

Research Progress of Wuling San and the Active Components of Its Constituent Herbs in Chronic Kidney Disease

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Abstract. Objective. To systematically review the current clinical application of the classical formula Wuling San (WLS) in chronic kidney disease (CKD), to explore in depth the mechanisms of action of the active components of its constituent herbs, and to provide a theoretical basis and research directions for the further development of WLS and the traditional Chinese medicine (TCM) prevention and treatment of CKD. Methods. Relevant domestic and international literature was retrieved. The clinical application of WLS and its modified formulations in common chronic kidney diseases—such as nephrotic syndrome, chronic glomerulonephritis and diabetic kidney disease—as well as the pharmacological actions of the core bioactive components of the five constituent herbs (*Poria cocos*, *Alismatis Rhizoma*, *Polyporus umbellatus*, *Atractylodis Macrocephalae Rhizoma* and *Cinnamomi Ramulus*) were summarized from the two dimensions of clinical research and basic-mechanism research. Results. When combined with conventional Western medical therapy, WLS and its modified formulations markedly enhance the clinical efficacy in CKD patients, improving renal-function indices, attenuating inflammatory responses and relieving edema. The underlying mechanisms mainly involve the regulation of multiple signaling pathways such as NF- κ B/NLRP3 and RAS/TGF- β 1/Smad, thereby exerting anti-inflammatory, antioxidant, anti-fibrotic and anti-apoptotic effects. Pachymic acid, alisma polysaccharides, ergosterol, atractylenolides and cinnamaldehyde, among others, are the key active constituents responsible for the reno-protective actions. Conclusion. Wuling San demonstrates definite therapeutic efficacy and broad research prospects in the treatment of chronic kidney disease.

Keywords: Wuling San; Chronic kidney disease; Active components; Mechanism of action; Clinical application.

1. Introduction

Chronic kidney disease (CKD) is extended damage to the structure and function of the kidneys caused by all kinds of factors, such as immune injury, metabolic disorders and changes in blood supply. It is now one of the major non-communicable diseases worldwide. According to epidemiological data, the age-adjusted prevalence of CKD in the general population has exceeded 10% [1], and with an increase in the proportion of people with hypertension and diabetes, so too has the incidence of CKD. It has a mild onset, no particular signs, and is not widely known among the public; thus, the disease-awareness rate in China is less than 12.5 per cent [2]. Therefore, a large number of patients miss the window for early treatment and later develop end-stage renal disease (ESRD), placing a heavy medical and economic burden on their families and society.

Currently, the Western medical system has introduced a stage- and stratum-based intervention approach for CKD. In the early stage (CKD 1-3), one needs to address the risk factors and add first-line renoprotective drugs, such as renin-angiotensin-aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors; at the same time, dietary modifications and symptom treatment for hypertension, hyperglycemia, hyperlipidemia and electrolyte disturbances should be carried out to prevent further harm to the kidneys. In Stage 4, the problem is how to correct complications such as renal anemia, secondary hyperparathyroidism and acid-base imbalance; in Stage 5, people will need to receive renal replacement therapy, such as dialysis or a kidney transplant [3]. However, the current regimens have obvious defects: first-line renoprotective drugs have definite contraindications and toxic side effects, thus limiting the eligible population; they can only slow down

the progression of the disease and are unable to reverse core organic lesions such as tubular atrophy and interstitial fibrosis; and renal replacement therapy in the end stage still faces problems such as donor shortage and frequent long-term complications. Therefore, in recent years, many complementary therapies have been proposed to address the issues of renal target-organ protection, low toxicity and long-term compatibility with Western medicine in chronic kidney disease (CKD).

Traditional Chinese medicine (TCM), with more than two thousand years of clinical practice, has developed a distinctive diagnostic and therapeutic system for the full-cycle prevention and management of CKD. Its holistic regulation, syndrome differentiation and multi-target coordination form a strong complement to the single-target, symptom-oriented Western approach, and offer notable advantages in the long-term management of CKD [4]. These advantages can be summarized in three respects. First, TCM interventions are not confined to local pathological repair of the kidney; rather, they simultaneously regulate systemic pathological states such as fluid-metabolism disturbance, immune imbalance and microcirculatory disorders, which is highly consistent with the multisystem involvement and multi-pathogenesis nature of CKD. Second, Chinese herbal compound formulas act in a multi-component, multi-pathway and multi-target manner; their mild and low-toxicity profile is well suited to the long-term management of CKD. Third, TCM can be combined with conventional Western therapy to enhance efficacy while reducing the toxicity of Western drugs, effectively delaying renal-function decline in non-dialysis patients and improving long-term prognosis. Wuling San, a classical formula recorded by Zhang Zhongjing in the Treatise on Cold Damage Diseases (Shanghan Lun) of the Eastern Han Dynasty, is a representative TCM prescription for promoting diuresis, warming yang and transforming qi to move water. It targets the pathogenesis of dysfunctional Sanjiao qi transformation and internal water–damp retention [5], which corresponds closely to clinical manifestations of CKD such as sodium–water retention, peripheral edema, oliguria, ascites and abnormal tubular water reabsorption. Existing clinical evidence indicates that WLS in combination with conventional Western therapy can effectively improve edema, proteinuria and renal interstitial edema in various CKD subtypes, including nephrotic syndrome, chronic glomerulonephritis, diabetic kidney disease, chronic renal insufficiency and ESRD. Its clinical applicability covers the entire CKD 1–5 disease course, providing a solid basis for full-cycle intervention.

Current studies on the single constituents of the five herbs of WLS (*Polyporus umbellatus*, *Poria cocos*, *Alismatis Rhizoma*, *Atractylodis Macrocephalae Rhizoma* and *Cinnamomi Ramulus*) are gradually improving; however, the synergistic mechanisms and dose–effect relationships by which the compound formula regulates the pathological progression of CKD have not yet been systematically summarized. Given the well-established clinical efficacy of WLS and its unique advantage in treating "water–damp" pathogenesis, the present paper systematically reviews the clinical controlled studies of WLS in different CKD subtypes, decodes the regulatory pathways by which the core active components of the five herbs (alisols, pachymic acid, ergosterol, atractylenolides and cinnamaldehyde) modulate renal inflammatory infiltration and interstitial fibrosis, and clarifies the intrinsic logic of the "sovereign-minister-assistant-envoy" combination. The aim is to provide a theoretical basis for the standardized clinical translation of WLS and for the optimization of integrated Chinese–Western intervention strategies for CKD.

2. Origin and Efficacy of Wuling San

Wuling San was first listed in the Treatise on Cold Damage Diseases (Shanghan Lun) by Zhang Zhongjing in the Eastern Han Dynasty. This is a classic formula for adjusting fluid metabolism that generally aims to increase urine output, reduce dampness in the body, warm Yang and move Qi. It is well suited to renal injury caused by disorders of fluid distribution and excretion. Its indications in the original text of Shanghan Lun overlap closely with the clinical manifestations of modern CKD: "floating pulse, dysuria, mild fever and polydipsia - Wuling San is indicated"; "After sweating, a floating and rapid pulse with vexation and thirst - Wuling San is indicated"; "Thirst with a desire to drink but vomiting immediately after drinking, called water counter-flow - Wuling San is indicated";

and "Distension is not relieved; the patient is thirsty, with dryness of the mouth, vexation and dysuria - Wuling San is indicated". These are further supported by the Synopsis of the Golden Chamber (Jin Gui Yao Lue), which states: "If a thin person has palpitations below the umbilicus, drools and suffers from epilepsy-like dizziness, it is water retention, and Wuling San is indicated".

Although the external forms described in the above classical passages are different, their fundamental pathogenesis is uniformly the same and all fall under the category of taiyang water-retention syndrome. The path of the disease is as follows: an unresolved external pathogen invades the bladder and impairs the function of qi transformation in the bladder, causing water retention in the lower jiao, disorder of fluid metabolism pathways, failure of fluids to ascend and moisten the mouth and tongue, and finally manifesting as a group of symptoms including dysuria, polydipsia, water counter-flow and dizziness.

Wuling San is a brief and strong formula composed of five herbs: *Alismatis Rhizoma*, *Poria cocos*, *Polyporus umbellatus*, *Atractylodis Macrocephalae Rhizoma* and *Cinnamomi Ramulus*, and they strictly adhere to the "sovereign-minister-assistant-envoy" principle of combination. *Alismatis Rhizoma* is used as a sovereign herb in a large dose; it is sweet, bland and cold in nature, can directly reach the lower jiao and bladder, promote diuresis, drain dampness and expel turbid water from the lower jiao. *Poria cocos* and *Polyporus umbellatus* are both bland and diuretic; therefore, they serve as minister herbs to help the sovereign herb increase the drainage of water and dampness in the lower jiao and relieve internal and external water retention. *Atractylodis macrocephalae rhizoma* is sweet, bitter and warm in nature, and enters the spleen and stomach meridians. It strengthens the spleen and dries dampness, thereby restoring the transportation and transformation of water and dampness in the middle Jiao, as shown in traditional Chinese medicine (TCM) theory. Paired with *Poria*, it strengthens the middle burner to cut off the source of water accumulation, and thus promotes normal fluid distribution. *Cinnamomi Ramulus* is pungent, sweet and warm; it corresponds to the bladder and heart meridians, and, first, it warms and regulates the Yang Qi of the lower Jiao, regulates the opening and closing function of bladder Qi transformation, and drives out water at its source; second, it can dispel residual exterior pathogens and thereby treat both the interior and the exterior. Generally speaking, the formula meets the requirements of "promoting diuresis without damaging vital Qi" and "warming Yang without generating heat"; it is a bland diuretic that also has the warming and transforming effects of Qi, and it also regulates the transport and transformation of the Middle Burner. At the same time, it opens the water-excretion path and restores visceral qi transformation to establish a dynamic equilibrium of fluid distribution and excretion for harmony between Yin and Yang in the body.

3. Clinical Studies of Modified Wuling San in Chronic Kidney Disease

3.1. Nephrotic Syndrome

Many clinical trials have shown that the modified Wuling San can treat nephrotic syndrome by reducing edema, regulating the immune response and decreasing the amount of protein in the urine. Huang Jia [6] conducted a clinical trial on 108 children with refractory nephrotic syndrome and found that Wuling San combined with Zhibai Dihuang Wan could effectively correct immune dysfunction, regulate the balance of immune cells and suppress abnormal release of inflammatory mediators; thus, urinary protein leakage decreased and the core pathological damage of the disease was improved. Wang Jingjing and others conducted a controlled study on 110 patients with nephrotic-syndrome-related edema [7]. The overall effective rate of the integrated Chinese-Western regimen (Wuling San + Western therapy) was 89.09%, which was significantly higher than that of the Western therapy alone group (74.55%). The combination of the two was also faster in reducing edema ((9.94 ± 2.18) days vs. (11.41 ± 3.25) days), indicating that Wuling San had a better effect on reducing edema.

A few other studies have also examined the effect of modified Wuling San on the modification of the formula and combination therapy. Xiao Yun and others [8] showed that the combination of Zhenwu Tang and Wuling San can reduce the level of inflammatory cytokines in patients with nephrotic

syndrome, relieve renal inflammatory injury, and improve kidney function; thus, it has good overall efficacy. Hu Maorong and others [9] used an internal-external combined therapy of modified Wuling San and acupoint application to treat refractory edema in nephrotic syndrome, and it was found that this all-round strategy further improved clinical effectiveness and offered an effective option for managing refractory edema. Li Ermin [10] used modified Wuling San with tacrolimus in 120 patients with nephrotic syndrome, and found that this combination effectively regulated immune function, repaired kidney damage, and achieved good control of the disease. For syndrome-differentiated precision treatment, Fu Huiling [11] focused on syndrome-differentiated precise treatment for adult primary nephrotic syndrome with a wind-water contention pattern and used Yuebi Jia Zhu Tang combined with Wuling San as adjuvant therapy; this study found that the combination significantly alleviated clinical symptoms, reduced proteinuria, suppressed renal inflammation and corrected immune imbalance, protected renal function and delayed disease progression, reduced the toxic side effects of Western drugs, and demonstrated the unique advantage of "enhancing efficacy and attenuating toxicity".

Clinical trials have shown that Wuling San and its modified formulas are effective in treating nephrotic syndrome to date. By blocking all paths to disease, they can relieve symptoms and improve the function of the kidneys in sick people; these have shown good clinical results and are safe.

In short, the present clinical data fully support the conclusion that Wuling San and all its modifications inhibit the progression of nephrotic syndrome through multiple pathways, such as immune regulation, anti-inflammation, reduced proteinuria, edema relief and protection of kidney function. They have shown certain efficacy in various types and degrees of nephrotic syndrome, and are now considered effective TCM formulas for treating this disease; further research on their mechanism and other applications is also being conducted.

3.2. Chronic Glomerulonephritis

Some clinical trials have shown that Wuling San and related or combined formulas can reduce the level of inflammatory cytokines and improve renal function in the treatment of chronic glomerulonephritis (CGN). Yang Jing and others conducted a clinical study [12] to add Wuling San to standard benazepril treatment for 104 patients with lung-kidney qi-deficiency CGN, and the results showed that combined therapy significantly reduced the levels of serum high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). Liu Fenghui et al. [13] treated 136 CGN patients with Wuling San combined with Xiaochaihu Tang and valsartan capsules; the 24-hour urinary protein, serum creatinine (SCr) and blood urea nitrogen (BUN) levels all improved significantly, and at the same time, serum matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1) and vascular endothelial growth factor (VEGF) levels were markedly downregulated, indicating a joint regulation of renal fibrosis and vascular endothelial injury pathways. Gu Weiqiang et al. [14] further investigated Yincheng Wuling San in CGN patients ($n = 95$) and found that it not only reduced 24-hour urinary protein, SCr and BUN levels, but also downregulated hs-CRP, IL-6 and interferon- γ (IFN- γ) expression and suppressed the mRNA transcription of Toll-like receptor 4 (TLR4) and nuclear factor- κ B (NF- κ B), thereby clarifying that it alleviates renal inflammation and improves renal function through the modulation of the TLR4/NF- κ B pathway.

In short, based on the above clinical data, it can be seen that Wuling San and its related formulas have many anti-inflammatory effects at the molecular level, help improve various indices of kidney function in patients with chronic glomerulonephritis (CGN), and offer promising clinical proof for TCM in treating CGN.

3.3. Diabetic Kidney Disease

Numerous clinical studies have demonstrated that the classical diuretic and damp-draining formula Wuling San, together with its modified compound prescriptions, can significantly improve renal

function, reduce urinary protein excretion and delay renal fibrosis in diabetic kidney disease (DKD). Chen Haishan et al. [15] treated 60 DKD patients with qi-deficiency and blood-stasis pattern using Buyang Huanwu Tang combined with Wuling San; the combined regimen effectively improved renal function, delayed the progression of renal injury and fibrosis, and significantly reduced urinary protein excretion. For DKD-associated edema, Liao Lizhen et al. [16] treated 88 DKD patients with edema using Wuling San combined with Wupi Yin; the treatment significantly increased urine output, alleviated peripheral edema and improved clinical symptoms.

Ma Chao [17] combined the modified Wuling San prescription with benazepril hydrochloride to treat 114 elderly patients with diabetic kidney disease in a study on combined Chinese-Western medication and special populations, and found that this regimen effectively regulated blood glucose, ameliorated renal-function injury, and corrected lipid-metabolism disorders. Jiang Zhixiang [18] treated 86 patients with DKD using a combination of Shenqi Dihuang Tang and Wuling San, and after treatment, the core renal function indicators, urinary albumin excretion rate (UAER), cystatin C (Cys-C), BUN and SCr were all significantly reduced.

3.4. Chronic Renal Insufficiency

Some clinical trials have shown that Wuling San can decrease urinary protein and improve kidney function in people with chronic renal insufficiency when combined with other formulas.

Wang Weiwei and others [19] have found that Shipi Wuling San, when used with conventional Western medicine, can improve the renal function of patients with chronic kidney disease, correct abnormal bone metabolism, enhance nutritional status and relieve symptoms of TCM clinical syndromes effectively. Focusing on stage-3 CKD, a severe stage of the disease, Tao Rui et al. [20] conducted a randomized controlled trial of 65 patients and found that modified Mahuang Fuzi Xixin Tang combined with Wuling San, in combination with conventional Western therapy, significantly reduced serum creatinine (SCr) more than compound α -ketoacid tablets ($(387.52 \pm 92.13) \mu\text{mol/L}$ vs. $(502.78 \pm 117.35) \mu\text{mol/L}$, $P < 0.01$); it also achieved a total effective rate of 87.5% and produced a more obvious improvement in TCM syndromes such as fatigue, soreness of the waist and legs, poor appetite and abdominal distension. Wang Rui and others [21] also found that Wuling San, when combined with abdominal acupuncture, reduced edema and decreased 24-hour urinary protein; at the same time, they increased serum albumin and reduced steroid-related adverse reactions.

3.5. End-Stage Renal Disease

Some clinical trials have shown that, when combined with other formulas, Wuling San can reduce inflammatory factors and improve the function of the kidneys in end-stage renal disease (ESRD). Chen Qiurong and others [22] examined hemodialysis patients with end-stage renal disease (ESRD) and found that Jiedu Gushen Tang combined with Wuling San reduced clinical symptoms, improved micro-inflammatory status, increased residual renal function, and optimized hemodialysis outcomes. Zhong Jin et al. [23] conducted a randomized controlled trial in 65 patients undergoing maintenance peritoneal dialysis to find that, in addition to standard therapy, Xiaochaihu Tang combined with Wuling San significantly improved residual renal function (RRF), reduced SCr, BUN and 24-hour urinary protein, downregulated IL-6, IL-8 and TNF- α levels, and suppressed peritoneal fibrosis by modulating the JAK2/STAT3 signaling pathway.

In brief, based on the current clinical data, Wuling San-based regimens have shown favorable results in various ways for patients with chronic kidney disease, such as improvement in renal function, reduction of inflammation, suppression of renal fibrosis, enhanced nutrition, and increased dialysis efficacy; thus, they provide reliable support for further clinical application and in-depth studies.

4. Mechanisms of Wuling San in the Treatment of Chronic Kidney Disease

With the deepening of modern research on TCM, studies of the mechanisms of Wuling San in CKD have progressed from overall pharmacodynamic evaluation to the level of molecular signaling

pathways and key targets. Multiple animal studies have systematically revealed the multi-target and multi-pathway reno-protective characteristics of Wuling San from different pathological models and intervention aspects.

Han Yuping and others [24] constructed a rat model of nephrotic syndrome induced by azithromycin and demonstrated that the extract of Wuling San had good diuretic and anti-edema effects; it reduced urinary protein, regulated lipid metabolism, increased serum albumin, alleviated renal histopathological injury, and also showed a strong synergistic effect when combined with the glucocorticoid prednisone.

Furthermore, Yang Ting and others [25] also conducted a comparative study and found that a modified Mahuang Wuling San reduced renal tissue damage more effectively than the original Wuling San in adriamycin-induced nephropathy rats, and showed superior effects in reducing urinary protein and recovering renal function.

In DKD mechanism studies, Chen Yanjun and others [26] found that Wuling San can inhibit renal fibrosis in db/db mice by regulating the nuclear factor- κ B/NLRP3 inflammasome signaling pathway. Rao Rui et al. [27] determined that Wuling San delays diabetic nephropathy through two routes: first, it downregulates the renal NF- κ B/NLRP3 pathway, reduces local inflammation and pro-inflammatory cytokine release, and dampens the inflammatory microenvironment that drives neutrophil extracellular trap (NET) formation at its origin; second, it suppresses neutrophil PAD4 and NADPH oxidase activity, reducing the production and glomerular deposition of NETs, and thus alleviates the toxic and mechanical injury to glomerular endothelial cells and preserves endothelial viability and barrier function. From a TCM perspective, the pathogenesis of DKD is generally traced back to spleen and kidney yang deficiency at the root, with the presentation of internal accumulation of water-damp and turbid toxins and stasis-blocked kidney collaterals; hyperactivation of the NLRP3 inflammasome is associated with excessive turbid heat and toxins, and an increase in NETs corresponds to palpable stasis and turbidity in the kidney collaterals; the two work together to create a vicious cycle of mutual production of toxins and stasis. Wuling San warms Yang, transforms Qi, promotes diuresis and drains Dampness; Alismatis Rhizoma, Polyporus and Poria drain Dampness and Turbidity to eliminate the cause of NLRP3 activation; Cinnamomi Ramulus warms and opens the collaterals to disperse NET-related stasis; and Atractylodes invigorates the Spleen and consolidates healthy Qi to stabilize immune homeostasis and enhance the clearance of pathological products, thereby addressing both the root and expression of the disease. It simultaneously interrupts the microscopic pathological loop of "toxin-generating stasis and stasis-promoting toxins", protects glomerular endothelial cells, reduces urinary protein, delays renal fibrosis and the progression of DKD.

In other types of CKD, Tang Yu et al. [28] have also found that Wuling San significantly reduced serum uric acid (SUA), SCr and BUN levels and alleviated renal histopathological damage in a rat model of uric acid nephropathy (UAN). Network pharmacology analysis and in vivo experiments have determined that the mechanism is associated with the endocrine resistance pathway, and several key targets include matrix metalloproteinase 2 (MMP2), insulin-like growth factor 1 receptor (IGF1R), tyrosine-protein kinase SRC, phosphatidylinositol-3-kinase catalytic subunit α (PIK3CA) and estrogen receptor 1 (ESR1). Xu Chang and others [29] constructed a rat model of renal water-metabolism disorder with high salt and aldosterone, and showed that Wuling San inhibits the activation of the mineralocorticoid receptor (MR), reduces renal sodium-water retention, and thus has renoprotective effects. In short, current basic research shows that Wuling San and its modifications regulate multiple core pathological links, such as inflammation and fibrosis signaling pathways, essential water-metabolism receptors, renal intrinsic cell function and metabolic disorders, thus exerting all-round renoprotective effects in various types of CKD and providing strong experimental support for its broad clinical application.

5. Anti-CKD Mechanisms of the Active Components of Individual Herbs in Wuling San

Using ultra-high-performance liquid chromatography-quadrupole time-of-flight tandem mass spectrometry (UHPLC-Q-TOF-MS), 21 prototype compounds absorbed into the blood after oral administration of Wuling San were identified, including alisol A, 23-acetyl alisol B, pachymic acid, atractylenolide I, atractylenolide III and cinnamaldehyde [30, 31]. Several of these active components act as diuretics via multiple targets and pathways, thus aligning well with the traditional Chinese medicine function of "draining dampness and turbidity". Therefore, these blood-absorbed components are expected to provide the pharmacodynamic material basis for Wuling San in the treatment of CKD.

5.1. *Poria cocos* (Fu Ling)

Retrieval from the TCMSP database and studies show that the main active components of *Poria cocos* are pachymic acid and lanostane-type triterpenoids, which have shown various therapeutic effects for chronic kidney disease and reduced apoptosis and fibrosis.

Mo Xun et al. [32] discovered that pachymic acid can promote renal function, reduce tubular epithelial injury, lower the levels of NGAL, KIM-1 and cleaved caspase-3, inhibit the expression of TNF- α , IL-1 β and MCP-1, suppress apoptosis, and directly bind to caspase-3 to inhibit caspase-8-mediated cleavage-based activation. Wang Ming [33] has shown that lanostane triterpenes and 3,4-seco-lanostane triterpenes in *Poria* peel can inhibit the RAS, Wnt/ β -catenin and TGF- β /Smad pathways to prevent kidney fibrosis. Liu Jingru and others [34] have shown that poricoic acid ZA and poricoic acid B can suppress renal fibrosis by regulating the RAS and TGF- β 1/Smad pathways. Wang Wei et al. [35] used C57 mice as subjects to find that pachymic acid downregulated TGF- β 1, phosphorylated Smad2/3 and MMP-9, and thus reduced obstructive hydronephrosis and interstitial fibrosis.

5.2. *Alismatis Rhizoma* (Ze Xie)

According to the TCMSP database and supporting literature, the main active components of *Alismatis Rhizoma* are alisma polysaccharides and alisols, which exert therapeutic effects on diabetic kidney disease and renal fibrosis via the PPAR- γ /LXR- α /ABCG1, TGF- β 1/Smad and Wnt/ β -catenin pathways.

Dong Yingying and others [36] showed that alisma polysaccharides activate the PPAR- γ /LXR- α /ABCG1 pathway to have renoprotective effects in a rat model of DKD. Wang Jinpiao and others [37] have confirmed that ethanol extract of *Alismatis Rhizoma* alleviates hyperuricemia induced by potassium oxonate in rats. Zhai Xinyu et al. [38] found that 23-acetyl alisol B inhibits RAS and ameliorates renal fibrosis by means of the TGF- β 1/Smad and Wnt/ β -catenin pathways; in addition, an aqueous extract of the combination of *Alismatis Rhizoma* and *Plantago semen* suppresses the formation of renal calcium-oxalate crystals induced by ethylene glycol and hydroxyvitamin in rats and thus protects the kidney.

5.3. *Polyporus umbellatus* (Zhu Ling)

Based on data from the TCMSP database and other studies, the main active components of *Polyporus umbellatus* are ergosterol and others; they can reduce renal fibrosis.

Liu Jingru and others [34] have reported that ergosterol suppresses both the RAS/TGF- β 1/Smad and RAS/Wnt/ β -catenin pathways to reduce renal fibrosis. Chen Lin and others [39] have found that ergosterol regulates the metabolism of tryptophan, lipids, energy and purines in CKD rats, thus inhibiting renal and interstitial fibrosis; combining *Polyporus* polysaccharide (PPU) with ergosterol can alleviate disturbances in the tryptophan metabolic pathway and repair of the intestinal barrier, as well as reduce inflammation and oxidative stress in a unilateral ureteric obstruction (UUO) model.

5.4. *Atractylodis Macrocephalae Rhizoma* (Bai Zhu)

Retrieval from the TCMSP database and related literature shows that the main active components of *Atractylodis Macrocephalae Rhizoma* include atractylenolides and *Atractylodes* polysaccharides, and they have anti-inflammatory and renoprotective effects.

Wu Yingzhi and others [40] studied a rat model of cardiorenal syndrome and found that atractylenolide I improved cardiac and renal function and reduced cardiac and renal inflammatory-cell infiltration; thus, it showed anti-inflammatory properties. Li Bingxin and others [41] have shown that *Atractylodes* polysaccharide + cyclophosphamide (CTX) can reduce renal damage induced by CTX, lower the level of renal malondialdehyde, increase antioxidant and enzyme activities; it is believed that this is due to modulation of the arachidonic acid metabolic pathway and alleviation of oxidative stress. Lin Shengfen et al. [42] found that atractylenolide III (AT-III) and its nano-formulation ZIF-8@AT-III can relieve intestinal-barrier injury in IgA nephropathy (IgAN) rats, reduce inflammation, downregulate diamine oxidase and D-lactate, upregulate tight-junction proteins, inhibit glomerular IgA deposition and protect the kidney; the nano-formulation ZIF-8@AT-III has better effects than AT-III alone.

5.5. *Cinnamomi Ramulus* (Gui Zhi)

Based on the TCMSP database and other research, the principal active components of *Cinnamomi Ramulus* are cinnamaldehyde, β -sitosterol, taxifolin and catechin. By regulating urate transporters and performing other functions, they have significantly reduced blood glucose and creatinine in the context of nephrotic syndrome, hyperuricemic nephropathy and diabetic kidney disease to mitigate renal damage and improve kidney function.

He Dan and others [43] have identified cinnamaldehyde as a likely key component by which Wuling San alleviates nephrotic syndrome, and a mechanism in the RAS pathway has been revealed. Sun Lu and others [44] have shown that β -sitosterol reduces UA, creatinine (CRE) and BUN in hyperuricemic mice, alleviates renal histopathological injury, inhibits xanthine oxidase (XOD) activity, and regulates urate transporters. Wu Fenfei and others [45] found that taxifolin can lower blood glucose, uric acid, creatinine and insulin in diabetic rats, relieve renal damage, and restore the expression of caveolin-1/NF- κ B signaling proteins. He Xiaojie and others [46] have shown that catechin reduces VEGF production in adriamycin-induced nephropathy rats by inhibiting it, and this effect is enhanced after microencapsulation.

6. Conclusion

Originally used for taiyang water-retention syndrome, Wuling San has been modified and combined with Western medicine and has produced marked efficacy in the treatment of various chronic kidney diseases. Its efficacy has been confirmed through objective indicators such as inflammatory cytokines and renal-function parameters, embodying the strength of TCM in "using the ancient to serve the present." At present, TCM research mainly focuses on the components of individual herbs, and the synergistic actions of the components within compound formulas have not received sufficient attention. Guided by pharmacological effects, the present review systematically summarizes the actions of the active components of each herb in Wuling San in chronic kidney disease, including regulation of apoptosis, anti-inflammatory, antioxidant and anti-fibrotic activities.

Wuling San is a well-known formula that warms the Yang and promotes diuresis, thus having broad research prospects for chronic kidney disease. However, the current clinical studies are still lacking in terms of evidence, have small sample sizes, are mostly single-center designs, lack long-term follow-up and recurrence data, and have imperfect efficacy-evaluation systems and clinical guidelines. Future research will employ a large-sample, multi-center, randomized controlled design, introduce modern detection technology, and integrate traditional Chinese medicine theories and diagnostic and therapeutic methods to provide scientific evidence for the evaluation of the effectiveness of TCM compound formulas and their standardized clinical application.

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