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Exploring the Main Patterns of Evidence and Medication Patterns and Target Prediction of Yang Xiaocui's Treatment of CKD Stage 3-4 Based on Data Mining

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Abstract:

Taking the Chinese medicine prescriptions of famous Chinese medicine practitioner Yang Xiaocui of Zunyi Hospital of Traditional Chinese Medicine for treating CKD stage 3–4 in the past 1 year as the source of data, the Chinese medicine prescriptions were analyzed for evidence type, frequency, association rules, and clustering by using Chinese medicine inheritance computation platform to obtain the main evidence type and core prescriptions, and on this basis, the research method of network pharmacology was used to screen the core targets and analyze them by KEGG pathway and GO function enrichment. The potential targets of HF drugs and diseases were studied to elucidate their mechanisms of action. A total of 158 outpatient medical records were collected, in which 153 Chinese herbal medicines were involved, including Huangqi, Shengdihuang, Chuanxiong, etc., which were mainly used to tonify deficiency, clear away heat and pacify the liver to calm the wind, and were mainly cold and sweet, and were mainly used in the liver meridian, spleen meridian and lung meridian, etc. Further, the frequency statistics and correlation analyzes were performed to obtain 10 high-frequency and 10 core drugs. By applying the research method of network pharmacology, the study explored the mechanism of action of the core group of Huangqi-Chuanxiong-Shengdihuang-Liuyuexue-Heichou (Qianniuzi), and found that its main active ingredients, such as quercetin, isorhamnetin and kaempferol, acted on the key targets of CA2, MAPT, ESR1, CYP19A1 and ESR2, and might be related to P53 signaling, insulin resistance, α-linolenic acid metabolism, inflammatory mediator regulation of TRP channels, longevity regulation pathway, and signaling pathway regulating stem cell pluripotency. Chinese herbal tonics are often used to treat CKD stage 3–4 by treating both the symptoms and the root cause, benefiting the kidney and draining the turbidity, with considerable clinical efficacy, and the HF drugs may play a therapeutic role through multiple signaling pathways, such as P53 signaling pathway, insulin resistance, and so on.

Keywords:

CKD

Data mining

Chinese medicine heritage computing platform

Network pharmacology

Medication patterns

Target prediction

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1. Introduction

Chronic kidney disease (CKD) is a chronic (duration of not less than 3 months) disease caused by primary or secondary glomerular disease, tubulopathy and renal vascular injury, which leads to structural damage and functional damage of the kidneys, accompanied by acid-base imbalance and metabolite retention [1]. Among them, chronic nephritis, hypertension and diabetes mellitus are the common causes of CKD, and the main clinical manifestations of this disease are proteinuria, haematuria, hypertension, and elevated blood creatinine [2]. Studies have shown that the prevalence of CKD among adults in China is 10.8%, involving about 119 million people [3], so CKD has now become a public health problem in China and even worldwide [4]. Compared with Western medical treatment, traditional Chinese medicine in China has better advantages in improving clinical symptoms, protecting residual renal function, and delaying complications in patients with CKD [5–7]. CKD stage 3–4 is an important transition period in the pathogenesis, and if properly treated, it can slow down the time to enter end-stage renal disease, reduce the drawbacks and economic pressures brought by renal replacement therapy, and improve the quality of patient's survival Dr Yang Xiaocui has been practicing medicine for more than 30 years. Yang Xiaocui has been practicing medicine for more than 30 years and has unique experience in the treatment of chronic kidney disease. By recording the cases of CKD stage 3–4 patients in Yang Xiaocui's outpatient medical records into the Chinese medicine inheritance computation platform, common Chinese medicine patterns and medication characteristics, prescription rules are mined and analyzed, commonly used medication groups and effective formulas are screened out, and then potential drug targets are predicted by using web-based pharmacology, further confirming Yang Xiaocui's clinical diagnosis and treatment. This will further confirm the scientific validity and effectiveness of Yang Xiaocui's clinical prescriptions and lay the theoretical foundation for possible animal experiments or clinical observations. Based on the effective prescription, the study can improve the clinical efficacy of treating CKD stage 3–4 patients, slow down the progression of patients to end-stage renal disease, prolong the survival period of patients, and improve the quality of life of patients with chronic kidney disease.

2. Information and methodology

2.1. Sources of prescription

The outpatient medical records of Yang Xiaocui, a famous Chinese medicine practitioner of Zunyi Hospital of Traditional Chinese Medicine, who treated CKD stage 3–4 from December 2022 to December 2023 were selected as the data source.

2.2. Prescription screening and data standardization

Inclusion criteria: (1) Meet the diagnostic criteria of CKD stage 3–4 in Western medicine; (2) Patients who meet the above TCM patterns according to the symptoms and signs; (3) Patients who are taking TCM decoctions or granules orally; (4) Patients who have complete clinical history, including at least the basic information of the patient, clinical manifestations, tongue and pulse, prescription and medicine, and the number of visits to the clinic is two or more; (5) Patients who have obvious clinical efficacy, such as the symptoms of the patient get better or the experimental examination improves after the follow-up visit.

Exclusion criteria: (1) Those who took replacement therapy or had renal replacement therapy at the data collection stage; (2) Those who combined with serious primary diseases of the liver, kidney, cerebrovascular, hematopoietic system and other organs; (3) Female patients who were pregnant or breastfeeding. The evidence type and formula composition in the prescriptions that met the criteria of screening were entered into Excel, and the names of evidence types and drugs were standardized according to the 2002 "Guidelines for Clinical Research of New Drugs in Traditional Chinese Medicine," the 2021 "Clinical Pathway of Chinese Medicine in Chronic Renal Failure" and the "Pharmacopoeia of the People's Republic of China."

2.3. Data analysis

The main types of evidence, drug frequency, efficacy, sexual flavour and categorization of drugs in TCM prescriptions were statistically analyzed, and the commonly used drug combinations and core formulas

were systematically analyzed.

2.4. Screening of core drug combinations for active ingredients and potential targets

The drug components were screened in the HERB database according to the Lipinski principle, and then the corresponding targets of each component were searched in turn, and the target gene names were standardized in the Uniprot database. The GeneCards database was searched with "chronic kidney disease" as the keyword to obtain CKD-related target genes. A Wayne diagram was drawn with the online mapping tool Venny 2.0 to obtain the common targets of active ingredients and diseases, i.e., the potential targets of the core drugs to improve CKD, and the common targets were analyzed by the STRING 11.0 online database (the highest confidence level parameter value was > 0.7).

2.5. Constructing a network diagram of disease-drug-target relationships

Drug compounds with the same target as the disease were screened and the network diagram of the relationship between the disease target and drug compounds was made using Cytoscape 3.9.1 software. The degree value of the compounds was calculated using the network analyzer tool, and the compounds with higher degree values were the main components that played a role in the core of Chinese medicine.

2.6. Extraction of key targets and construction of protein-protein interaction (PPI) network maps

The common targets were imported into the String database and the highest iso-confidence level of 0.700 was selected to obtain protein-protein interaction files for analysis. Potential target values were calculated using Cytoscape 3.9.1, and core target genes were assigned according to the degree of value.

2.7. GO function, KEGG pathway enrichment analysis

The GO function (Gene Ontology, GO) and KEGG pathway (Kyoto Encyclopedia of Genes and Genomes, KEGG) enrichment analysis of the obtained common targets were performed using the DAVID database, and the corresponding enrichment analyses were obtained, respectively ($P < 0.05$).

3. Results

3.1. Frequency analysis of certificate type

After the standardization of the evidence type names, the frequency analysis of the evidence types using the Chinese medicine inheritance computing platform yielded that among the 158 outpatient medical records with CKD stage 3–4 evidence types, the essential deficiency was dominated by spleen-kidney deficiency (57 times, 36.1%) and spleen-kidney yang deficiency (52 times, 32.9%), and the standardized solid evidence was dominated by blood stasis (75 times, 47.5%). See **Table 1** for details.

Table 1. Frequency and frequency of distribution of major evidence types in CKD stages 3–4

	Type of certificate (e.g. medical certificate)	Frequency	Frequency
Deficiency in essence	Deficiency of the spleen and kidney (TCM)	57	36.1%
	Deficiency of yang in the spleen and kidney (TCM)	52	32.9%
	Deficiency of both Qi and Yin (TCM)	21	13.3%
	Deficiency of Yin in the liver and kidney (TCM)	11	7%
	Deficiency of both Yin and Yang (TCM)	17	11%
Evidence-based	Water-dampness syndrome (TCM)	23	14.6%
	Damp-heat syndrome (TCM)	49	31%
	Evidence of blood stasis (TCM)	75	47.5%
	Evidence of intoxication by drowning (TCM)	11	7%

3.2. Analysis of the frequency and efficacy of Chinese herbal medicines and the 4 Qi's, five flavours and the attributed meridians

Statistical analyses of the prescribed Chinese medicines yielded 158 prescriptions involving a total of 153 Chinese medicines. The frequency of Chinese herbal medicines was mainly based on Huangqi (150), Shengdihuang (143), Chuanxiong (143), Jiangchan (139), Liuyuexue (138), etc. The efficacy of Chinese herbal medicines was mainly based on tonifying the deficiency (603), clearing heat (370), calming the liver and extinguishing the wind (309), (**Figure 1**). The flavour of the medicines was mainly based on coldness (861) and sweetness (1198), and the meridians were mainly based on the liver meridian, the spleen meridian and the lung meridian. The liver, spleen and lung meridians are the main meridians (**Figure 2**).

Table 2. The top 20 herbal medicines in terms of frequency in prescriptions for treating CKD stages 3–4

	Veterinary drug	Frequency
1	Huangqi	150
2	Shengdihuang	143
3	Jiangchan	143
4	Heichou	139
5	Dilong	138
6	Baichou	137
7	Chaihu	130
8	Longgu	122
9	Danggui	114
10	Taizishen	82
11	Danzhuye	54
12	Qianniuzi	52
13	Zhiqiao	50
14	Baishao	43
15	Cheqianzi	42
16	Yinyanghuo	37
17	Jinyinhua	34
18	Shigao	33
19	Sanleng	33
20	Weilingxian	31

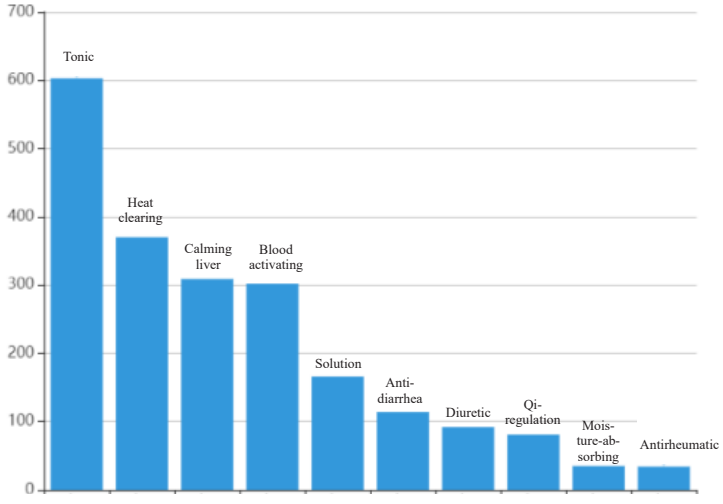

Figure 1. Histogram of the efficacy of Chinese herbal medicines for treating CKD stages 3–4.

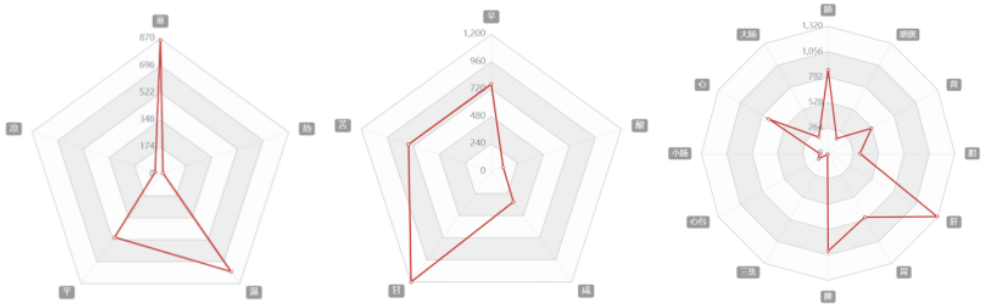

Figure 2. Radar chart of the frequency distribution of the four Qi, five flavours and attributed meridians of traditional Chinese medicine for treating CKD stages 3–4.

3.3. Analysis of the association rules of Chinese herbal formulas

The platform was set to have a support level of 50 and a confidence level of 0.7, and the top 10 drug combinations were obtained (**Table 3**). The association analysis of the obtained drug combinations resulted in the top 10 rules with the highest confidence level (**Table 4**), among which "Huangqi-Chuanxiong-Shengdihuang-Liuyuexue-Heichou-Dilong-Jiangchan" had the highest support, which indicated that this drug combination had the highest association in Chinese herbal formulae. Checking on "Network display" to get the network display of association rules (**Figure 3**).

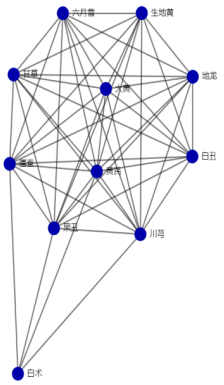

Figure 3. Display of the network of association rules of traditional Chinese medicines for treating CKD stage 3–4.

Table 3. Top 10 drug combinations in terms of frequency of herbal medicines for treating CKD stage 3–4 (times)

Serial number	Drug combinations	Frequency
1	Chuanxiong, Liuyuexue, Heichou, Dilong	99
2	Huangqi, Chuanxiong, Shengdihuang, Gancao	99
3	Shengdihuang, Jiangchan, Gancao	99
4	Jiangchan, Liuyuexue, Heichou, Gancao	99
5	Chuanxiong, Jiangchan, Liuyuexue, Heichou, Dilong	99
6	Huangqi, Liuyuexue, Heichou, Gancao	99
7	Huangqi, Shengdihuang, Dahuang	98
8	Huangqi, Chuanxiong, Jiangchan, Heichou, Gancao	98
9	Huangqi, Jiangchan, Heichou, Dahuang	98
10	Jiangchan, Liuyuexue, Heichou, Dahuang	98

Table 4. Top 10 drug combinations with herbal association rules for treating CKD stage 3–4

Serial number	Rules and regulations	Confidence level (math.)
1	Huangqi, Chuanxiong, Shengdihuang, Liuyuexue, Heichou, Dilong → Jiangchan	1
2	Liuyuexue, Heichou, Gancao, Dilong → Huangqi	0.99
3	Chuanxiong, Liuyuexue, Baichou → Jiangchan	0.99
4	Liuyuexue, Heichou, Baichou → Jiangchan	0.99
5	Chuanxiong, Liuyuexue, Heichou, Dahuang → Jiangchan	0.98
6	Chuanxiong, Shengdihuang, Liuyuexue, Baichou → Huangqi	0.97
7	Jiangchan, Dilong, Baichou → Liuyuexue	0.97
8	Shengdihuang, Liuyuexue, Heichou → Huangqi	0.97
9	Huangqi, Heichou, Baichou → Liuyuexue	0.96
10	Huangqi, Liuyuexue, Dilong → Heichou	0.96

3.4. Target prediction

3.4.1. Screening of core drugs and disease-related targets

Sixty-one active ingredients of Huangqi, Chuanxiong, Shengdihuang, Liuyuexue, Heichou (Qianniuzi) were screened (no active ingredients were retrieved for Dilong and Jiangchan), and a total of 953 targets were obtained after normalization and de-duplication processes, which were entered into the Cytoscape 3.9.1 software for numerical calculations and screened for degree ranking of the top 10 active ingredients (**Table 5**). After screening the target genes related to chronic kidney disease, the intersection of drug and disease targets were taken, and there were 141 targets (**Figure 4**). Disease targets overlapped with the targets of "Huangqi-Chuanxiong-Shengdihuang-Liuyuexue-Heichou (Qianniuzi)," which represented that the five core drugs could work on the disease through the relevant targets.

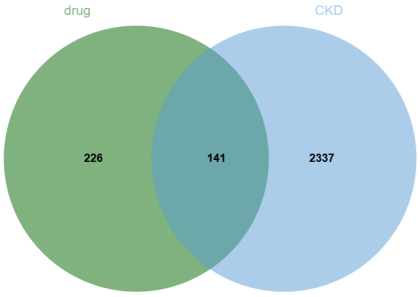

Figure 4. Wayne diagram of drug, CKD intersection targets.

3.4.2. Core drug-disease target networked presentation

By constructing a disease-drug target relationship network diagram, the relationship between drug compounds and disease targets can be shown more intuitively, and the compounds that play a major role can be predicted (**Figure 5**). In the diagram, the potential targets of drug action are represented by blue prismatic nodes, and the "Huangqi-Chuanxiong-Shengdihuang-Liuyuexue-Heichou (Qianniuzi)." Compound components were green, yellow, blue-green, pink and purple octagonal respectively represented by nodes, the higher the degree value of each node, the larger the node, the more important the node.

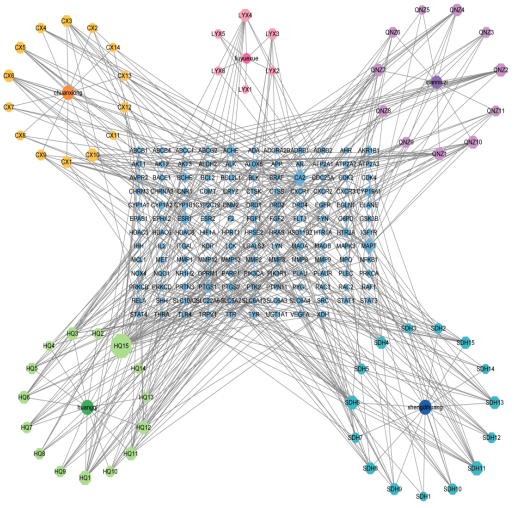

Figure 5. Core drug-disease target network map.

Table 5. Top 10 active ingredients by degree

Serial number	Herb ID	Ingredient name	Degree	Chinese medicine
1	HBIN041495	Quercetin	34	Huangqi
2	HBIN007657	3,5-Dimethoxystilbene	13	Huangqi
3	HBIN024020	Diincarvilone A	12	Shengdihuang
4	HBIN031114	Isorhamnetin	11	Huangqi
5	HBIN031753	Kaempferol	11	Huangqi
6	HBIN016163	Icaritin	11	Qianniuzi
7	HBIN038585	paederosidic acid	10	Liuyuexue
8	HBIN019690	Capsaicin	10	Huangqi
9	HBIN023828	Dihydrocapsaicin	10	Huangqi
10	HBIN013798	8-Prenylkaempferol	10	Qianniuzi

3.4.3. Prediction of relevant targets for core drug improvement before CKD

The common targets were imported into the String database to construct a protein-protein interaction (PPI) network graph (**Figure 6**). The values of potential targets were calculated using Cytoscape 3.9.1, resulting in an average degree value of 2.70. 50 targets exceeded the average degree value, and the larger the degree value, the larger the scope of action of the target. The larger the blue prismatic node in **Figure 5**, the greater the degree value of the node and the greater the impact on the disease. The information of the top 5 targets from high to low degree value (**Table 6**), among which CA2, MAPT, ESR1, CYP19A1, ESR2 and other target genes occupy a major position, which can be regarded as the key targets for the treatment of CKD.

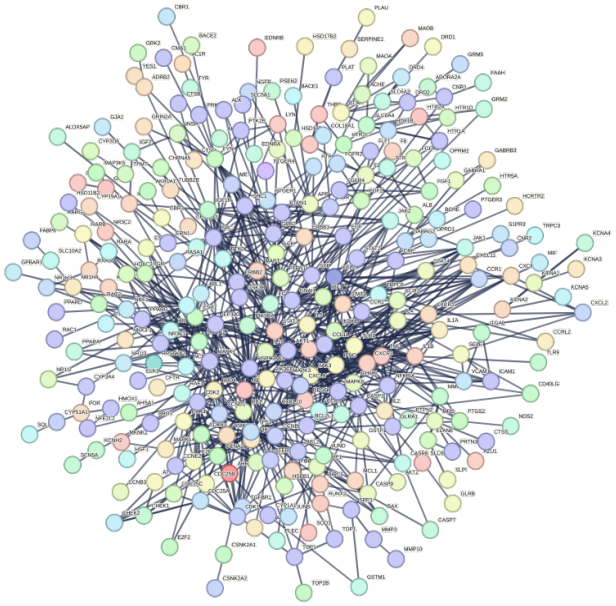

Figure 6. PPI network interoperability diagram.

Table 6. Top 5 key targets in terms of degree value

Serial number	Target name	Gene name	Degree
1	Carbonic Anhydrase 2	CA2	21
2	Microtubule Associated Protein Tau	MAPT	18
3	Estrogen Receptor 1	ESR1	11
4	Cytochrome P450 Family 19 Subfamily A Member 1	CYP19A1	9
5	Estrogen Receptor 2	ESR2	9

3.4.4. GO function and KEGG pathway enrichment analysis

The top 10 biological processes that were more significantly enriched in GO functional analysis included regulation of negative regulation of transcription by RNA polymerase II 1,B cell receptor signaling pathway, positive regulation of superoxide anion generation, positive regulation of blood vessel endothelial cell migration, epithelial cell proliferation, response to hydrogen peroxide, astrocyte activation, regulation of primary metabolic process, negative regulation of inflammatory response to antigenic stimulus, wound healing. The top 10 cell groups include IRE1-TRAF-ASK1 complex, peptidase inhibitor complex, NF-kappa B complex, insulin receptor complex, neuronal dense core vesicle, melanosome membrane, multivesicula body, clathrin-coated endocytic vesicle membrane, actin filament, lamellipodium. The top 10 molecular functions include long-chain fatty acid omega-1 hydroxylase activity, anandamide 11, 12 epoxidase activity, DNA binding domain binding, histone H3S 10 kinase activity, histone deacetylase regulator activity, nuclear estrogen receptor activity, interleukin-8 binding, dopachrome isomerase activity, carnitine 0-palmitoyltransferase activity, IMP dehydrogenase activity, and the bubble diagram of the GO enrichment analyses (**Figure 7**). The top 10 pathways in KEGG enrichment analysis (**Figure 8**), including p53 signaling pathway, insulin resistance, alpha-linolenic acid metabolism, inflammatory mediator regulation of TRP channels, longevity regulating pathway-multiple species, signaling pathways regulating pluripotency of stem cells, mTOR signaling pathway, apelin signaling pathway and Wnt signaling pathway.

4. Discussion

Chronic kidney disease has many causes and complex pathological mechanisms, and the main treatment measures mainly focus on delaying renal failure and relieving clinical symptoms, in which stages 3–4 are an important turning period of the disease, if not actively treated, GFR will significantly decline, renal function will accelerate the deterioration, and rapidly enter the end-stage renal disease. After entering into end-stage renal disease, the main means of treatment is renal replacement

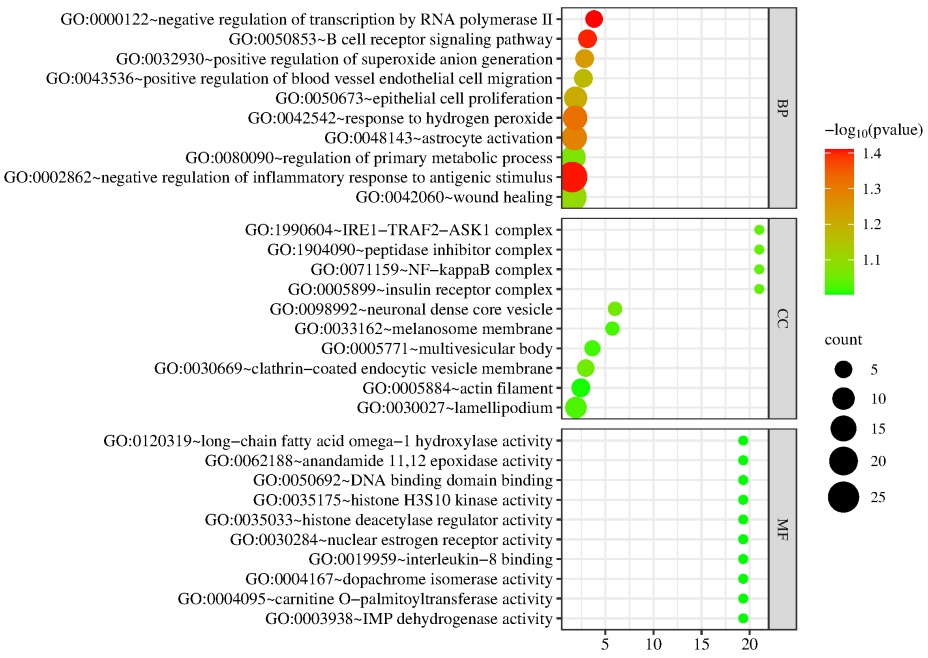

Figure 7. Bubble diagram of GO function analysis.

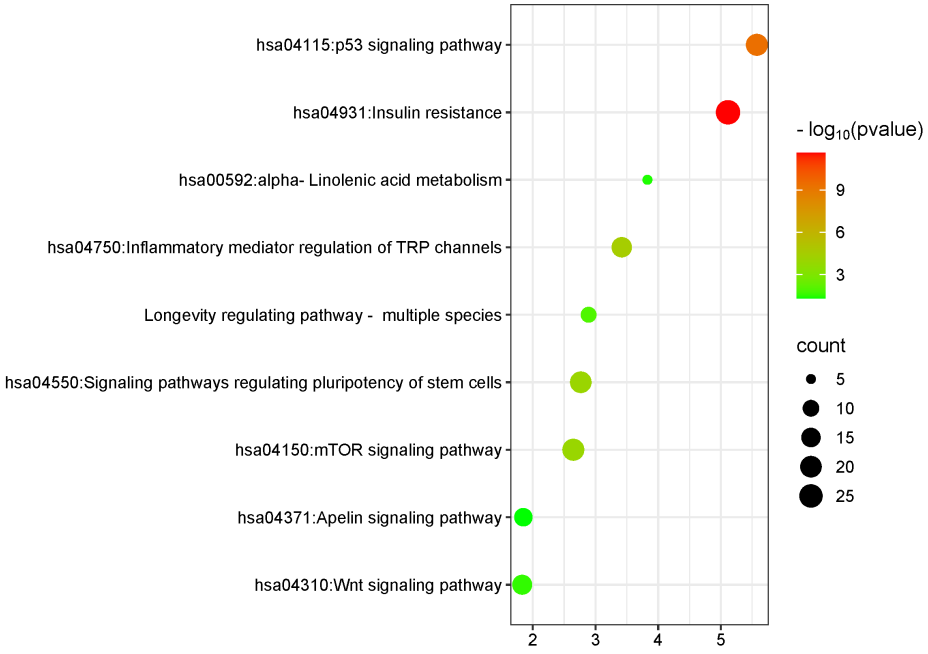

Figure 8. Bubble diagram of KEGG enrichment analysis.

therapy, but there are still many disadvantages of renal replacement therapy. Chinese medicine emphasizes evidence-based treatment and holistic treatment, which is not only simple, inexpensive, and easy to take for a long time, but also has an irreplaceable role in slowing down the process of renal failure and improving clinical symptoms.

As stated in "The Treatise on Typhoid Fever," "Guan is not allowed to urinate, and Ge is vomiting," therefore, chronic kidney disease is attributed to the category of "Guan Ge" in Chinese medicine, and clinically, according to the different clinical manifestations, such as oedema, lumbar pain, inability to urinate, and ammonia taste in the mouth, etc., chronic kidney disease should be attributed to the categories of "Shenfeng," "Shenlao," "Nidu," and "Longbi." According to Chinese medicine, the etiology

of CKD is complex, mainly due to internal and external causes, with external causes being external evils, drug damage, dietary strain and other factors, and internal causes being attributed to the deficiency of internal organs, with spleen and kidney deficiencies being the key [8].

Yang Xiaocui has been practicing medicine for more than 30 years and has unique experience in treating chronic kidney disease. As an inherited disciple of Zhang Daning, she inherited Zhang Daning's "Theory of Kidney Deficiency and Blood Stasis," "Theory of Heart-Kidney Axis System," and "Method of Tonifying the Kidneys and Activating Blood," and combined them with her experience in treating chronic kidney disease. In addition to the experience of "the theory of kidney deficiency and blood stasis," "the theory of heart-kidney axis system," "the method of tonifying the kidney and activating blood," and combining with the special geographic conditions of Guizhou, Yang Xiaocui put forward the rule of treatment for CKD, i.e., "benefiting the kidneys and draining the turbid." Chinese medicine believes that CKD stage 3–4 disease mechanism is mainly spleen and kidney deficiency, Yin and Yang, Qi and blood insufficiency, Qi and elevation dysfunction, so that the turbid evil diffuse congestion, is the basic deficiency standard solid. Yang Xiaocui believes that the main deficiency can be summarized as spleen and kidney deficiency, kidney deficiency and blood stasis, and the underlying reality can be manifested as internal dampness and turbidity, and stasis in the veins and channels, and proposes the treatment of "benefiting the kidneys and draining the turbid," and "dredging the liver, clearing the heart, and nourishing the blood" based on the identification of the viscera and organs. The present study is based on data mining. In the present study, data mining was used to collect statistics on Chinese herbal prescriptions for treating CKD stages 3–4, and it was found that in the treatment of CKD stages 3–4, Yang Xiaocui's treatments were dominated by spleen-kidney deficiency and spleen-kidney yang deficiency, and blood stasis was dominated by blood stasis. A total of 153 flavours of Chinese medicines were obtained, which were mainly tonic, heat-clearing, liver-relieving and wind-relieving, mostly cold, warm and flat, sweet, pungent and bitter and belonging to the liver meridian, the spleen meridian and the lung meridian. Cold and warm, and reconcile Yin and Yang, and use sweet and flat products to tonic, prevent and control warm, dry, greasy, and then with the method of XinKaiBitterDown to regulate the Qi, the overall to replenish the deficiency for the key. Yang Xiao Cui believes that "benefiting the kidneys" mainly includes replenishing Qi, warming Yang, nourishing Yin, so the evidence of the use of Huangqi, Taizishen, Baizhu, Fupenzi, Nvzhenzi, Mohanlian, and so on. In the aspect of "draining the turbid," it mainly includes inducing Qianniuzi, Chaihu, Danzhuye, Zhiqiao, Cheqianzi, Jiangchan, Dilong are often used in the diagnosis. An analysis of the association rules of 153 Chinese medicines shows that the core combination is "Huangqi-Chuanxiong-Shengdihuang-Liuyuexue-Heichou (Qianniuzi)," which embodies the method of "benefiting the kidneys and draining the turbid," achieving both symptomatic and fundamental effects.

It was found through network pharmacology that the core drug combination may improve CKD mainly through active ingredients such as quercetin, isorhamnetin, and kaempferol, which mainly act on the targets of CA2, MAPT, ESR1, CYP19A1, and ESR2. Among them, quercetin can play a protective role in the kidney through anti-oxidative stress and anti-inflammatory effects [9]. Isorhamnetin inhibits epithelial-mesenchymal transition formation and reduces extracellular matrix deposition, so it has a protective effect against renal fibrosis [10]. Kaempferol can inhibit the inflammatory response by mediating the inflammatory pathway, and it has been demonstrated that kaempferol also has an indirect protective effect against LPS and high glucose-induced pediculocyte damage by regulating the macrophage M1/M2 phenotypic transition [11]. Among the key targets, CA2 belongs to the zinc-containing enzyme family of lytic enzymes, which is mainly responsible for catalyzing the reversible hydration of carbon dioxide to form bicarbonate (HCO_3^-) and hydrogen (H^+) ions, and the deletion of this gene can lead to insufficient secretion of hydrogen ions in the distal renal tubules or insufficient reabsorption of bicarbonate ions from the proximal renal tubules, resulting in renal tubular acidosis [12], and CA2 can also hydrolyze cyanamide into urea [13], which is a major factor in acid-base metabolism and urea synthesis. It plays a great role in acid-base metabolism and urea synthesis. MAPT is a protein-coding gene that maintains

microtubule stability in cells and is mainly expressed in neuronal cells, lymphocytes and epithelial cells. Some studies have shown that abnormal expression of MAPT in renal clear cell carcinoma may be correlated with prognosis [14]. ESR1 and ESR2 are estrogen receptor and ligand-activated transcription factors, and they belong to the nuclear receptor superfamily and perform biological functions in a variety of ways [15]. CYP19A1 is a member of the cytochrome P450 enzyme superfamily. Cytochrome P450 proteins are monooxygenases that catalyze many reactions involved in drug metabolism and the synthesis of cholesterol, steroids and other lipids [16]. Some studies have shown that there is a correlation between ESR1, ESR2, and CYP19A expression and endometriosis, and there is a lack of research in the kidney, and the specific mechanisms are still being explored [17]. In conclusion, the above key targets are closely related to immune-inflammatory responses, acid-base metabolic processes and other processes. From the results of GO function analysis, it can be seen that the core drug combination "Huangqi-Chuanxiong-Shengdihuang-Liuyuexue-Heichou (Qianniuzi)" mainly regulates primary metabolic processes, vascular endothelial cell migration, epithelial cell proliferation, superoxide CKD can be improved by regulating the activity of histone deacetylase regulator, histone H3S10 kinase activity, DNA binding domain binding and other molecular activities. CKD has a complex pathological mechanism, and the development of inflammation, glomerular atrophy, and changes in interstitial fibrosis play an important role in its development, which can effectively slow down the progression of CKD by regulating the balance of acid-base metabolism *in vivo*, and regulating the transport and metabolism of intracellular substances [18]. Transport and metabolism can effectively delay glomerular atrophy and interstitial fibrosis, reduce the clinical symptoms of CKD and improve the quality of life of patients. From the results of KEGG enrichment analysis, it can be seen that the core drug combinations may mainly improve CKD by acting on the relevant pathways such as p53, which, as a nuclear transcription factor, can participate in the mitochondrial apoptosis pathway through the up-regulation of the expression of the target genes, and it has been demonstrated that p53 to activate the transcription of a variety of pro-apoptotic genes involved in mitochondrial apoptosis pathway [19], and the traditional Chinese medicines can improve the quality of life of the patients through the modulation of p53 and mitochondrial apoptosis pathway by regulating p53 and the mitochondrial apoptosis pathway [20]. Therefore, it can be hypothesized that "Huangqi-Chuanxiong-Shengdihuang-Liuyuexue-Heichou (Qianniuzi)" can improve CKD by regulating the balance of acid-base metabolism and slowing down renal fibrotic changes.

However, due to the limited number of medical records collected in this study, and the sources of cases were all outpatient clinics, the observation indexes were limited, which led to the possible bias of the experimental results, and there may be database aging, target collection errors or omissions in the part of the network pharmacological research, so it can only be used as a reference for preliminary prediction. The study found that ESR1, ESR2, CYP19A and other targets are the key targets of CKD, but the current research on this aspect is incomplete, this study also found that insulin resistance, alpha-linolenic acid metabolism, inflammatory mediator regulation of TRP channels, longevity regulating pathway-multiple species and other related pathways are related to the development of CKD, for these key targets and pathways that have not yet been clarified, the later can be achieved through the clinical. Randomized controlled trials and animal experiments will be conducted to further validate the findings of this study.

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Disclosure statement

The authors declare no conflict of interest.

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