Saudi Pharmaceutical Journal 28 (2020) 1138–1148

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Potential mechanisms of Chinese Herbal Medicine that implicated in the treatment of COVID-19 related renal injury

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ARTICLE INFO

Article history:
Received 14 June 2020
Accepted 6 August 2020
Available online 10 August 2020

Keywords:
COVID-19
Association rules
Network pharmacology
Renal/kidney injury
Chinese Herbal Medicine
Traditional Chinese Medicine

ABSTRACT

Clinical studies have shown that renal injury in Corona Virus Disease 2019 (COVID-19) patients has been a real concern, which is associated with high mortality and an inflammation/apoptosis-related causality. Effective target therapy for renal injury has yet been developed. Besides, potential anti-COVID-19 medicines have also been reported to cause adverse side effects to kidney. Chinese Herbal Medicine (CHM), however, has rich experience in treating renal injury and has successfully applied in China in the battle of COVID-19. Nevertheless, the molecular mechanisms of CHM treatment are still unclear. In this study, we searched prescriptions in the treatment of renal injury extensively and the potential mechanisms to treat COVID-19 related renal injury were investigated. The association rules analysis showed that the core herbs includes Huang Qi, Fu Ling, Bai Zhu, Di Huang, Shan Yao. TCM herbs regulate core pathways, such as AGE-RAGE, PI3K-AKT, TNF and apoptosis pathway, etc. The ingredients (quercetin, formononetin, kaempferol, etc.,) from core herbs could modulate targets (PTGS2 (COX2), PTGS1 (COX1), IL6, CASP3, NOS2, and TNF, etc.), and thereby prevent the pharmacological and non-pharmacological renal injury comparable to that from COVID-19 infection. This study provides therapeutic potentials of CHM to combat COVID-19 related renal injury to reduce complications and mortality.

1. Introduction

The outbreak of COVID-19 has quickly developed to a pandemic, bringing a severe challenge to global health. It has been confirmed that the angiotensin-converting enzyme II (ACE2) is the receptor for new coronavirus to enter cells (Zhou et al., 2020), same as SARS-CoV (Li et al., 2003). Several studies showed that ACE2 was highly expressed in the kidney, suggesting that the kidney may be one of the potential targets of COVID-19 (J. Chen et al., 2020; Y. Chen et al., 2020). Recently, the "Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Edition 7)" issued by the National Health Commission (NHC) of China (National Health Commission) suggested that the COVID-19 patients were found generally to have protein exudates in the glomerular balloon lumen. Pathological anatomy characteristics, such as tubular epithelial cells degeneration and shedding, hyaline casts, renal interstitial congestion, microthrombi and focal fibrosis, were also observed in autopsy. In addition, we reviewed the current clinical reports of COVID-19 and revealed that a remarkable fraction of patients had signs of kidney dysfunctions, including 59% with proteinuria, 44% with hematuria, 14% with increased levels of blood urea nitrogen, and 10% with increased levels of serum creatinine, although mild but worse than that in cases with other pneumonia (Li et al., 2020; Li et al., 2020). For patients with mild condition, 3–10.8% had elevated blood urea nitrogen and creatinine (Fan et al., 2020; Wang et al., 2020). For patients at critically stage, acute renal injury accounted for 29%, which was higher than cardiac injury (23%) (Yang et al., 2020). Moreover, in a study of 82 deaths, renal injury accounted for up to 31.7% (Zhang et al., 2020).

Abbreviations: CHM, Chinese Herbal medicine; COVID-19, Corona Virus Disease 2019; KEGG, Kyoto Encyclopedia of Genes and Genomes; CRRT, continuous renal replacement therapy; NHC, National Health Commission; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; CNKI, China National Knowledge Infrastructure; TCMSP, Traditional Chinese Medicine Systems Pharmacology; NCBI, National Coalition Building Institute; PPI, protein–protein interaction; AGE, Advanced Glycation End products; RAGE, Receptor of Advanced Glycation End products; PI3K, Phosphatidylinositol 3-kinase; AKT, Protein Kinase B; TNF, Tumor Necrosis Factor; PTGS1, Prostaglandin G/H synthase 1; PTGS2, Prostaglandin G/H synthase 2; NOS2, Nitric Oxide synthase; IL6, interleukin 6.

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2020.08.002
1319-0164/

Renal injury after coronavirus infection was common. A review of clinical studies of SARS found that although the overall proportion of patients with acute renal injury was 6.7%, the mortality rate of patients with acute renal injury was as high as 92% (Chu et al., 2005). In addition, renal injury was also common during MERS infection, and the mortality rate accompanied with renal injury was 67% (Zumla et al., 2015). In an in vitro experiment, it was shown that renal epithelial cells were more susceptible to MERS virus invasion than bronchial epithelial cells (Eckerle et al., 2013), while in pathological examination, high viral loads were detected in the renal tissue of SARS patients (Gu and Korteweg, 2007). There is evidence that the pathology and pathogenesis of COVID-19 coincides with MERS and SARS (Liu et al., 2020). These results indicate that development of acute kidney injury in patients with COVID-19 might be a crucial negative prognostic factor for survival (R. Q. Wang et al., 2020; S. Wang et al., 2020; Wang et al., 2020).

COVID-19 related renal injury includes the renal injuries during disease progression or from clinical treatments. There are three possible mechanisms of renal injury after COVID-19 infection: direct viral mediated, prolonged cytokine storm mediated, and drug-induced renal injury. ACE2, the receptor of COVID-19, is highly expressed in tubular cells; and the acute tubular necrosis was predominant in renal injury in SARS and MERS patients (Yang et al., 2020; Zumla et al., 2015). In addition, several clinical reports (Xu et al., 2020; Fan et al., 2020; Wang et al., 2020) have documented that patients with renal injury from COVID-19 infection have a higher systemic immune-inflammatory index. The release of a large number of proinflammatory cytokines can cause damage to kidney. Conventional treatment for COVID-19 pneumonia included antivirals and antimicrobials. Notably, the potential anti-COVID-19 drugs, ribavirin and ritonavir, have been shown to cause adverse effects of renal impairment in the treatment of COVID-19 (Cao et al., 2020; Chen et al., 2020).

For the treatment of renal injury, Western medicine routinely uses CRRT for supportive measure, and there is no targeted drug therapy (2012;; Zuk and Bonventre, 2016). However, the relevant reviews or medical records of Chinese Herbal Medicine (CHM) for the treatment of renal injury dated back to 2000 before, and many valuable experiences have been accumulated in this area. Therefore, CHM has certain advantages in the treatment of renal injury, and it is of particular importance to clarify its mechanisms of action in both traditional medicine and modern medicine. As regarding to COVID-19, a recent study found that CHM combined with antiviral medicine can prevent renal injury in patients with COVID-19 (Zheng et al., 2020); In this study, the feasibility and mechanism of CHM for preventing the renal injury that associated with COVID-19 is investigated based on the association rule analysis and network pharmacology.

2. Methods

The whole workflow was illustrated in Fig. 1.

2.1. Screening of prescriptions for clinical treatment of renal injury in CHM

CHM treatment has special advantages in the prevention and treatment of renal injury. We collected and summarized prescriptions with clear and definite reports on the clinical treatment of renal injury in CHM.

2.1.1. Source of prescriptions

Prescriptions for the treatment of renal injury in CHM clinical reports retrieved from databases such as CNKI (https://www.cnki.net/), VIP (http://www.cqvip.com/), and Wanfang (http://c.wanfangdata.com.cn/periodical), as well as empirical monographs about the treatment of renal injury by related distinguished veteran CHM practitioners were included.

2.1.2. Search method

The primary keywords of the search were "renal injury", and the secondary keywords were "immune function", "inflammation", "drug-induced", "proteinuria", "clinical", "renal failure", and "renal insufficiency".

2.1.3. Inclusion criteria

Prescriptions with reports in the clinical treatment of renal injury were included, e.g. clinical trials, case reports, and expert experience.

2.1.4. Exclusion criteria

Prescriptions with identical ingredients or causing kidney damage were excluded. Renal diseases unrelated to drug-induced, immunogenic and virus-induced renal injury, including renal calculi, congenital renal diseases, renal tumors, renal cysts and renal artery stenosis, were all excluded.

2.1.5. Normalization

Herb names were normalized with reference to "Chinese Pharmacopoeia (2015 Edition)" (2015 Edition). Standardized prescriptions were entered into Microsoft Excel. The source and composition of prescriptions were recorded, and consistency checkout and correction after information entry were conducted, so as to ensure the accuracy of data.

2.2. Analysis of the core herbs based on the association rules algorithm and exploration of the medication rules

R software (V3.6.1) was used to quantify the CHM fields using binary values. The occurrence of CHM was assigned a value of 1 and the absence was assigned a value of 0, and frequency statistics on the CHM were performed among all the prescription herbs recorded. Further analysis was performed by the association rules Apriori algorithm. Setting support $\geq$1%, confidence $\geq$50%, lift $\geq$1 and the number of anterior items $\leq$3 were used as mining conditions, and the association rule results were statistically analyzed. The visual association network was displayed for the CHM herbs with higher strength of association. The circle size indicated the degree of support; the larger the circle, the more chance the two herbs co-occurred. The color depth indicated the degree of improvement; the darker the color, the stronger the association between the two herbs.

2.3. Analysis of targets of core herbs

The main active ingredients of the core herbs were searched using the Chinese Herbal Medicine System Pharmacology Analysis Platform (TCMSP) (http://TCMspw.com/TCMsp.php). Oral absorption availability (OB) $\geq$ 30% and drug-likeness (DL) $\geq$ 0.18 were set as screening parameters. At the same time, this database was used to search target of the main active ingredients of the core herbs; and the obtained target information was normalized using the Uniport database to obtain the gene number of the key target corresponding to the ingredients in the core herbs.

2.4. Prediction of targets associated with renal injury after COVID-19 infection

Genes related to renal injury were obtained by searching with the keywords "renal injury" and "kidney injury" using the Gene-

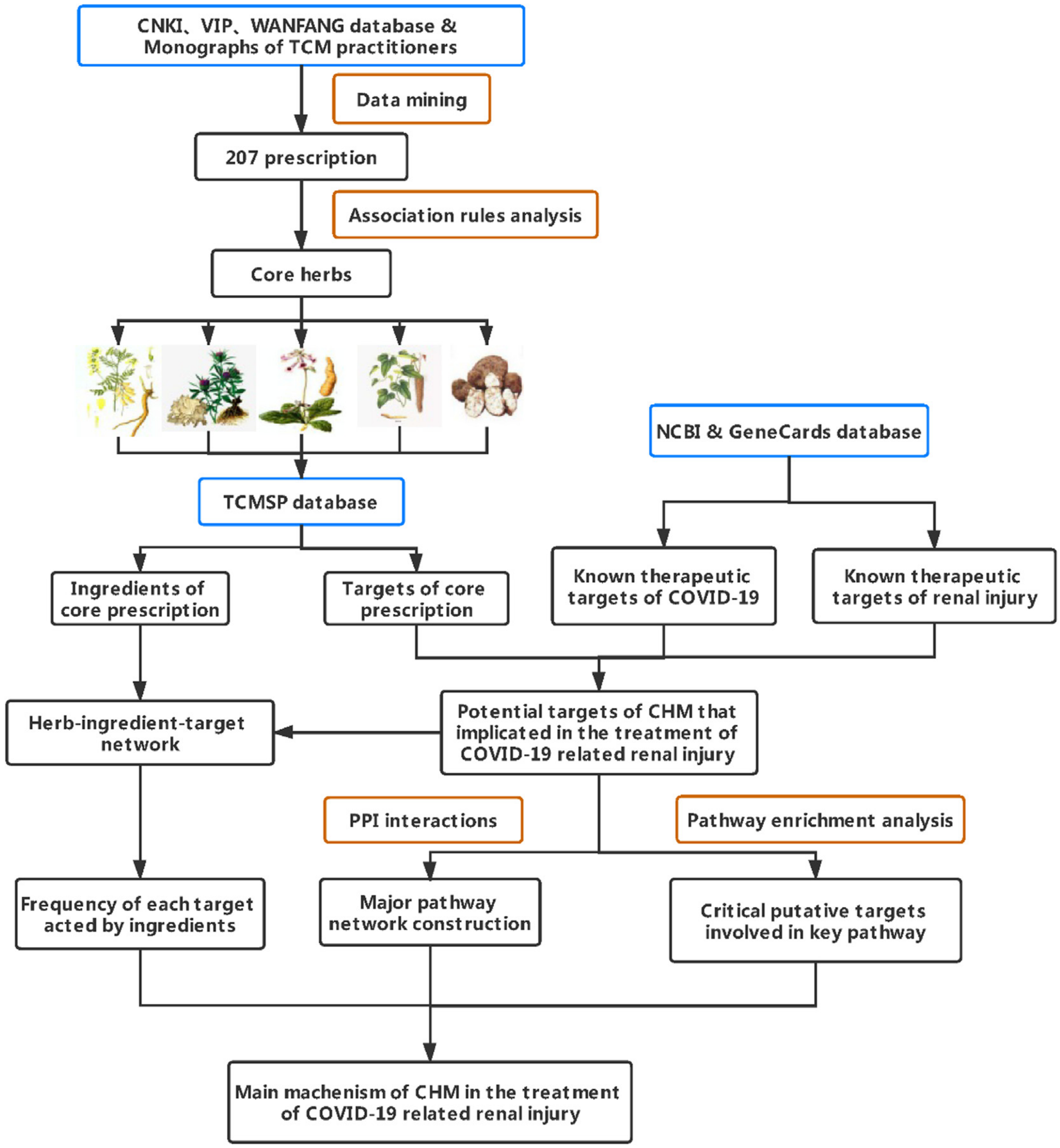

Fig. 1. The flowchart for deciphering the mechanisms of CHM implicated in the treatment of COVID-19 related renal injury. TCM, Traditional Chinese Medicine; CHM, Chinese Herbal Medicine; CNKI, China National Knowledge Infrastructure; TCMSP, Traditional Chinese Medicine Systems Pharmacology; NCBI, National Coalition Building Institute; PPI, protein–protein interaction.

Cards database (https://www.genecards.org/) and NCBI database (https://www.ncbi.nlm.nih.gov/). The species was selected as "Homo sapiens", and the related genes of COVID-19 were retrieved using the keyword "Novel coronavirus". Renal injury targets were mapped to those of COVID-19 using Venny plotting software (V2.1) to obtain potential targets of renal injury after COVID-19 infection. The predicted targets of the herbs were mapped with the targets of the disease to obtain the potential targets of the core herbs of CHM for the treatment of renal injury.

2.5. Screening of core active ingredients and targets

Cytoscape software (V3.7.2) was used to visually analyze the network pharmacology of all active ingredients and the potential targets of the core herbs of CHM for the treatment of renal injury, further to show the correlation and to analyze the number of targets of each active ingredient as well as the frequency of each target being acted by the active ingredient.

The potential targets of CHM core herbs for the treatment of renal injury were used to construct a target protein interaction (PPI) network through the STRING database. The position and role of targets with high frequency of action of active components in protein networks were further studied.

2.6. Enrichment analysis of target functional pathways

The core target genes were subjected to functional enrichment and major action pathway analysis, GO (Gene Ontology) enrichment and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis were conducted at $P < 0.01$ using the Bioconductor bioinformatics package. Enrichment analysis results were then visualized to reveal the possible mechanism of CHM in the treatment of renal injury.

3. Results

A total of 207 prescriptions related to the treatment of renal injury were collected. Through statistical analysis of frequency of the herbs in all the prescriptions recorded, it was concluded that the herbs with the highest frequency were *Radix Astragali* (Huang

Qi), *Poria* (Fu Ling), *Rhizoma Atractylodis macrocephalae* (Bai Zhu), *Radix Rehmanniae* (Di Huang), *Dioscoreae Rhizoma* (Shan Yao), *Radix Salviae liguliobae* (Dan Shen), *Rhizoma Alismatis* (Ze Xie), and *Herba Leonuri* (Yi Mu Cao); and the frequency of occurrence of each herb in all the prescriptions was counted (Table 1). CHM herb-type statistics showed that Diuretic Dampness Excreting medicinal and Qi Reinforcing medicinal were the most commonly used types of CHM, followed by Blood Activating medicinal, Antipyretic medicinal, Exterior Releasing medicinal, and Astringent medicinal. (Fig. 2).

In order to analyze the medication rules of CHM in the treatment of renal injury and to further screen the core herb combinations in the prescriptions for the treatment of renal injury, the herb association relationship with the top 20 degrees of improvement was selected, based on the association rule analysis of CHM prescriptions. The results suggested that the association and frequency of occurrence among *Radix Astragali (Huang Qi), Poria (Fu Ling), Rhizoma Atractylodis macrocephalae (Bai Zhu), Radix Rehmanniae (Di Huang)* and *Dioscoreae Rhizoma (Shan Yao)* were significantly higher than those of other herbs, suggesting that they were the core ingredients of CHM in the treatment of renal injury. (Fig. 3, Table 2).

In order to clarify the mechanism of action of the core herb combination and to further explore the key components for the efficacy, the ingredients from the five core herbs with DL > 0.18 and OB > 0.3 were obtained. To simplify the nomenclature of ingredients, their MOL IDs were obtained from TCMSP instead of ingredient names, and a total of 411 targets of the core herbs were further obtained.

To investigate the potential targets of core herbs that might be applied to the treatment of renal injury after COVID-19 infection, renal injury and COVID-19 related targets were collected and collated, and duplicate targets were eliminated, 8044 and 348 targets were included, respectively. Venny 2.1 mapping software was used to take the intersection of the targets regulated by the main active ingredients of five core herbs with the targets of COVID-19 and renal injury; and 60 targets were obtained. The core herbs may act on those targets to prevent and to treat renal injury after COVID-19 infection. It is worth noting that the intersected targets of the core herbs and COVID-19 can all act the targets of renal injury (Fig. 4).

In order to explore the frequency of 60 targets related to renal injury after COVID-19 infection that core herbs may act on, potential core targets and herbs were screened; and herbs-ingredients-targets were further analyzed by network analysis (Fig. 5).

Table 1
Frequency statistics of herbs associated with the treatment of renal injury.

No.	Herbs	Frequency	Percentage (%)
01	*Radix Astragali* (Huang Qi)	79	34.30
02	*Poria* (Fu Ling)	71	25.60
03	*Rhizoma Atractylodis macrocephalae* (Bai Zhu)	53	19.32
04	*Radix Rehmanniae* (Di Huang)	43	17.87
05	*Dioscoreae Rhizoma* (Shan Yao)	39	16.91
06	*Radix Salviae liguliobae* (Dan Shen)	35	16.91
07	*Rhizoma Alismatis* (Ze Xie)	35	16.43
08	*Herba Leonuri* (Yi Mu Cao)	34	14.98
09	*Radix Glycyrrhizae* (Gan Cao)	32	13.53
10	*Fructus Corni* (Shan Zhu Yu)	31	13.53
11	*Semen Plantaginis* (Che Qian Zi)	28	13.04
12	*Radix Angelicae sinensis* (Dang Gui)	27	12.56
13	*Rhizoma Imperatae* (Bai Mao Gen)	27	11.59
14	*Radix Aconiti Lateralis* (Fu Zi)	24	10.14
15	*Radix et Rhizoma Rhei(Da Huang)*	20	09.66

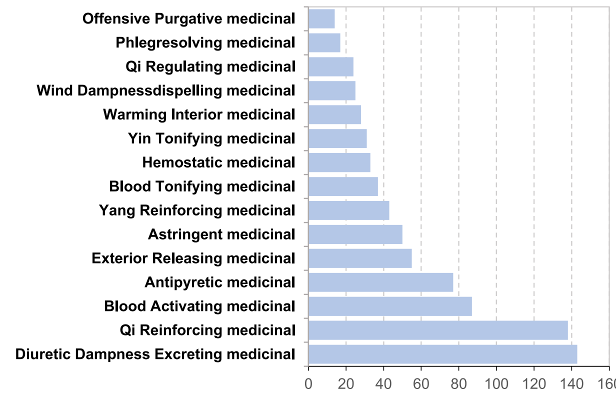

Fig. 2. Frequency of different CHM herb types in 207 prescriptions.

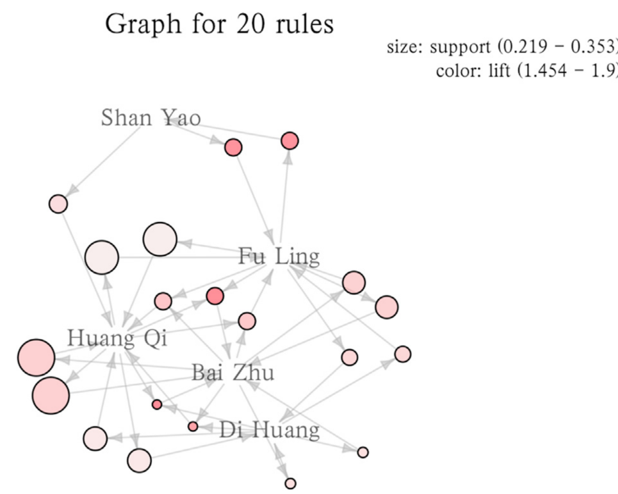

Fig. 3. Top 20 lift herbs of association rules analysis. The larger the circle, the more chance the two herbs co-occurred. The darker color indicated the stronger association between the two herbs.

Active ingredients that could act on targets associated with renal injury after COVID-19 infection were selected. A total of 20 core ingredients were included. It can be found that active ingredients modulate multiple targets; and the top listed ones, quercetin, kaempferol, formononetin, isorhamnetin, and diosgenin are mainly flavonoids and saponins, which generally have the effects of anti-inflammation and anti-tumor. They might have a relatively high value in the treatment of renal injury caused by COVID-19 infection (Table 3).

Statistical analysis of the number of times that each target was associated showed that PTGS2 (COX2), PTGS1 (COX1), NOS2, PPARG, and RELA were the most frequently associated targets, which were mainly associated with inflammation, oxidative stress, and apoptosis. Further, they may be the potential core targets of CHM in the treatment of renal injury after COVID-19 infection (Fig. 6).

Among them, PTGS2 or COX2 showed significantly higher frequency of association than other targets, which is an important factor in the inflammatory process. COX2 can be activated by TNF-α or NK-κB to promote IL6 production via activating PGE2, which in turn mediates a variety of inflammatory responses (Chen et al., 2013; Basudhar et al., 2017).

To further investigate the importance of core targets in biological processes, 60 intersection genes obtaining from ingredients and disease mapping were subjected to PPI network analysis on

Table 2
Association rules of herbs from 207 CHM prescriptions.

No.	rules	Support	Confidence	Lift	Total
1	Bai Zhu=>Huang Qi	0.3529	0.8800	1.6456	66
2	Huang Qi=>Bai Zhu	0.3529	0.6600	1.6456	66
3	Fu Ling=>Huang Qi	0.3369	0.7778	1.4544	63
4	Huang Qi=>Fu Ling	0.3369	0.6300	1.4544	63
5	Di Huang=>Huang Qi	0.2888	0.7941	1.4850	54
6	Huang Qi=>Di Huang	0.2888	0.5400	1.4850	54
7	Bai Zhu=>Fu Ling	0.2834	0.7067	1.6314	53
8	Fu Ling=>Bai Zhu	0.2834	0.6543	1.6314	53
9	Shan Yao=>Huang Qi	0.2620	0.8305	1.5531	49
10	Shan Yao=>Fu Ling	0.2567	0.8136	1.8782	48
11	Fu Ling=>Shan Yao	0.2567	0.5926	1.8782	48
12	Bai Zhu-Fu Ling=>Huang Qi	0.2567	0.9057	1.6936	48
13	Bai Zhu-Huang Qi=>Fu Ling	0.2567	0.7273	1.6790	48
14	Fu Ling-Huang Qi=>Bai Zhu	0.2567	0.7619	1.8997	48
15	Di Huang=>Fu Ling	0.2513	0.6912	1.5957	47
16	Fu Ling=>Di Huang	0.2513	0.5802	1.5957	47
17	Di Huang=>Bai Zhu	0.2246	0.6176	1.5400	42
18	Bai Zhu=>Di Huang	0.2246	0.5600	1.5400	42
19	Di Huang-Bai Zhu=>Huang Qi	0.2193	0.9762	1.8255	41
20	Di Huang-Huang Qi=>Bai Zhu	0.2193	0.7593	1.8931	41

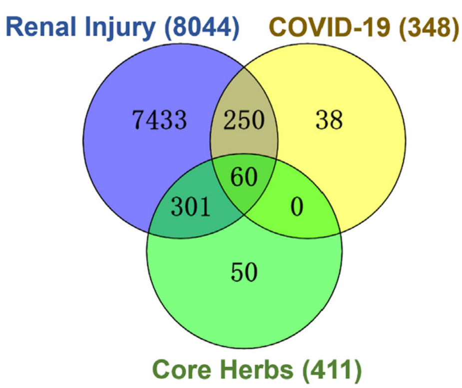

Fig. 4. Potential targets of core herbs in the treatment of renal injury related to COVID-19. The total of renal injury targets is 8044, COVID-19 targets is 348, and core herbs targets is 411, individually; and their intersected targets is 60.

the STRING platform. Where nodes represent proteins, each line represents the interaction relationship between proteins and proteins, and the more lines indicate the greater correlation. It can be seen that IL6, PTGS2 (COX2), PTGS1 (COX1), NOS2, CASP3, TNF, PPARG, RELA and other targets are in the core position in the network. IL6 is a clinical warning indicator for critical illness in the "China Novel Coronavirus Diagnosis and Treatment Scheme" and a potential factor mediating the inflammatory storm. The above targets may play an important role in the treatment of renal injury by CHM after COVID-19 infection (Fig. 7).

Through GO (Gene Ontology) biological process enrichment analysis and KEGG (Kyoto Encyclopedia of Genes and Genomes) signaling pathway enrichment analysis, the main pathways that the above CHM acts were obtained. It mainly acts on 100 biological process ($P < 0.05$) and 165 signaling pathways ($P < 0.05$). The results showed that the biological processes or pathways such as cytokine receptor binding, cytokine activity, receptor ligand activity, phosphatase binding, protein phosphatase binding, AGE-RAGE

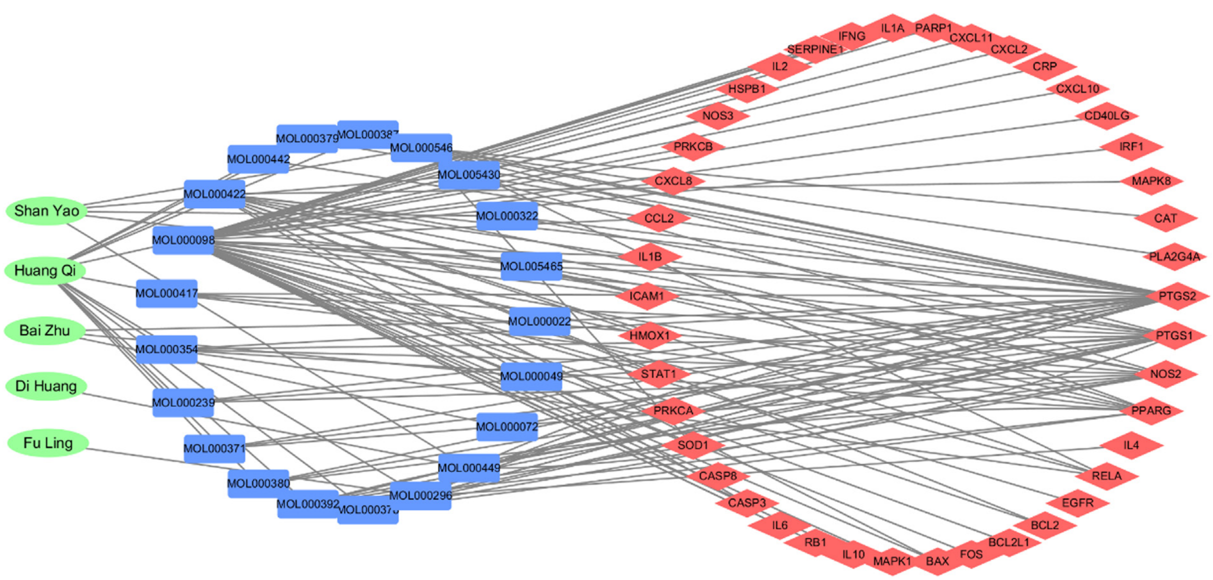

Fig. 5. Network of herb-ingredient-target. The interactions of components were connected with lines.

Table 3
Top 20 ingredients with the highest number of targets.

MOL ID	Name	Count	BO(%)	DL
MOL000098	Quercetin	38	46.43	0.28
MOL000422	Kaempferol	13	41.88	0.24
MOL000392	formononetin	6	69.67	0.21
MOL000354	isorhamnetin	5	49.60	0.31
MOL000546	diosgenin	5	80.88	0.81
MOL000449	Stigmasterol	4	43.83	0.76
MOL000296	hederagenin	4	36.91	0.75
MOL000378	7-O-methylisomucronulatol	4	74.69	0.30
MOL000417	Calycosin	4	47.75	0.24
MOL000380	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c] chromen-3-ol	3	64.26	0.42
MOL000371	3,9-di-O-methylnissolin	3	53.74	0.48
MOL000239	Jaranol	3	50.83	0.29
MOL000387	Bifendate	2	31.10	0.67
MOL005430	hancinone C	2	59.05	0.39
MOL000322	Kadsurenone	2	54.72	0.38
MOL005465	AIDS180907	2	45.33	0.77
MOL000049	3β-acetoxyatractylone	1	54.07	0.22
MOL000022	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol	1	63.37	0.30
MOL000442	1,7-Dihydroxy-3,9-dimethoxy pterocarpene	1	39.05	0.48
MOL000072	8β-ethoxy atractylenolide III	1	35.95	0.21

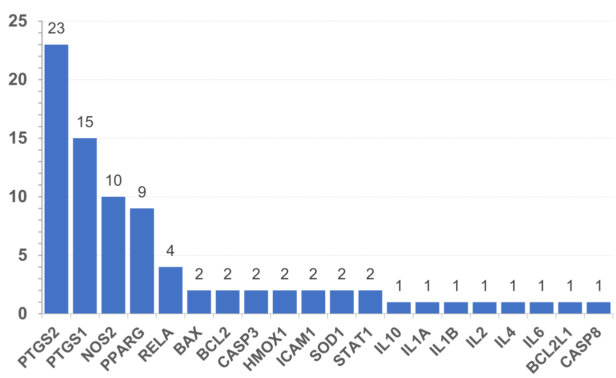

Fig. 6. Frequency of the targets acted by ingredients.

signaling pathway, PI3K-AKT pathway, TNF pathway, IL17 pathway, MAPK pathway, and apoptosis pathway had high degree values, which may be the core mechanism to explain why the core herbs of CHM can be applied to the treatment of renal injury after COVID-19 infection (Fig. 8).

4. Discussion

Combined with current clinical reports, the common causes of COVID-19-induced renal injury may be related to virus, immune system and drug, and its core mechanism is related to inflammation and apoptosis. The conventional treatment to renal injury is continuous renal replacement therapy (CRRT), which is only suitable for supportive treatment of critically ill patients, and there is still no effective treatment strategy. CHM provides good methods and experiences in dealing with renal injury, while its mechanism has not been clarified.

In the theory of CHM, the principle of "mother–child relationship" from five-element theory is often practiced in Chinese Herbal Medicine; the lung belongs to gold, the kidney belongs to water, and gold (mother) generates water (child), so lung disease often causes renal injury. Visconti et al. (2016) found that a variety of physiological processes depended on the co-regulation of the kidney and lung, and thus the lung and kidney were closely related in acute and chronic diseases. CHM had the concept of taking care of the kidney when curing pulmonary diseases, and clarifying the potential mechanism of CHM in the treatment of renal injury after COVID-19 infection will help to exert the advantages of CHM in clinical practice and improve clinical efficacy.

In order to provide a reference for clinical prevention and treatment of renal injury after COVID-19 infection, we systematically collated the prescriptions related to the treatment of renal injury. *Radix Astragali* (Huang Qi), *Poria* (Fu Ling), *Rhizoma Atractylodis macrocephalae* (Bai Zhu), *Radix Rehmanniae* (Di Huang), *Dioscoreae Rhizoma* (Shan Yao), *Radix Salviae liguliobae* (Dan Shen), *Rhizoma Alismatis* (Ze Xie), *Herba Leonuri* (Yi Mu Cao), *Radix Glycyrrhizae* (Gan Cao), etc., were among the most frequently used herbs. From the results of association rules analysis, it can be seen that Huang Qi, Fu Ling, Bai Zhu, Shan Yao, Di Huang are the core herbs in CHM prescriptions for the treatment of renal injury. Among them, Huang Qi excels at securing the exterior, which is excellent for tonifying Qi. Fu Ling is renowned for clearing damp, which specializes in treatment of edema. Bai Zhu invigorates the spleen and Qi, which plays the role of clearing damp together with Fu Ling. Di Huang enters the two meridians of the liver and kidney, which is good at tonifying the Yin, and is one of the most essential herbs for tonifying the kidney. From the characteristics of core herbs, the main treatment of renal injury in CHM is tonifying Qi and benefiting kidney, and clearing damp and promoting diuresis. According to the classification of CHM herbs efficacy, statistical analysis revealed that the frequency of Diuretic Dampness Excreting medicinal and Qi Reinforcing medicinal were the highest, followed by Blood Activating medicinal, Antipyretic medicinal and Exterior Releasing medicinal, which suggested that most of the pathogenesis were related to phlegm-dampness and Qi deficiency, as well as blood stasis, pathogenic heat and wind. In the process of syndrome differentiation and treatment, it is often used flexibly depending on the different course of disease and patient's constitution.

The ingredients of the core herbs were searched by database and visualized by the method of network pharmacology, and the core ingredients were selected, including quercetin, kaempferol, formononetin, isorhamnetin, astragaloside isoflavanthin, attractylone, diosgenin, stigmasterol, sitogluside, kadsurenone, and aesculin. Among them, the interaction between quercetin and the targets was found with the highest frequency, and it was found that quercetin could reduce the production of cytokines (IL-6, TNF-α, IL-1β, and cox-2), inhibit MAPKs and NF-κB signaling pathways, and then reduce inflammatory damage (Spagnuolo et al., 2018). Besides, kaempferol helps to reduce the inflammatory response associated with COX2 expression (Kang et al., 2018). In addition, astragaloside isoflavanthin can regulate the immune sys-

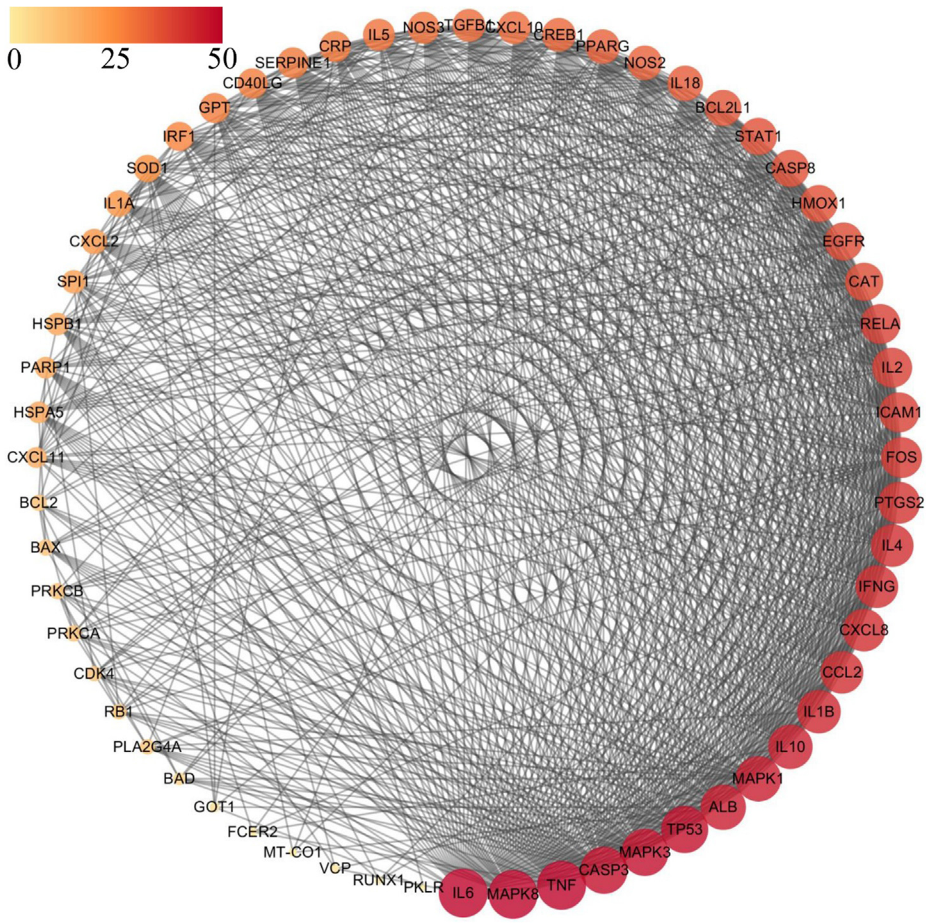

Fig. 7. Protein-protein interaction (PPI) network of the intersection targets of core components and renal injury. The larger the circle indicates the more chance the two proteins interact. The color index indicates the count of interactions, where the darker the more interactions.

tem and enhance the body's function of producing interferon (Yang et al., 2014). Formononetin has pharmacological effects such as lowering blood pressure, regulating inflammatory responses and lipid metabolism (Chen et al., 2018). Attractylone may inhibit apoptosis by regulating PI3K-AKT pathway and other mechanisms (Liu et al., 2017). Diosgenin can reduce apoptosis by regulating PI3K/Akt, ERK and JNK signaling pathways (Hsieh et al., 2017). Furthermore, ingredients such as stigmasterol, sitogluside, kadsurenone, and aesculin also have anti-inflammatory, antioxidant, and inhibitory effects on apoptosis (Agatonovic-Kustrin et al., 2018; Ma et al., 2018). The above ingredients may play the role of preventing renal injury by acting on multiple targets in oxidative stress, inflammation, or apoptotic pathways.

In order to determine the core targets, it was found that PTGS2, IL6, PTGS1, TNF-α, NOS2, PPARG, and RELA, etc., may play an important role in the treatment of renal injury by CHM after COVID-19 infection by counting the frequency of active ingredients acting on different targets, as well as the interaction network between targets. Among them, PTGS2 and PTGS1, also known as COX2 and COX1, are the most frequently interacted targets by ingredients of core herbs. COX1/2 are often induced by various inflammatory stimuli and injurious factors, being one of the major pharmaceutical targets for anti-inflammatory medicine. COX1/2 can directly promote the production of IL6 via activating PGE2. IL6, the target with the highest degree value in PPI network, is a clinical warning indicator for critical illness according to the "China Novel Coronavirus Diagnosis and Treatment Scheme". Moreover, the core herbal targets (IL6, IL1A/B, IL2, etc.,) are key players in triggering inflammatory storm and subsequently exacerbating COVID-19 disease to critically ill stage. Inflammation storm attributes to renal damage as well. In addition, targets such as TNF-α, NOS2, PPARG, and RELA, are closely related to oxidative stress, inflammation, or apoptosis.

It is worth mentioning that active ingredients of CHM herbs have been screened out for their potential to interfere the binding of covid-19 to ACE2 (Niu et al., 2020); ACE2 was highlighted, as it was found high in kidney, which increases the risk for renal related complications in COVID-19 patients. However, the beneficial role of ACE2 could also protect patients from getting worse after infection. For instance, in mice model, infected with the SARS virus or treated with the SARS spike protein, the expression of ACE2 plays a protective role by cutting Ang II for avoidance of lung function failure happened (Kuba et al., 2005; Imai et al., 2005). This complicated role of ACE2 gives ways to the major causes of renal injury that were found from our analysis, namely inflammation storm and anti-apoptosis.

Through GO and KEGG analysis, it was shown that cytokine receptor binding, cytokine activity, receptor ligand activity, phosphatase binding, protein phosphatase binding, AGE-RAGE signaling pathway, PI3K-AKT pathway, TNF pathway, IL17 pathway, MAPK pathway, and apoptosis pathway may be important pathways for the application of CHM in the treatment of renal injury after COVID-19 infection. Among them, the degree of AGE-RAGE pathway is significantly higher than other pathways, which can activate MAPK signaling pathway, and then activate NF-κB, causing the expression and release of a large number of pro-inflammatory

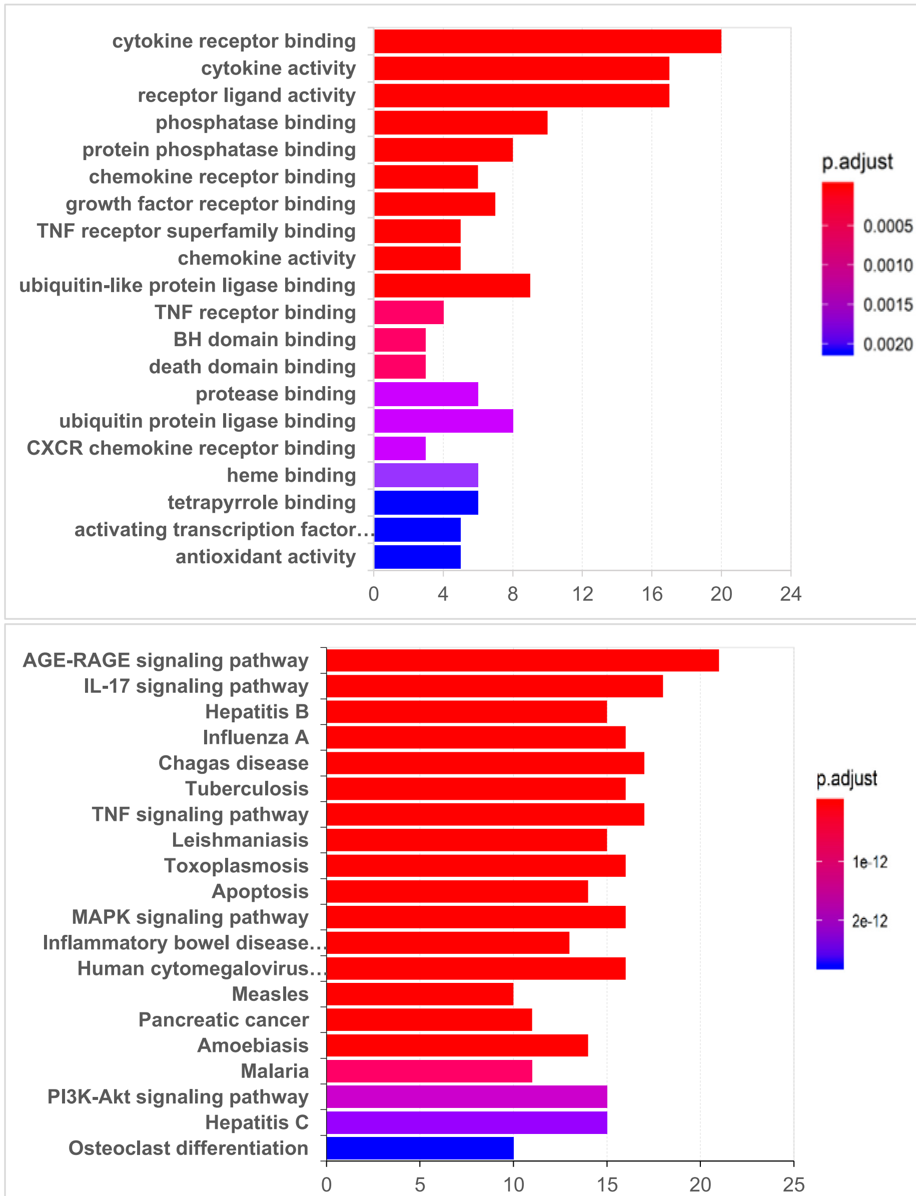

Fig. 8. Top 20 pathways of the core targets from GO and KEGG enrichment analysis.

cytokines and growth factors. PI3K-AKT pathway is involved in the regulation of various cellular functions such as cell proliferation, differentiation, apoptosis and glucose transport, in which AKT can release NF-κB from the cytoplasm and regulating cellular inflammation and apoptosis. The IL-17 family can activate signaling pathways such as MAPK and NF-κB and induce the expression of antimicrobial peptides, cytokines and chemokines. Based on the above analysis, the potential mechanisms of CHM that implicated in the treatment of COVID-19 related renal injury can be summarized (Fig. 9). Furthermore, in order to clarify the directionality of interaction of core herbs with their core targets (COX1/2, IL6, TNF-α, CASP3, etc.,), we systematically assessed their relationships via literature searching. Consistent results were illustrated in Fig. 9, where a few key players of inflammation storm were found being unanimously inhibited by one or more core of herbs.

Inflammation and apoptosis and other immune regulation-related steps are mainly involved after making a general survey at the pharmacological effects of ingredients, classification of targets, biological processes and pathways. Studies have confirmed that CHM prescriptions and CHM monomers mainly protect the kidney and treat renal injury by reducing inflammation, inhibiting apoptosis, necrosis and inhibiting oxidative stress (Li et al., 2019). Analysis of the pharmacological effects of the core herbs showed that Huang Qi is good at tonifying Qi and can play a therapeutic role in renal dysfunction and pathological changes through anti-oxidation (Han et al., 2017). The main mechanisms of action include inhibiting the expression of TNF-α and COX2, relieving apoptosis and necrosis of renal cells (Fan et al., 2005), inhibiting levels of interleukin to reduce renal inflammation (Li et al., 2017), and reducing the possibility of microthrombosis by inhibiting MAPK pathways, which in turn protects the kidney (Ma et al., 2017). Besides, Huang Qi ameliorates renal fibrosis via the inhibition of CASP3 activation (Xu et al., 2014). In addition, studies have shown that astragalus can inhibit the expression of BAX protein in the kidney and has a protective effect on multiple organs (Fei et al., 2016). Fu Ling has the effect of inducing diuresis to reduce edema,

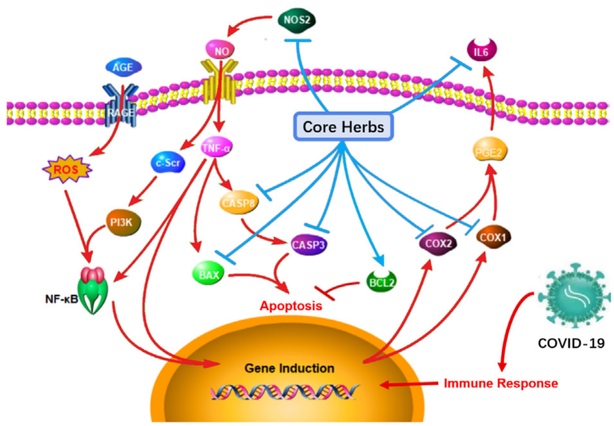

Fig 9. Key mechanisms of CHM core herbs that implicated in the treatment of renal injury of COVID-19 patients. Core herbs have been reported to inhibit the inflammatory targets, as marked by blue arrow. And the inflammatory response was marked by red arrow.

at the same time, Poria polysaccharide can improve human immune function and improve renal fibrosis by inhibiting MAPK pathway (Feng et al., 2019). Poria acid activates RAS/TGF-β/Smad axis in kidney cells and inhibits oxidative stress injury in the kidney (Ming et al., 2017). Moreover, Bax and CASP3 expression was decreased by Fu Ling, resulting in anti-apoptotic effect to protect kidney (Lee et al., 2013). Bai Zhu is commonly used to invigorate the spleen to regulate water in kidney, according to CHM theory. Studies have demonstrated that Atractylodes macrocephala can reduce chronic kidney disease-induced inflammation and muscle atrophy by inhibiting the PI3K-Akt pathway (Wang et al., 2019). At the same time, it can reduce the production of proinflammatory mediators NO, reduce the levels of TNF and IL, and then relieve the damage of renal cells (Ishii et al., 2020). Meanwhile, it can reduce CASP3 activation and may enhance immunity (Guo et al., 2012). Shan Yao has the effect of tonifying kidney, and it can inhibit the PI3K-Akt pathway, stimulate monocyte proliferation, up-regulate SOD2, and then protect kidney cells (Zhao et al., 2018). Study shows that Shan Yao can Alternatively, Shan Yao extract can reduce IL-1β, IL-6, and TNF-α levels to reduce renal inflammation (Qiao et al., 2019). Di Huang is often used to treat kidney diseases. Acteoside, the main nature component of Di Huang, can inhibit the excessive release of proinflammatory cytokines, prevent the synthesis of TGF-β1, and reduce the inflammatory injury of renal cells by regulating the chemotaxis and proliferation of Th22 lymphocytes (Gan et al., 2018). Besides, the iridoid glycoside in Di Huang can significantly decrease ROS generation, levels of inflammatory cytokine TNF-α, IL-1β, and IL-6 in renal podocyte injury, meanwhile, Inhibit cell apoptosis via decreasing the expression of CASP3, BAX, NOX4, TLR4, MyD88, p-p38 MAPK, p-IκBα and NF-κB nuclear translocation, as well as increasing BCL2 expression to protect kidney (Chen et al., 2019).

In addition, for drug-induced renal injury, it has been shown that Huang Qi can protect against gentamicin-induced renal injury by inhibiting oxidative stress response and inflammatory factors (Wang et al., 2019). The triterpenoids extracted from Fu Ling have protective effects on cisplatin nephrotoxicity, and the mechanism is related to the anti-apoptotic activity of the ingredients (Lee et al., 2017). Extracts of Shan Yao have protective effects on renal injury induced by non-steroidal anti-inflammatory drugs (NSAID) such as paracetamol. Pathological sections show that it can effectively inhibit the necrosis and disintegration of renal tubules (Lee et al., 2002). Diosgenin in Shan Yao can protect acetaminophen-induced liver injury from niacin induced renal injury by inhibiting inflammation and oxidative stress (Zhang et al., 2017). Formononetin can prevent methotrexate-induced oxidative stress, inflammation, and renal injury in rats by upregulating the Nrf2/HO-1 signaling pathway (Huang et al., 2017). In the "Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Edition 7)", antiviral drugs as well as common antibacterial drugs are used for conventional medicine treatment, and most of them have adverse effects of renal impairment, or are contraindicated in patients with renal insufficiency, including remdesivir, lopinavir, ritonavir and ribavirin (Grein et al., 2020; Han et al., 2020; Wang et al., 2020). Antiviral drugs mainly lead to crystalline renal injury. The mechanisms of injury relate to damage to mitochondria, interference with tubular transport, and increase of oxidative stress (Pannu and Nadim, 2008; Douros et al., 2018).

Furthermore, some of the core herbs, e.g. Huang Qi, Fu ling, Bai Zhu and Shan Yao have been used in many TCM remedies for combating COVID-19, therefore, the beneficial effects from these core herbs are beyond their renal protection. Intriguingly, a clinical report of 98 patients who administered of "Qin-Fei-Pai-Du" decoction (QFPD), which encompassed 3 out of 5 our core herbs, reported an above 90% curative rate based on clinical lab results, with no death or deterioration to severe stage (R. Q. Wang et al., 2020; S. Wang et al., 2020; Wang et al., 2020). Besides, a controlled clinical trial of 52 patients from Hubei Province found that compared with those treated Western Medicine (33.3%), patients treated with integrated Chinese Herbal and Western Medicine (including Bai Zhu, Fu Ling and Di Huang) were less likely to deteriorate to severe stage and damage the kidney (5.9%) (Zheng et al., 2020).

5. Conclusion

CHM protects the kidney through the mechanisms of anti-oxidation, inhibition of inflammation and apoptosis pathways. Herein, 207 prescriptions for clinical treatment of renal injury were sorted out. Further, association rules analysis showed that the core herbs implicated in treatment of renal injury includes Huang Qi, Bai Zhu, Fu Ling, Shan Yao and Di Huang. They could regulate core pathways (AGE-RAGE, PI3K-AKT, TNF pathway, etc.) via interactions of ingredients (quercetin, formononetin, soniferol, etc.,) on targets (PTGS2 (COX2), PTGS1 (COX1), NOS2, IL6, CASP3, and TNF, etc.) to prevent the pharmacological and non-pharmacological renal injury comparable to that from covid-19 infection. Therefore, the application of CHM in treatment of renal injury after COVID-19 infection can not only improve the quality of life of patients, but also prevent drug-induced renal injury.

In summary, CHM is promising to protect the kidney in the clinical practice of COVID-19 pneumonia to provide ideas in order to reduce the incidence of severe disease and mortality in patients.

Funding

This work was supported by the Beijing research fund for double first-class and high-level talents (No. 1000041510053).

Author contribution

TL directed the research and revised the manuscript; TH performed the research and wrote the paper; RQ and CQ modified the tables and figures and revised the manuscript; ZW, YZ and XS revised the manuscript. All authors have read and approved the manuscript.

Acknowledgement

The authors would like to thank professor Yan Feng, in Communication University of China, and Dr Biyuan Liu, Dr Yuanfeng Zhang, Dr Xinqi Deng, Dr Xiting Wang in Beijing University of Chinese Medicine, for their help to provide constructive advice.

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