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Research Progress on the Treatment of Diabetic Nephropathy with Traditional Chinese Medicine

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Abstract: Diabetic nephropathy, one of the primary chronic microvascular complications of diabetes, demonstrates distinct advantages in TCM treatment. This approach effectively alleviates clinical symptoms and improves patients' quality of life. Through holistic regulation and personalized therapeutic principles, TCM exhibits unique efficacy in reducing urinary protein levels and protecting renal function. Its multi-target, multi-pathway mechanism provides innovative approaches for disease prevention and control, while offering patients expanded treatment options. In clinical practice, TCM applications not only help delay disease progression but also reduce side effects associated with Western medications, achieving more comprehensive therapeutic outcomes. This paper examines both internal and external TCM therapies. The internal treatment section analyzes mechanisms and clinical efficacy using selected common herbs and classical formulas, while external treatments, though serving as adjunct therapies, play an indispensable role in preventing and managing diabetic nephropathy.

1. Introduction

Diabetic kidney disease (DKD), a prevalent secondary renal disorder in China, is also one of the primary chronic microvascular complications of diabetes. In its early stages, DKD typically presents with subtle symptoms and minimal manifestations, later progressing to clinical presentations such as [1] proteinuria and edema, ultimately leading to end-stage renal disease. According to estimates by the International Diabetes Federation, China's diabetic population is projected to exceed 174 million [2] by 2045. With the growing number of diabetes patients, the incidence of DKD has correspondingly increased. The substantial medical costs associated with end-stage renal replacement therapy not only impose heavy financial burdens on families but also significantly reduce patients' quality of life. Consequently, the prevention and treatment of DKD have become a focal point of public concern. Traditional Chinese medicine (TCM) has demonstrated remarkable efficacy in managing DKD and slowing disease progression. This review summarizes recent research advancements in TCM-based therapies for DKD.

2. Understanding of DKD between traditional Chinese medicine and modern medicine

2.1. Traditional Chinese medicine's understanding of DKD

In traditional Chinese medicine, diabetes was termed "Xiao Ke" (consumptive thirst), first documented in the "Su Wen: Discussion on Rare Diseases". Although diabetes nephropathy lacks explicit historical records, it falls under the category of "lower consumption" in the Xiao Ke syndrome differentiation system. Wang Kuntang's Ming Dynasty text "Zheng Zhi Zhun Sheng: Xiao Dan" states: "... frequent thirst with greasy discharge corresponds to lower consumption (as described in the classics as kidney consumption)." Ancient medical texts categorize this condition under "Xiao Ke," "kidney consumption," and "guan ge" (kidney obstruction). Professor Nan Zheng proposed the TCM diagnosis "Xiao Ke Shen Bing" [3] for diabetes nephropathy, which was officially recognized in 2010 and included in the "Terminology of Traditional Chinese Medicine". Historians attribute its development to congenital deficiencies, dietary imbalances, emotional disturbances, and organ dysfunction, with spleen-kidney deficiency being the primary cause. The underlying pathology involves blood stasis, dampness, and pathogenic toxins. Emperor Huizong of Song noted in "Sheng Ji Zong Lu": "Long-term Xiao Ke damages kidney qi. As the kidneys govern water metabolism, their deficiency disrupts qi transformation, impairing fluid regulation and causing edema." Professor Nan Zheng [4] identified "toxin damage to kidney meridians" as a common pathogenic factor. Professor Zhao Yuyong [5] synthesized clinical observations, proposing "kidney meridian stasis" as the fundamental mechanism, emphasizing meridian unblocking therapy. Professor Lv Renhe[6] developed the "micro-carcinoma" theory, focusing on resolving blood stasis. Master Zhou Zhongying[7] emphasized heat-stasis in mid-to-late stages, advocating heat-clearing, blood-cooling, and essence-consolidation therapies.

In traditional Chinese medicine (TCM), the understanding of diabetic nephropathy extends beyond etiological analysis to encompass detailed observation of its clinical manifestations and progression patterns. Through centuries of clinical practice, ancient physicians identified characteristic symptoms including cloudy urine, edema, and fatigue, attributing these to impaired spleen-kidney function. The Jingyue Quanshu (Complete Book of Jingyue) states: "Prolonged diabetes leads to sinking essence qi, causing undigested food to form turbid urine". This underscores the intrinsic connection between diabetic nephropathy and spleen-kidney deficiency. Furthermore, generations of practitioners emphasized emotional factors in disease development, noting that excessive worry or emotional distress could exacerbate symptoms. Guided by these insights, TCM treatment for diabetic nephropathy focuses on holistic regulation and syndrome differentiation, with the core objective of restoring yin-yang balance in the body. This unique theoretical framework provides crucial guidance for modern TCM approaches in managing this condition.

2.2. Modern medical understanding of DKD

Modern medicine identifies the pathogenesis of diabetic kidney disease (DKD) [8-10] as involving genetic factors, impaired glucose metabolism, altered renal hemodynamics, dysregulated lipid metabolism, hypertension, vasoactive substances and growth factors, oxidative stress, and other contributing factors. According to the Mogensen staging criteria for diabetic nephropathy, DKD is classified into five stages: Stage I (acute glomerular hyperfiltration), Stage II (normal proteinuria), Stage III (early diabetic nephropathy), Stage IV (clinically advanced diabetic nephropathy), and Stage V (renal failure). For DKD diagnosis, it must be confirmed whether the condition stems from diabetes. Chinese researchers unanimously agree that a diagnosis of diabetes-induced nephropathy requires meeting at least one of three criteria: (1) Massive proteinuria; (2) Diabetic retinopathy; or (3) Microalbuminuria in type 1 diabetes patients with chronic kidney disease of any stage and over 10

years of diabetes history.

With the deepening of research on the pathogenesis of diabetic kidney disease (DKD), modern medicine has gradually recognized the critical role of inflammatory responses and immune mechanisms in its development. Studies indicate that persistent hyperglycemia induces chronic inflammation in renal tissues, leading to tubulointerstitial fibrosis and glomerulosclerosis. Meanwhile, various cytokines such as transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) play significant roles in DKD progression. These factors promote extracellular matrix accumulation and thickening of the glomerular basement membrane through complex signaling pathways.

3. Internal treatment of Traditional Chinese Medicine

3.1. Combination of drugs

According to literature review [11,12], the most frequently used combinations were rhubarb-huangqi and Danshen-huangqi.

3.1.1. Rhubarb-astragalus

The earliest record of rhubarb appears in the "Shennong Bencao Jing" (Classic of Materia Medica). As a bitter-cold herb classified under purgatives, it is renowned for clearing heat, reducing fire, cooling blood, detoxifying, eliminating accumulations, promoting menstruation, and resolving dampness-induced jaundice. Astragalus, on the other hand, serves as a tonic herb that strengthens qi, consolidates the exterior, reduces edema, and replenishes vital energy. When combined, these herbs achieve the dual therapeutic effect of tonifying deficiencies and purging excesses. In late-stage diabetic nephropathy characterized by phlegm-stasis accumulation and systemic weakness, this formula effectively addresses the pathogenesis of qi deficiency and blood stasis. Studies [13,14] indicate that rhubarb-astragalus formulations may leverage active compounds like quercetin and kaempferol to target key biological pathways including tumor protein P53 (TP53), protein kinase B1 (AKT1), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF). By modulating signaling pathways, they demonstrate therapeutic potential for diabetic nephropathy (DKD). Clinical trials [15] showed that oral administration of raw rhubarb powder combined with intravenous astragalus injection in 30 DKD patients achieved effective symptom control and reduced protein leakage, demonstrating clinical value in disease prevention and management.

3.1.2. Salvia miltiorrhiza and Astragalus membranaceus

Salvia miltiorrhiza, first documented in the "Shennong Bencao Jing" (Classic of Materia Medica), is characterized by its bitter taste and slightly cold nature. It effectively promotes blood circulation, resolves stasis, alleviates pain, and reduces blood heat to eliminate abscesses. The "Bencao Huiyan" (Compendium of Materia Medica) states: "Salvia miltiorrhiza excels in entering the blood system, resolving stasis, regenerating tissues, regulating menstruation, and unblocking meridians." Astragalus membranaceus enhances qi and spleen function while promoting diuresis and reducing edema. When combined with astragalus, they synergistically enhance qi-boosting, blood-activating, and stasis-resolving effects. The mechanism of Astragalus-salvia combination in treating diabetic nephropathy (DKD) [16] primarily involves active components like quercetin, salvianolic acid II A, kaempferol, and luteolin, which act on target molecules such as ADRB2, CASP3, VCA1, and MYC. These components interact with multiple signaling pathways including AGE/RAGE, MAPK, and HIF-1 to combat diabetic complications. In DKD patients, intestinal flora imbalance disrupts the intestinal barrier, triggering inflammatory responses, oxidative stress, and fibrosis that worsen renal damage.

This herbal formula helps protect the intestinal barrier, regulate gut microbiota metabolites, safeguard glomerular filtration barriers, and break the vicious cycle between gut and kidney [17]. Clinical observations [18] show that a 50-50 treatment group using Astragalus-salvia injection achieved a 94.0% overall efficacy rate in relieving clinical symptoms of DKD patients.

3.2. Ancient formula treatment

3.2.1. Shenqi Dihuang Decoction

Shenqi Dihuang Decoction, first documented in Shen Jin 'ao's Qing Dynasty text "Xizhu: The Origin and Development of Miscellaneous Diseases", is formulated with Liuwei Dihuang Pills as its base formula. By incorporating Astragalus and Ginseng, it effectively nourishes qi-yin (vital energy) and strengthens kidney function while supporting spleen health, making it suitable for treating diabetic nephropathy (DKD) characterized by dual deficiency of qi and yin [19]. The therapeutic mechanism involves 50 active compounds such as quercetin, kaempferol, phytosterols, and dioscin, which interact with 133 biological targets across 167 signaling pathways to regulate cell proliferation, growth, and inflammatory responses [20]. Research indicates that Shenqi Dihuang Decoction reduces vascular endothelial cell adhesion (VEGF) and T-cell adhesion-associated protein-1 (TGF-β1) expression in renal tissues of DKD model rats, thereby improving glomerular filtration rate and reducing inflammatory reactions in renal tissue, ultimately contributing to the treatment of DKD.

Clinical studies [21] demonstrate that modified Shenqi Dihuang Decoction (a traditional Chinese herbal formula) effectively treats stage IV diabetic nephropathy with qi-yin deficiency and blood stasis, while delaying progression of diabetic kidney disease (DKD). For early-stage diabetic nephropathy (DN) [22], this modified formula regulates glucose and lipid metabolism, reduces inflammatory responses, decreases 24-hour urinary protein and microalbumin/creatinine levels, and lowers serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) in patients. These therapeutic effects mitigate renal damage caused by inflammation and slow the progression of DN.

3.2.2. Bu Yang Huan Wu Tang

Buxiang Huanwu Decoction, derived from the classic text "Yi Lin Gai Cuo" (Revised Medical Forest), contains essential ingredients: Astragalus, Paeonia, Angelica tail, Chuanxiong (Ligusticum), Safflower, Earthworm, and Peach Kernel. This formula demonstrates therapeutic effects in replenishing qi, promoting blood circulation, and unblocking meridians, particularly effective for treating diabetic nephropathy (DKD) with qi deficiency and blood stasis patterns. Research indicates that Buxiang Huanwu may delay disease progression through multiple mechanisms including suppressing inflammatory responses, regulating signaling pathways, and combating oxidative stress. Specifically, it enhances glucose metabolism, reduces lipid levels, improves hypercoagulability, and protects renal function [23]. Additionally, the decoction activates the Nrf2/HO-1 signaling pathway to mitigate oxidative damage, inhibit fibrotic factor expression, reduce pathological damage in mouse models, and slow the progression of diabetic nephropathy [24].

Clinical observations [25] indicate that Bu Yang Huan Wu Tang (Yang-Nourishing Five-Ingredient Decoction) significantly alleviates symptoms in diabetic nephropathy patients, reduces overall blood glucose levels and 24-hour urine microalbumin excretion rate, while regulating the body's stress response. In a study involving 102 diabetic kidney disease (DKD) patients [26], the treatment group achieved an 88.2% overall efficacy rate. When blood glucose and blood pressure were effectively controlled, the decoction demonstrated reduced blood viscosity, decreased renal vascular resistance index, increased renal blood flow, and marked improvement in renal

microcirculation. The three consecutive measurements of urinary albumin excretion rate (UAER) showed significant reduction, indicating therapeutic effects on stage III DKD.

3.2.3. Angelica Blood Tonic Decoction

Whengui Buxue Decoction, derived from the classic text "Distinguishing Between Internal and External Injuries", is a renowned formula for tonifying qi and blood. Composed of Astragalus membranaceus and Angelica sinensis in a 5:1 ratio, this herbal formula works through three key mechanisms to treat diabetic nephropathy [27]: By reducing endoplasmic reticulum stress in hyperglycemic kidneys, it modulates autophagy activity, decreases apoptosis in renal tissue cells of diabetic nephropathy rats, alleviates inflammatory responses, and reduces abnormal extracellular matrix accumulation in the glomerular mesangial zone, thereby exerting therapeutic effects. The formula improves renal function indicators in DKD patients by suppressing miR-21 expression to regulate autophagy activity in renal tubular cells [28]. Additionally, it demonstrates significant kidney-protective and disease-prolonging effects by improving mitochondrial dysfunction in DKD rat renal tubular cells, reducing ROS expression, mitigating oxidative stress, and decreasing inflammatory responses in renal tubular cells, ultimately lowering proteinuria levels [29].

In a clinical study involving 60 patients with confirmed diabetic kidney disease (DKD) [30], the use of Angelica and Codonopsis Blood-Tonic Decoction demonstrated significant therapeutic effects. Key indicators including UAER (Urine Clearing Excretion Rate), Ccr (Serum Creatinine Clearance), 24-hour PRO (24-hour Proteinuria Quantification), and serum inflammatory factor levels showed marked suppression of disease progression and improved prognosis. Analysis of 96 DKD patients [31] revealed that the decoction exhibited significantly higher clinical efficacy, better TCM syndrome scores, and lower adverse reaction rates compared to the control group, confirming its safe and effective treatment for diabetic nephropathy.

3.2.4. Zhenwu Decoction

Zhenwu Decoction, derived from the "Treatise on Cold Damage Diseases" and formulated by Zhang Zhongjing, the medical sage of the Eastern Han Dynasty, contains processed aconite root, white atractylodes rhizome, poria cocos, peony root, and ginger. It is effective in warming yang energy, promoting diuresis to reduce edema, and tonifying kidney and spleen functions. This formula is indicated for treating diabetic nephropathy (DKD) with spleen-kidney yang deficiency syndrome. Literature review [32] demonstrates that Zhenwu Decoction exerts multifaceted biological effects through immune regulation, oxidative stress response, and stress-induced reactions, targeting multiple pharmacologically active components and therapeutic pathways to modulate DN characteristics. A "Chinese herbal medicine-chemical components-disease targets" network [33] has been established. Specifically targeting key DKD biomarkers including TNF, AKT1, IL6, PTGS2, and MAPK8, the active chemical constituents of Zhenwu Decoction—such as β-sitosterol, kaempferol, stigmasterol, hederagenin, and 3β-acetoxyatractylone—target disease mechanisms through their bioactive compounds.

Clinical observations [34] indicate that Zhenwu Decoction demonstrates therapeutic efficacy in diabetic nephropathy. It effectively reduces blood glucose levels, promotes urinary albumin excretion, decreases proteinuria, and lowers creatinine clearance rate, thereby alleviating renal impairment. When administered alongside standard therapy, the modified Zhenwu Decoction significantly improves clinical symptoms and enhances renal function in patients with stage IV spleen-kidney yang deficiency type diabetic nephropathy (DN) [35].

4. External treatment of Traditional Chinese Medicine

4.1. Chinese herbal enema

Through comparative analysis of TCM syndrome scores, renal function changes, and treatment efficacy after 4 weeks[36], it was found that the modified Da Huang Fu Zi Tang enema formula demonstrated significant therapeutic effects in treating stage IV diabetic nephropathy. This approach effectively alleviated symptoms while markedly improving renal function and quality of life for patients with intermediate-to-late stage disease. For end-stage diabetic nephropathy, the combination of traditional Chinese medicine enema retention and hemodialysis showed [37] clinical symptom relief, reducing dialysis frequency from three times weekly to twice weekly while decreasing complications during treatment.

4.2. Auricular patching

Ear Acupoint Patch Therapy[38]: Using Wangliubingzi (a traditional Chinese herb), this therapy targets key acupoints including Endocrine, Sanjiao, Kidney, Adrenal, Pancreas, Gallbladder, Liver, Insomnia, and Ear Migen. Comparative studies demonstrate its effectiveness in reducing 24-hour urinary microalbumin levels and alleviating symptoms in diabetic nephropathy (DKD) patients, confirming its efficacy as an external treatment for DKD. Professor Zhao Jinxi [39]: The primary focus is on four acupoints—Lung, Spleen, Liver, and Kidney—which are crucial for early-stage DKD management. These points leverage their qi-tonifying, blood-activating, and tissue-dispersing properties to prevent pathogen retention while preserving vital energy during heat-clearing processes.

5. Conclusion

Traditional Chinese Medicine (TCM) theory posits that diabetic nephropathy manifests as a fundamental pathogenesis characterized by underlying deficiency and superficial excess. To address this pathological pattern, TCM practitioners apply syndrome differentiation and treatment principles based on medicinal properties and therapeutic effects. This study screened commonly used combinations such as rhubarb astragalus and astragalus salvia, along with classical formulas including Shenqi Dihuang Decoction, Buxiang Huanwu Decoction, Danggui Buxue Decoction, and Zhenwu Decoction, analyzing their mechanisms of action and evaluating clinical efficacy. Literature review indicates that these herbal pairings and ancient prescriptions can effectively improve renal function, delay renal failure progression, and enhance patient prognosis. However, current research on paired herbal therapy for diabetic nephropathy remains limited. As TCM falls within the realm of precision medicine, variations in dosage ratios often hinder achieving desired therapeutic outcomes. Unclear dosing, ratio specifications, or preparation methods may compromise clinical effectiveness, complicating mechanism interpretation and variability. Consequently, these pairings are rarely used alone in practice. While TCM external therapies serve as adjunct treatments, their role should not be underestimated—they effectively alleviate symptoms and enhance overall treatment efficacy.

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