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Mechanistic investigation of Quercetin in the management of complications of Diabetes mellitus by Network Pharmacology

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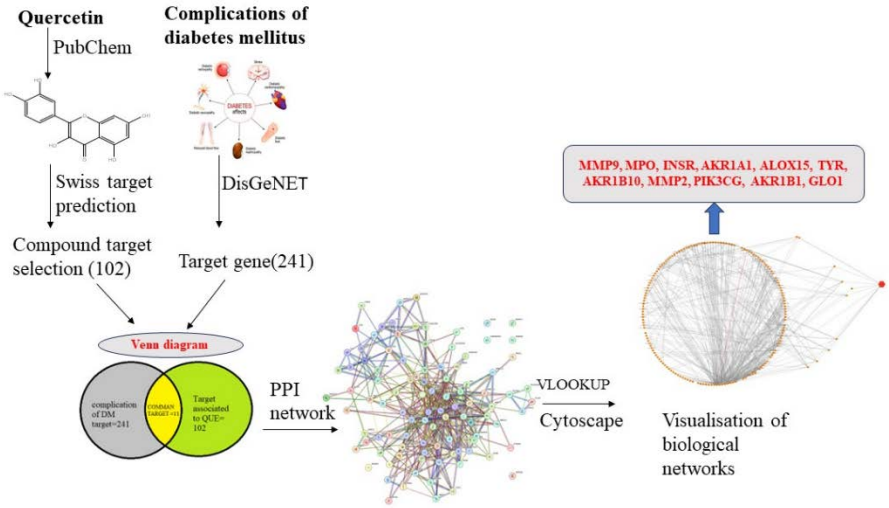
ABSTRACT



Quercetin is a health supplement that can assist in managing complications associated with diabetes. This study employed modern methods such as network pharmacology to investigate the mechanism by which quercetin protects against diabetes-related complications. Various comprehensive databases (Pubchem, Swiss target prediction database, SEA database, String database, Disgenet database) were used to obtain quercetin-associated targets and genes related to diabetes mellitus complications. The obtained targets were analyzed and intersected to obtain mapping targets, and a protein-protein interaction (PPI) network was constructed to identify candidate targets. These targets were then ranked to obtain key targets. The major pathways for quercetin obtained from the KEGG pathway were MMP9, MPO, INSR, AKR1A1, ALOX15, TYR, AKR1B10, MMP2, PIK3CG, AKR1B1, GLO1 found to be responsible for management and control of diabetes-associated complications.

Keywords: Network pharmacology, Quercetin, Diabetes complications, Hyperglycemia, Protein-Protein Interaction

INTRODUCTION

Diabetes, the most prevalent major metabolic illness and one of the top five killers globally, is characterized by persistent hyperglycemia linked to anomalies in the metabolism of carbohydrates, proteins, and lipids.[1]

The National Diabetes Committee has embraced T1DM, T2DM, and GTM diabetes. Diabetes will contribute, if left untreated, to various serious health problems affecting smaller and large vessels. The microvascular risks affect the renal system, the most expensive complication of diabetes, with persistent kidney failure (nephropathy) and nerve injury (neuropathy) increasing the likelihood of diabetic foot ulcers and/or amputations. Additionally, retinal degeneration (retinopathy) and macrovascular diseases such as peripheral artery disease, coronary heart failure, and stroke can cause blindness. The disturbance of the body's vascular system, combined with a hyperglycemic disease, is due to compromised digestion of sugars, protein, and electrolytes.[2]

One of the most prevalent and well-researched dietary flavonols, quercetin can be found in berries, apples, green tea, citrus fruits, green leafy vegetables, seeds, flowers, buckwheat,

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bark, broccoli, almonds, and olives. An aglycone, quercetin is commonly found in fruits and vegetables as glycoconjugates such as quercetin glycoside, quercetin glucuronide, quercetin rutinoside, etc.[3]

Quercetin has been demonstrated in numerous studies, particularly recent ones, to have positive therapeutic effects in treating a variety of human ailments, including diabetes. Quercetin may aid in reducing blood sugar and improving insulin sensitivity because it has potent anti-diabetic properties. Numerous elements and signalling pathways related to insulin resistance and the pathophysiology of type 2 diabetes appear to be impacted by quercetin. TNF, NFKB, AMPK, AKT, and NRF2 are a few of the factors that quercetin affects. Quercetin also influences the major pathways involved in the aetiology of these issues, making it useful in both preventing and treating diabetic complications like diabetic nephropathy, cardiovascular issues, neuropathy, delayed wound healing, and retinopathy. The anti-inflammatory and antioxidant properties of quercetin may be responsible for these advantageous effects.[4–7]

Andrew Hopkins was the first to propose network pharmacology, an emerging discipline based on the theory of systems biology that examines the network of biological systems and identifies particular signal nodes to develop multi-target therapeutic molecules.[8] Network pharmacology emphasizes multi-channel regulation of signalling pathways, which enhances the therapeutic effect of drugs, lowers the side and toxic effects, and increases predictability, increasing the success rate of clinical trials for new drugs and reducing the cost of drug research and development.[9,10]

This research paper aimed to investigate the mechanism of quercetin in the management of complications of diabetes mellitus through network pharmacology.

MATERIALS AND METHODS

This experimental study consists of six components: collection of active targets of quercetin, screening of disease targets in complications of diabetes mellitus, construction of Drug-Active Ingredient-Target Gene Disease Network, construction of Protein-Protein Interaction (PPI) network of targets in complications of diabetes mellitus, identification of common genes of interactions, and network construction in Cytoscape.[11]

2.1 Collection of Active Targets of quercetin

To identify the targets of quercetin, the Swiss databases were searched using the keyword "quercetin".[12] The identification of target genes required CANONICAL SMILES, which were collected from two databases: PubChem and ChEMBL.[13] The SEA and Swiss Target Prediction databases were used to estimate the most probable targets of quercetin based on 2D and 3D similarity with known activities in the databases. All unique targets obtained were considered to be regulated by quercetin. [14,15]

2.2 Screening of Disease Targets in complication of diabetes mellitus

To identify genes associated with complications of diabetes mellitus,[16] we used DisGeNET, a database of gene-disease associations. This platform is known for having a vast collection of genes and variants linked to human diseases. We searched the database using the keywords "complications of diabetes mellitus" and "Homo sapiens" to retrieve relevant information.[17]

2.3 Construction of Drug-Active Ingredient-Target Gene Disease Network

In Section 2.1, we identified the target genes for the compound quercetin. Similarly, in Section 2.2, we screened target genes related to diabetes complications. We then matched and mapped the two sets of target genes and identified the common genes as the key targets for quercetin in treating diabetes complications. We used Cytoscape 3.10.0 software to build a relationship network between the drug, active ingredient, target gene, and disease. We then analyzed this network topologically using the "Analyze network" function to better understand how quercetin works in treating diabetes complications.[18]

2.4 Construction of Protein-Protein Interaction (PPI) Network of DFU Targets

To search for known and predicted Protein-Protein Interactions (PPI), the String database (https://cn.string-db.org/) was used. Further inputted the common targets of quercetin and Disease Targets in the complication of diabetes mellitus into the String database, selected the study species as human ("Homosapiens"), set the confidence threshold to be greater than 0.4, and hid disconnected nodes in the network. Then used the downloaded.tsv file in String with R 4.0.4 language software to process the data and drew the PPI diagram based on the degree value (degree). Finally, the top 20 PPI core gene targets were obtained.[19]

2.5 Identification of common genes of interactions

It is done with advanced skills in Microsoft Excel. create an Excel sheet of disease genes and compound target genes with the help of 'VLOOKUP' FORMULA[20] Common genes of interaction are identified. GO, KEGG Functional Enrichment Analysis. The species was limited to "Human," and the enriched entries with q values (corrected P values) less than 0.05 were retained and sorted according to the size of the q values.

2.5 Network construction in Cytoscape

The network was created and styled using Cytoscape 3.10.0, an open-source software platform that visualizes complex networks and integrates them with attribute data. This network's nodes represent proteins, and the edges represent protein interactions. The Network Analyzer plug-in of Cytoscape was used to analyze the network topology parameters, including the "degree" of targets in the PPI network. The targets with the highest "degree" values were identified as key targets for quercetin protection against complications of diabetes mellitus.

RESULT AND DISCUSSION

Network pharmacology was performed for quercetin as a potential treatment for managing diabetes mellitus complications.

3.1 Searching quercetin-associated Targets:

A total of 102 targets of quercetin were obtained from Swiss target prediction. The targets were ranked based on their probability of being targeted by the compound. The canonical smiles used for quercetin were obtained from PubChem and are

as follows: C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O.

3.2 Searching genes related to DFU:

Complications of diabetes mellitus are associated with 241 human genes, which were identified using the Disgenet database (https://www.disgenet.org). The Venn diagram illustrates how each database source contributed to determining the protein-target information. It also shows the role of each protein-target (PT) prediction method in determining quercetin's targeting ability. In the diagram, the grey circle represents the target predicted in complications of diabetes mellitus, while the green circle represents the target involved in quercetin. Furthermore, the Venn diagram (**Figure 1)** demonstrates the disease and compound target**.**

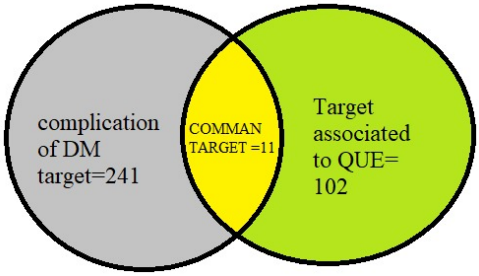

Figure 1: Venn diagram represents a common target for quercetin

3.3 Protein-protein interaction:

The PPI network was created using the String database (https://string-db.org/) KEGG pathway file to analyze the complications of diabetes mellitus concerning quercetin. The network consists of 120 associated targets where each node represents all the proteins produced by a single protein-coding gene locus. The colored nodes represent query proteins and their first shell of interactors, whereas the white nodes represent the second shell of interactors. Empty nodes indicate proteins of unknown 3D structure, while filled nodes represent proteins with some 3D structure that can be either known or predicted. The edges on the network symbolize protein-protein associations. The PPI network contains 99 nodes and 489 edges, with an average "degree" value of 9.88, which is the mean number of connections per node. Please refer to **Figure 2** for the visual representation of the PPI network.

3.4 Identification of common genes of interactions:

The formula VLOOKUP (C: C, I2:I456,1, FALSE) from MS Excel was used to identify the common genes (MMP9, MPO, INSR, AKR1A1, ALOX15, TYR, AKR1B10, MMP2, PIK3CG, AKR1B1, GLO1) associated with the management of complications of diabetes mellitus and target interacting with QUERCETIN. To clarify the mechanism of quercetin in treating the complications of diabetes mellitus, the Cytocape software (https://cytoscape.org/) was used to build the relationship network of "drug-active ingredient-target gene-disease". The "Analyze network" function in the software was then used to perform topological analysis on the network, as shown in **Figure 3**.

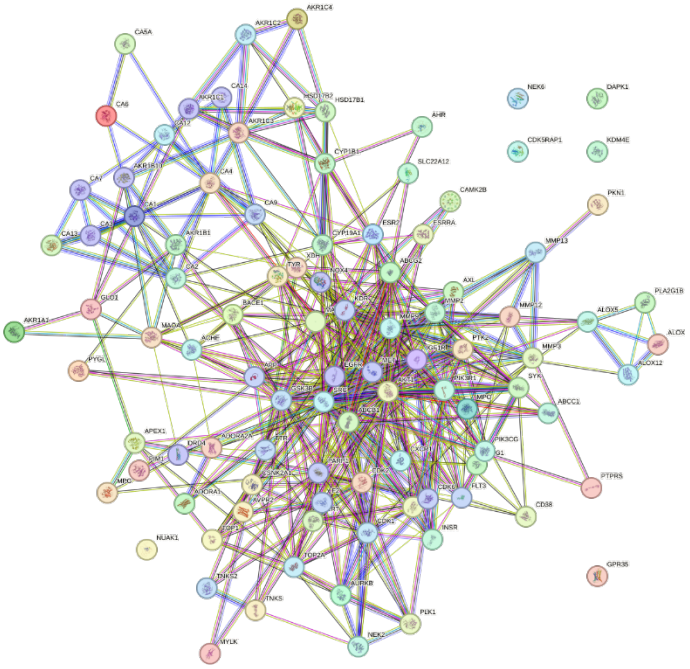

Figure 2: PPI network of quercetin

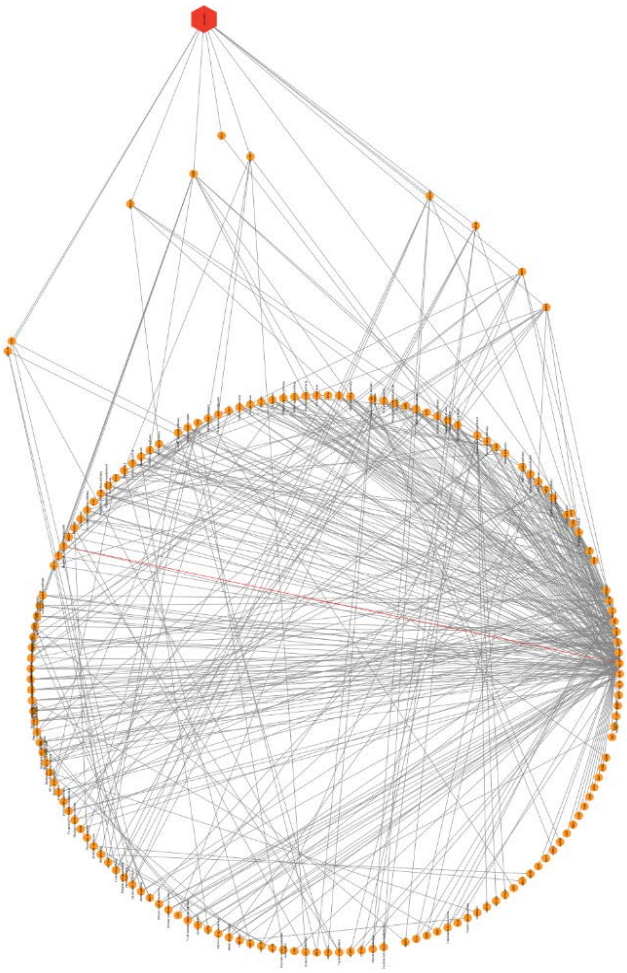

Figure 3: Network analysis of quercetin

Network pharmacology-based approach is to use computational methods to find putative binding proteins for a given compound. In this study, 11 potential targets of these components were identified by network pharmacology. Biological process and pathway enrichment analysis of these targets demonstrated that quercetin could exert an anti-diabetic effect by regulating various biological processes through different pathways. The detailed action pathways of 11 targets such as MMP9, MPO, INSR, AKR1A1, ALOX15, TYR, AKR1B10, MMP2, PIK3CG, AKR1B1, GLO1 through network pharmacology in the management of complications of diabetes mellitus is as MMP9 stimulates 10 pathways such as proteoglycan in cancer, pathways of cancer, prostate cancer, estrogen signaling pathway, Relaxin signaling pathway, Leukocyte transendothelial migration, IL-17 signaling pathway, TNF signaling pathway, Fluid shear stress and atherosclerosis. INSR stimulates 10 other pathways such as the MAPK signaling pathway, Fox O signaling pathway, HIF-1 signaling pathway, insulin resistance, Insulin signaling pathway, mTOR signaling pathway, Longevity regulating pathway, Non-alcoholic fatty liver disease, AMPK signaling pathway, Regulation of lipolysis in adipocytes. AKR1A1 stimulates 3 pathways: metabolic pathways, glycerolipid metabolism, and pentose and glucuronate interconversions. ALOX15 stimulate 5 pathways such as linolic acid metabolism, serotonergic synapse, arachidonic metabolism, metabolic pathway, necroptosis. TYR involved in stimulation of tyrosine metabolism, metabolic pathway and melenogenisis. AKR1B10 involved in galactose metabolism, fructose and mannose metabolism, glycerolipid metabolism, and Pentose and glucuronate interconversion, folate biosynthesis and metabolic pathway. MMP2 stimulate estrogen signaling pathway, relaxin signaling pathway, Fluid shear stress and atherosclerosis, leukocyte transendothelial migration, bladder cancer, GrNH signaling pathway, proteoglycan in cancer and pathways of cancer. PIK3CG affects oxytocin signalling pathway, platelet activation, cholinergic synapse and metabolic synapse. AKR1B1involved in galactose, fructose and mannose metabolism, glycerolipid metabolism, and pentose and glucuronate interconversions, folate biosynthesis and metabolic pathway. MPO is activated by quercetin. GLO1target metabolic pathway.

CONCLUSION

This study scientifically investigates the pharmacological mechanism of quercetin in the treatment of complications of diabetes mellitus through network pharmacology. The performed study concludes that quercetin can be effectively proposed in the management of complications of diabetes mellitus by inhibiting the action of 11 targets such as MMP9, MPO, INSR, AKR1A1, ALOX15, TYR, AKR1B10, MMP2, PIK3CG, AKR1B1, GLO1 through network pharmacology. It is concluded that quercetin containing extracts and formulations can reduce the complications associated with diabetes mellitus by the management of above-mentioned targets.

Abbreviations: Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), Matrix metalloproteinase 9 (MMP9), Myeloperoxidase (MPO), Insulin receptor (INSR), Aldehyde reductase (AKR1A1), Arachidonate 15-lipoxygenase (ALOX15), Tyrosinase (TYR), Aldo-keto reductase family 1 member B10 (AKR1B10), Matrix metalloproteinase 2 (MMP2), PI3-kinase p110-gamma subunit (PIK3CG), Aldose reductase (AKR1B1), Glyoxalase I (GLO1)

REFERENCES

1. D.K. Yang, H.-S. Kang. Anti-diabetic effect of cotreatment with quercetin and resveratrol in streptozotocin-induced diabetic rats. *Biomol. Ther*. **2018**, 26 (2), 130.
2. S.A. Mezil, B.A. Abed. Complication of diabetes mellitus. *Annal. Romanian Society for Cell Biology* **2021**, 1546–1556.
3. R. Dhanya. Quercetin for managing type 2 diabetes and its complications, an insight into multitarget therapy. *Biomedicine & Pharmacotherapy* **2022**, 146, 112560.
4. L. Yan, M. Vaghari-Tabari, F. Malakoti, et al. Quercetin: an effective polyphenol in alleviating diabetes and diabetic complications. *Crit. Rev. Food Sci. Nutrition* **2022**, 1–24.
5. N. Murugesan, C. Damodaran, S. Krishnamoorthy. Niosomal formulation of Quercetin and Resveratrol and in-vitro release studies. *J. Integr. Sci. Technol.* **2022**, 10 (2), 134–138.
6. N. Murugesan, C. Damodaran, S. Krishnamoorthy, M. Raja. In-vitro evaluation of synergism in antioxidant efficiency of Quercetin and Resveratrol. *Chem. Biol. Let.* **2023**, 10 (2), 534.
7. N. Murugesan, C.P. Damodaran. Antioxidant activity of synergistic quercetin resveratrol. *J. Mol. Chem.* **2023**, 3 (1), 581.
8. Y. Dong, Q. Zhao, Y. Wang. Network pharmacology-based investigation of potential targets of astragalus membranaceous-angelica sinensis compound acting on diabetic nephropathy. *Scientific reports* **2021**, 11 (1), 19496.
9. A.L. Hopkins. Network pharmacology. *Nat. biotechnol.* **2007**, 25 (10), 1110–1111.
10. L.I. Shao, B. Zhang. Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chinese J. Natural Med.* **2013**, 11 (2), 110–120.
11. K. Chen, Y. Deng, S. Shang, et al. Network Pharmacology-Based Investigation of the Molecular Mechanisms of the Chinese Herbal Formula Shenyi in the Treatment of Diabetic Nephropathy. *Frontiers in Medicine* **2022**, 9, 898624.
12. G. Zu, K. Sun, L. Li, et al. Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus. *Scientific rep.* **2021**, 11 (1), 22959.
13. S. Feng, T. Wang, L. Fan, et al. Exploring the potential therapeutic effect of Eucommia ulmoides–Dipsaci Radix herbal pair on osteoporosis based on network pharmacology and molecular docking technology. *RSC advances* **2022**, 12 (4), 2181–2195.
14. M. Davies, M. Nowotka, G. Papadatos, et al. ChEMBL web services: streamlining access to drug discovery data and utilities. *Nucl. Acids Res.* **2015**, 43 (W1), W612–20.
15. Q. Chen, X. Chen, X. Chen, et al. Computational biomedical modeling and screening for prediction of molecular mechanisms of Simiao Pill against hyperuricemia. *Journal of Molecular Liquids* **2023**, 381, 121827.
16. L. Zhang, S. Lu, Z. Hu, et al. Prediction of the anti-inflammatory effects of bioactive components of a Hippocampus species-based TCM formulation on chronic kidney disease using network pharmacology. *Tropical Journal of Pharmaceutical Research* **2021**, 20 (11), 2355–2362.
17. J. Piñero, J.M. Ramírez-Anguita, J. Saüch-Pitarch, et al. The DisGeNET knowledge platform for disease genomics: 2019 update. *Nucleic acids res.* **2020**, 48 (D1), D845–D855.
18. Y. Wang, X. Zhang, M. Duan, et al. Identification of potential biomarkers associated with acute myocardial infarction by weighted gene coexpression network analysis. *Oxidative medicine and cellular longevity* **2021**, 2021.
19. Y. Yin, Q. Wu, Z. Wang, Y. Kang, X. Xie. AMU: Using mRNA Embedding in Self-Attention Network to Predict Melanoma Immune Checkpoint Inhibitor Response. *medRxiv* **2022**, 2022–10.
20. T. Tohge, A.R. Fernie. Combining genetic diversity, informatics and metabolomics to facilitate annotation of plant gene function. *Nat. prot.* **2010**, 5 (6), 1210–1227.