DOI: 10.53469/jcmp.2026.08(05).29

Research Progress on the Regulation of Macrophage Polarization by Traditional Chinese Medicine in the Prevention and Treatment of Immune Injury in Diabetic Nephropathy

Changmei Ning[1], Peng Xiong[1,2,*]

[1]The First Clinical Medical College of Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Diabetic nephropathy (DN) is one of the serious microvascular complications of diabetes, which is mainly caused by non-enzymatic glycosylation of the basement membrane of blood vessels, which in turn leads to microvascular damage, which will rapidly develop into chronic renal failure if not treated in time, and immune damage plays an important role in its pathogenesis. Macrophage polarization plays a key role in the immune inflammatory response in diabetic nephropathy. In recent years, some progress has been made in the research on the regulation of macrophage polarization by traditional Chinese medicine in the prevention and treatment of immune injury in diabetic nephropathy. This article reviews the relationship between macrophage polarization and immune damage in diabetic nephropathy, the mechanism of TCM regulation of macrophage polarization, and the clinical application prospects.***

Keywords: Diabetic nephropathy, Macrophage polarization, Immune impairment, Chinese medicine**.**

1. Introduction

Diabetic nephropathy (DN) is one of the common chronic complications of diabetes, with a highly complex pathogenesis linked to multiple factors. In this process, immune and inflammatory responses play a significant role in the onset and progression of DN. As key immune cells, the polarization state of macrophages is closely associated with immune-mediated damage in DN [1]. Currently, Western medical treatments for DN include comprehensive management such as glycemic control, blood pressure reduction, lipid regulation, and improved circulation. However, long-term treatment is often associated with poor patient compliance, numerous side effects, and long-term efficacy that remains to be verified [2]. Traditional Chinese Medicine (TCM) offers unique advantages in the prevention and treatment of DN. Compared to Western medicine alone, TCM treatment has fewer side effects, making it suitable for DN patients requiring long-term medication [3]. It also allows for individualized treatment based on the patient's specific condition and constitution. Through a comprehensive, multi-targeted, and multi-pathway approach, TCM aims to regulate the body's overall physiological functions [4]. In addition to alleviating systemic symptoms (such as fatigue, edema, and soreness in the lower back and knees), TCM can also improve renal function. When combined with Western medical treatments—such as the concurrent use of antidiabetic, antihypertensive, and lipid-lowering medications — it can produce synergistic effects, enhancing overall therapeutic efficacy while effectively protecting the kidneys and preventing further damage [5]. In recent years, an increasing number of studies have focused on the regulatory role of TCM in macrophage polarization, offering new insights for the prevention and treatment of DN.

2. The Relationship Between Macrophage Polarization and Immune-Mediated Damage in Diabetic Nephropathy

2.1 Types of Macrophage Polarization

Macrophages are innate immune cells widely distributed throughout the human body. They are highly plastic and can adapt to changes in the local microenvironment; under different microenvironmental stimuli, they can polarize into classically activated M1-type and alternately activated M2-type macrophages [1]. M1-polarized macrophages primarily secrete pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), LPS, IFN-γ, interleukin-1β (IL-1β), and IL-6, which exert their effects through signaling pathways such as NF-κB and STAT1, thereby promoting inflammation and immune activation; M2-polarized macrophages primarily secrete anti-inflammatory cytokines, such as IL-4, IL-13, IL-10, and transforming growth factor-β (TGF-β), which exert their effects through signaling pathways such as STAT6 and PI3K/Akt, thereby exerting anti-inflammatory, tissue-repair-promoting, and immunoregulatory effects [6].

2.2 Relationship Between Macrophage Polarization and Immune Damage in Diabetic Nephropathy

Macrophages play a crucial role in the pathogenesis of diabetic nephropathy (DN). The signaling molecules and cytokines involved in macrophage polarization exert central regulatory roles in mechanisms such as metabolism, inflammation, fibrosis, and mitochondrial autophagy in DN [7]. Factors such as a high-glucose environment and oxidative stress can induce macrophage polarization toward the M1 phenotype, leading to the release of large amounts of

pro-inflammatory cytokines and exacerbating renal inflammation and immune damage [1]. Li X et al.[8] found that GBP2 (guanylate-binding protein 2), as a key gene in the pathological progression of DN, is a promising prognostic biomarker and intervention target; it promotes M1 macrophage polarization by activating the Notch1 signaling pathway, thereby accelerating the progression of DN. Concurrently, M1 macrophages are induced and activated by lipopolysaccharide (LPS) and interferon-γ (IFN-γ), leading to the release of pro-inflammatory mediators that exacerbate inflammation and tissue damage, thereby playing a role in the progression of renal fibrosis [9]. Conversely, M2 macrophages can alleviate renal inflammation, inhibit renal fibrosis, and promote renal tissue repair by secreting anti-inflammatory cytokines (IL-13, IL-4) and growth factors [6]. The sequential appearance of these two types of macrophages not only protects the body against pathogen invasion but also terminates inflammation and repairs tissues at the appropriate time. In patients with DN, an imbalance in their polarization state (increased M1 pro-inflammatory macrophages and decreased M2 anti-inflammatory macrophages) exacerbates renal immune damage and inflammatory responses. Therefore, regulating macrophage polarization to promote M2 polarization while inhibiting M1 polarization, thereby restoring the balance of macrophage polarization, may be an effective strategy for preventing and treating immune-mediated damage in DN.

3. Mechanisms of Traditional Chinese Medicine in the Prevention and Treatment of Immune-Mediated Damage in Diabetic Nephropathy

3.1 Modulation of Immune and Inflammatory Responses

3.1.1 Inhibition of Pro-inflammatory Cytokine Release

Inappropriate or excessive release of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6) may disrupt the balance of the immune system, thereby inducing inflammatory responses or causing functional impairment of the immune system, which in turn leads to renal damage. Certain TCM formulas and single herbs can protect the kidneys by inhibiting signaling pathways such as NF-κB and MAPK, thereby reducing the release of pro-inflammatory cytokines and alleviating renal inflammatory responses. Research by Jin Yuqiu et al. [10] demonstrated that Zhenwu Decoction (Poria, Paeonia, Ginger, Atractylodes, and Processed Aconite) reduces the production of inflammatory factors and alleviates renal inflammatory damage by downregulating the expression of key molecules in the ROCK/IKK/NF-κB pathway and inhibiting NF-κB activation. It also significantly lowers serum levels of pro-inflammatory factors such as IL-1β, IL-6, IL-8, and TNF-α, while increasing levels of the anti-inflammatory factor IL-10. Animal studies by Liu Jia et al. [11] demonstrated that in rats treated with Huangqin Decoction (Scutellaria baicalensis, Paeonia lactiflora, fried Glycyrrhiza uralensis, and Ziziphus jujuba), the phosphorylation levels of NF-κB in renal tissue, as well as the protein expression levels of NLRP3, ASC, Caspase-1, IL-1β, and GSDMD were significantly reduced. This may alleviate renal damage in DN by inhibiting the NF-κB/NLRP3/Caspase-1 pyroptosis pathway, exerting immunomodulatory, anti-inflammatory, antioxidant, and anti-fibrotic effects, while levels of inflammatory factors (IL-1β and IL-18) were also significantly reduced.

3.1.2 Promotion of Anti-inflammatory Cytokine Secretion

In the pathological progression of DN, anti-inflammatory cytokines (such as IL-4, IL-10, and IL-13) play a key role. They can reduce immune-mediated damage by inhibiting the production and activation of pro-inflammatory cytokines, while simultaneously promoting the repair of damaged renal tissue. Traditional Chinese medicine can regulate immune balance by modulating the function of immune cells to promote the secretion of anti-inflammatory cytokines. Research findings by Wang Chuan et al. [12] indicate that serum pro-inflammatory cytokines (IL-6, TNF-α) and anti-inflammatory cytokines (IL-10) are closely associated with diabetes and are involved in the entire process of diabetes and its vascular complications. The anti-inflammatory cytokine IL-10 exerts an immunosuppressive effect by inhibiting the release of immune mediators by mononuclear macrophages and suppressing the production of pro-inflammatory cytokines in serum. Clinical research by Wang Xin et al. [13] shows that a self-formulated compound formula (Asparagus cochinchinensis, Ophiopogon japonicus, Trichosanthes kirilowii, Xiagucao, Ge gen, and Huai shanyao) has the efficacy of tonifying qi and nourishing yin. It exerts a significant anti-inflammatory effect by stimulating the release of the anti-inflammatory factor IL-10. Furthermore, this formula demonstrates the potential to enhance insulin sensitivity. This personalized combination of Chinese herbal medicines effectively alleviates inflammatory responses by specifically regulating the body's immune response, thereby aiding in the treatment of diabetic nephropathy (DN).

3.2 Regulatory Signaling Pathways

3.2.1 NF-κB Signaling Pathway

NF-κB is an important transcription factor that plays a key role in inflammatory responses. Traditional Chinese medicine can reduce the polarization of M1 macrophages while promoting the polarization of M2 macrophages by inhibiting the NF-κB signaling pathway. Feng Y et al. [14] found that HOXD9/APOC1 is a key factor causing podocyte damage in diabetic nephropathy (DN) and that it induces M1 macrophage polarization via the NF-κB signaling pathway, thereby exacerbating the progression of DN. Research by Zhao Limin et al. [15] demonstrated that the hyperglycemic environment in DN, by upregulating miR-203 expression, can inhibit NF-κB activation, reduce the expression of inflammation- and fibrosis-related factors, and alleviate structural damage to renal tissue and renal function decline in rats. A related study by Chen Yi et al. [16] found that silybin alleviates renal damage in DN by regulating the TLR4/NF-κB and TNF-α/ROS/P38 MAPK pathways, inhibiting their activation, and reducing oxidative stress. Research by Zhang Yao et al. [17] indicates that a high-sugar environment can induce increased TLR4 expression in renal tubular epithelial cells, thereby activating the NF-κB pathway, promoting the release of inflammatory factors, and consequently exacerbating inflammatory responses and fibrosis. In contrast,

the modified Shengjiang San formula (Rhubarb, Bombyx silkworm, Turmeric, Cicada slough, Astragalus, Smilax glabra, Epimedium) can protect renal function by alleviating renal inflammation and fibrosis through the inhibition of the TLR4/NF-κB and Raf/MEK pathways. Research by Jiang Yifan et al. [18] showed that quercetin can improve diabetes-induced renal damage; its protective effect may be related to the inhibition of the HMGB1/RAGE/NF-κB inflammatory signaling pathway, thereby reducing renal inflammatory responses and cellular apoptosis. Experimental studies by Yang Wen et al. [19] indicated that the Qi-tonifying, Yin-nourishing, and Blood-activating Formula (raw Astragalus, raw Rehmannia, Cuscuta, Centella asiatica, processed Rheum, and leech) alleviates renal pathological damage, reduces proteinuria, and improves renal function in rats with diabetic nephropathy (DN) by inhibiting the NF-κB/COX-2 inflammatory pathway, providing a molecular biological basis for the use of this formula in the treatment of DN. Research by Song Kaiming et al. [20] showed that in the Yiqu Yangyin Huoxue Formula group, the expression levels of the Nrf2 gene and protein in rat kidney tissue increased, while the expression levels of the NF-κB p65 and NFATc1 genes and proteins decreased. This effect may be achieved by regulating the Nrf2/NF-κB/NFATc1 signaling pathway, thereby inhibiting oxidative stress and inflammatory responses in the body, alleviating renal pathological damage, protecting renal function, and reducing urinary protein.

3.2.2 PI3K/Akt Signaling Pathway

The PI3K/Akt signaling pathway plays a crucial role in cellular growth, motility, proliferation, survival, and metabolism. It is involved in pathological changes in renal tissue and influences the progression of diabetic nephropathy (DN). Some traditional Chinese medicines can alleviate renal inflammation by activating the PI3K/Akt signaling pathway, thereby promoting the polarization of macrophages toward the M2 phenotype. Research by Chen Lei et al. [21] indicates that oxidative stress and inflammatory responses are key pathogenic mechanisms of DN. The hyperglycemic environment associated with diabetes exerts antioxidant, anti-inflammatory, and anti-apoptotic effects by activating the PI3K/Akt/Nrf2 signaling pathway, thereby protecting renal cells from damage. Research by Wang Xiaowei et al. [22] indicated that cnidicin can upregulate SIRT1 expression, reduce urinary microalbumin in rats with DN, alleviate the degree of renal fibrosis, and improve renal pathological damage; this effect may be related to the inhibition of the PI3K/Akt/mTOR pathway. Experimental research by Zhong Juan et al. [23] showed that chuanxiongzine can promote renal autophagy and improve renal pathological changes by inhibiting the PI3K/Akt/mTOR signaling pathway while simultaneously upregulating the expression level of the autophagy marker protein LC3B and the LC3B-II/LC3B-I ratio. Network pharmacology and animal studies by Song Yangyang et al. [24] indicate that Yunu Jian (Gypsum, Rehmannia glutinosa, Anemarrhena asphodeloides, Ophiopogon, Achyranthes) can upregulate the protein expression of PI3KCA and VEGFA in the kidney tissue of DN rats, while downregulating the expression of EGF and the autophagy-related genes ATG5 and Beclin 1. Its mechanism of action may be related to the PI3K/Akt/mTOR signaling pathway, achieving therapeutic effects by regulating the autophagy process. Animal studies by Wu Jinmei et al. [25] demonstrated that both Astragalus and Pueraria root exhibit significant hypoglycemic effects. Their mechanism may be related to changes in the expression of key factors in the PI3K/Akt signaling pathway (Insulin, Insulin Receptor, IRS-2, PI3K, Akt2, GSK-3β, GLUT-4, etc.) in the PI3K/Akt signaling pathway. By fully stimulating the binding of Ins to InsR, they activate the PI3K/Akt signaling pathway, promoting glucose uptake and utilization by skeletal muscle, thereby maintaining glucose metabolic balance.

3.2.3 AMPK Signaling Pathway

AMPK is an energy sensor that plays a crucial role in cellular metabolism (carbohydrate and lipid metabolism), cellular transcription, apoptosis, and energy balance. Traditional Chinese medicine can regulate macrophage metabolism by activating the AMPK signaling pathway, promoting M2 macrophage polarization, improving renal interstitial fibrosis, and preventing and treating DN. Research by Ye Yuyan et al. [26] indicates that dapagliflozin can protect the glomerular filtration barrier and reduce proteinuria by activating the AMPK/mTOR-autophagy signaling pathway, thereby delaying the progression of DN. Research by Xue Jian et al. [27] showed that Perilla frutescens leaf extract can significantly improve renal function in rats with a DN model by activating the Sesn2/AMPK/mTOR signaling pathway and promoting localized autophagy in the glomeruli. Research by Cui Xiao et al. [28] indicates that in a state of DN, the AMPK/mTOR pathway is inhibited, leading to impaired autophagy and lysosomal function; however, berberine can restore autophagy and lysosomal function by activating the AMPK/mTOR pathway, thereby alleviating kidney damage. Research by Liu Xufeng et al. [29] revealed that astragalus polysaccharides, by upregulating the activity of AMPK and SIRT1, promote the deacetylation of FOXO1, enhance its DNA-binding capacity, and consequently increase the expression of antioxidant genes, suppress oxidative stress, and activate the autophagy process (AMPK/SIRT1/FOXO1 signaling pathway), thereby improving glucose and lipid metabolism and reducing renal damage in rats with diabetic nephropathy (DN). Clinical and experimental studies by Liu Shilin et al. [30] indicated that the Jiedu Tongluo Yishen Concentrated Pills (containing hazelnut flower, wine-processed rhubarb, smilax glabra, motherwort, astragalus, salvia, ginseng, tangerine peel, goji berries, raspberries, Cicada Shed, Dragon's Blood) can upregulate the expression of nephrin, Podcin, WT-1, LC3II/LC3I, and Beclin-1, while downregulating P62, p-mTOR/mTOR expression, and upregulate p-AMPK/AMPK and Sirt3 expression. This suggests that its mechanism may be related to the promotion of podocyte autophagy via the AMPK/mTOR/Sirt3 pathway, thereby improving the overall condition of rats with diabetic nephropathy (DN), lowering blood glucose and lipid levels, reducing urinary protein production, improving pathological damage to renal tissue structure, and protecting renal function.

3.2.4 The NLRP3 Signaling Pathway

NLRP3 is an intracellular pattern recognition receptor that, upon sensing various endogenous and exogenous stimuli, recruits proteins to assemble into a complex capable of

mediating proenzyme activation; this complex is known as the NLRP3 inflammasome. Macrophages can inhibit the assembly and activation of the NLRP3 inflammasome in a non-enzyme-dependent manner by inhibiting NLRP3 binding [31]. Xie Qin-jiao et al. [32] randomly divided 40 SPF-grade SD male rats into a control group, a model group, an enalapril group, and a He Shen Wan group, with 10 rats in each group. The rats were fed a high-fat, high-sugar diet, and administered streptozotocin via intraperitoneal injection. Fasting blood glucose levels ≥16.7 mmol/L and 24-hour urine protein levels ≥30 mg were used as indicators of successful DN model establishment. The enalapril group and He Shen Wan group were administered equivalent doses of enalapril and He Shen Wan via oral gavage for 8 weeks, respectively, while the control and model groups received equal volumes of saline via oral gavage. The results indicate that He Shen Wan (comprising Syaeonzi, Dioscorea, calcined oyster shell, calcined dragon bone, and Phellodendron) can improve podocyte damage in DN rats, lower blood glucose, blood lipid, and serum creatinine levels, reduce urinary protein excretion, and improve renal function. Its mechanism of action may be related to the inhibition of NRT2/NLRP3 inflammasome pathway activation.

3.3 Regulation of Metabolism

3.3.1 Glucose Metabolism

Patients with DN often present with glucose metabolism disorders, and a high-glucose environment can induce macrophage polarization toward the M1 phenotype. Traditional Chinese medicine can alleviate the inflammatory response of macrophages by regulating glucose metabolism, improving insulin resistance, and lowering blood glucose levels. A clinical study by Yang Yang et al. [33] demonstrated that Urine-Toxicity-Clearing Granules (containing rhubarb, astragalus, white atractylodes, sophora flavescens, poria, plantain, white peony, processed polygonum multiflorum, Morus alba bark, and Salvia miltiorrhiza) has the effects of strengthening the spleen and tonifying the kidneys, invigorating qi and clearing turbidity, and promoting diuresis and draining dampness. Its components, such as Astragalus and Rheum, possess anti-inflammatory and hypoglycemic effects. As an adjunctive treatment for patients with diabetic nephropathy (DN), it can effectively improve glucose metabolism indicators, reduce inflammatory responses, and help improve renal function, with good safety. A study by Xu Hui et al. [34] demonstrated that the modified Si Ni Tang formula (Astragalus, Asarum, Cinnamomum cassia, Paeonia lactiflora, Millettia reticulata, Polygonum multiflorum stem, Coptis, Angelica sinensis, Dried ginger, and Fried licorice) possesses effects such as nourishing and invigorating blood, regulating qi and unblocking meridians, tonifying qi and fortifying the exterior, and promoting yang and transforming qi. By regulating patients' glucose and lipid metabolism levels, it helps significantly improve clinical efficacy and quality of life in patients with type 2 diabetes. Fu Shaojie et al. [35] demonstrated through network pharmacology research that isoliquiritigenin and emodin, as active components in traditional Chinese medicine, target glucose transporter 1 (GLUT 1) as a potential mechanism of action. By acting through multiple targets and pathways, they directly and indirectly regulate GLUT 1, thereby exerting a therapeutic effect on diabetic nephropathy (DN). Animal studies by Bai Guirong et al. [36] showed that Lycium polysaccharides (LBP) correct glucose metabolism disorders and improve insulin resistance by regulating the expression of glucose transporter 4 (GLUT4), thereby controlling blood glucose levels. Experiments by Zhou Haiyan et al. [37] indicated that Astragalus polysaccharides significantly reduced blood glucose levels in diabetic rats by alleviating endoplasmic reticulum stress, upregulating Bcl-2 expression, downregulating Bax expression, inhibiting pancreatic islet cell apoptosis, and improving islet function. Tie Defu et al. [38] conducted cellular and animal studies based on network pharmacology, showing that Jinqi Hypoglycemic Tablets (Astragalus, Coptis, and Lonicera) activate insulin signaling pathways, promote glycogen synthesis, and inhibit gluconeogenesis through multi-target, multi-organ synergistic effects. This significantly reduces blood glucose and lipid levels in mice with type 2 diabetes, enhancing systemic glucose homeostasis and insulin sensitivity. Research by Li Ke et al. [39] indicates that total flavonoids from (Tengcha) can significantly improve glucose metabolism in rats with type 2 diabetes, a mechanism potentially related to the upregulation of the IRS-1/PI3Kp85/AKT/GLUT4 signaling pathway. Research by Wang Lei et al. [40] indicated that the herbal tea "Qianxiao Cha" (comprising green tea, lotus leaf, mulberry leaf, loquat leaf, and honeysuckle) can lower blood glucose by improving insulin resistance through increased expression of glucose transporters (GLUT).

3.3.2 Lipid Metabolism

Dyslipidemia is also a common complication of diabetic nephropathy (DN). Traditional Chinese medicine can regulate lipid metabolism, lower blood lipid levels, and reduce lipid deposition in the kidneys, thereby influencing the polarization state of macrophages. A clinical study by Li Guixia et al. [41] demonstrated that patients with DN presenting with patterns of deficiency of both qi and yin, damp-heat, and blood stasis all exhibit lipid metabolism disorders and endothelial dysfunction. An experimental study on diabetic rats by Han Dong et al. [42] showed that astragaloside A can effectively reduce blood lipid and glucose levels in experimental rats by enhancing antioxidant enzyme activity and inhibiting oxidative stress damage. Research by Wang Lei et al. [40] indicates that Zhanxiao Tea can significantly reduce TNF-α, IL-6, and blood lipid levels in rats with impaired glucose tolerance (IGT) by decreasing the secretion of inflammatory factors. A clinical study by Jiang Yanan et al. [43] showed that the Lipid-Lowering and Kidney-Nourishing Formula (Astragalus, Rehmannia glutinosa, Cornus officinalis, Lycium barbarum, Salvia miltiorrhiza, Alisma orientale, Cuscuta chinensis, Achyranthes bidentata, Paeonia suffruticosa, Bupleurum chinense, Prunus persica, Citrus reticulata, Gynostemma pentaphyllum, Trichosanthes kirilowii, and Scrophularia ningpoensis) can effectively improve the quality of life in patients with stage III–IV diabetic nephropathy (DN) by regulating blood lipids, lowering blood glucose and proteinuria, and improving renal function. A study by Feng Zhaohai et al. [44] demonstrated that the addition of the Kidney-Nourishing, Liver-Regulating, and Spleen-Strengthening Formula (Astragalus, Ginseng, Prepared Rehmannia, Cornus officinalis, Dioscorea, Poria, Moutan, Alisma, Bupleurum, Rheum, Polygonum cuspidatum,

Lotus leaf, Polygonum multiflorum, Hawthorn) demonstrated significant advantages over a control group receiving Western medicine alone in improving renal function, correcting dyslipidemia, and reducing proteinuria in patients with DN, while exhibiting high clinical safety. Animal studies by Shao Yang et al. [45] demonstrated that Astragalus flavonoids, Astragalus saponins, and Pueraria flavonoids downregulate inflammation-related factors, enhance lipid metabolism, and restore insulin sensitivity through the ADPN/AdipoR1/ AMPK/PPARα and ADPN/AdipoR1/P38MAPK/GLUT4 pathways.

4. Clinical Application Prospects of Traditional Chinese Medicine in Regulating Macrophage Polarization for the Prevention and Treatment of Diabetic Nephropathy

With its multi-target and multi-pathway mechanisms of action, TCM demonstrates unique advantages within the modern medical system. It can serve not only as an independent therapeutic modality but also be combined with modern medical treatments to collectively improve the therapeutic outcomes for diabetic nephropathy (DN). Specifically, TCM can be used in combination with hypoglycemic, antihypertensive, and lipid-lowering drugs to exert synergistic effects, thereby reducing the burden on the kidneys and delaying disease progression. Current clinical studies have demonstrated that when TCM is used in combination with sodium-glucose cotransporter 2 (SGLT-2) inhibitors, ACEIs, or ARBs, it effectively reduces proteinuria and protects renal function while simultaneously controlling blood glucose and blood pressure.

Although TCM has made some progress in regulating macrophage polarization to prevent and treat DN, most current research remains at the basic research stage. Most studies have focused on animal experiments and in vitro cell experiments, and the specific mechanisms by which TCM influences macrophage polarization and the underlying signaling pathways remain unclear. Furthermore, although some TCM formulas or individual components have shown potential therapeutic effects, there is currently a lack of large-scale, multicenter clinical trials to validate their efficacy and safety.

In the future, to further promote the application of TCM in the treatment of DN, we need to conduct in-depth clinical research to verify the actual efficacy and safety of TCM in preventing and treating immune-mediated damage in DN. At the same time, it is necessary to conduct in-depth research into the specific mechanisms by which TCM regulates macrophage polarization, particularly those related to inflammatory factors and signaling pathways, to provide a theoretical basis for the development of new therapeutic approaches. Furthermore, based on the mechanisms of action of TCM, we need to explore novel therapeutic methods and develop new drugs or therapies to provide more treatment options for patients with DN, better leverage the advantages of TCM, and open up new avenues for the treatment of DN.

5. Conclusion

In summary, traditional Chinese medicine (TCM) shows great promise in the prevention and treatment of immune-mediated damage in diabetic nephropathy (DN) by modulating macrophage polarization. Through various mechanisms — such as regulating immune and inflammatory responses, influencing key signaling pathways, and modulating metabolic processes—TCM effectively promotes M2 macrophage polarization while inhibiting M1 macrophage polarization, thereby restoring the M1/M2 balance and significantly reducing renal inflammation and immune-mediated damage. Modern research indicates that certain active components of TCM and herbal formulas are the primary means by which TCM regulates macrophage polarization. By influencing signaling molecules and cytokines involved in the macrophage polarization process, they significantly reduce inflammatory factor levels in patients with DN, improve renal function, and achieve regulation of the macrophage polarization state. In the future, more detailed clinical and experimental studies are needed to further elucidate the specific mechanisms by which TCM regulates macrophage polarization and to apply these findings to clinical practice, thereby providing more effective and safer treatment options for patients with DN. This will represent a positive exploration of the integration of traditional and modern medicine and is expected to offer new therapeutic strategies for the prevention and treatment of DN.

References

[1] Chen Zhichao, Lin Qiaoni, Sun Liya, et al. The Role of Macrophage Activation and Polarization in Diabetes and Its Related Complications, and Traditional Chinese Medicine Interventions [J/OL]. Chinese Journal of Experimental Formulary, 1–15 [2024-12-19].

[2] Wang Sihai, Fang Zhaohui, Li Yufan, et al. Research Progress on the Internal Treatment of Diabetic Nephropathy with Traditional Chinese Medicine [J]. Journal of Henan University (Medical Edition), 2024, 43(05): 313-317+340.

[3] Zhu Qing, Han Jiarui, Pang Xinxin, et al. Research Progress on the Prevention and Treatment of Diabetic Nephropathy with Traditional Chinese Medicine Based on the AMPK Signaling Pathway [J/OL]. Pharmacology and Clinical Application of Traditional Chinese Medicine, 1-13 [2024-12-20].

[4] Pei Wenli, Shi Xiaowei, Lian Guan, et al. Mechanisms of Action of Traditional Chinese Medicine in the Prevention and Treatment of Diabetic Nephropathy [J]. Journal of Practical Traditional Chinese Internal Medicine, 2023, 37(12): 16-19.

[5] Li Xin, Yang Xiaojun, Liu Leliang. Clinical Observation of 45 Cases of Early Diabetic Nephropathy Treated with Integrated Traditional Chinese and Western Medicine [J]. Chinese Ethnic and Folk Medicine, 2024, 33(20): 98-102.

[6] Youssef N, Noureldein MH, Riachi ME, Haddad A, Eid AA. Macrophage polarization and signaling in diabetic kidney disease: a catalyst for disease progression. Am J Physiol Renal Physiol. 2024 Mar 1;326(3):F301-F312.

[7] Wang WR, Wang XH, Yan L, Zeng Q, Zhan T, Zhan JY, Li JX, Yu RH. [Potential pathways for traditional Chinese medicine intervention in diabetic kidney disease:

macrophage polarization]. Zhongguo Zhong Yao Za Zhi. 2024 Aug;49(15):4044-4053.
[8] Li X, Liu J, Zeng M, Yang K, Zhang S, Liu Y, Yin X, Zhao C, Wang W, Xiao L. GBP2 promotes M1 macrophage polarization by activating the notch1 signaling pathway in diabetic nephropathy. Front Immunol. 2023 Aug 9;14:1127612.
[9] Dai Jiazhen, Xing Haiyan. A Study on the Role of Macrophage Polarization in Renal Fibrosis from the Perspective of the Theory of Yin and Yang [J/OL]. Journal of Traditional Chinese Medicine, 1–10 [2024-12-20].
[10] Jin Yuqiu, Chen Guangshun, Bai Min, et al. Mechanistic Study on the Regulation of Key Molecules in the ROCK/IKK/NF-κB Pathway by Zhenwu Decoction to Improve Renal Inflammatory Damage in Mice with Spleen-Kidney Yang Deficiency-Type DN [J]. Chinese Journal of Traditional Chinese Medicine, 2023, 48(18): 5041-5048.
[11] Liu Jia, Yan Baofei, Zhang Jingzheng, et al. Effects of Huangqin Decoction on the NF-κB/NLRP3/Caspase-1 pyroptosis pathway in the kidneys of rats with diabetic nephropathy [J]. Chinese Journal of Bioengineering, 2022, 42(11): 109-116.
[12] Wang Chuan, Zhao Wen. Observation of Changes in Serum Pro-inflammatory Cytokines (IL-6, TNF-α) and Anti-inflammatory Cytokines (IL-10) Levels in Patients with Diabetes and Hypertension [J]. New World of Diabetes, 2018, 21(14): 57-58.
[13] Wang Xin, Chen Shi. Effects of a Standardized Traditional Chinese Medicine Formula on the Secretion of the Anti-inflammatory Factor Interleukin-10 in Patients with Type 2 Diabetes [J]. Henan Journal of Traditional Chinese Medicine, 2014, 34(05):884-886.
[14] Feng Y, Zhang Y, Gao F, Liu M, Luo Y. HOXD9/APOC1 axis promotes macrophage M1 polarization to exacerbate diabetic kidney disease progression through activating NF-κB signaling pathway. Hereditas. 2024 Nov 7;161(1):40.
[15] Zhao Limin, Li Yajing, Zhang Yonggang, et al. Effects of miR-203 on renal fibrosis in rats with diabetic nephropathy via targeted regulation of the PEG3/NF-κB signaling pathway [J]. Chinese Journal of Immunology, 2023, 39(11): 2275–2281.
[16] Chen Yi, Yang Taiwang, Wang Mingsheng. Study on the Alleviation of Renal Injury in Rats with Diabetic Nephropathy by Silymarin via the Co-inhibition of the TLR4/NF-κB and TNF-α/ROS/P38MAPK Pathways [J]. Clinical Medicine Practice, 2023, 32(05): 348-352.
[17] Zhang Yao, Gao Fei, Song Ruijing, et al. Investigation of the Mechanism of Action of Modified Shengjiang San in Inhibiting Renal Inflammation and Fibrosis in Diabetic Rats Based on the TLR4/NF-κB and Raf/MEK Pathways [J]. Pharmacology and Clinical Application of Traditional Chinese Medicine, 2022, 38(05): 20-27.
[18] Jiang Yifan, Li Xiaorong, Geng Jiayi, et al. Quercetin alleviates diabetic-induced renal injury in rats by inhibiting the HMGB1/RAGE/NF-κB signaling pathway [J]. Journal of Southern Medical University, 2024, 44(09): 1769-1775.
[19] Yang Wen, Song Chundong, Chen Chenchen, et al. Investigation of the Mechanism of Renal Protection by the "Yiqi Yangyin Huoxue" Formula in Rats with Diabetic Nephropathy Based on the NF-κB/COX-2 Inflammatory Pathway [J]. Journal of Traditional Chinese Medicine, 2023, 51(04): 21-26.
[20] Song Kaiming, Song Chundong, Duan Fengyang, et al. Investigation of the Mechanism of Action of the Qi-tonifying, Yin-nourishing, and Blood-activating Formula in Rats with Diabetic Nephropathy Based on the "Kidney Governs the Bones" Theory and the Nrf2/NF-κB/NFATc1 Pathway [J]. Shizhen: Traditional Chinese Medicine and Pharmacy, 2023, 34(02): 277-280.
[21] Chen Lei, Shen Zhouji, Guo Fei. Protective Effects of the PI3K/Akt/Nrf2 Pathway on Diabetic Nephropathy [J]. Chemistry of Life, 2024, 44(10): 1823-1830.
[22] Wang Xiaowei, Yu Xiaozhu, Guo Erxia, et al. Effects of Cnidicinin on Fibrosis and HSP90, SIRT1 in Rats with Diabetic Nephropathy via the PI3K/Akt/mTOR Pathway [J]. Chinese Journal of Gerontology, 2023, 43(06):1446-1450.
[23] Zhong Juan, Chen Jing, Qing Yao, et al. Chuanxiongzine Improves Renal Damage in Rats with Diabetic Nephropathy by Inducing Autophagy via Inhibition of the PI3K/Akt/mTOR Pathway [J]. Tianjin Medicine, 2019, 47(04):395-400.
[24] Song Yangyang, Wang Yijin, Zhuang Shuting, et al. Network pharmacology study and experimental validation of Yunu Jian in the treatment of diabetic nephropathy [J]. Fujian Journal of Traditional Chinese Medicine, 2023, 54(03): 35–42.
[25] Wu Jinmei, Fan Ying, Liu Qian, et al. Investigation of the Effects of the Astragalus and Pueraria Combination on Glucose Metabolism in Skeletal Muscle of Diabetic Rats Based on the PI3K/Akt Signaling Pathway [J]. Journal of Liaoning Traditional Chinese Medicine, 2019, 46(06): 1308-1311.
[26] Ye Yuyan, Wang Peng, Fang Xia, et al. Study on the Mechanism of Dapagliflozin in Improving Renal Injury in a Diabetic Nephropathy Rat Model Based on the AMPK/mTOR Autophagy Signaling Pathway [J]. Journal of Integrated Traditional and Western Medicine of Zhejiang, 2024, 34(10): 905-909+914.
[27] Xue Jian, Qiao Chen. Study on the Improvement of Renal Injury in Rats with Diabetic Nephropathy by Perilla Frutescens Leaf Extract via the AMPK/mTOR Autophagy Signaling Pathway [J]. Journal of Traditional Chinese Medicine, 2023, 51(09): 18-22.
[28] Cui Xiao. Mechanistic Study on Berberine's Improvement of Diabetic Nephropathy via Regulation of Autophagy-Lysosome Function Through the AMPK/mTOR Pathway [D]. Tianjin Medical University, 2020.
[29] Liu Xufeng, Feng Jia, Wang Shujin, et al. Effects and Mechanisms of Astragalus Polysaccharides on Oxidative Stress and Autophagy in Rats with Diabetic Nephropathy [J]. Journal of Shanxi Medical University, 2023, 54(03): 343-351.
[30] Liu Shilin. A Study on the Characteristics of Toxic Pathogen Syndrome in Diabetic Nephropathy and the Mechanism of Action of Detoxifying, Collateral - Unblocking, and Kidney-Nourishing Concentrated Pills [D]. Changchun University of Traditional Chinese Medicine, 2024.

[31] Cheng Z, Huang M, Li W, et al. HECTD3 inhibits NLRP3 inflammasome assembly and activation by blocking NLRP3-NEK7 interaction. [J]. Cell Death & Disease, 2024, 15(1): 86-86.
[32] Xie Qinqiao, Tang Yu, Zhang Weining. He Shen Wan Regulates the Nrf2/NLRP3 Inflammasome Pathway to Improve Podocyte Damage in Diabetic Nephropathy [J/OL]. Journal of Traditional Chinese Medicine, 1-8 [2024-12-15].
[33] Yang Yang. Effects of Urinqing Granules as an Adjuvant Therapy on Glucose Metabolic Indicators and Inflammatory Responses in Diabetic Nephropathy [J]. Journal of Tianjin University of Traditional Chinese Medicine, 2024, 43(07): 595-599.
[34] Xu Hui. Effects of Modified Sini Tang on Glucose Metabolism, Lipid Metabolism, and Glucose Transporter 4 in Elderly Patients with Type 2 Diabetes [J]. Electronic Journal of Clinical Medicine and Pharmacy, 2019, 6(64): 1-2+4.
[35] Fu Shaojie, Zhang Li, Wang Xueyao, et al. Investigation of the Mechanism of Traditional Chinese Medicine in Treating Diabetic Nephropathy with Glucose Transporter 1 as a Potential Target [J]. Journal of Clinical Nephrology, 2022, 22(10):819-826.
[36] Bai Guirong, Luo Li, Xie Xiaomin, et al. Effects of Lycium polysaccharides on insulin resistance and GLUT4 expression in skeletal muscle of type 2 diabetic rats [J]. Journal of Ningxia Medical University, 2020, 42(05): 528-531.
[37] Zhou Haiyan. Study on the Effects of Astragalus Polysaccharides on Endoplasmic Reticulum Stress and Bcl-2 and Bax Expression in Type 2 Diabetic Rats [D]. Anhui University of Chinese Medicine, 2015.
[38] Tie Defu. Treatment of Type 2 Diabetes by Jinqi Jiangtang Tablets via Multi-target Synergistic Multi-organ Action [D]. Guangdong Pharmaceutical University, 2022.
[39] Li Ke. Mechanistic Study of Total Flavonoids from Tengcha on Skeletal Muscle Insulin Resistance in Rats with Type 2 Diabetes [D]. Beijing University of Chinese Medicine, 2021.
[40] Wang Lei. Effects of Xianxiao Tea on TNF-α, IL-6, and Glucose Transporter Expression in the Liver and Skeletal Muscle of Rats with Impaired Glucose Tolerance [D]. Zhejiang University of Traditional Chinese Medicine, 2016.
[41] Li Guixia, Huang Lei, Dai Zeliang, et al. A Study on the Correlation Between Traditional Chinese Medicine Syndromes of Diabetic Nephropathy and Endothelial Function and Lipid Metabolism [J]. Chinese Folk Medicine, 2023, 31(12): 92-95.
[42] Han Dong. Study on the Hypoglycemic, Lipid-Regulating, and Antioxidant Effects of Astragaloside A on Experimental Diabetic Rats [J]. Journal of Modern Integrated Traditional and Western Medicine, 2016, 25(04):360-364.
[43] Jiang Yanan. Clinical Observation on the Treatment of Stage III–IV Diabetic Nephropathy by the Lipid-Lowering and Kidney-Nourishing Formula Through Regulation of Abnormal Lipid Metabolism [D]. Heilongjiang University of Traditional Chinese Medicine, 2024.
[44] Feng Zhaohé. A Clinical Study on the Treatment of Lipid Metabolic Disorders in Diabetic Nephropathy Using the Kidney-Nourishing, Liver-Regulating, and Spleen-Strengthening Formula [D]. Shandong University of Traditional Chinese Medicine, 2022.
[45] Shao Yang. Effects of Effective Formulations of Astragalus and Pueraria Root on Glucose and Lipid Metabolism and Inflammatory Responses in Skeletal Muscle of Diabetic Rats [D]. Liaoning University of Chinese Medicine, 2022.