, and the presence of binding sites confirms ligand-protein interactions [12]. In this study, TRPC6 (PDB ID: 6UZ8) was selected for molecular docking due to its pivotal role in pain signaling in diabetic neuropathy. Structural analysis of TRPC6, in complex with the agonist AM-0883, reveals important binding site information that is valuable for drug discovery. Mutation studies have also identified key residues essential for channel activity, underscoring the therapeutic relevance of TRPC6 modulation [13].

Additionally, absorption, distribution, metabolism, excretion, and toxicity (ADMET) predictions were conducted using pkCSM to assess the pharmacokinetic and safety profiles of the compounds. pkCSM is a free web-based tool that utilizes graph-based modeling to predict ADMET properties, including gastrointestinal absorption, distribution (e.g., central nervous system penetration), metabolism by liver enzymes like CYP450, excretion through the renal system, and toxicity risks such as hepatotoxicity and mutagenicity. These predictions provide an initial pharmacokinetic profile of a compound, helping to identify the most promising candidates for further drug development [14].

The aim of this study is to evaluate the pharmacological potential of quercetin and its derivatives—rutin, quercitrin, rhamnazin, rhamnetin, isoquercitrin, hyperoside, isorhamnetin, tamarixetin, and tamarixetin-3-o-glucosidase—as alternative treatments for diabetic neuropathy, specifically targeting TRPC6.

Methods

Preparation of protein target and ligand

The TRPC6 protein structure (PDB ID: 6UZ8) was downloaded in .pdb format from the RCSB Protein Data Bank (http://www.rcsb.org/). Using AutodockTools 1.5.7, the protein structure was prepared by removing unnecessary components such as water molecules. Polar hydrogens were then added, and charges were assigned to the protein. The native ligand, (5-chlorospiro[1,2-dihydroindole-3,4'-piperidine]-1'-yl)-[(3R)-2,3-dihydro-1,4-benzodioxin-3-yl]methanone (R0D), was separated from the protein, and the processed receptor was saved in .pdbqt format for further analysis [15].

Validation of molecular docking

To validate the molecular docking protocol, AutodockTools 1.5.7 was used. A grid box was set with center coordinates (X=170.343, Y=144.902, Z=132.757) and dimensions (X=24 Å, Y=30 Å, Z=30 Å). Re-docking was performed using AutoDock 4.2.6, where the native ligand was re-bound to the receptor protein to assess the accuracy of the docking procedure [16]. Validation was confirmed by calculating the root mean square deviation (RMSD) between the re-docked and original ligand positions. An RMSD value of ≤ 2 Å was considered acceptable, validating the docking protocol for use with the test compounds [17].

Preparation and optimization of compound structures

The structures of quercetin and its derivatives—rutin, quercitrin, rhamnazin, rhamnetin, isoquercitrin, hyperoside, isorhamnetin, tamarixetin, and tamarixetin-3-o-glucosidase—were obtained from the MolView website (https://molview.org). The compounds were

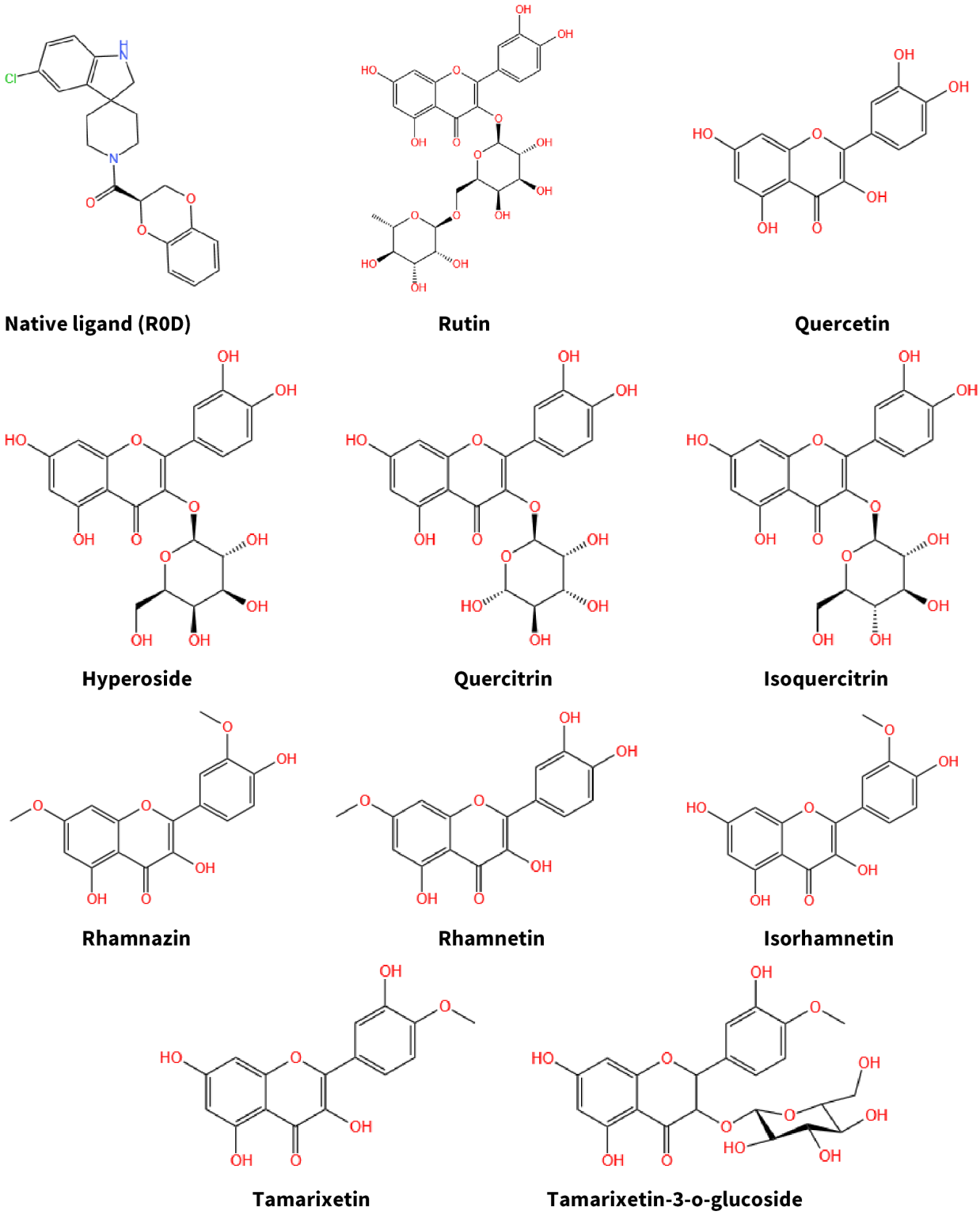

Figure 1. Structure of the native ligand and quercetin along with its derivatives

Table 1. Validation of the protein with its native ligand

Receptor	Ligand	RMSD	ΔG (kcal/mol)	Ki (μM)	Amino acid residues	Number of hydrogen bonds
6UZ8	R0D	1.04	-4.22	803.70	709-Gly, 706-Val, 705-Tyr, 702-Asn	3

Table 2. Results of Lipinski's analysis for quercetin and its derivatives

Compounds	MW (g/mol)	Log P	HBA	HBD	MR
Quercetin	302	2.0109	7	5	74.050
Quercitrin	448	0.297	11	7	104.862
Isoquercitrin	464	-0.7306	12	8	106.273
Rutin	610	-1.8788	16	10	137.495
Hyperoside	464	-0.7306	12	8	106.273
Rhamnazin	330	2.6168	7	3	83.824
Rhamnetin	316	2.3138	7	4	78.937
Isorhamnetin	316	2.3139	7	4	78.937
Tamarixetin	316	2.3139	7	4	78.937
Tamarixetin-3-o-glucoside	494	-0.4711	12	7	115.66

assessed according to Lipinski's rule of five, which includes molecular weight (MW <500 daltons), LogP (<5), hydrogen bond donors (HBD <5), hydrogen bond acceptors (HBA <10), and molar refractivity (MR: 40-130). Geometric optimization of the structures was performed using Avogadro software to ensure stability, and the optimized structures were saved in .pdbqt format for molecular docking [18].

Molecular docking of compounds

The optimized structures of quercetin and its derivatives were docked to the prepared TRPC6 protein using AutoDock 4.2.6. The grid box dimensions from the validation step (X=24 Å, Y=30 Å, Z=30 Å) were applied. The docking results provided the conformation with the lowest binding energy, indicating the strength of the potential interaction between each compound and the TRPC6 protein [15].

Data analysis

The interactions between the ligands and the TRPC6 protein were analyzed using Biovia DS software. Key parameters such as binding affinity (ΔG), inhibition constant (Ki), amino acid residues involved, and the number of bonding interactions were evaluated [18]. The ligand's affinity for the protein was determined based on the binding energy, with more negative values indicating stronger binding. The molecular interactions were visualized in both 2D and 3D formats using Biovia DS to ensure the accuracy and quality of the ligand-protein interactions [19] [15]. The compound with the highest binding affinity was further analyzed for its ADME properties using the pkCSM web tool (https://biosig.lab.uq.edu.au/pkcsm/).

Results

The root mean square deviation (RMSD) value is a key parameter for assessing the accuracy of the molecular docking validation process. The validation results of the protein with its native ligand are summarized in Table 1.

Quercetin and its derivatives were evaluated based on Lipinski's rule of five using the SCFBio tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp), and the analysis results are presented in Table 2.

Validation of the protein was conducted by re-docking the native ligand (R0D) to its binding site in TRPC6. The re-docking results, showing the overlay of the re-docked R0D (red) with the native ligand (blue), are displayed in Figure 2. All optimized ligands were

Table 3. Molecular docking results of quercetin and its derivatives with TRPC6 (PDB ID: 6UZ8)

Ligand	ΔG (kcal/mol)	Ki (mM)	Amino acid recidues	Number of hydrogen bonds
Quercetin	-3.17	4.75	705-Tyr, 709-Gly, 706-Val, 702-Asn	5
Quercitrin	-2.20	24.55	702-Asn, 706-Val	2
Isoquercitrin	-1.43	88.76	702-Asn, 705-Tyr, 706-Val	6
Rutin	-0.29	612.62	702-Asn, 705-Tyr, 706-Val, 709-Gly,	4
Isorhamnetin	-3.21	4.44	705-Tyr, 709-Gly, 706-Val	4
Rhamnazin	-3.24	4.20	705-Tyr, 709-Gly, 706-Val	4
Rhamnetin	-3.25	4.17	706-Val, 709-Gly, 705-Tyr, 702-Asn	5
Tamarixetin	-3.27	4.00	705-Tyr, 709-Gly, 706-Val, 702-Asn	5
Tamarixetin-3-o-glucoside	-1.73	53.84	706-Val, 705-Tyr, 710-Val	4
Hyperoside	-1.37	98.88	702-Asn, 709-Gly, 706-Val	4

Table 4. ADME analysis results for tamarixetin

	Parameter	Tamarixetin
Absorption	Water solubility (log mol/l)	-3.007
	$CaCO_2$ Permeability (Log P_{app} in 10^{-6} cm/s)	0.002
	Intestinal absorption (human) (%)	73.005
Distribution	VDSS (humans) (log L/Kg)	1.089
	BBB Permeability (log BB)	-1.161
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	No
	CYP2D6 inhibitor	Yes
	CYP3A4 inhibitor	No
Excretion	Total clearance (log ml/min/kg)	0.508
Toxicity	AMES toxicity	No
	Hepatotoxicity	No

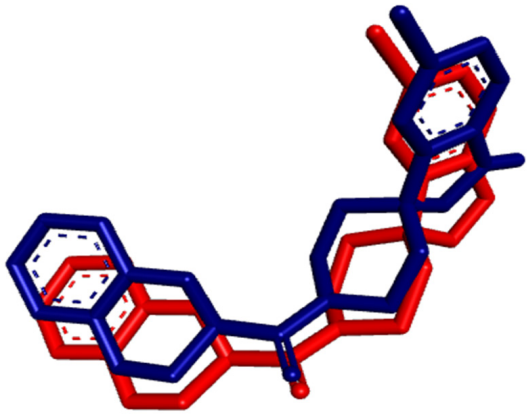

Figure 2. Overlay of re-docked R0D (red) with the native ligand (blue)

docked at the same active site as R0D, and the docking outcomes for all ligands are shown in Table 3.

Among the tested compounds, tamarixetin, a flavonoid derivative, exhibited the strongest interaction with TRPC6, with a binding energy of -3.27 kcal/mol. This interaction involves key residues 702-Asn, 705-Tyr, 706-Val, and 709-Gly, as illustrated in Figure 3.

Tamarixetin, which demonstrated the most promising activity as a potential TRPC6 antagonist, was further analyzed for its ADME properties using the pkCSM web tool (https://biosig.lab.uq.edu.au/pkcsm/). The results of this analysis are provided in Table 4.

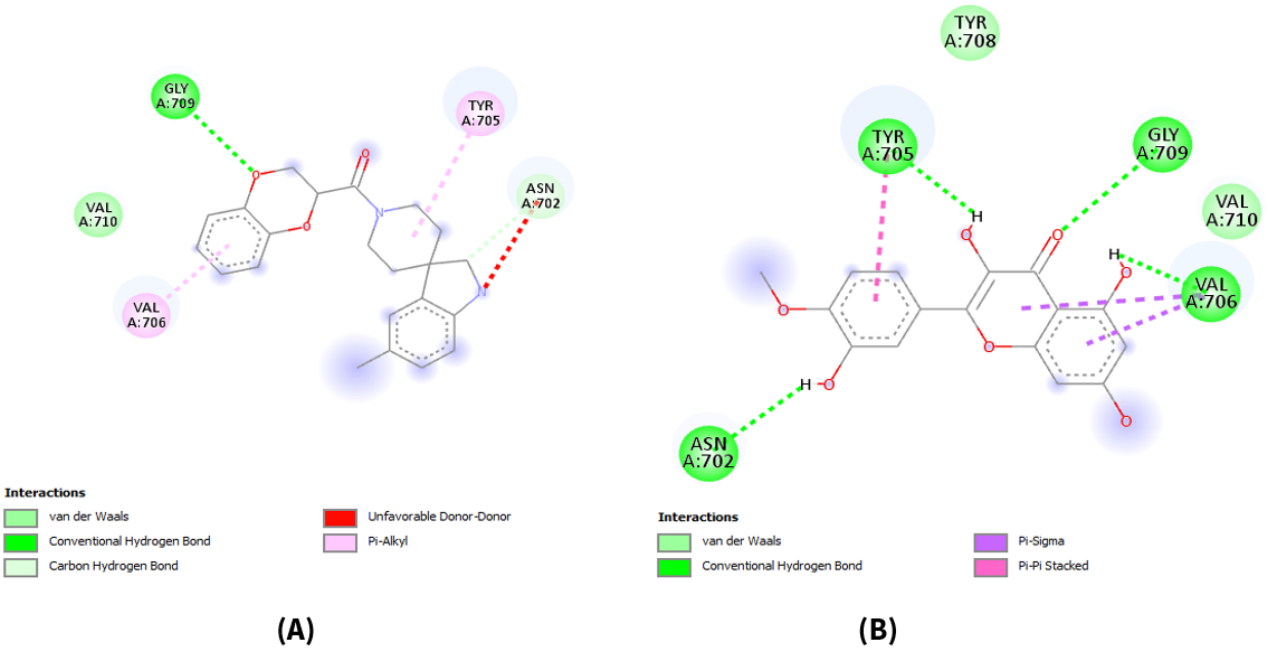

Figure 3. 2D visualization of interactions between TRPC6 and ligands. (A) the native ligand and (B) tamarixetin

Discussion

In silico studies play a crucial role in drug discovery, offering validated protocols for predicting the interaction between potential ligands and target proteins. This study used computational medicinal chemistry and molecular docking to explore quercetin and its derivatives as ligands for TRPC6. AutoDock software facilitated the docking process, predicting binding models and affinities between the TRPC6 receptor and the quercetin derivatives. This approach is advantageous as it reduces both time and cost in early-stage drug discovery [20][11].

All compounds were analyzed according to Lipinski's rules, with the results presented in Table 2. Lipinski's rule of five includes key parameters such as the lipid/water partition coefficient (Log P), which should range from -0.4 to 5, and molecular weight, which should not exceed 500 Da for optimal membrane permeability [21]. A higher molecular weight corresponds to increased hydrophobicity, reflected in a higher Log P value. Highly hydrophobic molecules are often more toxic, as they tend to remain embedded in the lipid bilayer longer and disperse widely throughout the body, reducing their binding selectivity to the target enzyme. Conversely, if the Log P value is too low, the molecule may struggle to pass through the lipid bilayer. Furthermore, compounds with a higher hydrogen bonding capacity—due to a greater number of hydrogen bond donors and acceptors—require more energy for absorption. Overall, Lipinski's rules provide an assessment of a compound's ability to passively diffuse through cell membranes [21][22].

The protein preparation process aimed to optimize the target protein structure for docking by removing its native ligand and eliminating water (H_2O) molecules. The removal of water enhances the potential interaction between the test compound and the target protein. Additionally, polar hydrogens were added, and charges were assigned to mimic the physiological conditions of the human body. This ensures that the molecular structure reflects the proper charge and atom distribution. Before docking, it is essential to add missing atoms (such as hydrogen, and occasionally non-hydrogen atoms) to ensure the protein structure is complete [23].

Protein validation was achieved by re-docking the native ligand, R0D, to TRPC6, the receptor protein (Figure 2). R0D binds to the agonist-binding site within TRPC6, located in a cavity adjacent to the extracellular membrane, formed by the S6 and pore helices of neighboring subunits [13]. RMSD is a key parameter for assessing the accuracy of binding mode predictions, with values ⩽ 2 Å considered reliable for docking validation [17]. Table 1 shows that the TRPC6 protein (PDB ID: 6UZ8) achieved an RMSD value of 1.04 Å, meeting the validation criteria. This allows for accurate docking of

quercetin and its derivatives to the active site of TRPC6, using the provided 3D coordinates.

To determine the compound with the best affinity for TRPC6, the free energy value (ΔG) was used as an indicator. A more negative ΔG value signifies greater stability in the binding interaction between the ligand and the receptor, indicating a stronger interaction [24]. The negative ΔG value represents the system reaching equilibrium under constant temperature and pressure. The magnitude of this value reflects the strength of the protein-ligand association, providing an important measure of complex stability or ligand binding affinity [25].

Tamarixetin, a flavonoid derivative, demonstrated the strongest interaction with TRPC6, exhibiting a binding energy of -3.27 kcal/mol and interacting with key residues such as 702-Asn, 705-Tyr, 706-Val, and 709-Gly (Figure 3). These amino acids are located in the active site of TRPC6 [13]. Visualization of the docking results confirmed a similarity in the binding mode of tamarixetin and the native ligand R0D, particularly at residues 702-Asn, 705-Tyr, and 706-Val. Both tamarixetin and R0D formed comparable numbers of hydrogen bonds, with 5 and 3 bonds, respectively.

The ADME analysis for tamarixetin is summarized in Table 4. Absorption was assessed by measuring human intestinal absorption (HIA) and CaCO2 permeability (from the human colon adenocarcinoma cell line-2). A compound is considered poorly absorbed if its intestinal absorption is less than 30% [14]. Tamarixetin showed good absorption, with an HIA of 73.005%. However, its CaCO2 permeability was low, as it did not exceed the logPapp threshold of 0.9 for high permeability [14].

The volume of distribution at steady state (VDss) indicates how well a drug distributes into tissues compared to plasma [14]. The higher the VDss, the more drug is distributed to tissues compared to plasma. A compound is considered well distributed to tissues if log VDss > 0.45 and poorly distributed if log VDss < -0.15 [14]. Tamarixetin exhibited good tissue distribution with a log VDss value of 1.089, indicating effective tissue penetration. However, its ability to cross the blood-brain barrier (BBB) was limited, as indicated by a log BB value of less than -1, which suggests poor brain penetration [16].

Cytochrome P450 enzymes play a critical role in drug metabolism, and inhibitors of these enzymes can significantly affect drug pharmacokinetics. Tamarixetin was found not to be a substrate for key enzymes like CYP2D6 and CYP3A4. In terms of elimination, tamarixetin demonstrated relatively high total clearance, suggesting it would be effectively excreted from the body.

Based on these findings, tamarixetin interacts with TRPC6 through the formation of hydrogen bonds, similar to the native ligand R0D. This suggests that tamarixetin may have comparable affinity for TRPC6 as R0D, making it a potential antagonist of TRPC6 [16]. Furthermore, the predicted toxicity results indicate that tamarixetin is non-toxic in both AMES toxicity and hepatotoxicity assays.

Conclusion

Ten quercetin derivatives were predicted to have activity as TRPC6 antagonists, with tamarixetin showing the highest binding affinity among them. Despite its promising interactions with TRPC6, tamarixetin's affinity is still relatively lower than that of R0D, the native ligand. To enhance tamarixetin's antagonistic potential against TRPC6, structural modifications focusing on strengthening its lipophilic interactions are recommended. These adjustments could improve its binding affinity and overall effectiveness as a potential therapeutic agent for diabetic neuropathy.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

RP and MAP performed the molecular docking study and data analysis. AHS supervised the docking process, while WNA provided oversight for both the manuscript and the docking procedure. GPM, HNA, NRY, NKE, IKC, and CA contributed to the initial draft of the manuscript. All authors were involved in the final writing and have approved the final version of the manuscript.

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