Study on the Mechanism of Coptis Chinensis in the Treatment of Diabetic Nephropathy Based on Network Pharmacology

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Abstract: To investigate the therapeutic effects of Coptis chinensis on diabetic nephropathy using systematic pharmacological techniques. The TCMSP database was used to search the main components and related targets of Coptis chinensis; the GeneCards and CTD databases were used to screen the disease targets of diabetic nephropathy, and the intersection of the targets and disease targets was taken and plotted in Venn diagram; the target protein interaction (PPI) network was constructed from STRING database; the DAVID 6.8 online tool was used to GO and KEGG enrichment analyses were performed using DAVID 6.8 online tool to obtain the key signaling pathways of Coptis chinensis acting in diabetic nephropathy. Fourteen effective components of Coptis chinensis and 186 targets were obtained from the TCMSP database, and 3358 diabetic nephropathy targets were obtained from the summary of two databases, GeneCards and CTD. 118 intersecting targets of Coptis chinensis components and diabetic nephropathy diseases were obtained, and the core targets were TP53, MAPK1, AKT1, RELA, TNF, CAV1, RXRA, which may act on MAPK signaling pathway and PI3K-Akt signaling pathway to regulate the inflammatory response and oxidative stress generated by diabetic nephropathy process, thus reducing the disease symptoms. Coptis chinensis can exert its mechanism of action for the treatment of diabetic nephropathy through multiple components with multiple targets and pathways.

1 INTRODUCTION

Diabetic nephropathy is mostly a kidney injury induced by microvascular complications of diabetes mellitus, which presents early with persistent albuminuria (or albuminuria excretion rate of >300 mg/d or 200 μg/min) and a progressive reduction in glomerular filtration rate (GFR) (Selby and Taal 2020; Thipsawat 2021). The International Diabetes Federation Diabetes Map estimated that in 2011, 366 million people worldwide (8.3% of adults) had diabetes, and this number will increase to 552 million by 2030 (Alicic, Rooney and Tuttle 2017; Reutens 2013). Risk factors for the development of DN from cross-sectional studies include genetic susceptibility, hypertension, hyperglycemia, hyperfiltration, smoking, and high protein diet. Therefore, the clinical treatment of diabetic nephropathy is mainly symptomatic and includes glycemic control, hypertension treatment, hyperlipidemia, smoking cessation, protein restriction and renal replacement therapy (Ayodele, Alebiosu and Salako 2004; Navaneethan, Zoungas, Caramori, Chan, Heerspink, Hurst, Liew, Michos, Olowu, Sadusky, Tandon, Tuttle, Wanner, Wilkens, Lytvyn, Craig, Tunnicliffe, Howell, Tonelli, Cheung, Earley, Rossing, de Boer and Khunti 2021). In recent years, with the proposed new use of old drugs, the hypoglycemic, lipid-regulating, anti-inflammatory, cardiovascular function-improving, and blood pressure-lowering effects of Coptis chinensis are being proposed. Zhenxian Qinet al. (Qin, Wang, Liao, Wu and Li 2018)found that Coptis chinensis could reduce fasting blood glucose levels, improve tolerance to glucose, and restore serum levels of the four lipids in diabetic mice. Coptis chinensis also affects macrophages and inhibits the production of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, and is able to regulate the NF-κB signaling pathway, which further regulates the production of various pro-inflammatory enzymes and cytokines(Yan, Yingchao, Zhangliu, Xianli, Si, Siyi and Jihong 2020). In this paper, based on systems biology, we integrate pharmacology and computer technology to explore the potential active ingredients and action targets of Coptis chinensis and to deeply reveal its drug action mechanism.

2 METERIALS AND METHODS

2.1 Screening of Components and Targets of Coptis Chinensis

Capturing the relationship between drugs, targets and diseases using TCMSP (Traditional Chinese Medicine

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Systems Pharmacology Database and Analysis Platform). Fill in the input box to get the composition, relevant targets, and relevant.

2.2 Screening of DN Disease Targets and Intersecting Genes

Using "Diabetic Nephropathies" as a keyword, genes with direct evidence of experimental validation and treatment were screened in the CTD database and supplemented by the Gene cards database. The total number of targets involved in diabetic nephropathy was obtained by collating the two databases. Venny was then used to integrate the intersection of the targets of Coptis chinensis components with the targets of diabetic nephropathy disease, and finally the intersection genes were derived. Coptis chinensis exerts its therapeutic effect on diabetic nephropathy through these intersecting genes.

2.3 Network Diagram of Active Ingredient-Interacting Genes of Flos Daturae and the Construction of Protein-Protein Interaction Network

The obtained intersection genes were sorted out and corresponded to the active ingredients of Coptis chinensis one by one. Cytoscape 3.9.1 software was used to construct a network diagram of the active ingredients of Coptis chinensis - intersection targets, in which the connecting lines represent the interconnection between the ingredients and the targets, and the size of the nodes represents the size of the node degree value. The more the number of connecting lines between nodes, the larger the nodes are and the larger the degree value is. And the visualization analysis of the intersection protein network structure is performed using String database.

2.4 GO and KEGG Enrichment Analysis

GO illustrates gene functions from three parts of data: cellular components, molecular functions, and biological processes. KEGG helps to understand the high-level functions and utilities of biological systems from genomic and molecular perspectives. GO and KEGG enrichment analysis is performed through the CAVID database and the results are visualized using gadgets.

3 RESULTS

3.1 Coptis Chinensis Components and Targets

The TCMSP database was used to obtain information that Coptis chinensis contains 48 ingredients with 596 targets. The ingredients were screened according to OB≥30% and DL≥0.18, resulting in 14 ingredients, and those without action targets were removed. As shown in Table 1, 11 active ingredients were finally obtained. The target information was pre-screened according to the 14 components and duplicate values were removed, resulting in 186 targets, and the target protein names were calibrated to the official names by Uniprot database, and non-human genes were excluded.

Table 1 Active components and target information of Coptis coptidis

Mol ID	Molecule Name	AlogP	OB (%)	DL	Target
MOL000098	quercetin	1.5	46.43	0.28	151
MOL002903	(R)-Canadine	3.4	55.37	0.77	31
MOL002904	Berlambine	2.49	36.68	0.82	20
MOL000785	palmatine	3.65	64.6	0.65	19
MOL001454	berberine	3.45	36.86	0.78	17
MOL002894	berberrubine	3.2	35.74	0.73	13
MOL002897	epiberberine	3.45	43.09	0.78	11
MOL001458	coptisine	3.25	30.67	0.86	9
MOL002668	Worenine	3.73	45.83	0.87	7
MOL000622	Magnograndiolide	1.18	63.71	0.19	4
MOL002907	Corchoroside A_qt	1.34	104.95	0.78	2

MOL013352	Obacunone	2.68	43.29	0.77	0
MOL008647	Moupinamide	2.86	86.71	0.26	0
MOL000762	Palmidin A	4.52	35.36	0.65	0

3.2 Diabetic Nephropathy Disease Targets and Crossover Genes

With "Diabetic Nephropathies" as the key word, 3586 target genes of diabetic nephropathy were obtained in CTD and Gene cards database. Through Venny analysis, there are 118 intersection targets between Coptis chinensis components and diabetic nephropathy (Fig.1).

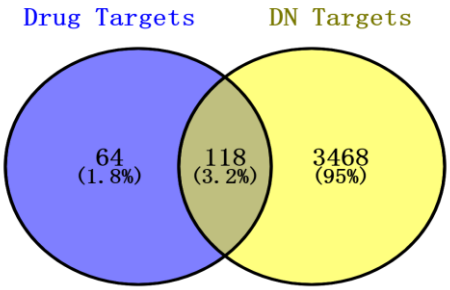

Fig.1 Venny Diagram of intersection Target of Coptis chinensis and Diabetic Nephropath

3.3 The Results of the Related Network Diagram Are Shown

Except for Magnolialactone which did not act on the intersection targets, the remaining 10 active ingredients of Coptis chinensis were collated with 118 intersection targets and the ingredient-target network diagram was constructed by Cytoscape 3.9.1 (Fig.2). Red triangles represent the active ingredients of Coptis chinensis and green dots represent the intersection targets. It can be concluded that among all the components of Coptis chinensis, quercetin has the largest node connection value.And among all the targets, the innermost circle of targets is more closely associated with the component of Coptis chinensis. The Protein-Protein Interaction Networks (PPI) of 118 overlapping genes was constructed by using STRING database, the interaction score was set to the highest confidence level (0.900), the unrelated nodes were deleted, and the other parameters were kept as the default parameters (Fig.3). The goals of centrality, proximity to centrality and node connectivity greater than the average were screened, and TP53, MAPK1, AKT1, RelA, tumor necrosis factor, CAV1 and RXRA were obtained as core proteins.

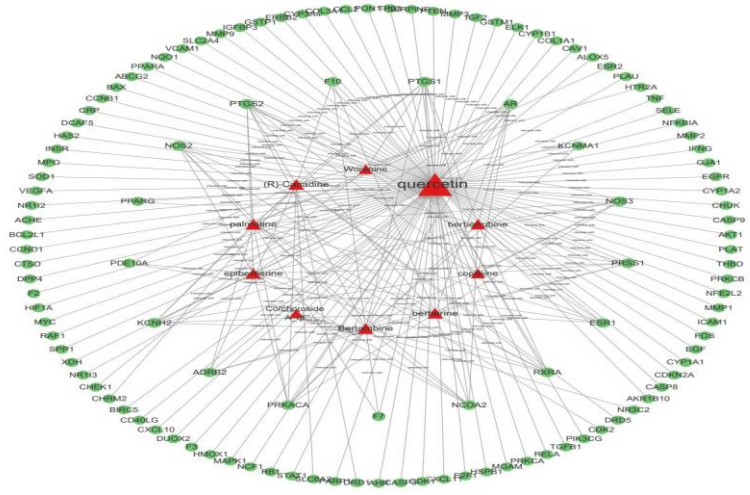

Fig.2 Coptis chinensis component-intersection gene network map

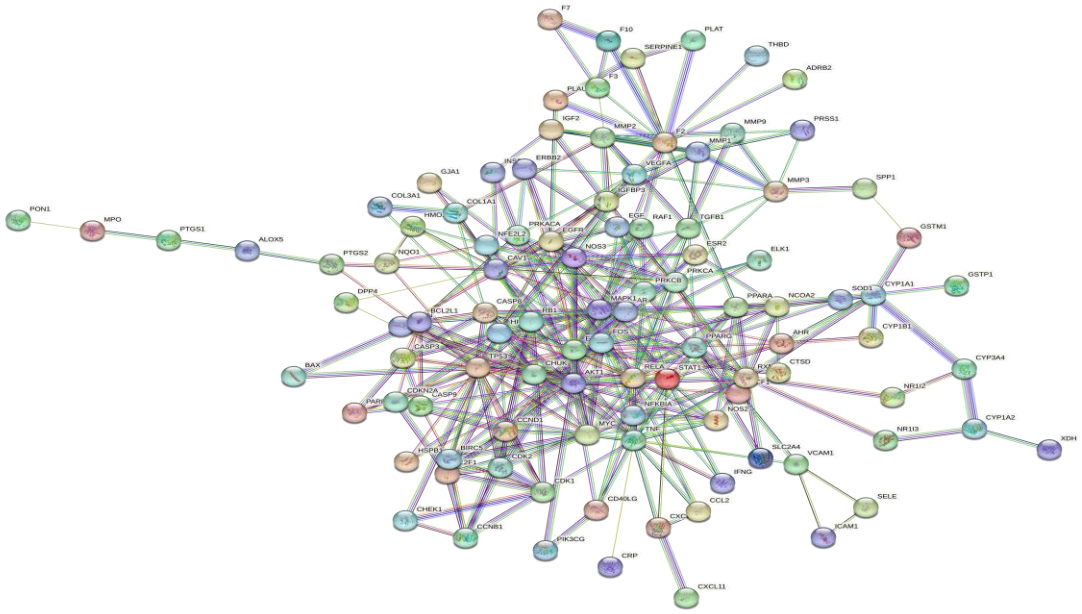

Fig.3 PPI diagram of overlapping genes

3.4 GO and KEGG Enrichment Analysis Results

Import the targets whose center value, compactness value and node connection value are all greater than the average, such as TP53, MAPK1, AKT1, RELA, TNF, CAV1, RXRA, into the DAVID database. The results of GO and KEGG enrichment analysis of Coptis chinensis were obtained. The biological processes involved include 13 biological processes, including positive regulation of gene expression, positive regulation of DNA template transcription, signal pathway mediated by lipopolysaccharide, regulation of RNA polymerase II promoter, signal pathway mediated by tumor necrosis factor and I κ B kinase / NF- κ B signal transduction (Fig.4). The cell components involved are polymer complexes. The four biological functions involved are the same protein binding, enzyme binding, transcriptional regulatory region sequence-specific DNA binding and protein kinase binding. According to the order from large to small according to Count, the first 20 KEGG pathways were screened to draw the enrichment bubble diagram. Coptis chinensis can improve diabetic nephropathy through MAPK signal pathway and PI3K-Akt signal pathway (Fig.5).

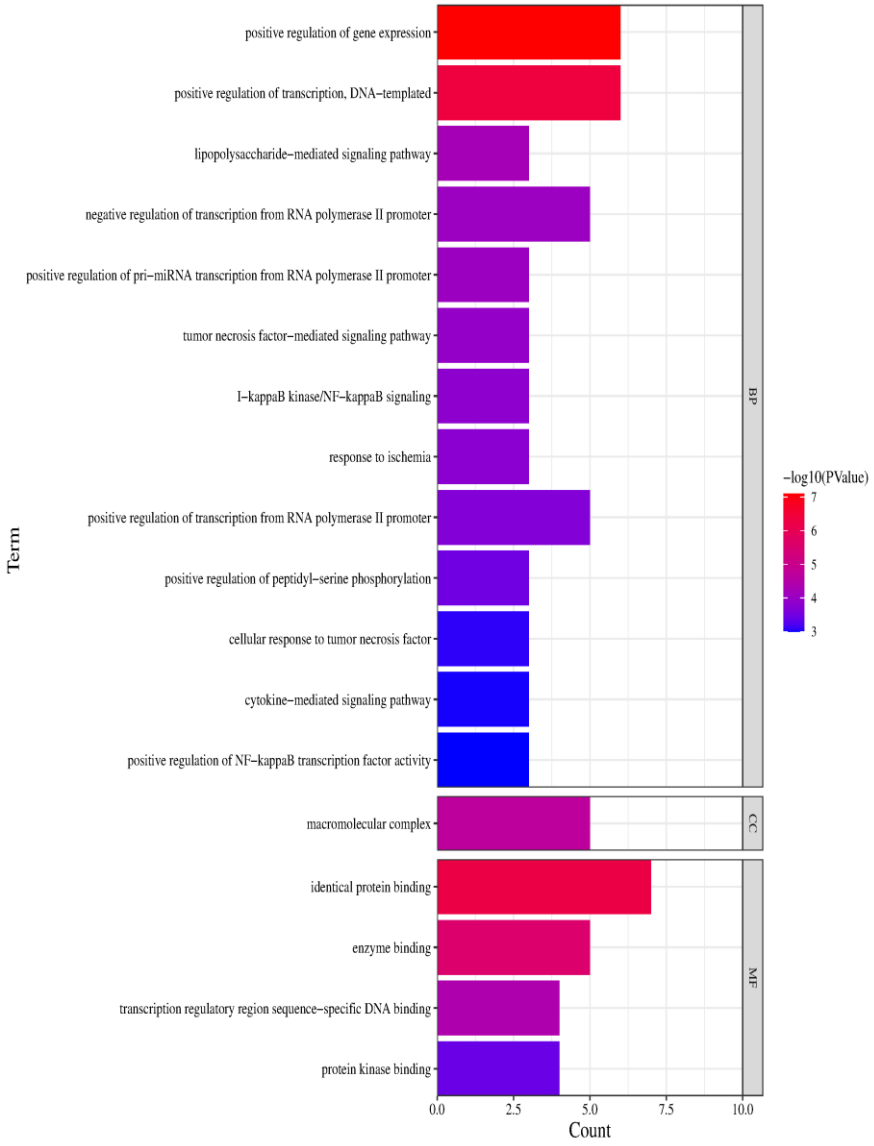

Fig.4 GO enrichment analysis network of the targets of Coptis chinensis

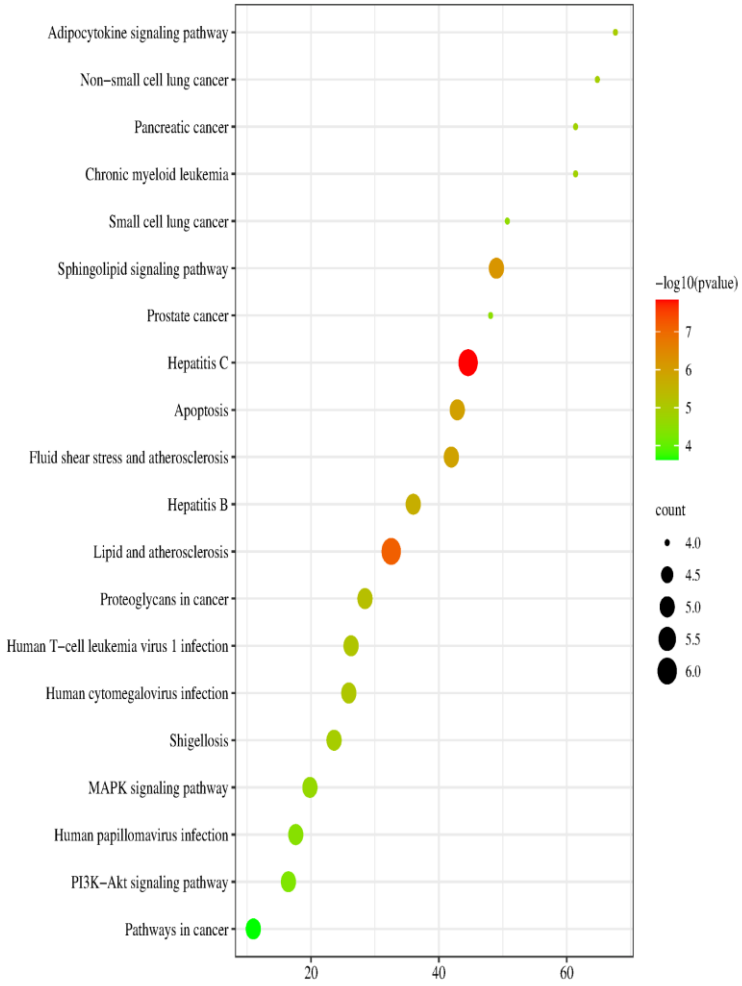

Fig.5 KEGG enrichment analysis network of the targets of Coptis chinensis

4 Conclusion

Diabetic nephropathy (DN) is a kidney damaging disease caused by long-term hyperglycemia, and its pathogenesis is related to various factors such as disorders of glucose metabolism and altered hemodynamics. The main active ingredient of Coptis chinensis was found to be quercetin, a plant polyphenol with lipid peroxidation inhibiting, anti-inflammatory and antiviral effects, through the TCMSP database(Li, Yao, Han, Yang, Chaudhry, Wang, Liu and Yin 2016). Its antioxidant effect is mainly on glutathione, enzyme activity, signal transduction and reactive oxygen species(Xu, Hu, Wang and Cui 2019). Chen Tielong et al. found that quercetin reduced the upregulation of TNF-α-induced apoptosis and also reversed the upregulation of adhesion molecules (ICAM-1, VCAM-1 and E-selectin) by inhibiting the activation of NF-κB and AP-1 (Chen, Zhang, Zhu, Liu, Chen, Wang and He 2020). Analysis of the network diagram of flavopiridol components-targets as well as the PPI network diagram yielded TP53, MAPK1, AKT1, RelA, TNF, CAV1 and RXRA as key targets.TP53 is an oncogene that plays an important role in the regulation of immune responses and systemic inflammation by "signaling" to promote senescence and/or triggering cell death through apoptosis, and also by inhibiting the inflammatory transcription factor NF-κB to suppress the development of inflammation (Sul and Ra 2021). AKT is a serine/threonine kinase that plays an important role in cellular metabolism, transcriptional.

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