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Network Pharmacology-Based Approach to Unveil the Therapeutic Mechanism of *Viburnum opulus* L. on Glomerulonephritis

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ABSTRACT

This study aimed to investigate the potential targets and pathways of the bioactive compounds of *Viburnum opulus* L. – a plant recognized in ethnopharmacology for its therapeutic applications in renal disorders - on glomerulonephritis (GN) disease. The phytochemical profile of *V. opulus* was obtained from review articles in the literature on plant contents. GN-associated target genes were retrieved from the GeneCards database, and interaction mapping was conducted using Cytoscape 3.10.0. The intersection of compound - target - disease was imported into the STRING database to create a PPI network. GO and KEGG enrichment analyses were applied to define the biological functions of the targets. A molecular docking study simulated the binding capabilities of key targets and active ingredients. A total of 9 bioactive constituents were identified from *V. opulus*, with rutin and quercetin demonstrating the highest binding affinities. The resulting compound–target interaction network consisted of 125 nodes and 358 edges. Central hub proteins within the PPI network included TP53, SRC, and EGFR indicating their potential role in the mechanism of action. GO and KEGG analyses suggested that the treatment of GN by *V. opulus* mainly involves the generation of cellular response to chemical and oxidative stress, protein tyrosine kinase activity, transcription regulatory complex, and other biological processes. The results of KEGG enrichment analysis indicate that *V. opulus* mainly involves some pathways, such as chemical carcinogenesis-receptor activation, EGFR tyrosine kinase inhibitor resistance in the treatment of GN. Molecular docking data presented that rutin and quercetin have the highest affinity score with TP53, SRC, and EGFR proteins. Overall, this study reveals the active compounds and potential molecular pathways of *V. opulus* in the treatment of GN and presents a source for further basic studies.

Keywords: *Viburnum opulus,* Glomerulonephritis, Network pharmacology, Molecular docking.

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Introduction

The kidneys play a crucial role in filtering metabolic waste from the body. The microscopic building blocks in its structure are called glomeruli [1]. Glomerulonephritis (GN) is a disease that causes impaired kidney function as a result of inflammation of the glomeruli [2]. It is important to produce an effective drug for the treatment of GN.

Ethnopharmacology is the science of using traditional medicines and practices derived from plants for healing purposes. Ethnobotanical studies have been utilised to develop a safe method for many diseases with the therapeutic properties of plants from ancient times to the present day [3].

Viburnum opulus L. is a plant in the Adoxaceae family, interesting for both its decorative and medicinal uses, known colloquially as gilaburu, guelder rose, European cranberrybush, and is widespread in Europe, Russia, North Africa, and North Asia. *V. opulus* is traditionally preferred in the treatment of many diseases such as colds, coughs, tuberculosis, rheumatic pains, ulcers, stomach and kidney ailments [4].

Network pharmacology is a modern approach to understanding drug targets, mechanisms of action and side effect profiles by analysing the complex interactions of biological systems [5]. In contrast to the traditional single-target focus of pharmacology, network-based approaches recognise that a drug can interact with many biomolecules and cellular pathways. This method aims to systematically study drug-gene, drug-protein, and drug-disease relationships using bioinformatics, systems biology, computational modelling and data mining techniques [6]. In particular, multi-targeted drug design has great potential in the areas of better understanding of disease mechanisms and personalised medicine [5]. In recent years, herbal medicines have emerged as an important research area for polypharmacological strategies.

Molecular docking is a computational method used to imagine how a ligand (drug candidate molecule) binds to a target protein. This technique is of great importance, especially in drug discovery, analysis of protein-ligand interactions, and elucidation of biomolecular mechanisms. Molecular docking helps to determine the optimal conformation and affinity by assessing the binding site, interaction energy, and stability [7].

In this research, we aimed to determine the therapeutic qualities of *V. opulus* in the treatment of GN using network pharmacology and molecular docking approaches. By using in slico analysis to investigate the bioactive contents and molecular mechanisms of *V. opulus* in GN treatment, it was aimed to provide useful data for further research.

Materials and Methods

Network Analysis

The active compounds belonging to *V. opulus* plant are arranged and given in Table 1 from the articles in the literature in which the contents of the plant were determined by using various extraction methods and chromatographic techniques [4,8]. GN disease targets were obtained by searching associated genes in GeneCards (https://www.genecards.org/) with the keyword 'glomerulonephritis' [9]. Target genes of *V. opulus* were obtained from the SwissTargetPrediction (http://www.swisstargetprediction.ch/) database [10]. Potentially active components of *V. opulus* and their matching targets were loaded into Cytoscape 3.10.0, and a network model including GN components and targets was created [11] (Figure 1). The jvenn database was used to find the intersection of the active ingredients in the plant and the overlapping targets of GN (http://www.bioinformatics.com.cn/static/others/jvenn/example.html) [12]. In order to obtain information about the protein interaction network of genes intersecting *V. opulus* and GN, it was transferred to the STRING (https://string-db.org/) database and analysed by identifying the species as 'homo sapiens' [13]. Protein-protein interaction (PPI) data were analysed, then target nodes with BC and CC degree scores above the median values in the PPI network were identified and 10 potential core targets were chosen for further analysis. Within the scope of gene ontology (GO) analysis, Metascape (https://metascape.org/gp/index.html#/main/step1) tool was used for the evaluation of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways together with cellular components (CC), molecular functions (MF) and biological processes (BP) and SRPLOT (https://www.bioinformatics.com.cn/srplot) was used for visualisation [14,15].

Molecular Docking

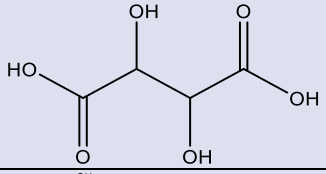
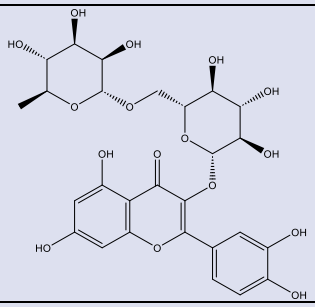
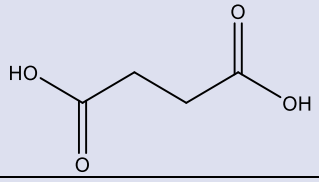
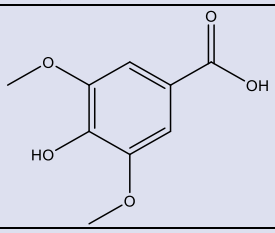
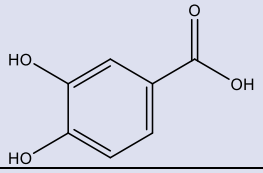
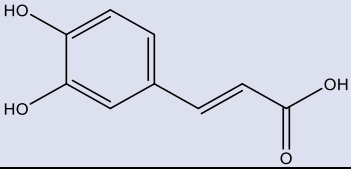
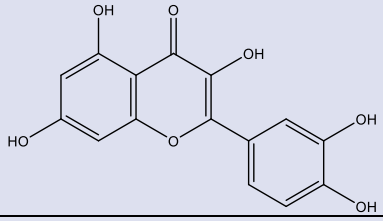
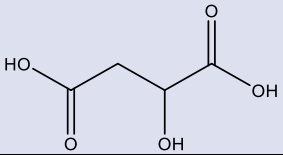
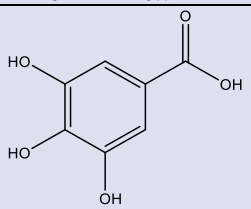
For the molecular docking study, which examines the binding of two molecules (receptor–ligand) and is frequently used in the fields of structural biology and drug design, the three-dimensional (3D) structure of the target protein was obtained from the RCSB PDB database (http://www.rcsb.org/) [16]. The three-dimensional (3D) molecular structures of the 9 ligands identified in the plant content were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [17]. Ligand binding model and interaction analysis were performed using the Maestro Schrödinger package software. Since the receptors obtained from the PDB database were not suitable for direct docking calculations, they were subjected to a structural optimisation process. In this process, hydrogen atoms were added to the receptor, partial charges were assigned, and the missing loops in the chains were completed. Water molecules within 3 Å (Angstrom) of the binding site in the crystal structure were removed from the system. In order to model the receptor and ligand interaction in accordance with biological conditions, the system was minimised at pH 7.4, and ligands were prepared at the same pH conditions [18].

Results

The molecular structures and IUPAC names of the 9 active components organised according to the literature are taken from Pubchem and given in Table 1 [4,8,17].

The network between the active compounds in *V. opulus* and GN is represented by a node. The relationship between the component and the target is represented by a connecting line. As shown in Figure 1, there are 125 nodes and 358 edges.

Table 1. Potential active compounds of *V. opulus* [4,8,17].

Compound	Molecular Structure	IUPAC Name
Tartaric acid		(2R,3R)-2,3-dihydroxybutanedioic acid
Rutin		2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one
Succinic acid		butanedioic acid
Syringic acid		4-hydroxy-3,5-dimethoxybenzoic acid
Protocatechuic acid		3,4-dihydroxybenzoic acid
Caffeic acid		(E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid
Quercetin		2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one
Malic acid		2-hydroxybutanedioic acid
Gallic acid		3,4,5-trihydroxybenzoic acid

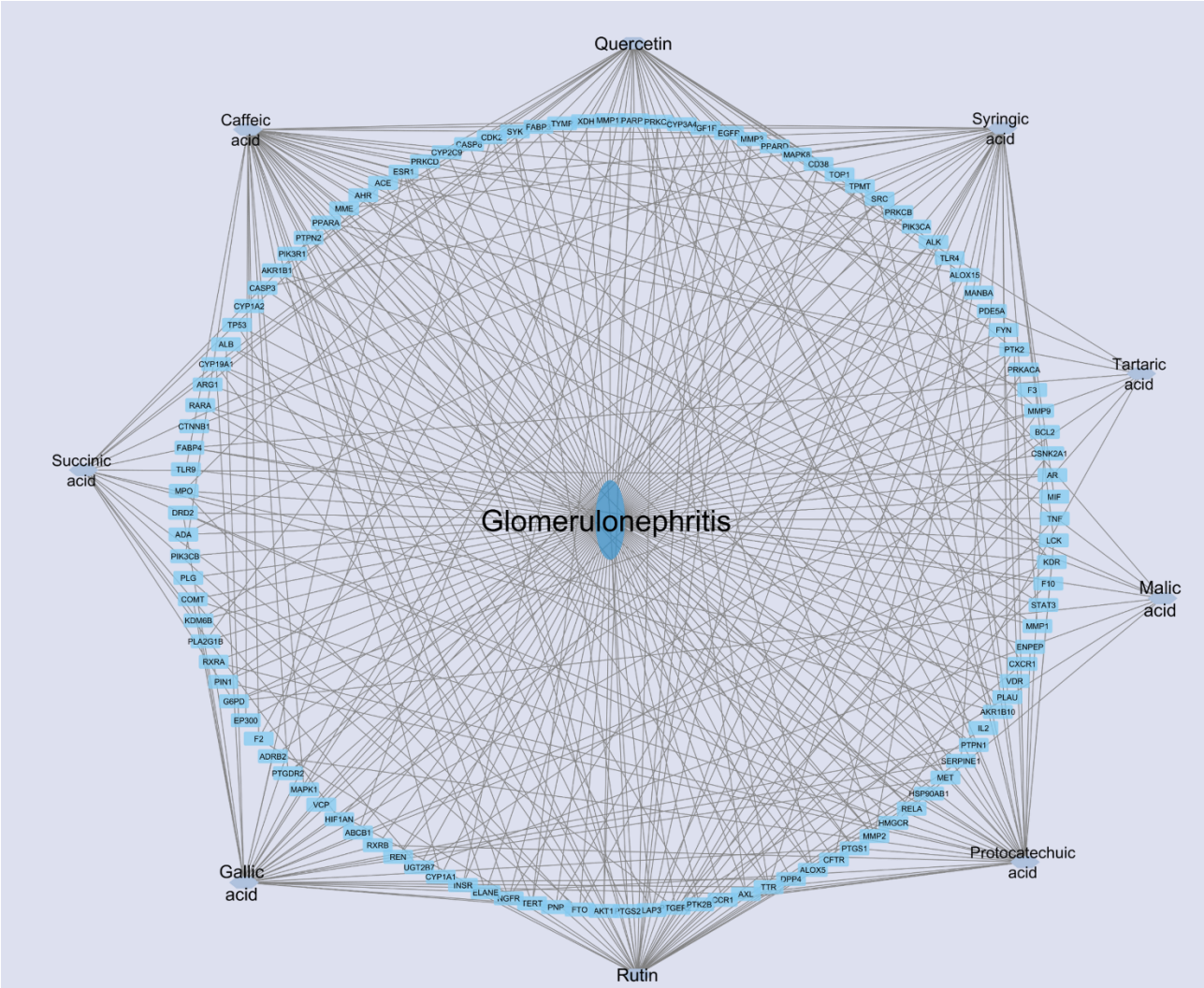


Figure 1. Bioactive coumpounds and corresponding targets network of *V. opulus* of GN. The ellipse in the centre represents the disease. Hexagons represent 9 phytochemical compounds. Blue rectangles represent 358 potential target genes of *V. opulus*.

When looking at the Venn diagram results, there are 114 common targets between *V. opulus* targets and GN disorder targets (Figure 2).

The protein-protein interaction (PPI) network was analysed by transferring the drug-disease intersection genes to the STRING database and as a result, an interaction network containing 106 nodes and 581 edges was created (Figure 3).

The degree values of the first ten targets were evaluated according to DC (Degree Centrality), BC (Betweenness Centrality) and CC (Closeness Centrality) criteria as shown in Table 2. As a result of this analysis, the top 10 proteins were TP53, SRC, EGFR, STAT3, CTNNB1, TNF, AKT1, BCL2, PTGS2 and ESR1 (Figure 3).

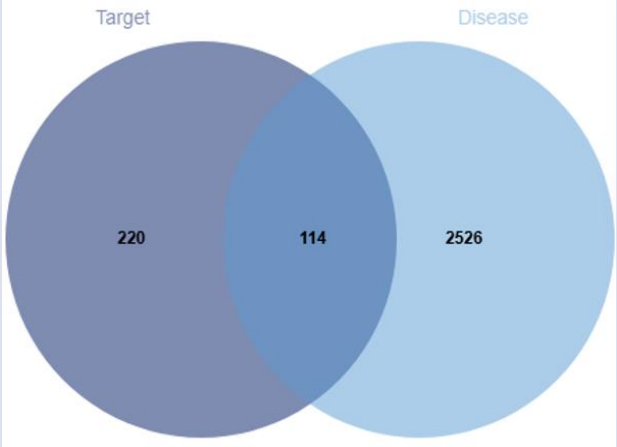


Figure 2. Venn diagram shows genes between GN and *V. opulus*

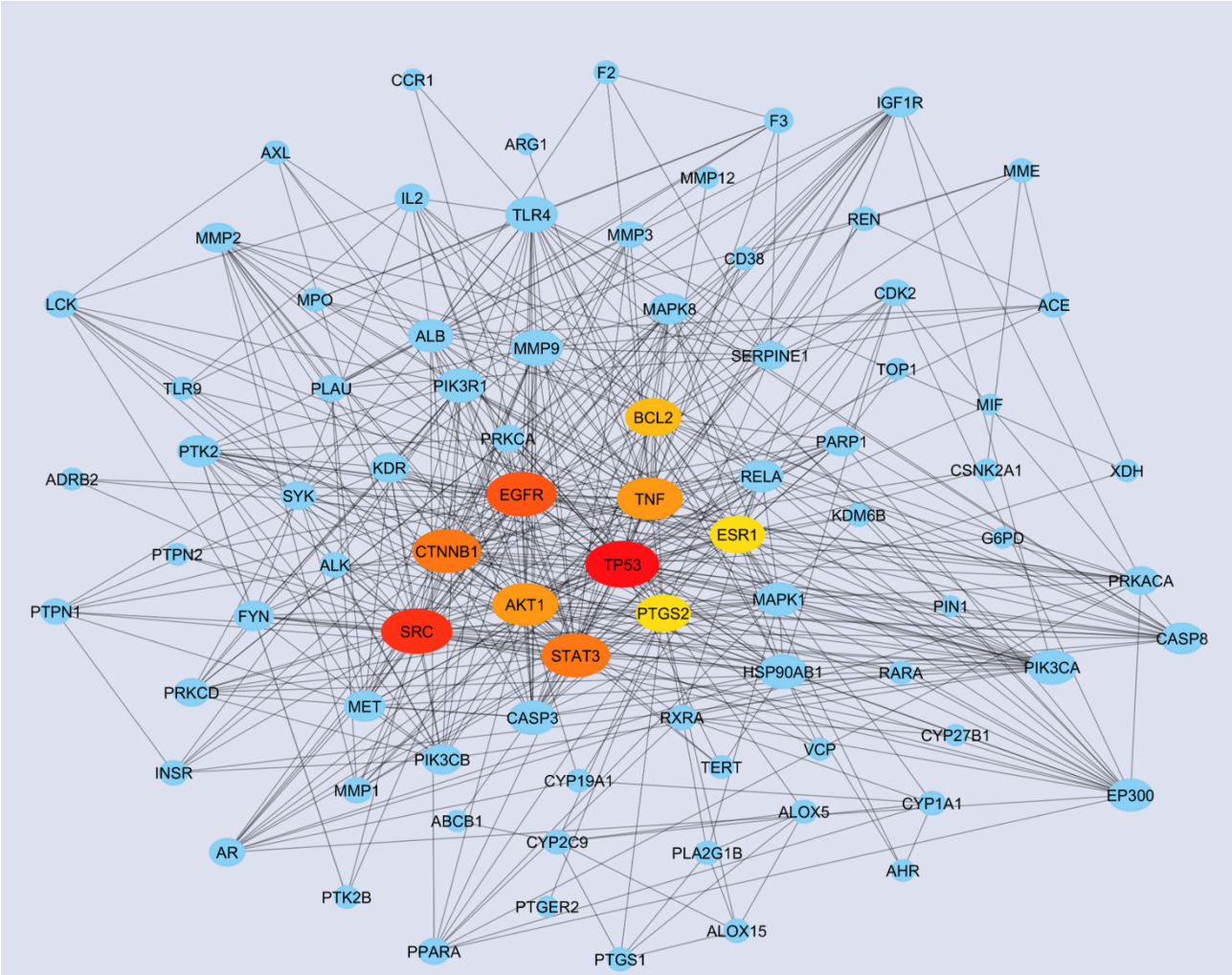


Figure 3. The PPI network of *V. opulus* and GN targets. Nodes Express proteins (The colors from yellow to red express the degree of binding between protein). Edge express protein-protein interaction.

Table 2. Some data on attributes of the top 10 target according to the degree value.

Name	Score	Betweenness Centrality	Closeness Centrality
TP53	40	0.12813816862591176	0.5706521739130435
SRC	38	0.06527801831039313	0.5440414507772021
EGFR	37	0.05731073423629428	0.5614973262032086
STAT3	36	0.07122806909889566	0.5497382198952879
CTNNB1	36	0.054655771432631	0.5614973262032086
TNF	34	0.10591636291065458	0.5585106382978723
AKT1	34	0.05521460279319312	0.5585106382978723
BCL2	27	0.02951844026402951	0.5329949238578681
PTGS2	26	0.03372253267195596	0.525
ESR1	26	0.05514466457790829	0.5147058823529412

The 114 intersection targets obtained were mapped to their biological processes (BP), GO molecular functions (MF) and cellular components (CC) through the Metascape database and SRPLOT was used for visualisation. The first 30 items were selected from the terms obtained by GO analysis. As shown in Figure 4, GO (Gene Ontology) analysis shows the enrichment scores of genes under three different ontology categories (BP: Biological Process, CC: Cellular Component, MF: Molecular Function). In the BP category, oxidative stress response, chemical stress response, response to drugs and response to reactive oxygen species are the most enriched biological processes. In the CC category, vesicle lumen, membrane microdomains and extrinsic membrane components are the most prominent cellular components. In the MF category, protein tyrosine kinase activity, phosphatase binding, transcription coactivator binding and serine-type peptidase activity are the most enriched molecular functions. Figure 5 reveals that biological pathways associated with cancer, metabolic diseases and infections were enriched, with the most significant pathways being chemical carcinogenesis, lipid metabolism and cancer-related processes, with bubble size indicating the number of genes and colour scale indicating statistical significance.

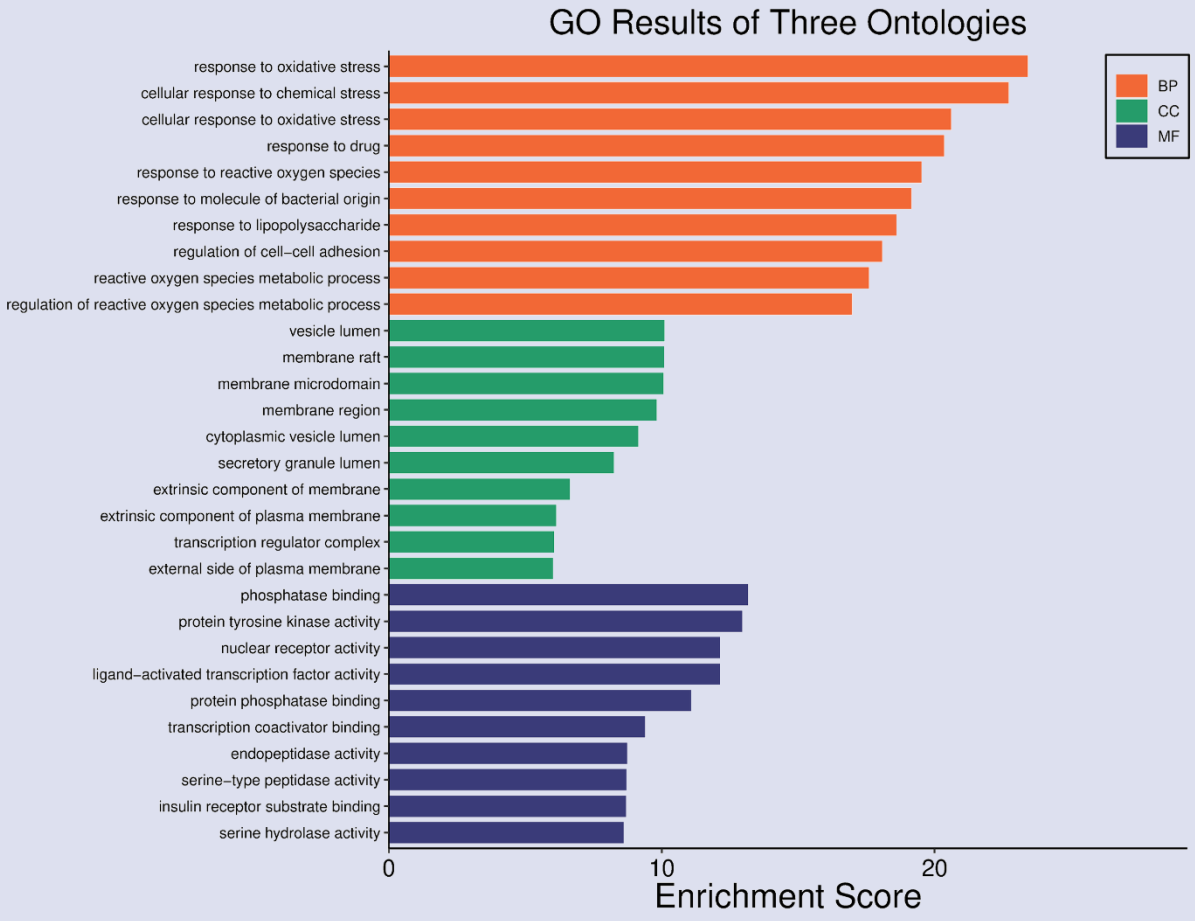


Figure 4. Top 10 GO terms of hub genes.

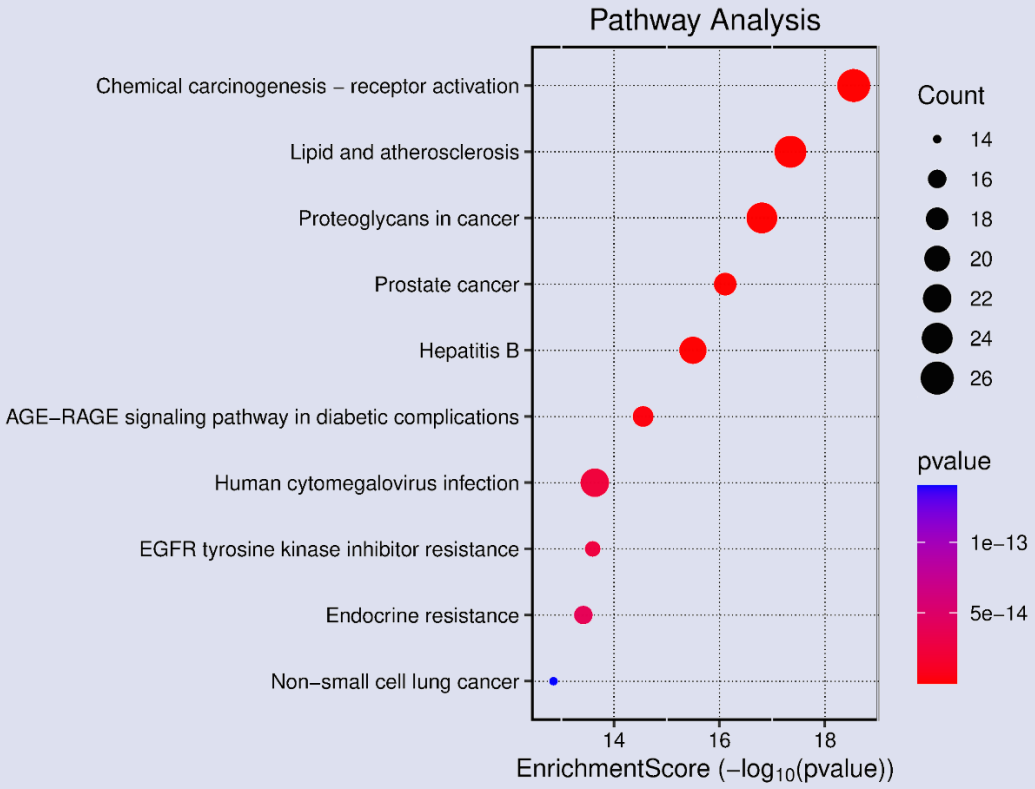


Figure 5. Top 10 KEGG pathway of hub genes

According to the molecular docking informations presented in Table 3 and Table 4, among the 9 active compounds in the plant, rutin and quercetin are the compounds with the best docking score with genes. It is seen that these compounds belonging to the flavonoid group have the lowest binding energy (highest binding affinity) compared to other compounds.

Table 3. Molecular docking results of rutin

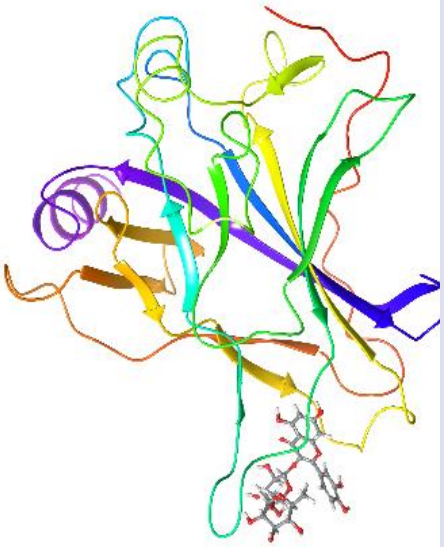
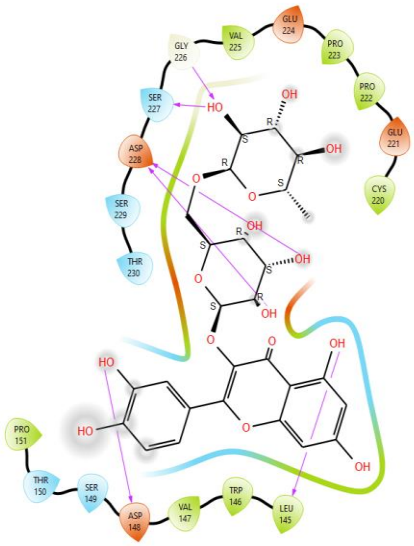
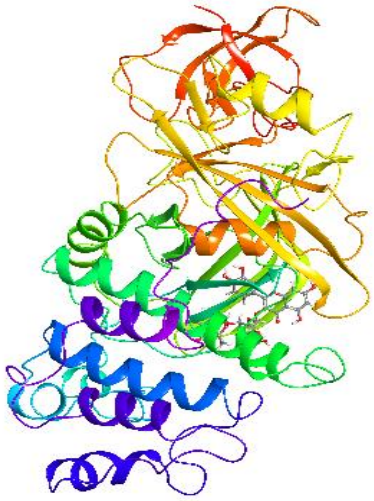
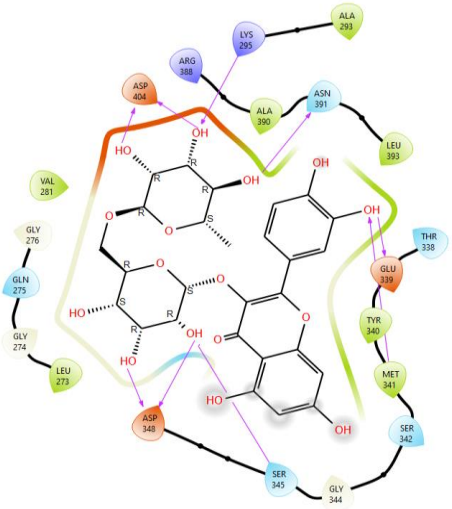
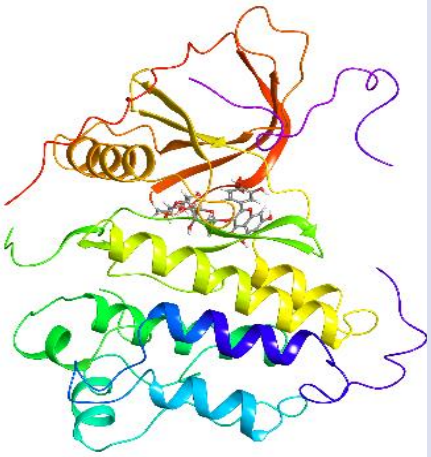
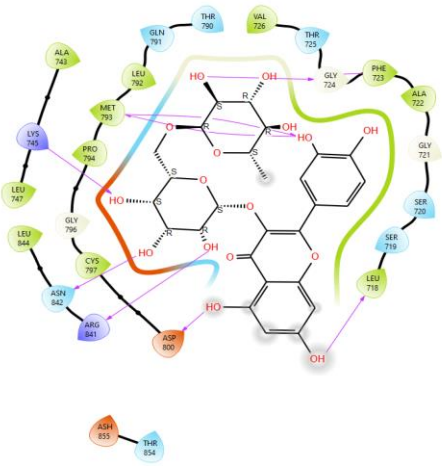
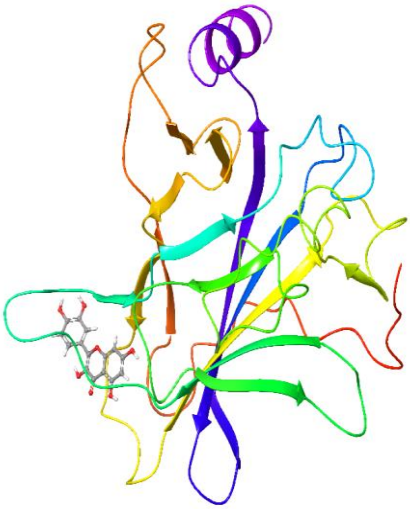
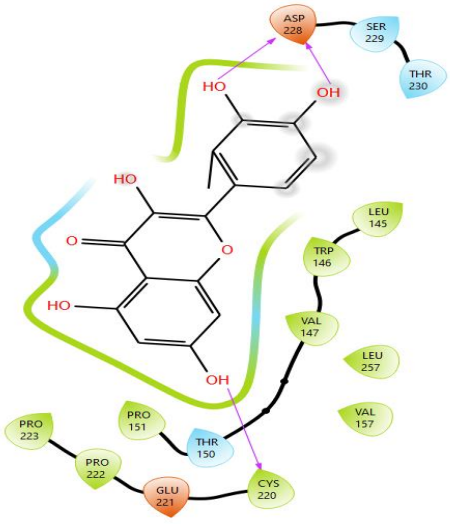
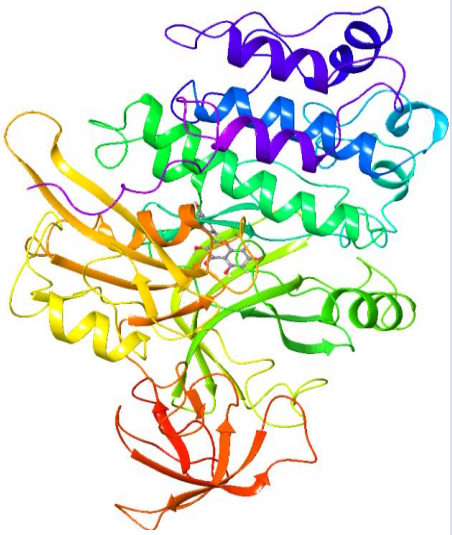
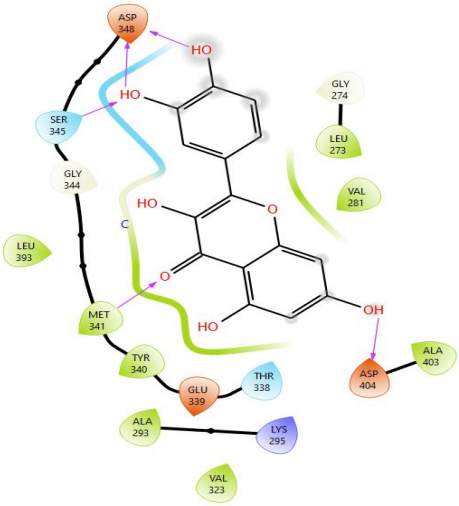
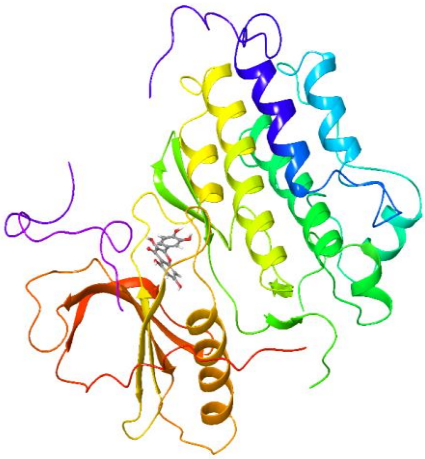
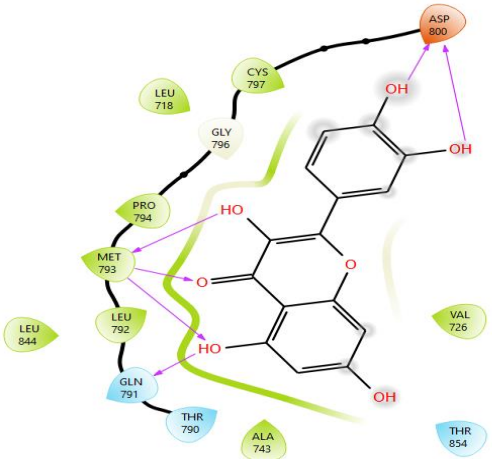
Target	3D Structure	2D Structure	Docking Score
TP53 (8DC7) - Rutin			-7.862
SRC (1A07) - Rutin			-9.939
EGFR - (2ITN) Rutin			-9.153

Table 4. Molecular docking results of quercetin

Target	3D Structure	2D Structure	Docking Score
TP53 (8DC7) - Quercetin			-6.021
SRC (1A07) - Quercetin			-7.719
EGFR (2ITN) - Quercetin			-8.625

Molecular docking consequences showed that rutin and quercetin can interact well with TP53, SRC and EGFR proteins. Rutin formed 2 hydrogen bonds with amino acid ASP228 and one hydrogen bond with amino acids ASP148, LEU145, GLY226, SER227 in TP53 protein. The molecular docking score was determined as -7,862 kcal/mol. Rutin formed two hydrogen bonds at positions ASP348 and ASP404 and one hydrogen bond at positions LYS295, GLU339, MET341, SER345, ASN391 in SRC protein. The molecular docking score was determined as -9.939

kcal/mol. In EGFR protein, rutin formed a hydrogen bond with the amino acids MET793, GLY724, PHE723, LEU718, ASP800, ARG841, ASN842, LYS745. The molecular docking score was determined as -9.153 kcal/mol.

Quercetin created 2 hydrogen bonds with ASP228 amino acid and one hydrogen bond with CYS220 amino acid in its interaction with TP53 protein. The molecular docking score was determined as -6,021 kcal/mol. Quercetin created two hydrogen bonds with amino acid ASP348 and one hydrogen bond with amino acids SER345, MET341, ASP404 in its interaction with SRC protein. The molecular docking score was determined as -7,719 kcal/mol. Quercetin formed three hydrogen bonds with amino acid MET793, two hydrogen bonds with amino acid ASP800 and one hydrogen bond with amino acid GLN791 in its interaction with EGFR protein. The molecular docking score was determined as -8.625 kcal/mol.

In molecular docking studies, the affinity between receptor and ligand is stronger if the binding energy is lower than -5 kcal/mol [19]. Accordingly to the molecular docking results we obtained, the binding energies show that all of them are lower than -5 kcal/mol. The lowest binding energy is between SRC and rutin (-9.939 kcal/mol), while the docking of TP53 and quercetin has the highest binding energy (-6.021 kcal/mol).

Rutin and quercetin connect well to three key targets (TP53, SRC and EGFR) and based on this, we guess that these bioactive ingredients may act an important role in the treatment of GN.

Discussion

The incidence of kidney diseases, one of the most common chronic diseases on a global scale, is gradually increasing, and this situation is considered an important issue in the field of health [20]. GN is a condition of damage to the glomeruli caused by acute or chronic inflammation, and this process can affect each of the basement membrane, mesenchyme, and capillary endothelium that make up the glomerular structure [2]. Studies have shown that *V. opulus*, which is popularly used to reduce kidney stones, can be used as an important non-invasive herbal treatment method that facilitates the passage of ureteral stones. In various experimental studies, it has been explained that *V. opulus* facilitates the passage of <10 mm ureteral stones and can be used as an alternative herbal treatment material [21]. In this research, the goal was to determine the potential molecular mechanism of *V. opulus* plant by network pharmacology and molecular docking applications to have information about its therapeutic properties in GN disease.

Using both papers by Polka et al. (2019) and Kajszczak et al. (2020), 9 chemical constituents with common intersections were compiled [4,8]. These 9 chemical components can be divided into groups as organic acids (tartaric acid, succinic acid, malic acid), phenolic acids (gallic acid, syringic protocatechuic acid, caffeic acid), and flavonoids (rutin-quercetin). The human immune system secretes various pro-inflammatory mediators, contributing to the activation and recruitment of immune cells. However, excessive production of these components can lead to the development of different chronic diseases [22]. Phenolic compounds, which are known to have many protective properties for living organisms, can show their anti-inflammatory effects by inhibiting the production or activity of pro-inflammatory mediators that are overproduced in the organism [23]. Flavonoids, also commonly known as hydroxylated polyphenols, have many properties (analgesic, anti-proliferative, antioxidant, anticancer, anti-angiogenic, anti-microbial, anti-inflammatory, anti-viral, and anti-malarial) [24–26]. In a research on the protective effect of quercetin on sepsis-induced lung damage, it was observed that quercetin can reduce the amount of ROS in the lung tissue of rats with sepsis, increase SOD, APX and CAT activities, and reduce the expression of study-related (HMGB1) protein [27]. In addition, it was found that quercetin regulates the effect of reducing inflammation and oxidative stress by down-regulating the expression of Toll-like receptor protein [28]. According to these findings, it is promising that these 9 different bioactive components may have therapeutic effects in the treatment of GN, but further research is needed.

In this study, through the PPI network containing 114 common genes, the top 10 core genes with high ranking value were obtained, namely TP53, SRC, EGFR, STAT3, CTNNB1, TNF, AKT1, BCL2, PTGS2, and ESR1 genes. TP53 is a tumour suppressor gene and has an essential role in vital reactions such as controlling the cell cycle, responding to DNA disorders, and apoptosis (programmed cell death). TNF-α has an effect on inflammation in serum levels [29,30].

On the other hand, within the scope of this study, GO and KEGG enrichment applications were applied to investigate the mechanism of action of *V. opulus* in GN treatment. GO results expressed that the target genes were mainly took part in regulation of oxidative stress response, generation of cellular response to chemical and oxidative stress, regulation of drug response, regulation of secretory granule lumen, activation of transcription regulatory complex and external part of plasma membrane, tyrosine kinase activity, phosphatase binding, ligand-activation of transcription factors, transcription coactivator binding, serine-type peptidase and hydrolase activity.

The results of KEGG enrichment analysis indicate that *V. opulus* in GN treatment mainly involves some pathways, such as EGFR tyrosine kinase inhibitor resistance, chemical carcinogenesis-receptor activation. Dysregulation or abnormal activation of receptor tyrosine kinases (RTKs) has compensatory functions against EGFR inhibition. Currently, many clinical trials are underway intending to solve and prevent TKIs resistance in various inflammatory conditions and cancers. The EGFR-TKIs offer a promising first-line strategy for further clinical events in inflammatory diseases [31].

Rapidly progressive glomerulonephritis (RPGN) is a disease characterised by quick loss of renal function with the lesions in the glomeruli, accumulation of proliferation of intrinsic glomerular cells. Nowadays, a link between the HB-EGF-EGFR pathway and RPGN in a mouse model of nephritis has been described. However, HB-EGF-deficient mice were found to show EGFR phosphorylation and were resistant against RPGN. The inhibition pharmacologically of EGFR has been shown to effectively reduce glomerular damage and ameliorate acute renal failure in this animal model [32]. Future studies are needed to further investigate the role of HB-EGF and EGFR in the pathogenesis of GN. Recent studies have shown that EGFR activation also play a role in to the many renal diseases. like GN. In this case, the indication that *V. opulus* may be effective as an EGFR tyrosine kinase inhibitor in the treatment of GN suggests that the use of this plant in the treatment of GN may be promising for clinical applications [33].

Chen et al. (2012) reported that when SRC activation is induced, it mediates sustained EGFR phosphorylation and TGF-β expression. [34]. These data suggest that SRC is a important factor of renal fibrosis. Another study presented that activation of c-Src is consistent with the mesangial proliferation in GN [35]. Jalal and Kone (2006) showed that SRC activates the NF-κB in GN and inflammatory host responses [36]. Since mesangial cell proliferation is the defining mechanism in GN, these results suggest that c-Src is critically involved in the pathogenesis of this disease. In addition, Gruden et al. (2003) suggested that SRC is involved in the insulin-like growth factor-induced production of VEGF (vascular endothelial cell growth factor), which is involved in the pathogenesis of early renal impairment in diabetes [37]. Wu et al. (2015) revealed in their study that inhibition of SRC by PP2 caused a decrease in Bax-Bcl-2 and caspase-3 levels in the kidneys of diabetic mice [38]. Some common pathological changes, such as activation of renal fibroblasts and inflammation, are regulated by SRC Family Kinases (SFKs). Therefore, knocking out one SFK may not be sufficient to prevent pathological effects. Therefore, with the combined use of highly selective inhibitors and gene silencing techniques, further studies are necessary to explain clearly the relative participation of SFK members in pathologies [39].

p53, an important part of defence mechanisms against DNA damage, is a critical protein that prevents tumour formation by regulating repair processes, limiting cellular growth, and inducing apoptosis when necessary [40]. Although the role of p53 in tumour formation is well established, recent studies suggest that p53 plays roll in the beginning and attending of various kidney disorders. The drug studies suggest that clinical targeting of p53 may make way as a novel therapeutic approach for acute and chronic kidney disease [41]. This demonstrates the potential benefits of targeting p53 to suppress progressive kidney injury and chronic kidney injury (CKD) [42]. In conclusion, in this study, while investigating the potential mechanism of *V. opulus* in the treatment of GN, based on the results of network pharmacology, the screening results of the active components of the plant and the screening results of the targets in the PPI network, the bioactive components of rutin and quercetin as the most effective compound were screened in further analyses. As a result of molecular docking, it was determined that rutin and quercetin compounds showed the highest degree of molecular binding with TP53, SRC, and EGFR proteins. According to the molecular docking results, it was found that rutin and quercetin compounds can bind very well to these three proteins and have the lowest binding energy. This shows that the protein-bioactive compound combinations obtained are the most stable.

There are still some limitations in this study. Current network analysis techniques need to be improved and optimized. Also, the accuracy and sensitivity of database data need to be further increased, and the margin of error needs to be reduced. At the same time, according to the literature, compounds or targets that have not been validated or have never been recorded may not have been included in our study. Although the 9 active ingredients selected in this study were identified as the most important bioactive components of this plant, it should always be considered that they may not fully represent the plant content in reality. Therefore, pharmacodynamic experiments and molecular biology experiments should definitely be planned in the future to further confirm our research results. Since the effects of the potential active constituents herein on GN have not been proven by controlled experiments, we believe that the research area is of great interest, and the importance of this research is great.

Conclusion

This study revealed the preliminary investigation of the main chemical contents and possible mechanism of *V. opulus* in the treatment of GN, based on network pharmacology and molecular docking techniques. Our research shows that rutin and quercetin may be the important basic active components of *V. opulus* with therapeutic nature, and the protein targets TP53, SRC, and EGFR may be potential therapeutic target of *V. opulus* in the treatment of GN. The effective components of *V. opulus* plant may provide therapeutic agents in GN disease through TP53, SRC, and EGFR pathways. In addition, this study will support a reference for further studies on the mechanism of *V. opulus* in the treatment of GN.

Conflict of Interest

The authors declare that they have no conflicting interests.

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