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Research Article

An Integrated Analysis of Network Pharmacology and Molecular Docking to Explore the Active Component and the Underlying Mechanism of Cuscutae Semen in Membranous Nephropathy

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Abstract

Aims/purpose: To analyze the bioactive components of Cuscutae Semen, the targets and the underlying mechanism in Cuscutae Semen against Membranous Nephropathy (MN), to provide the data support for Cuscutae Semen applications in MN.

Methods and results: An aggregate of 443 drug targets and 460 MN targets were obtained from the databases, there were 24 overlapped targets being determined as potential therapeutic targets of Cuscutae Semen against MN. Through centrality analysis, PTGS2 and ALOX5 is screened as core target and its bindings with kaempferol are further validated by molecular docking. By conducting Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses for drug targets, disease targets and the shared targets, arachidonic acid metabolism signaling pathway is found, indicating the potential mechanism of Cuscutae Semen in the treatment of MN.

Conclusion: Cuscutae Semen could ameliorate the renal injury in MN by targeting multi-targets and multi-pathways including arachidonic acid metabolism, those data may provide the novel insights into further study of the drug discovery in MN.

Keywords: ALOX5; Cuscutae Semen; Membranous nephropathy; Network Pharmacology; PTGS2

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Introduction

Cuscutae Semen, which is called Tu-si-zi in Chinese, is a kind of dried mature seed in the Convolvulaceae family. It mainly distributes in China, Korea, Pakistan, Vietnam, India and Thailand. Cuscutae Semen has been widely prescribed by Chinese medicinal practitioners to treat oligoasthenozoospermia or dyszoospermia including Five Seeds Combo (wu zi yan zong wan, a well-known traditional Chinese herbal formula) [1,2]. It could also play the important role in a classic Chinese herbal prescription for nourishing the kidney and activating blood circulation named Bushen Huoxue recipe (BSHXR), which is effectively used to treat failed pregnancy and its complications [3]. What is more, Cuscutae Semen is also used to tonify deficiency of liver and kidney, spleen and kidney deficiency and diarrhea [4]. Specifically, it is reported that Cuscutae Semen could maintain reproduction of human beings through promoting the migration and invasion of EVT cells by increasing MMP9 expression and prevent miscarriage by activating Notch, AKT, and MAPK signaling pathways [5]; the evidences of animal studies in both sex demonstrated that Cuscutae Semen could play significant role in maintaining reproductive system functions [2,6-10]; Cuscutae Semen also has been proven that it could contribute to regulate several genes related to hearing loss [11], depression [12], liver fibrogenesis [13], leukopenia [14]. Specially, traditional clinical experiences and modern studies demonstrated that Cuscutae Semen also could help to alleviate the symptoms of kidney diseases. For example, Hui-Ting Liang et al. isolated and verified b-sitosterol, stigmasterol, astragalin, quercetin, kaempferol, apigenin, isorhamnetin, isoquercitrin, hyperoside and rutin in Cuscutae Semen by electrospray ionization ion trap mass spectrometry (ESI-MS), 1H and 13C NMR technique, and found matrine, sesamin, isorhamnetin, quercetin and beta-sitosterol had the better effect on actue and chronic kidney disease [15].

Membranous Nephropathy (MN) is a kind of autoimmune diseases and one of the leading causes of nephrotic syndrome. MN exhibits heterogenous outcomes with approximately 30% of cases progressing to end-stage renal disease and ranks second popular in primary glomerulonephritis in renal biopsy cases in China [16]. the patient often faces potential complications of nephrotic syndrome including edema and hypo-albuminemia. For its characteristic and mechanism, nowadays corticosteroids and the alkylating agents chlorambucil or

cyclophosphamide are widely used, but comes with other adverse effects. New strategy still remains to investigated. traditional Chinese medicines such as Tripterygium wilfordii and Astragalus membranaceus shed light on MN treatment [17]. In this article, we explored whether Cuscutae Semen would be the new strategy treatment to MN and analyze its possible targets and obtaining potential indigents for further study through network pharmacology methods and molecular docking.

Methods

Active ingredients and target prediction of cuscutae semen

The active ingredients of Cuscutae Semen were retrieved in TCMSP database (https://old.tcmsp-e.com/tcmsp.php). The ingredients which passed the ADME screening criteria (oral bioavailability OB≥30% and drug-likeness DL≥0.18) were imported into the TCMSP platform to analyze the targets in the Swiss Target prediction database, and the validated targets with the species "Homo sapiens" were screened and imported into the Genecard database (https://www.genecards.org/) and standardized to the officially recognized gene names.

Construction of the active ingredient-target network of cuscutae semen

Cytoscape 3.8.0 software was used to build and to analyze "active ingredient-target" network diagrams of "Cuscutae Semen." The "node" and "edge" represented the ingredients or targets and the relationship between them. The network parameters including degree, betweenness, and closeness were analyzed using the Network Analyzer plug-in tool of Cytoscape 3.8.0. By analyzing these network parameters, the key active ingredients, targets, and their relationships in "Cuscutae Semen" were also analyzed.

MN-related target analysis

We retrieved the GeneCards (https://www.genecards.org/) for potential targets of MN treatment using the keyword "Membrannous Nephropathy", and then the retrieval results from the three databases were exported (the duplicates were removed to obtain the final disease targets for MN).

PPI network construction and key target screening

Protein-protein interaction (PPI) networks were performed using Cytoscape 3.8.0. The active ingredient targets of Cuscutae Semen, and MN targets, were successively entered into Cytoscape 3.8.0 to generate the PPI network. The intersection of the two PPI networks was extracted using the Merge plugin tool of Cytoscape 3.8.0, and analyzed the properties of each node in the intersection network using CytoNCA.

Pass-through enrichment analysis

For pass-through enrichment analysis, KEGG pathway enrichment analysis was performed; bioinformatic analysis was performed using the OECloud tools (https://cloud.oebiotech.com) for KEGG analysis.

Molecular docking

To verify the reliability of the key targets of Cuscutae Semen in the treatment of MN, we performed molecular docking between the potential active ingredients and key targets. The 3D structures of the key target proteins (resolution<2A) were obtained from the PDB database (https://www.rcsb.org). The 3D structures of the active ingredients were obtained through the PubChem platform. PyMOL was applied to remove ligands and water molecules. AutoDock Tools 1.5.6 was used to hydrogenate the target proteins, calculate the charge number, and determine the AD4 type of the atoms. And then, the built-in plugins software, autogrid 4 software and autodock 4 software were used to determine the binding energy of the best docking site between the active ingredients and target proteins. Finally, PyMOL was used to draw a molecular docking map and derive the docking hydrogen bond distance and docking target name for optimization and output.

Results

Active ingredients and target acquisition of cuscutae semen

Retrieving the active ingredients of Cuscutae Semen in the TCSMP database according to the admission criteria (the oral bioavailability greater than 30% and higher than 0.18), 11 active ingredients of Cuscutae Semen were obtained, and sophranol was skipped because of the unknown structures. The basic information including Molecule number, Molecule name, Molecule weight, Oral Bioavailability (OB) and Drug Likeness (DL) of main active ingredients in Cuscutae Semen were shown in the table 1.

Mol number	Mol name	Mol weight	OB (%)	DL
MOL005944	matrine	248.41	63.77	0.25
MOL001558	sesamin	354.38	56.55	0.83
MOL006649	sophranol	264.41	55.42	0.28
MOL000354	isorhamnetin	316.28	49.60	0.31
MOL000098	quercetin	302.25	46.43	0.28
MOL005440	Isofucosterol	412.77	43.78	0.76
MOL000422	kaempferol	286.25	41.88	0.24
MOL000184	NSC63551	412.77	39.25	0.76
MOL000953	CLR	386.73	37.87	0.68
MOL005043	campest-5-en-3beta-ol	400.76	37.58	0.71
MOL000358	beta-sitosterol	414.79	36.91	0.75

Table 1: The potential active ingredients in Cuscutae Semen.

Abbreviations: OB, oral bioavailability; DL, drug likeness.

Potential targets analysis

The above 10 active ingredients of Cuscutae Semen in Swiss Targetprediction database (http://www.swisstargetprediction.ch/) were retrieved to predict the related biological targets. There were 460 MN-related targets and 243 drug targets were obtained; after 243 drug targets and 460 disease targets were imported into Venny 2.1, there were a total of 24 overlapped targets (Figure 1); and then we analyzed the PPI network of potential therapeutic MN targets and screened the more important targets, 24 overlapped targets were exported to construct a PPI (Protein-Protein Interaction) network. These targets are directly or indirectly related to MN. PTGS2 and MMP9 are proteins that makes most interactions with other target proteins (Table 2 & Figure 2).

Visualization of MN pathway enrichment analysis for cuscutae semen treatment on MN

24 targets were imported into OECloud tools for KEGG pathway enrichment analysis. The results showed that KEGG enrichment, involved 15 pathways. The top 14 entries of KEGG significance,

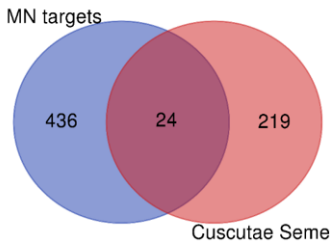

Figure 1: Venn diagrams of drug targets and disease targets.

name	NCC	Degree	Cloneness	Betweenness	Clustrering Coefficient
MMP9	12	12	15.66667	83.56905	0.36364
PTGS2	11	11	15.33333	94.70952	0.4
MPO	9	9	14.16667	31.21429	0.5
HIF1A	9	9	14	32.26667	0.52778
XDH	8	8	13.83333	62.77619	0.46429
NOS2	6	6	12.5	1.4	0.86667
MMP2	6	6	12.33333	5.43333	0.73333
MME	5	6	12.25	37.85952	0.26667
ALOX5	5	5	11.66667	7.01667	0.7
AKR1B1	2	5	12	51.9	0.2
NR3C1	4	4	11.33333	0	1
FABP1	3	4	10.75	41.3	0.33333
PTK2	4	4	10.66667	2.56667	0.66667
DPP4	4	4	11.25	14.65476	0.5
ALK	2	3	10.25	3.33333	0.33333
TTR	2	2	9.08333	0	1
SLC5A2	2	2	8.28333	0	1
CXCR1	2	2	9.5	0	1
PLA2G1B	2	2	9.41667	0	1
FABP3	1	1	7.2	0	0
PRKCD	1	1	7.75	0	0

Table 2: Common genes of drug targets and disease targets in figure 1.

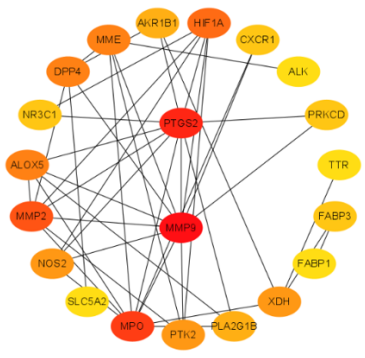

Figure 2: The active ingredient-target network map in Cuscutae Semen. The hexagon represents the target of the action of the active ingredient; the quadrilateral represents the 21 active ingredients (3 genes were skipped for they are could not be translated into proteins).

according to the Log10 (P) values, were plotted in bubble diagrams, as figure 3 shows. The KEGG analysis mainly contained pathways in cancer, arachidonic acid metabolism, drug metabolism,endocrine resistance and so on in Membranous Nephropathy.

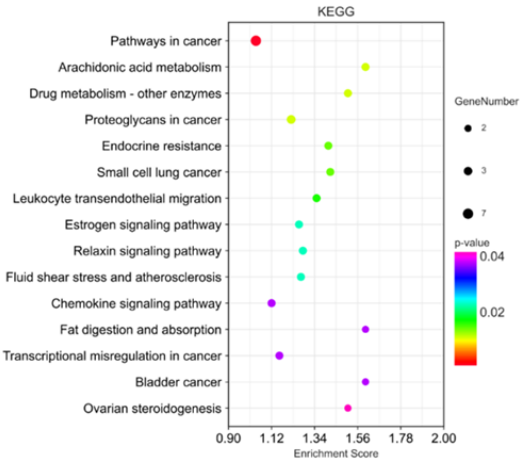

Figure 3: Bubble chart of enrichment bubbles of KEGG analysis targets for the treatment of MN by Cuscutae Semen.

Active compounds analysis

In order to predict the effective monomer components for further research, we firstly set specific one extract and the subset of figure 2 to explore which extract would be effective to membrane nephropathy, the results showed Venn figures of top three extracts, as shown in figure 4. According to table 3, kaempferol, isorhamnetin and quercetin may be important components of Cuscutae Semen in regulating the development of membranous nephropathy because these extracts share most common targets.

Figure 4: A subset of predicted components of (A) kaempferol, (B) isorhamnetin, and (C) quercetin and components of Cuscutae Semen that intersect with targets of MN respectively.

Molecular docking

Molecular docking is a tool for predicting how a protein interacts with small molecules (ligands) using molecular computational methods [1]. In this study, according to the above results, we chose kaempferol as ligand and PTGS2 AKR1B1, ALOX5, PTK2 and CFTR as proteins to perform the molecular docking. The results indicated that the receptor-ligand interaction between drugs and proteins includes hydrophobic interactions and polar interactions. According to table 4 and figure 5, AKR1B1 have strong binding interactions with kaempferol. What is more, we observed that PTGS2 and ALOX5 binds to kaempferol obviously, which revealed that Cuscutae Semen is involved with arachidonic acid metabolism pathway. This is coincident with what we obtained in figure 3.

Compo-nent	Kaempferol	Isorhamnetin	Quercetin
Common Targets	AKR1B1	XDH	AKR1B1
	XDH	AKR1B1	XDH
	ALOX5	ALOX5	ALOX5
	MMP9	MPO	MPO
	MMP2	PTK2	PTK2
	TTR	MMP9	MMP9
	MPO	MMP2	MMP2
	PTK2	CXCR1	CXCR1
	CXCR1	ALK	ALK
	ALK	PLA2G1B	PLA2G1B
	PLA2G1B	TTR	TTR
	PTGS2		
	CFTR		

Table 3: Common targets of each component in figure 4.

ligand	Target proteins	Affinity (kcal/mol)
kaempferol	PTGS2	-8.2
	AKR1B1	-13.2
	ALOX5	-11.5
	PTK2	-8.2
	CFTR	-10.9

Table 4: Results of Molecular Docking Between ingredients of Cuscutae Semen and the predicted Targets.

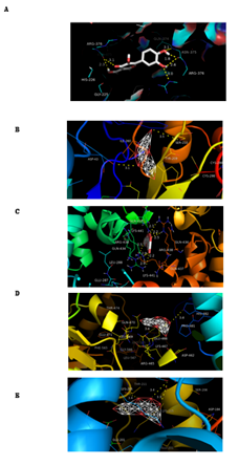

Figure 5: Molecular models of the binding of kaempferol, extracts of Cuscutae Semen, to the PTGS2 and kaempferol binding to PTGS2 (A), AKR1B1(B), ALOX5(C), PTK2(D) and CFTR(E) shown as 3D diagrams.

(Abbreviation: PTGS2: Cyclooxygenase-2; AKR1B1: Aldose reductase; ALOX5: Arachidonate 5-lipoxygenase; PTK2: Focal adhesion kinase 1; CFTR: Cystic fibrosis transmembrane conductance regulator)

Discussion

Based on the above speculation, we browse the literature and found that components in table 1 and figure 4 (but not limited to) have certain reports in the treatment of different kinds of kidney diseases. It is reported that kaempferol is the precursor of coenzyme Q (CoQ) cycle in cells in kidney, and protects renal tissue from oxidative stress by increasing the content of coenzyme, which clarifies the regulated role of kaempferol in CoQ cycle, providing a molecular basis for recognizing kaempferol's participation in the regulation of intracellular oxidative stress signaling. Kaempferol also shows protective effect in a unilateral ureteral obstruction model induced fibrosis via activating BMP 7-Smad 1/5 pathway in renal fibroblasts, thus reduces interstization of renal fibroblasts, and inhibits interstitium of renal tubular epithelial cells through hedgehog pathway [18-20]. Moreover, kaempferol suppresses tubular epithelial cell apoptosis, autophagy response [21], inflammatory response and decreased oxidative stress injury caused by cisplatin, cadmium chloride, calcium chloride [22], and carbon tetrachloride [23], which are negatively regulated by NF-κB pathway [24,25] to alleviate acute and chronic renal injury. In addition, kaempferol effectively inhibits podocyte apoptosis and promotes the transformation of M1-macrophages to M2-macrophages in diabetic nephropathy animals [26], thus reducing cytokines production [27,28] such as TGF- β and IL-6; on the other hand, kaempferol also increase the activity of nitric oxide by increasing the production of GSH and SOD [29]. A large number of literatures reported the significant effect of kaempferol on inhibiting ROS generation and inhibiting apoptosis in injured kidney. Cechinel-Zanchett et al. reported that kaempferol promotes sodium and chloride excretion and diuresis in a hypertensive rat model [30]. Overall, a large body of reports suggests that kaempferol is involved in the regulation of [31] of inflammatory response in renal disease, thereby exerting a renal protective effect. The current report of isorhamnetin mainly focus on its treatment of osteoporosis [32], alleviating obesity and diabetes [33,34], breast tumors and other gynecological tumors [35] It is said that it plays a protective role in cardiovascular disease and neurological diseases, especially the effects of inhibiting proliferation and differentiation and antioxidant, anti-inflammation and so on [36]. isorhamnetin also involved in regulating the production advanced glycation products (AGEs, advanced glycoxal end-products) in renal and hepatic cells [36]; besides, isorhamnetin is involved with AChE/BChE/COX2/NOX [37]. Diabetic rats treated with isorhamnetin lower fasting blood glucose and increase the content of renal autophagosomes [38], suggesting its important effect in treating diabetic nephropathy. A large number of reports have clarified that quercetin alleviates the development of various types of kidney diseases. It stops nephrotoxic damage in rats caused by 5-fluorodixine, cisplatin [39] and novel coronavirus N protein [40], down-regulates the level of KIM-1 and NGAL in the kidney and serum and deactivates RAS system [41,42] in kidney cortical renal tubular epithelial cells [43]; Treating STZ-induced diabetic rats with quercetin approves endothelial dysfunction [44] by deactivating NRF2/HO-1 pathway, thus reducing ferroptosis [45], inflammatory response and tissue oxidative stress [46,47] in renal tubular epithelial cells and glomerular mesangial cells [48-50]. Besides, quercetin has been reported that it participates in regulating the metabolism of fructose and purine, so as to be a potential to alleviating hyperuricemia and gout [51]. Quercetin is a new strategy treatment of acute and chronic renal diseases nowadays; further study remains to be elucidated.

Matrine has been reported to significantly reduce blood glucose, urinary albumin content and improve renal function in KKAY mice [52]. In doxorubicin-treated rats, scientists observed that matrine inhibits the activation of Treg/Th 17 cells by down-regulating Foxp3 and Rorγt, so as to decrease levels of IL-6, IL-10, TGF- β, and IL-10 [53]. Meanwhile, for acute kidney injury caused by cisplatin, the treatment of matrine inhibits NF-kB signaling pathway, reducing oxidative stress production, improving mitochondrial function by inhibiting SIRT 3-OPA 1 pathway, thus alleviating symptoms of acute kidney injury [54]. Matrine also reveals antifibrotic effect in glomerulonephritis rats [55]. The role of sesamin in treating kidney disease is relatively rarely reported. As we can see, sesamin alleviates kidney injury induced by immunosuppressants cyclophosphamide and fluoride [56], its intervention improves kidney function, increases the amount of antioxidants and reduce oxidants, meanwhile inhibiting apoptotic [57]. Sesamin also approves hyperlipidemia rats by downregulating α-SMA and Col-IV, thus inhibiting renal fibrosis [58]. In the 2-kidney 1 clip-induced hypertensive rat model and high fructose-drink rat model [59], sesamin treatment was found to improve endothelial cell dysfunction and decrease blood pressure [60] Meanwhile, sesamin was reported to be associated with regulating macrophages. Mouse macrophages stimulated by LPS shows lowering ubiquitination of HO-1 and less M1-macrophages after semamin treatment [61], which indicates its anti-inflamation effect.

Network pharmacology analysis in this article confirmed that kaempferol, quercetin, isorhamnetin, matrine and sesamin in Cuscutae Semen may be devoted to new treatment strategy to MN. Moreover, we found that quercetin and isorhamnetin is widely studied and has been clarified effective in the inflammatory response of kidney and immune system, and sesamin and matrine are rarely reported to treat kidney disease. They are potential therapeutic agents for nephropathy due to their anti-fibrosis, anti-inflammatory and anti-oxidative stress injury effects.

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Conflict of Interests

There is no conflict of interest in this article.

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