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Understanding the Therapeutic Potential of Quercetin and Resveratrol: Computational Insights into Anti-Diabetic Activity †

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Abstract

The global population is aging rapidly, with those aged 60 and above expected to reach 2.1 billion by 2050. This shift is driving a rise in chronic diseases, including diabetes, which is projected to affect 592 million people by 2035. These trends highlight the urgent need for novel therapeutic strategies and better understanding of disease mechanisms. Resveratrol and quercetin, two widely recognized polyphenols, are highly valued for their potent antioxidant and anti-inflammatory properties, demonstrating significant promise in mitigating and improving diabetic conditions by addressing core pathological features such as oxidative stress and insulin resistance. This study leverages computational chemistry techniques to elucidate the putative mechanisms of action of resveratrol and quercetin within the context of diabetic pathogenesis. To achieve this, a target prediction analysis was performed for both molecules using SwissTargetPrediction and EpigeneticTargetProfiler, followed by a structure-based target fishing utilizing TargetFisher. From the list of the predicted targets, we selected three key enzymes: Monoamine Oxidase A (MAO-A) and Monoamine Oxidase B (MAO-B), mitochondrial enzymes linked to oxidative stress and inflammation in diabetic conditions, and Insulin-like Growth Factor 1 Receptor (IGF-1R), which activates signalling pathways essential for insulin sensitivity and beta-cell function. These targets were chosen due to their established roles in metabolic signalling and oxidative pathways relevant to diabetes progression. Molecular docking analyses indicated the potential of quercetin and resveratrol to modulate the function of these enzymes and to confirm viability to continue exploring the therapeutic potential of these natural products in both combating metabolic aging and managing diabetic disease.

Keywords: resveratrol; quercetin; metabolic anti-aging; diabetes; target prediction; molecular docking

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1. Introduction

Aging is an inevitable biochemical process that results in the body's inability to regenerate itself, and especially in Western civilizations, it is often accompanied by a high risk of chronic diseases, including cancers, cardiovascular, metabolic and neurodegenerative disorders [1]. Polyphenols are a well-known group of phytochemicals

fundamentally composed of phenolic rings. They are plant-derived compounds found in various types of fruits and vegetables. These secondary metabolites serve a protective function in plants, shielding them from environmental influences and biological stress. When consumed as part of the human diet, polyphenols are known to help prevent various age-related diseases. They are particularly recognised for their antioxidant properties and their role in protecting against oxidative stress [2]. The oral administration of polyphenol quercetin led to significant benefits for diabetic patients, suggesting its potential as a supplementary agent in clinical practice as a beneficial intervention for metabolic disorders [3]. Polyphenol resveratrol influences multiple metabolic pathways by increasing cellular glucose uptake, altering glucose metabolism, preserving β-cell function, modulating insulin secretion, and reducing insulin resistance. These mechanisms underlie its beneficial effects on diabetic nephropathy, cardiomyopathy and vasculopathy, inflammation and oxidative stress, apoptosis and autophagy regulation, diabetes-associated ocular diseases, and gastrointestinal complications in diabetic patients [4]. Nonetheless, the precise mechanisms of action (MoA) underlying the effects of these natural compounds remain to be fully elucidated and confirmed.

This research was undertaken to gain insights into the possible protein targets for these two natural products in a diabetes context. The two compounds investigated (resveratrol and quercetin) are believed to act via phenolic radicals to carry out their antioxidant effects, and therefore involved in ROS-sequestering events; however, binding to protein targets is likely an important element of their secondary modulating action within the cell, there is a strong likelihood that, these interactions significantly contribute to the compounds' secondary, pleiotropic effects. Conventional anti-diabetic agents and non-traditional compounds were selected as a benchmarking set to compare their interactions with a subset of relevant predicted targets. The anti-diabetic drugs pioglitazone, rosiglitazone and metformin were included due to their known direct or indirect effects on one of the three target proteins, while the primary anti-diabetic action of rosiglitazone and pioglitazone is mediated by PPAR-gamma, they can also function as MAO-B inhibitors [5,6], a function more associated with an off-target mechanism. Additionally, the anti-neoplastic agents linsitinib and picropodophyllin were selected, as their observed mechanisms of action have demonstrated interaction with at least one of the three target proteins [7,8] and a recognised impact on patient glucose homeostasis.

2. Materials and Methods

2.1. Target Prediction

The SwissTargetPrediction platform (http://www.swisstargetprediction.ch accessed 15 July 2025) was utilized within this study to analyze resveratrol and quercetin, aiming to successfully predict and select their most relevant targets. This system for small chemical molecules employs 2D and 3D similarity algorithms relative to known ligands. The probability of target prediction is expressed as a numerical score ranging from 0 to 1 [9]. Furthermore, two complementary prediction tools were utilized: Epigenetic Target Profiler (http:2//www.epigenetictargetprofiler.com/, accessed 1 September 2022), a web server dedicated to predicting epigenetic targets of small molecules, and Target Fisher (https://gqc.quimica.unlp.edu.ar/targetfisher, accessed 18 July 2025), a structure-based method that combines target-specific machine learning models with docking results for predicting biological activities.

2.2. Structure Preparation of Ligands and Proteins

The three-dimensional structures of selected protein targets, IGF-1R (PDB ID: 3LWO), MAO-A (PDB ID: 2Z5X), and MAO-B (PDB ID: 2BYB), were downloaded from

the RCSB Protein Data Bank. The solvent molecules were removed from all selected protein structures before computational studies and missing hydrogens were added using Vega ZZ ver. 3.2.4.9 software. The isomeric SMILES strings of quercetin and resveratrol, as well as of rosiglitazone, pioglitazone, metformin, linsitinib and picropodophyllin were obtained from the PubChem database "https://pubchem.ncbi.nlm.nih.gov (accessed on 17 July 2025)". The SMILES strings of selected compounds were converted into mol2 format using VEGA ZZ. Likewise, fixing atomic potentials and assigning atom charges of ligands were performed in VEGA ZZ software.

2.3. Prediction of Protein Ligand Interactions

Virtual screening studies were executed by Auto Dock Vina ver. 1.1.2 software with Vega ZZ software as a graphical user interface. The crystalized ligand of each protein structure was used to define the docking site. The dimensions of the grid box size(x,y,z) were set to: (a) 29 Å, 24 Å,29 Å(IGF-1R), (b) 24 Å, 24 Å,24 Å(MAO-A), (c) 24 Å, 24 Å, 24 Å(MAO-B). The grid centres (x, y, and z) coordinates had the following values: (a) −13.5, 13, and −32,5 (IGF-1R), (b) 40.6, 26.85, and −14.8 (MAO-A), and (c) 52.56, 156.3, and 26.1 (MAO-B) [10,11]. The exhaustiveness value was set to 50, while the binding modes value was set to 5. All screened compounds were ranked by binding energy (in kcal/mol) based on the AutoDock Vina scoring function (a more negative value indicates higher binding affinity). In addition, the 2D diagram of protein–ligand interactions were verified using the Discovery Studio Visualizer program.

3. Results and Discussion

3.1. Target Prediction

An analysis of the SwissTargetPrediction results for resveratrol and quercetin was conducted and a subset of the protein targets was considered for further study (Table 1) Both quercetin and resveratrol were predicted to have 100 protein targets. However, the score ranges differed: quercetin's scores spanned from 0.19 to 1, while resveratrol's range was broader, from 0.0 to 1.

The results were leading to the identification of MAO-A and IGF-1R as possible targets for action for people with diabetes. MAO-B was included as a relevant potential target due to its role in generating oxidative stress. Inhibition of MAO-B has been shown to reduce hydrogen peroxide production, thereby alleviating oxidative damage that contributes to insulin resistance and diabetic complications.

Table 1. A subset of predicted targets quercetin and resveratrol obtained using SwissTargetPrediction.

Target Name	Common Name	Probability Quercetin	Probability Resveratrol
NADPH oxidase 4	NOX4	1.0	0
Monoamine oxidase A	MAO -A	1.0	1.0
Insulin-like growth factor	IGF-1R	1.0	0.049
Cytochrome P450 19A1	CYP19A1	1.0	0.058
Epidermal growth factor	EGFR	1.0	0.049
Tyrosine-protein kinase receptor	FLT3	1.0	0
Arachidonate 5-lipoxygenase	ALOX5	1.0	0.058

IGF-1R showed high probability as a target for quercetin and a moderate one for resveratrol, but it represents an important therapeutic avenue in diabetes therapy due to the frequent disruption of the INSR/IGF-1R signaling pathway in insulin resistance. Its

overactivation may contribute to insulin resistance in peripheral tissues, influence pancreatic β-cell function, and—as is the case with MAO enzymes—participate in the regulation of oxidative stress and the inflammatory response, both of which play significant roles in the progression of diabetes-associated diseases and the proven link between diabetes and certain tumors whose treatment targets IGF-1R [12]. MAO-A has a high probability of being a target for both molecules, quercetin and resveratrol. Considering its role in oxidative stress, it was selected as a target in this study alongside MAO-B. On one hand, elevated oxidative stress affects insulin signaling and contributes to insulin resistance and hyperglycemia; on the other hand, one of the diabetes-related complications is neurodegeneration, which is also closely linked to MAO enzymes.

3.2. Molecular Docking

The potential therapeutic effects of the natural polyphenols resveratrol and quercetin in diabetic patients were further evaluated through molecular docking against three target monoamine oxidase A (MAO-A), monoamine oxidase B (MAO-B) and insulin-like growth factor 1 receptor (IGF-1R). The docking was conducted for both polyphenols and a set of reference compounds, including linsitinib, picropodophyllin, rosiglitazone, pioglitazone, and metformin. The binding energy results for each molecule with MAO-A, MAO-B, and IGF-1R suggest that most compounds exhibit favourable binding to all three proteins (Table 2).

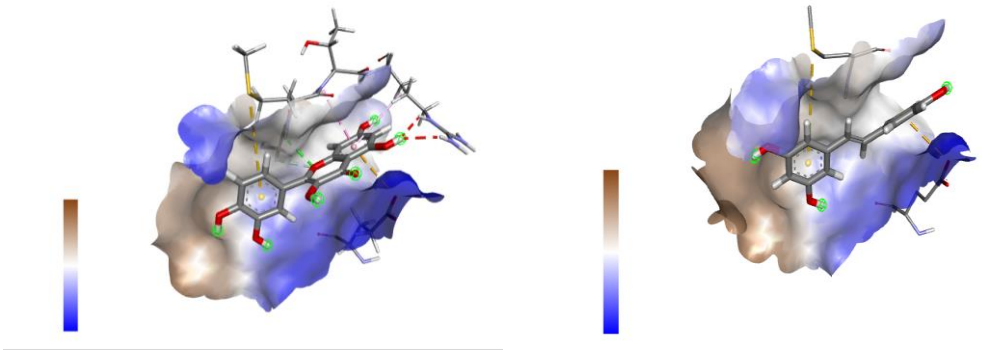
Table 2. Predicted binding energies (kcal/mol) of selected molecules against MAO-A, MAO-B, and IGF1R.

Molecule Name	Terapeutical Indication	MAO-A	MAO-B	IGF1R
Linsitinib	anticancer	−8.1	−9.8	−5.9
Metformin	antidiabetic	−5.6	−4.8	−4.2
Picropodophyllin	anticancer	6.5	−9.2	−7.5
Pioglitazone	antidiabetic	−8.2	−10.2	−6.8
Rosiglitazone	antidiabetic	−8.1	−9.7	−6.9
Quercetin	antiox	−7.8	−9.4	−6.9
Resveratrol	antiox	−8.4	−8.5	−6.5

The results show that resveratrol exhibited the strongest affinity toward MAO-A (–8.4 kcal/mol) and MAO-B (–8.5 kcal/mol), comparable to rosiglitazone (–8.1 and –9.7 kcal/mol) and pioglitazone (–8.2 and –10.2 kcal/mol). Quercetin showed strong binding to MAO-B (–9.4 kcal/mol) and IGF-1R (–6.9 kcal/mol), nearly identical to rosiglitazone. Interestingly, both linsitinib (–8.1, –9.8) and picropodophyllin (6.5, –9.2) drugs developed primarily as anticancer agents, whose mechanism of action involves direct IGF-1R inhibition, and also have demonstrated notable interactions with MAO enzymes. The calculated docking scores exhibited similarity with the TargetFisher results, except for the quercetin-MAO-B interaction, where the docking score indicated more favourable interactions.

Metformin, a first-line antidiabetic drug, showed the weakest binding to all three targets, which is consistent with its mechanism of action that does not involve direct enzyme inhibition with these targets.

The 3D protein ligand plots indicate favourable poses of quercetin and resveratrol within the binding site, as shown in Figure 1.



(**a**) (**b**)

Figure 1. Most favourable poses of studied molecules within the binding site shown as a surface coloured according to hydrophobicity (hydrophobic—brown, hydrophilic—blue): (**a**) quercetin-IGF-1R; (**b**) resveratrol-IGF-1R.

Furthermore, ligand– IGF-1R interactions were analysed using linsitinib interactions as a reference compound and compared to quercetin and resveratrol interactions (Figure 2). Although linsitinib, resveratrol, and quercetin interact with similar amino acid residues within the binding site, the nature of their interactions differs. For example, Glu1046 forms a conventional hydrogen bond with linsitinib, while interacting through pi-anion interactions with both quercetin and resveratrol. Arg1158 forms a conventional hydrogen bond with linsitinib, but displays an unfavourable donor–donor interaction with both quercetin and resveratrol. Met1156 engages in a pi–sulfur interaction with linsitinib and forms a conventional hydrogen bond with quercetin. Val1053 is involved in a pi–alkyl interaction with both linsitinib and resveratrol.

Quercetin and resveratrol exhibit a favourable interaction potential with IGF1R; however, their binding scores are lower compared to their interactions with other targets. In the context of our analysis, this suggests that these agents exert a stronger influence on the consequences of diabetic disease as antioxidants via MAO enzymes. However, it certainly indicates the potential for research into the use of these two products in antineoplastic therapy.

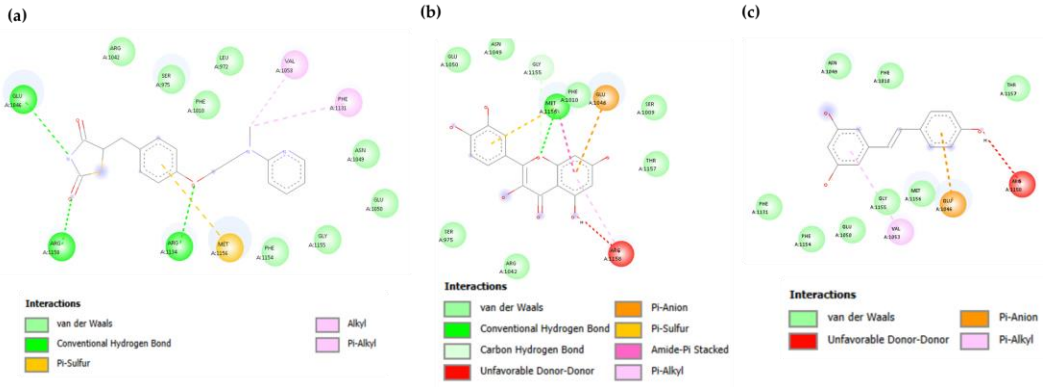


Figure 2. 2D Ligand–protein interactions plots: (**a**) IGF-1R-linstinib interaction; (**b**) IGF-1R-quercetin interaction; (**c**) IGF-1R resveratrol interaction.

The ligand-protein interaction analysis for MAO-A was conducted by comparing rosiglitazone with quercetin and resveratrol. The most significant structural similarities in their binding modes are: IleA335 an alkyl/pi-alkyl interaction was observed with this residue across all three ligands; PheA208, Rosiglitazone forms a pi donor hydrogen bond,

whereas quercetin and resveratrol exhibit a pi-pi stacked interaction with this residue; TyrA44, a conventional hydrogen bond was present with this residue for all three ligands.

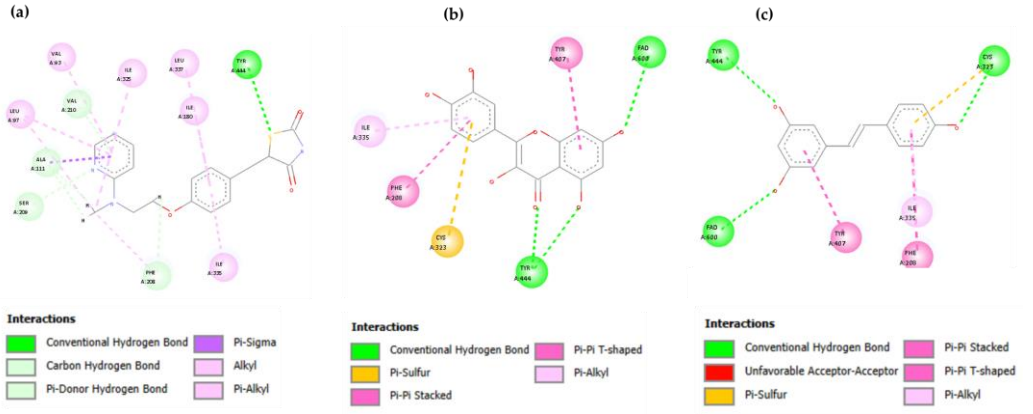


Figure 3. 2D Ligand–protein interactions plots: (**a**) MAO-A-rosiglitazone interaction; (**b**) MAO-A-quercetin interaction; (**c**) MAO-A-resveratrol interaction;.

Regarding MAO-B as a target, the interactions of quercetin and resveratrol were compared with that of pioglitazone, and the following observations were made: IleA199 forms an alkyl interaction with pioglitazone and a conventional hydrogen bond with resveratrol, generaly larger compounds such as pioglitazone and rosiglitazone are docked better in a crystal structure where Ile 199 adopts the 'open' conformation that is not needed for little molecules [13]; CysA172 forms a pi–sulfur interaction with pioglitazone, a pi–alkyl interaction with resveratrol, and a carbon hydrogen bond with quercetin; LeuA171 forms a carbon-hydrogen bond with pioglitazone and pi–alkyl interactions with both quercetin and resveratrol; TyrA398 engages in a pi-pi stacked interaction in all three cases. The interaction of quercetin with Tyr 435 is interesting, as it provides an advantage in the increased potency of MAO-B inhibition by utilising a key hydrophobic environment in the enzyme's active site (Figure 4) [13].

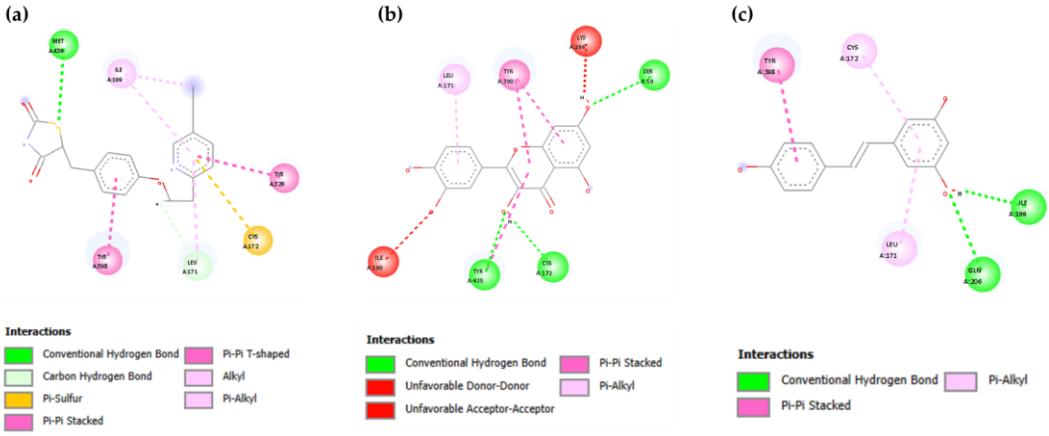


Figure 4. 2D Ligand–protein interactions plots: (**a**) MAO-B-pioglitazone interaction; (**b**) MAO-B-quercetin interaction; (**c**) MAO-B-resveratrol interaction.

4. Conclusions

Although resveratrol and quercetin are not recognised as conventional antidiabetic drugs, their well-documented antioxidant and anti-inflammatory effects suggest significant potential in alleviating diabetes-related symptoms and complications. Their increasing use as dietary supplements among diabetic patients highlights the importance of

understanding their molecular interactions with key disease-related targets. This study contributes to that understanding by comparing the binding profiles of quercetin and resveratrol with those of established antidiabetic agents (pioglitazone and rosiglitazone) and selected antineoplastic compounds (linsitinib and picropodophyllin), which may exert secondary metabolic effects.

Importantly, the study focuses on non-conventional protein targets associated not only with diabetes itself but also with common comorbidities, particularly those related to ageing, by including classic antidiabetic drugs such as rosiglitazone and pioglitazone—analysed here at their off-target sites—as well as investigational antineoplastic agents like linsitinib, not just because in a certain way they influence metabolic pathways indirectly but also because significant common biological processes, molecular functions, and pathways from Type 2 diabetes (T2D) are linked to the development of hepatocellular carcinoma HCC and colorectal cancer CRC [12]. The results of this research, to be confirmed experimentally, suggest that diabetic patients, who often suffer from multiple comorbid conditions, could benefit from the complementary use of natural polyphenols such as quercetin and resveratrol. These two molecules exhibit promising yet still underexplored in terms of their polypharmacology and effects on epigenetic targets, interactions with targets relevant to both metabolic and age-associated disorders, warranting further investigation into their therapeutic potential.

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