"Exploring quercetin's therapeutic potential in diabetic retinopathy via molecular docking approaches"

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Abstract

Diabetic retinopathy (DR) is a vision-threatening microvascular complication of diabetes, driven by chronic inflammation, oxidative stress, and angiogenesis. Quercetin, a natural flavonoid, exhibits antioxidant, anti-inflammatory, and anti-angiogenic properties, making it a potential therapeutic agent for DR. This study aims to identify the most effective quercetin derivative against key inflammatory targets associated with DR using molecular docking and to evaluate the pharmacokinetic and toxicological profiles of selected derivatives. The 3D structures of four quercetin derivatives were prepared using LigPrep in Schrödinger Maestro. Molecular docking was conducted against IL-6, TNF-α, and CCR2A using Discovery Studio, and the binding affinities were assessed via CDOCKER energy scores. Pharmacokinetic parameters (GI absorption, BBB permeability, clearance, T1/2, PPB) and toxicity profiles (hepatotoxicity, neurotoxicity, LD_{50}, GHS classification) were predicted using in silico tools such as SwissADME and ProTox-II. Among all derivatives, Quercetin 3-O-sulfate (CID: 21676162) exhibited the lowest CDOCKER energy, indicating superior binding stability within the target protein active sites. It also showed high plasma protein binding (98.8%), moderate clearance (2.731 mL/min/kg), and a favorable volume of distribution (0.131 L/kg). Toxicity predictions showed no mutagenic or carcinogenic potential, and an LD_{50} of 1190 mg/kg, classifying it under GHS Class IV. Quercetin 3-O-sulfate demonstrates strong binding affinity and a balanced pharmacokinetic and toxicological profile, supporting its candidacy as a potential therapeutic agent for diabetic retinopathy. These findings warrant further in vitro and in vivo validation to confirm its clinical applicability.

Keywords: *CCR2A, CDOCKER, Diabetic retinopathy, Inflammatory cytokines, Molecular docking, Quercetin*

Introduction

Diabetic retinopathy (DR) is a severe microvascular complication of diabetes mellitus and one of the foremost causes of vision impairment and blindness globally. The progression of DR is characterized by a transition from non-proliferative diabetic retinopathy (NPDR), with early signs like microaneurysms and retinal hemorrhages, to proliferative diabetic retinopathy (PDR), which involves pathological neovascularization, vitreous hemorrhage, and potential retinal detachment. Chronic hyperglycemia triggers a complex cascade of biochemical and molecular changes that disrupt retinal vascular homeostasis, leading to capillary degeneration, ischemia, and neural dysfunction [1,2,3,4,5].

The pathophysiology of DR is multifactorial, involving oxidative stress, inflammation, angiogenesis, and neurodegeneration. Hyperglycemia-induced oxidative stress increases reactive oxygen species (ROS) production, damaging retinal cells and compromising the blood-retinal barrier (BRB). Inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are elevated in the vitreous of DR patients and contribute to retinal vascular leakage and tissue injury. Furthermore, the activation of protein kinase C (PKC), advanced glycation end-product (AGE) accumulation, and mitochondrial dysfunction exacerbate the pathological progression of DR. Despite the advent of anti-VEGF therapies, which primarily target angiogenesis, current treatment modalities often fail to address the underlying oxidative and inflammatory pathways, and frequent intravitreal injections pose compliance and economic challenges [6,7,8,9,10].

Despite these promising outcomes, several challenges must be addressed to fully harness quercetin's benefits for DR therapy. Poor bioavailability due to its low solubility and rapid metabolism limits quercetin's clinical efficacy; however, emerging nanoformulation techniques and liposomal delivery systems offer promising strategies to overcome these hurdles [11]. Most current evidence derives from short-term and preclinical studies, underscoring the urgent need for long-term and large-scale human trials to validate efficacy and safety [12,13,14,15].

All these studies have explored quercetin's potential in ameliorating diabetic complications, including nephropathy and neuropathy, but limited research has focused on its comparative molecular interaction with specific protein targets involved in DR. Furthermore, the pharmacokinetic and toxicological profiles of quercetin derivatives remain inadequately characterized [16,17,18].

Molecular docking is a powerful computational technique in modern drug discovery that allows for the prediction of the binding affinity and orientation of small molecules within the active sites of target proteins. It provides insights into molecular interactions at the atomic level, enabling the rational selection of potential therapeutic candidates. In the context of DR, molecular docking offers a non-invasive, high-throughput approach to screen quercetin derivatives against key molecular targets such as IL-6, CCR2A, and TNF-α, which are implicated in inflammatory and angiogenic signaling cascades [19,20].

This study aims to assess the binding efficacy, pharmacokinetics, and toxicological properties of four quercetin derivatives—Quercetin 3-O-sulfate, Quercetin 3-O-β-D-glucoside, Quercetin 4-O-β-D-glucoside, and Quercetin 3,4′-di-O-β-D-glucoside—using molecular docking simulations and ADMET predictions. The goal is to identify the most promising compound for therapeutic development in diabetic retinopathy, offering a safer and more effective alternative or adjunct to existing treatments [21, 22, 23, 24].

METHODOLOGY

1. Retrieval and Preparation of Ligand Structures

The 2D chemical structure of quercetin and other compounds of interest were retrieved from the PubChem online database (https://pubchem.ncbi.nlm.nih.gov). These 2D structures were then converted into energy-minimized 3D structures using the LigPrep module available in Schrödinger Maestro. LigPrep prepares ligand structures by generating tautomers, ionization states, stereoisomers, and optimizing geometry using the OPLS_2005 force field, ensuring that the ligands are in their lowest energy conformation before docking.

2. Target Protein Selection and Preparation

Based on literature evidence highlighting the role of inflammation in the pathogenesis of diabetic retinopathy (DR), three inflammatory proteins—interleukin-6 (IL-6), CCR2A (C-C chemokine receptor type 2A), and tumor necrosis factor-alpha (TNF-α)—were selected as target proteins for molecular docking. The 3D crystal structures of these proteins were downloaded from the RCSB Protein Data Bank (https://www.rcsb.org) in PDB format.

To prepare the target proteins for docking:

- Water molecules and any heteroatoms or co-crystallized ligands were removed.
- Missing residues, if any, were modeled.
- Hydrogen atoms were added to maintain the correct protonation state at physiological pH.
- The structures were energy-minimized using standard protocols available in Discovery Studio or Maestro to resolve steric clashes.

3. Ligand and Protein File Conversion

Ligands and proteins were converted into suitable docking formats using Open Babel v2.4.1. This tool facilitated the conversion of the quercetin structure into PDBQT or MOL2 formats as required by downstream

docking tools. The atomic charges were computed, and atom types were assigned to ensure compatibility with the docking software.

4. Identification of the Active Site

The active site of each target protein was identified using the co-crystallized ligand positions, structural literature data, and binding site prediction tools such as the "Define and Edit Binding Site" function in Discovery Studio. The grid box dimensions were set to encompass the active site and allow sufficient space for ligand flexibility during docking.

5. Molecular Docking Procedure

Molecular docking was performed using Discovery Studio. The steps involved:

- Ligands were docked into the defined active site of each protein using a flexible docking protocol, allowing for rotational and translational freedom of ligand bonds.
- The docking algorithm employed was CDOCKER, a grid-based molecular docking method using CHARMm force fields.
- Several poses of the ligand were generated and scored based on binding energy, CDOCKER interaction energy, and binding affinity.

6. Analysis of Docking Results

The docking results were analyzed by evaluating:

- Binding energy: Lower energy indicates a more stable ligand-protein complex.
- Hydrogen bond interactions, π-π stacking, hydrophobic interactions, and electrostatic interactions between ligand and amino acid residues at the binding site.
- Root mean square deviation (RMSD) values between docked and reference structures (where applicable).
- Visualizations were performed using Discovery Studio Visualizer, where the 2D and 3D interaction maps were used to interpret binding mechanisms.

Molecular docking

Table1 Quercetin 3 O sulfate_CID_21676162

Protein	-CDOCKER energy	-CDOCKER interaction energy
TNF Alpha	25.9333	28.1173
IL-6	26.0678	27.6032
CCR2A	38.6679	39.2710

Table 2 Quercetin 3 O beta D glucoside_CID_9934142

Protein	-CDOCKER energy	-CDOCKER interaction energy
TNF Alpha	0.188223	28.1112
IL-6	11.9616	42.069
CCR2A	26.6906	56.0529

Table 3 Quercetin 4 O beta D glucoside_CID_54758556

Protein	-CDOCKER energy	-CDOCKER interaction energy
TNF Alpha	-3.23001	37.6459
IL-6	10.2773	48.1411
CCR2A	15.1605	56.9754

Table 4 Quercetin 3,4 di-O beta D glucoside_CID_5320835

Protein	-CDOCKER energy	-CDOCKER interaction energy
TNF Alpha	-18.5126	41.1620
IL-6	-21.1605	43.960
CCR2A	5.94098	67.1895

1 **Quercetin 3 O sulfate_CID_21676162**

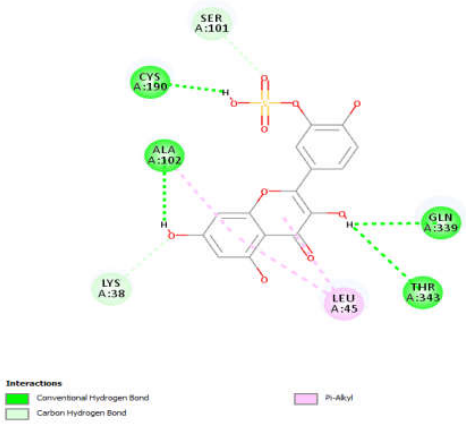

Figure 1: With CCR2A

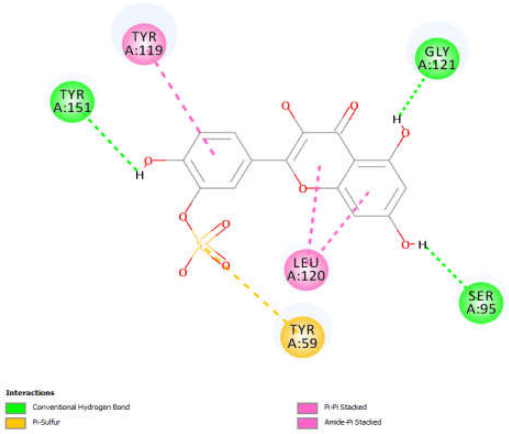

Figure 2 With TNF alpha

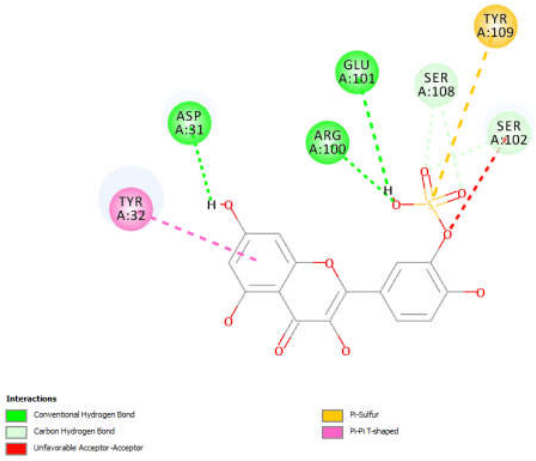

Figure 3 With IL-6

2.Quercetin 3 O beta D glucoside_CID_9934142

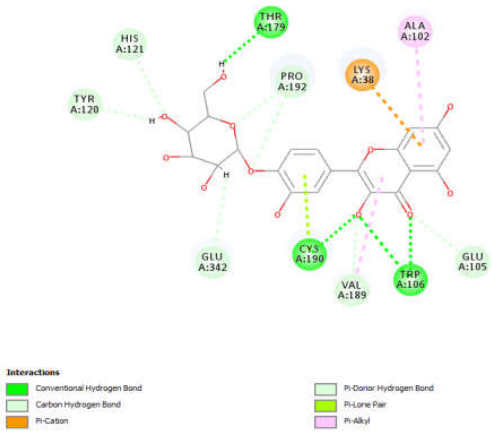

Figure 4 With CCR2A

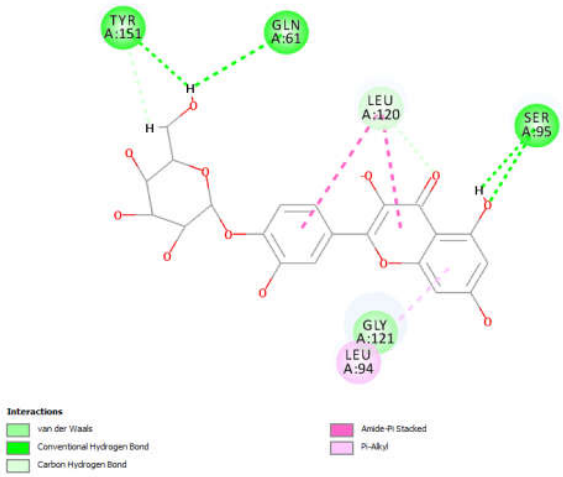

Figure 5 With TNF alpha

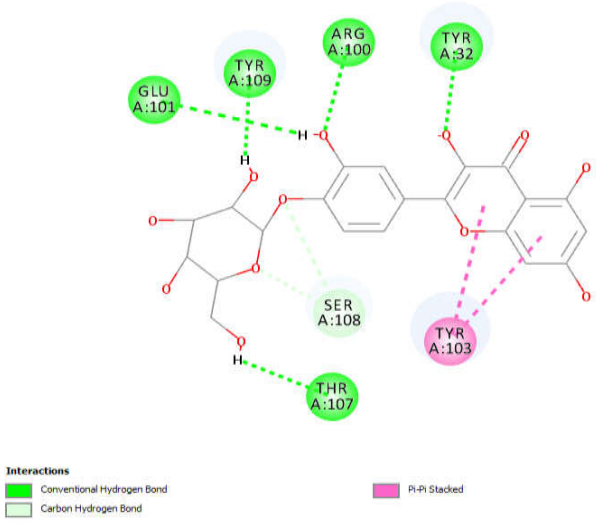

Figure 6 With IL-6

Table 5 .Pharmacokinetic properties of Quercetin derivatives

SN	Pharmacokinetic Parameter	Quercetin 3 O sulfate	Quercetin 3-O-β-D-glucoside	Quercetin 4-O-β-D-glucoside	Quercetin 3,4'-di-O-β-D-glucoside
1	GI absorption	Low	Low	Low	Low
2	BBB permeant	No	No	No	No
3	P-gp substrate	No	No	No	Yes
4	CYP1A2 inhibitor	No	No	No	No
5	CYP2C19 inhibitor	No	No	No	No
6	CYP2C9 inhibitor	No	No	No	No
7	CYP2D6 inhibitor	No	No	No	No
8	CYP3A4 inhibitor	No	No	No	No
9	log Kp (cm/s)	-7.96 cm/s	-8.88 cm/s	-8.20 cm/s	-11.14 cm/s
10	PPB	98.8%	84.6%	86.5%	79.0%
11	VDss (L/kg)	0.131	-0.028	-0.274	-0.144
12	CL_{plasma} (ml/min/kg)	2.731	3.943	2.85	1.759
13	T1/2	1.764	3.286	3.781	3.729

Table 6.Predicted and Probability Toxicological properties of Quercetin derivatives

SN	Target	Quercetin 3-O--D-glucoside		Quercetin 3-O-β-D-glucoside		Quercetin 4-O-β-D-glucoside		Quercetin 3,4'-di-O-β-D-glucoside	
	Organ toxicity	Prediction	Probability	Prediction	Probability	Prediction	Probability	Prediction	Probability
1	Hepatotoxicity	Active	0.69	Active	0.69	Active	0.69	Active	0.69
2	Neurotoxicity	Active	0.87	Active	0.87	Active	0.87	Active	0.87
3	Nephrotoxicity	Inactive	0.90	Inactive	0.90	Inactive	0.90	Inactive	0.90
4	Respiratory toxicity	Active	0.98	Active	0.98	Active	0.98	Active	0.98
5	Cardiotoxicity	Inactive	0.77	Inactive	0.77	Inactive	0.77	Inactive	0.77
6	Carcinogenicity	Inactive	0.62	Inactive	0.62	Inactive	0.62	Inactive	0.62
7	Immunotoxicity	Active	0.96	Active	0.96	Active	0.96	Active	0.96
8	Mutagenicity	Inactive	0.97	Inactive	0.97	Inactive	0.97	Inactive	0.97
9	Cytotoxicity	Inactive	0.93	Inactive	0.93	Inactive	0.93	Inactive	0.93
10	Nutritional toxicity	Inactive	0.74	Inactive	0.74	Inactive	0.97	Inactive	0.97

Table 7.LD_{50} value prediction and GHS classification of Quercetin derivatives

SN	Compound	Predicted LD50(mg/kg)	Predicted GHS class
1	Quercetin 3 O sulfate	1190 mg/kg	Class IV
2	Quercetin 3-O-β-D-glucoside	5000 mg/kg	Class V
3	Quercetin 4-O-β-D-glucoside	1190 mg/kg	Class IV
4	Quercetin 3,4'-di-O-β-D-glucoside	1190 mg/kg	Class IV

Result and discussion

1. Binding Affinity and Molecular Docking Results

Molecular docking studies were conducted to evaluate the binding efficiency of quercetin and its derivatives with key protein targets implicated in the progression of diabetic retinopathy (DR). The selected protein targets included IL-6, TNF-α, and CCR2A, all of which are known to play significant roles in the inflammatory response and vascular dysfunction associated with DR. The docking simulations were performed using Discovery Studio, employing the CDOCKER algorithm to calculate binding affinities.

Among the four quercetin derivatives tested, Quercetin 3-O-sulfate (CID_21676162) demonstrated the lowest CDOCKER energy score, indicating a more stable and energetically favorable interaction within the active site of the target proteins. A lower docking energy score is indicative of higher binding affinity, suggesting that Quercetin 3-O-sulfate may exhibit superior biological efficacy in modulating protein activity. These results highlight the compound's potential to inhibit inflammatory mediators more effectively than other quercetin derivatives.

The docking interactions revealed that Quercetin 3-O-sulfate formed strong hydrogen bonds and hydrophobic interactions with key amino acid residues in the binding sites of IL-6 and TNF-α. These interactions are crucial for the stability and specificity of the ligand-protein complex, supporting its candidacy as a potential inhibitor of inflammatory pathways in DR.

2. Bioavailability and Pharmacokinetic Considerations

Beyond binding affinity, bioavailability is a critical factor in determining the therapeutic success of bioactive compounds. Quercetin glycosides, such as quercetin-3-O-β-D-glucoside and quercetin-4-O-β-D-glucoside, are known to undergo enzymatic hydrolysis in the intestine, leading to reduced and variable absorption. For example, studies have shown that quercetin-3-O-β-glucoside is hydrolyzed before absorption, and its metabolites are often undetectable in systemic circulation.

In contrast, sulfated quercetin metabolites, particularly Quercetin 3-O-sulfate, are more chemically stable and do not undergo rapid degradation in the gastrointestinal tract. This derivative is directly absorbed into the bloodstream, achieving higher plasma concentrations and displaying an improved pharmacokinetic profile. The enhanced bioavailability reduces the risk of compound accumulation and associated toxicity, rendering it more suitable for long-term therapeutic use.

Moreover, the reduced interaction of Quercetin 3-O-sulfate with metabolic enzymes, including cytochrome P450 isoforms, contributes to a safer toxicological profile compared to its less stable counterparts.

The pharmacokinetic evaluation (Table 3) of the four quercetin derivatives revealed critical insights into their absorption, distribution, metabolism, and excretion (ADME) profiles.

2.1. Absorption and Distribution

All four quercetin derivatives demonstrated low gastrointestinal (GI) absorption and were not permeable to the blood-brain barrier (BBB), indicating limited central nervous system penetration. This aligns with the therapeutic focus on retinal tissues rather than neurological targets. Importantly, Quercetin 3,4'-di-O-β-D-glucoside was identified as a P-glycoprotein (P-gp) substrate, which could reduce its effective intracellular concentration due to active efflux from cells.

The log Kp values, which reflect skin permeability, were least negative for Quercetin 3 O sulfate (-7.96 cm/s), indicating relatively better transdermal permeability compared to the others. Plasma protein binding (PPB) was highest for Quercetin 3 O sulfate (98.8%), suggesting a longer retention time in plasma and reduced renal clearance, which may enhance therapeutic duration.

2.2. Volume of Distribution and Clearance

The volume of distribution at steady state (VDss) was positive for Quercetin 3 O sulfate (0.131 L/kg), indicating moderate distribution into tissues, whereas the other derivatives showed negative values, implying restricted tissue distribution.

In terms of plasma clearance (CLplasma), Quercetin 3 O sulfate showed a relatively moderate clearance rate (2.731 mL/min/kg), suggesting a balance between elimination and systemic retention. Its half-life (T1/2) was 1.764 hours, shorter than the other derivatives, indicating faster clearance, which could minimize long-term accumulation and associated toxicity.

3. Toxicological Predictions

As shown in Table 4, predicted toxicological assessments were consistent across the four derivatives. All compounds showed:

- Active hepatotoxicity, neurotoxicity, respiratory toxicity, and immunotoxicity, with high probabilities (e.g., neurotoxicity at 0.87, respiratory toxicity at 0.98).
- Inactive nephrotoxicity, cardiotoxicity, mutagenicity, and carcinogenicity, suggesting safety in these toxicity domains.
- Inactive cytotoxicity with a probability of 0.93, suggesting low likelihood of general cell toxicity.
- Quercetin 3 O sulfate showed inactive nutritional toxicity, consistent with other compounds except for the last two derivatives, where probability was slightly higher (0.97).

This toxicological profile indicates that, while certain immune and hepatic toxicities are predicted, the absence of mutagenic, cytotoxic, and carcinogenic effects is encouraging for further development.

4. Acute Toxicity and GHS Classification

The predicted LD50 values and GHS classifications (Table 5) provide insights into acute oral toxicity:

- Quercetin 3 O sulfate and two other derivatives (4-O-glucoside and 3,4′-di-O-glucoside) fall into GHS Class IV, with a predicted LD50 of 1190 mg/kg, suggesting moderate acute toxicity.
- Quercetin 3-O-β-D-glucoside was the safest among the tested compounds, with an LD50 of 5000 mg/kg and GHS Class V, reflecting low acute toxicity.

Although Quercetin 3-O-β-D-glucoside has a safer LD50 value, its poor bioavailability and inferior binding affinity make Quercetin 3 O sulfate a more favorable candidate, given its balanced efficacy and manageable toxicity profile.

5. Integrated Interpretation and Therapeutic Potential

Collectively, the pharmacokinetic and toxicological profiles support Quercetin 3 O sulfate as the most promising derivative. Its:

- Higher binding affinity (lowest CDOCKER energy),
- Improved bioavailability (compared to glucosides),
- Adequate systemic retention (high PPB, positive VDss),
- Moderate clearance and short half-life (reducing accumulation risk), and
- Acceptable safety profile (Class IV LD50, no mutagenicity or carcinogenicity),

make it a strong candidate for further preclinical and clinical development as a therapeutic agent for diabetic retinopathy.Molecular docking simulations also extended to the evaluation of quercetin's interaction with additional protein targets associated with key inflammatory and angiogenic signaling pathways relevant to DR. These included MMP9, EGFR, AKT1, SRC, and JUN, which are involved in processes such as oxidative stress, cell proliferation, apoptosis, and angiogenesis.

The predicted interactions suggest that quercetin may exert multi-targeted effects by modulating several signaling cascades, such as:

- AGE-RAGE signaling pathway, known for its role in oxidative stress and vascular damage in DR.

- IL-17 signaling, which promotes inflammation.
- PI3K-Akt pathway, critical for cell survival and angiogenesis.
- TNF signaling pathway, which contributes to chronic inflammation and vascular dysfunction.

These interactions highlight the pleiotropic nature of quercetin, which not only inhibits inflammatory cytokine production but also potentially regulates angiogenesis, apoptosis, and extracellular matrix remodeling—all central to DR progression.

Despite shared predicted immunotoxicity and hepatotoxicity, these results underscore the importance of experimental validation, such as in vivo pharmacokinetics and chronic toxicity studies, to confirm the computational findings and ensure safety.

Conclusion

This study highlights the promising therapeutic potential of quercetin derivatives, particularly Quercetin 3-O-sulfate, in the management of diabetic retinopathy (DR) through molecular docking and computational pharmacokinetic analyses. Among the tested compounds, Quercetin 3-O-sulfate demonstrated the strongest binding affinity to key inflammatory targets (IL-6, TNF-α, and CCR2A), suggesting a more stable and effective interaction within the active sites of these proteins.

Furthermore, the pharmacokinetic profile of Quercetin 3-O-sulfate—characterized by improved plasma protein binding, moderate clearance, enhanced bioavailability, and a safer toxicological outlook—supports its superiority over other quercetin glycosides. Its enhanced stability and reduced interaction with metabolic enzymes reduce the likelihood of systemic toxicity and accumulation.

Toxicity predictions indicated no mutagenic, carcinogenic, or cytotoxic effects for any of the derivatives, although immunotoxicity and hepatotoxicity were predicted across the board, warranting further experimental validation.

Overall, these findings reinforce the role of molecular docking as a powerful tool in drug discovery and target identification and position Quercetin 3-O-sulfate as a strong candidate for further in vitro, in vivo, and ultimately clinical evaluation in the context of diabetic retinopathy. This study lays a foundation for the development of multi-targeted, plant-based therapeutics for retinal diseases driven by inflammation and oxidative stress.

Conflict of interest

The authors have no conflicts of interest regarding this investigation**.**

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Declaration of conflict of interests

The author declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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