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STUDY ON NATURAL HERBAL MEDICINAL SUBSTANCES IN KIDNEY DISEASES

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Abstract: Chronic kidney disease (CKD) is a leading cause of life lost worldwide (Chen et al., 2019). The contributing factors to progression of CKD include parenchymal cell loss, chronic inflammation, fibrosis and reduced regenerative capacity of kidney (Ruiz-Ortega et al., 2020). The complications of CKD, e.g. anemia, are associated with increased risks of death (Fishbane and Spinowitz, 2018). The prevalence and mortality of CKD are rapidly increasing, illustrating the shortcomings of current therapeutic approaches. Research aiming to identify novel therapies for CKD is required to prevent disease progression and to prevent death. In recent years, herbal medicine has demonstrated its potential as an alternative therapy to treat numerous diseases, and which is attracting greater attention and being applied to control CKD. However, some of herbal medicines have been found to be nephrotoxic when incorrectly utilized. Thus, the proper usage of herbal medicine is necessary to avoid the nephrotoxicity. The goal of this research topic is to provide a forum to advance research of herbal medicine towards CKD therapies. Thirty-seven contributions covering the listed research topics have been submitted to this special issue.
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Introduction:

The use of herbal remedies dates to ancient times. The term ‘herb’ is often utilized freely to allude not just to herbaceous plants yet in addition to bark; roots; leaves; seeds and product of trees, bushes, and woody vines; and concentrates of a similar that are esteemed for their exquisite, fragrant, or therapeutic characteristics (Craig, 2004). Herbal medicine is the utilization of therapeutic plants for counteractive action and treatment of sicknesses, where it ranges from conventional and mainstream solutions of each nation to the utilization of standardized natural concentrates (Firenzuoli and Gori, 2007). It has been perceived that from 1981 to 2002, 16.4% of new chemical entities correspond to molecules containing a pharmacophore derived directly from natural products. Due to the toxicity issues of synthetic compounds, herbal medicines are preferred in treating or curing many diseases in recent times. The utility of plants being employed for therapeutics, relay on the fact that they produce a vast and diverse assortment of organic compounds, commonly referred to as secondary metabolites (Croteau et al., 2000). These metabolites may act separately, additively, or in cooperative energy to enhance wellbeing. The different constituents present in plants such as bitter substances help in absorption, alkaloids help in mood enhancement while tannins play a powerful role as natural antibiotics (Winslow and Kroll, 1998; Gurib-Fakim, 2006). Thereby, therapeutically herbal medicines are being now employed in the treatment of cancer (Huang et al., 2009), cardiovascular disease (Mashour et al., 1998), diabetes (Kim et al., 2006), disorders of the central nervous system (Carlini, 2003), respiratory disorders (Asadbeigi et al., 2014), infectious diseases (Kitazato et al., 2007) and for immune-compromised diseases (Managoli, 2008). Owing to the wide plethora of utility of herbs in treating various ailments in humans, several studies has been conducted to provide a scientific basis for their use in treating various diseases including chronic kidney disease. Chronic kidney disease (CKD) is typically and widely described as a reduction in glomerular filtration rate over months and years. It is reported that there are 697.5 million cases of CKD worldwide resulting a prevalence rate of 9.1%. The global all-age prevalence is increased to 29.3% during 1990–2017 with stable age-standardized prevalence, and 1.2 million deaths occurred due to CKD in 2017 (Bikbov et al., 2020). It is surveyed that reliably 3200,000 people accomplish end-stage renal disease (ESRD); at present, it is amid the three reasons for

mortality and predominance rate changes from 8 to 16% everywhere throughout the world. CKD is mostly associated with conditions such as diabetes, hypertension, obesity, hyperlipidemia (Hruska et al., 2010), and non-alcoholic fatty liver disease (Targher et al., 2011), which behave as initiator as well as progressive factor for the disease (Levey and Coresh, 2012). As the genetic and non-genetic factors are also responsible for CKD, it has been reported that DNA damage due to reactive oxygen species (ROS) overproduction and nucleic acid oxidation occurs in CKD (Khan et al., 2016). The kidney dysfunction is demonstrated by glomerulosclerosis and tubulointerstitial fibrosis through processes such as inflammation, proliferation, apoptosis, and fibrosis. Moreover, renal remodeling results in the release of chemokines like angiotensin II, cytokines, and growth factors like transforming growth factor-beta 1 (TGF β1). These growth factors trigger intracellular signal transduction pathways exposed to arbitrate the response to the damage of renal cells. Mitogen-activated protein kinases (MAPK), Rho-associated coiled-coil kinase, nuclear transcription factor β, and Jun N-terminal kinase/stress-activated protein kinase have also been implicated in renal cellular responses (El Nahas and Bello, 2005; Tomson and Bailey, 2011; Gajjala et al., 2015). The elementary diagnostic parameters which are commonly used to detect CKD include measurement of serum creatinine, glomerular filtration rate (GFR), and urinary albumin levels (Jha et al., 2013). The classic treatment for CKD initiates with preventing and monitoring the symptoms related to its co-morbid disease. CKD treatment aims to decelerate the advancement to ESRD. It has been speculated that β-blockers, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors has definite contributions in the therapeutic aspects of CKD. Furthermore, medications for CKD proceed with other conceivably harming frameworks and procedures, including endothelin, fibrosis, oxidation, and propelled glycation, at different phases of advancement(Snyder and Pendergraph, 2005; Bakris et al., 2006; Levin et al., 2008; Turner et al., 2012). However, the pharmaco-therapeutic management of renal dysfunction is complex and, in an average patient with dialysis, includes at least a combination of 12 medications. This intricate nature of therapy may lead to medication-related problems. These problems are in turn related to overdosages, adverse drug reactions, improper drug selection, etc. (Cardone et al., 2010). Correspondingly, immunosuppressive drugs and corticosteroids are also not very supportive in improving renal dysfunction. Handful clinical and pre-clinical studies have accounted for the strong evidence of herbs being effective in the treatment of CKD. The basic concept being adapted by this medicinal system is the restoration of imbalance between nature and body for the management of any specific disease (Zhong et al., 2015). Due to the multifaceted nature of CKD and the concurrence of several risk factors, the treatment for CKD should also consider herbal drugs that act through numerous pathways with least or no adverse reactions. Several classical medicinal systems have exploited amalgamate of herbs which have gained the interest of modern scientists to perform an in-depth analysis of its use in CKD. Thus, the current review is undertaken to study the herbs which has been suggested useful for the treatment of **CKD.**

Reviews of Herbal Medicine in Prevention of Kidney Disease

Zhao et al. summarized recent studies on the efficiency of Chinese herbal medicine commonly used for the treatment of kidney disease. As a conclusion, Chinese herbal medicine has been shown to have effects of anti-inflammatory, anti-oxidative, anti-apoptotic, autophagy, and anti-fibrotic: these pharmacological properties could account for the therapeutic approach in treating CKD. Given the critical role of mitochondrial dysfunction in developing CKD, Tian et al. have summarized the efficiency of herbal formulae on mitochondrial dysfunction, providing novel insights into the rationale in developing new drugs to prevent and/or to treat CKD. Supporting this notion, a mini review by Li et al. has summed up the therapeutic effect of herbal medicine in CKD via targeting mitochondrial dynamic. Anemia is one of the most common complications in CKD patients. Here, Li et al. have performed meta-analysis to assess the efficacy of a herbal formula, Jianpi Bushen, in treatment of patients suffering from CKD anemia. This study demonstrated that Jianpi Bushen showed good efficacy in treating CKD anemia. In parallel, Feng et al. have summarized clinical outcomes of herbal medicine in treating idiopathic membranous nephropathy, one of the main types of CKD. This article has led to a new idea for treatment of idiopathic membranous nephropathy. In addition, Yu et al. have performed a network meta-analysis to investigate the efficacy of Chinese herbal injections in treating primary nephrotic syndrome. This study supports the clinical usage of herbal injection in clinic. A review by Shao et al. has summarized the pharmacological effects of herbal medicines in progression of autosomal dominant polycystic kidney disease, which paves a direction to develop effective herbal drugs for therapeutic usage. In summary, these review articles are providing different lines of scientific evidence supporting efficacy and mechanistic action of herbal medicine in CKD and its associated diseases.

Herb and Herbal Formula for CKD

Herbal medicine, either as a single herb or in a formulated mixture, has been reported to exhibit protective role in CKD. Kidney fibrosis is the common final pathway of CKD. In this topic, three articles have focused on therapeutic effects of herbal extracts against renal fibrosis in rats. Wang et al. have performed lipidomic analysis to reveal the effect of *Polyporus umbellatus* extract on adenine-induced lipid metabolism disorder in rats. Their findings suggest that the extract of *P. umbellatus* could protect renal fibrosis by regulating fatty acyl metabolism. Sari et al. have elucidated the efficacy of *Centella asiatica* extract in restoring kidney fibrosis in an unilateral ureteral obstruction model. The results showed that treatment with *C. asiatica* extract could improve kidney fibrosis by reducing mesenchymal transition, collagen deposition and inflammation. In addition, Ning et al. have found that the treatment with genistein, an isoflavone, was able to increase expression of renal alkylation repair homolog 5, as well as to reduce expression of RNA m6A levels in unilateral ureteral occlusion-induced renal fibrosis. Besides, He et al. have shown that the in-take of rhein and curcumin mixture, major active ingredients of Bu-Shen-Huo-Xue herbal formula, could markedly improve renal fibrosis in CKD rats.

Recently, gut microbiota have been proposed to contribute development and progression of CKD. In this special issue, four articles have presented the roles of herbal medicine in remodeling dysbiosis of CKD rats. Al-Asmakh et al. have explored potential effects of gum acacia, a natural gum consisting of hardened sap of two species of acacia tree, i.e. *Acacia Senegal* and *Vachellia* (*Acacia*) *seyal*, on gut microbiome, particularly in the amount of short chain fatty acids, and which further illustrated its beneficial effects in CKD rat model. These results support that the renal protective function of gum acacia, and the mechanism of which may be involved in improving growth of beneficial bacteria in gut, and thereafter which stimulates release of short chain fatty acids. Tu et al. have demonstrated that the extract of *Abelmoschus manihot* could protect renal damage by remodeling gut dysbiosis and inhibiting microinflammation triggered from intestinal metabolites. These findings provide information on the role of *A. manihot* in delaying CKD progression. Moreover, Guan et al. have explored the renal protection of herbal mixture containing *Scutellaria baicalensis* and *Sophora japonica*. This herbal mixture was able to low blood pressure and to reverse renal injury in a rat model of hypertensive nephropathy. The involvement of microbiota, short chain fatty acids and metabolites in gut has been proposed to be responsible for action of the herbal mixture. Lastly, Li et al. have demonstrated the effect of Zhen Wu Tang, a classic herbal decoction from ancient China, in ameliorating kidney injury in rats having immunoglobulin A nephropathy. Again, the adjustment of intestinal flora and the restoration of metabolism homeostasis are proposed to be the outcome of Zhen Wu Tang treatment.

Moreover, three articles have focused on other aspects of therapeutic benefits in treating CKD. First, exosomal miRNA profiling has been revealed in CKD rats. Liu et al. have found that 4 exosomal miRNAs were markedly disturbed, and which could be modulated by Jian-Pi-Yi-Shen formula, a Chinese herbal decoction, in adenine-induced CKD rats. Second, the positive response of a herbal formula Yi-Qi-Jian-Pi-Xiao-Yu-Xie-Zhuo on muscle atrophy in CKD rats has been investigated, and the mechanism of which has been proposed to be involved in modulating IGF-1/PI3K/Akt signaling (Xia et al.). The article by Zhou et al. has shown that Jian-Pi-Yi-Shen herbal formula could restore renal oxidative injury by activating nuclear factor (erythroid-derived 2)-like 2 signaling in CKD rats.

Herbal Medicine for Diabetic or Other Kidney Diseases

Diabetic kidney disease is one of the leading causes of end-stage renal disease, and it is therefore of great importance to delay the progression of diabetic kidney disease. Three articles are presented in this topic assessing renal protective effects of herbal medicine in diabetic animal models. Wang et al. have demonstrated that Bu-Shen-Huo-Xue herbal decoction effectively regulated high blood glucose and renal function in diabetic mice, and the underlying mechanism of which was proposed to have an involvement of inhibition of Rac1/PAK1/p38MAPK signaling. Another study by Li et al. have revealed that Tang Shen herbal formula could attenuate diabetic kidney injury and reduce pyroptosis of tubular epithelia via TXNIP-NLRP3-GSDMD axis in diabetic rats. The third article by Xuan et al. is revealing the effect of Yiqi Jiedu Huayu herbal decoction in diabetic nephropathy. Treatment with Yiqi Jiedu Huayu herbal decoction improved renal pathological damage and renal function, and the mechanism of which might be related to downregulation of mTOR pathway via PI3K/Akt and AMPK pathways. Apart from herbal decoction, Yang et al. have reported the effect of Huidouba, a Tibetan medicine derived from the nest of *Atypus karschi*, in diabetic nephropathy. Having an intake of Huidouba could down regulate the expression of Nox4 and relieve the oxidative injury in podocytes and proteinuria of diabetic nephropathy rats. Taken together, the aforementioned articles

provide possible therapeutic strategies for treatment of diabetic kidney disease.

In addition, the therapeutic functions of herbal medicine on other kidney diseases have included here. Zhen-Wu-Tang, a well-known traditional Chinese herbal formula, restored renal dysfunction in immunoglobulin A-mediated nephropathy rat model, and the action of was revealed to be triggered by regulating exosome secretion in inhibiting NF-κB/NLRP3 pathway (Li et al.). Chao et al. have employed untargeted lipidomics to reveal action mechanism of *Orthosiphon stamineus* extract in treating nephrolithiasis. They found that the anti-stone effect of *O. stamineus* extract was closely related to glycerolphospholipid-mediated oxidative stress and inflammatory response. In parallel, Xiong et al. have investigated the effect of I-BET151, a small-molecule inhibitor targeting the bromodomain and extra-terminal (BET) protein, on the development of hyperuricemic nephropathy, which supports the notion that BET inhibition may have therapeutic potential in prevention and treatment of the problem.

Active Ingredients in Herbal Medicine for CKD

Ten articles are focused on identifying active ingredients within herbal medicine to treat CKD. Fucoidan, a natural compound of *Laminaria japonica*, was reported to ameliorate renal injury-related calcium-phosphorous metabolic disorder and bone abnormality in CKD mineral and bone disorder rats by targeting FGF23-Klotho signaling axis (Liu et al.). These data provide pharmacological evidence of fucoidan in the treatment of this disease. Ning et al. have shown that genistein could restore renal fibrosis by increasing alkylation repair homolog 5 to regulate epithelial-to-mesenchymal transition in unilateral ureteral occlusion-induced animal model. The result provides new insight into the function of m6A modification in CKD progression. Emodin, the most important component of *Rheum palmatum*, was being prepared in nanoparticles to form an emodin-nanoparticle system. This combination possessed higher stability and better colon adhesion in therapeutic effect on CKD (Lu et al.). He et al. have revealed that rhein and curcumin had a synergistic effect in ameliorating CKD, which provides an important explanation on the synergy of rhein and curcumin from a pharmacokinetic viewpoint. Tu et al. have demonstrated that total flavones, containing rutin, hyperoside, isoquercitrin, and quercetin extracted from *A. manihot*, could regulate the amounts of gut microbiota and its metabolites, and which inhibit microinflammation by targeting autophagy-mediated macrophage polarization in CKD rats. Saikosaponin D, a triterpene saponin isolated from *Bupleurum falactum*, was shown to inhibit peritoneal fibrosis in rats by regulating TGFβ1/BMP7/Gremlin1/Smad pathway (Liu et al.). Astragaloside II protected podocyte injury and mitochondrial dysfunction in diabetic rats, possibly *via* a co-modulation of nuclear factor (erythroid-derived 2)-like 2 and PTEN-induced putative kinase signaling (Su et al.). Li et al. have shown that scutellarin, a biologically active flavonoid derived from *Erigeron breviscapus*, restored renal injury *via* increasing cellular communication network factor 1 expression and suppressing nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome in hyperuricemic nephropathy mice. Cui et al. have investigated the effect of oleuropein, an active ingredient of *Ilex pubescens*, on acute kidney injury model. Their findings showed that oleuropein attenuated lipopolysaccharide-induced acute kidney injury both *in vitro* and *in vivo* by suppressing dimerization of toll-like receptor. Zhou et al. have reported that glycyrrhetinic acid, a bioactive component of *Glycyrrhiza uralensis*, protected renal tubular cells against oxidative insult. The regulation of JNK-connexin 43-thioredoxin signaling is proposed to play a crucial role in this action. Taken together, these findings can offer promising candidates for new drugs against CKD.

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