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Research Progress of Traditional Chinese Medicine in Treating Diabetic Nephropathy Based on TLR4/NF-κB Signaling Pathway

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Abstract: ***Diabetic Nephropathy (DN) is one of the most severe microvascular complications of diabetes, and its pathogenesis is closely associated with inflammation, oxidative stress, and apoptosis mediated by the TLR4/NF-κB signaling pathway. In recent years, traditional Chinese medicine (TCM) has demonstrated significant renal protective effects by multi-target regulation of this pathway through active monomer components and compound formulations. This article comprehensively reviews recent domestic and international research on the mechanisms and advances in TCM treatment of DN by inhibiting the TLR4/NF-κB pathway, providing a theoretical basis for the clinical prevention and treatment of DN. It also highlights the need for further clinical studies and mechanistic exploration in the future.***

Keywords: Traditional Chinese medicine, TLR4/NF-κB signaling pathway, Diabetic Nephropathy**.**

1. Introduction

Diabetic Nephropathy (DN) is one of the most severe microvascular complications of diabetes and a leading cause of end-stage renal disease and chronic kidney disease. The persistent hyperglycemic state it induces damages renal blood vessels, leading to a gradual decline in kidney function and ultimately resulting in uremia. According to data from the International Diabetes Federation, in 2021, 536.6 million adults aged 20–79 worldwide had diabetes, and this number is projected to rise to 783.2 million by 2045 [1]. Approximately 30% of patients with type 1 diabetes and 40% of those with type 2 diabetes will eventually develop symptoms of diabetic nephropathy, with the global incidence of diabetes complicated by DN ranging from about 20% to 40% [2]. The pathogenesis of DN is complex and is currently believed to result from the combined effects of genetic factors, inflammation, insulin resistance, oxidative stress, among others. The exact mechanisms have not yet been fully elucidated [3]. Studies have found that DN is characterized mainly by glomerular basement membrane thickening, reduced glomerular filtration rate, albuminuria, and podocyte loss [4]. However, extensive research indicates that cellular biological mechanisms such as oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and ferroptosis play significant roles in the development and progression of DN. Current conventional treatments for DN primarily focus on reducing body weight, controlling blood pressure and blood sugar levels, and using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) as first-line medications for DN [5]. In recent years, traditional Chinese medicine (TCM) has made considerable progress in treating DN, attracting increasing attention due to its multi-target, multi-component, and multi-pathway approach, leveraging the advantages of syndrome differentiation and holistic regulation [6].

Research has found that the Toll-like receptor 4 (TLR4)/nuclear factor kappa-B (NF-κB) pathway plays a crucial role in regulating the pathophysiological processes of DN. It specifically modulates inflammatory responses, apoptosis, oxidative stress, and other processes, thereby influencing the progression of DN. This pathway is a key signaling route for the prevention and treatment of DN. This article reviews the mechanisms by which TCM modulates the TLR4/NF-κB signaling pathway in DN and discusses advances in related research. Through in-depth study of TCM in treating DN, we aim to provide a more solid theoretical basis for the prevention and treatment of DN with TCM and offer new perspectives and ideas for future drug development.

2. Overview of the TLR4/NF-κB Signaling Pathway

Toll-like receptors (TLRs) are a class of pattern recognition receptors that detect infection by activating the innate immune system. They recognize pathogen-associated and damage-associated molecular pattern ligands, thereby activating related pathways, promoting the release of inflammatory factors, and mounting a response [7]. Each member of the TLR family detects pathogen-associated molecular patterns derived from different microbial pathogens, such as viruses, bacteria, and fungi. TLR4, one of the earliest discovered members of the TLR family, is widely distributed in various tissues and cells of the body. It consists of three parts: an extracellular domain, an intracellular structure, and a transmembrane structure. The extracellular domain contains multiple leucine-rich repeats responsible for recognition, while the intracellular domain contains a Toll/interleukin-1 receptor (TIR) domain, which is critical for initiating downstream pathways.

NF-κB is a downstream effector of the TLR4 signaling pathway and regulates the expression of a large number of genes. It plays an important role in inflammatory responses, tissue damage, and apoptosis. In the resting state, the NF-κB dimer (p65, p50) binds to the inhibitory protein IκB, forming a complex that resides in the cytoplasm. When cells are stimulated, the IκB kinase β (IKKβ) complex is activated, leading to the phosphorylation of IκB. This promotes the

dissociation of the proteasome, releasing the NF-κB dimer, which then participates in processes such as inflammation and fibrosis [8].

Upon activation, TLR4 transmits signals through the adaptor protein myeloid differentiation factor 88 (MyD88). MyD88 enables auto-phosphorylation of interleukin-1 receptor-associated kinase (IRAK) and binds to tumor necrosis factor receptor-associated factor 6 (TRAF6) [9]. TRAF6 is a RING domain E3 ubiquitin ligase. Once activated, TRAF6 promotes the polyubiquitination of target proteins, subsequently recruiting transforming growth factor-β-activated kinase 1 (TAK1). This leads to the phosphorylation and degradation of IκB, acting on NF-κB and activating the NF-κB pathway, thereby inducing the expression of genes involved in inflammation and immune responses. Additionally, TLR4 can be activated through a MyD88-independent pathway, which requires the participation of the TIR-domain-containing adapter-inducing interferon-β (TRIF) and TRIF-related adaptor molecule (TRAM). Upon stimulation, TLR4 recruits TRIF, which directly binds to TRAF6 via its N-terminal TRAF6-binding motif, subsequently activating TAK1 and ultimately the NF-κB pathway.

3. Role of TLR4/NF-κB Signaling Pathway Activation in Diabetic Nephropathy

In the early stages of diabetes, macrophages present in renal tissue secrete oxygen free radicals and inflammatory mediators [3], leading to glomerulosclerosis and subsequent renal tissue damage in patients. Therefore, an increase in TLR4 expression not only reflects the extent of renal damage and changes in renal function but also indicates the progression of systemic inflammation. Chronic renal inflammation mediated by hyperglycemia is a critical component in the pathogenesis of diabetic nephropathy. The overexpression of inflammatory factors during the development and progression of diabetic nephropathy is also a major contributor to renal fibrosis and eventual renal failure [10]. The TLR4/NF-κB pathway is a classic inflammation-related signaling pathway, and its expression changes play a significant role in the initiation and progression of inflammatory responses in the body.

TLR4 can activate nuclear factor kappa B (NF-κB) through both myeloid differentiation factor 88 (MyD88)-dependent and MyD88-independent pathways, mediating downstream signal transduction. This leads to increased expression of pro-inflammatory cytokines such as TNF-α and IL-1β, which further activate NF-κB, resulting in an amplification of inflammatory signals [11] and exacerbation of renal damage. Under normal conditions, NF-κB exists in the cytoplasm in an inactive state as a heterotrimeric complex composed of p50, p65, and inhibitory IκB. Due to the presence of inhibitory IκB and the absence of relevant activation signals, NF-κB remains inactive. In unstimulated cells, NF-κB is freely present in the cytoplasm. Once stimulated, NF-κB translocates to the nucleus and promotes the release of various inflammatory factors, such as TNF-α, IL-1β, and MCP-1 [12].

MCP-1, upon entering the bloodstream, induces the accumulation of immune cells like macrophages in renal tissue, increasing extracellular matrix deposition [13]. TNF-α can alter the permeability of the glomerular basement membrane, stimulate fibroblast proliferation, and cause structural changes in renal blood vessels [14]. IL-1 also mediates neutrophil infiltration, triggers endothelial cell damage, and induces the release of other inflammatory factors, forming a cascade reaction [15]. The release of these inflammatory factors accelerates the occurrence and progression of DN. Numerous studies have reported increased expression of inflammatory factors such as IL-1β, IL-6, and TNF-α in the kidneys of diabetic nephropathy rat models, while downregulating the expression of these inflammatory factors can alleviate the inflammatory response in diabetic nephropathy rats [16].

4. Treatment of Diabetic Nephropathy through TLR4/NF-κB Signaling Pathway Regulation by Traditional Chinese Medicine

4.1 Traditional Chinese Medicine Understanding of Diabetic Nephropathy

In Traditional Chinese Medicine (TCM), there is no exact equivalent term for Diabetic Nephropathy (DN). Based on ancient TCM texts and its clinical manifestations, it can be categorized under “Xiao Ke” (wasting-thirst), “Shen Xiao” (renal consumption), “Niao Zhuo” (turbid urine), and “Xu Lao” (deficiency fatigue). Prolonged Xiao Ke consumes qi and damages yin, impairing organ function, and is often accompanied by pathogenic factors such as phlegm, stagnation, blood stasis, and toxins. The primary pathogenesis involves “spleen and kidney deficiency, qi and yin deficiency, phlegm-dampness, and blood stasis.” The fundamental treatment principles focus on tonifying the kidney and spleen, replenishing qi and nourishing yin, and promoting blood circulation to remove stasis.

Targeted therapy for DN is a current research hotspot. Although existing medications can alleviate symptoms, they often fail to halt the progression to end-stage renal disease. Traditional Chinese medicine, with its unique advantages of multi-target synergy and multi-pathway regulation, specifically targets the TLR4/NF-κB signaling pathway. It demonstrates significant efficacy in improving renal injury and delaying disease progression.

4.2 Chinese Herbal Extracts

Dioscorea has effects such as eliminating phlegm, promoting digestion and diuresis, relaxing tendons and activating blood circulation, and preventing malaria. Dioscin, a natural steroid extracted from it, possesses anti-inflammatory and antioxidant properties. Cai [17] et al. found that dioscin effectively ameliorates streptozotocin (STZ)-induced DN in mice by inhibiting the inactivation of the TLR4/NF-κB pathway and reducing the secretion of inflammatory cytokines, thereby improving renal function. Strobilanthes sarcorrhiza C is a Chinese herbal medicine with both culinary and medicinal uses. It functions to tonify the kidney, nourish yin, clear heat, and detoxify. Chen [18] et al. demonstrated that CTS (extract of Strobilanthes sarcorrhiza root) primarily alleviates DN by regulating glycerophospholipid metabolism. The phenolic extract of Strobilanthes sarcorrhiza root may mitigate DN by inhibiting the NF-κB pathway, thereby reducing inflammatory

responses and fibrosis in renal tissue. Psoralea corylifolia enriching kidney and strenthening Yang-qi. It is primarily indicated for kidney deficiency with cold diarrhea, enuresis, spermatorrhea, and frequent urination. Isobavachalcone (ISO), an active compound extracted from the dried ripe fruit of Psoralea corylifolia, has anti-inflammatory, antioxidant, and insulin resistance-improving effects. Dong [19] et al. discovered that ISO reduces the production of pro-inflammatory mediators in damaged renal tissue and high glucose (HG)-treated human renal glomerular endothelial cells (HRGECs), blocks the NF-κB pathway, prevents STZ-induced glomerular tissue apoptosis in vivo, and counteracts HG-induced growth inhibition of HRGECs in vitro. It effectively lowers BUN, Scr, and 24 hr urinary protein levels, thereby improving renal damage and pathological manifestations.

Astragalus membranaceus invigorating qi, strengthening the body surface resistance, arrests sweating, promotes tissue regeneration, and reduces edema. Astragalus Polysaccharide (APS), the most effective bioactive component naturally extracted from Astragalus, exhibits broad pharmacological effects, including anti-inflammatory, antioxidant, and hypoglycemic activities. Guo [20] et al. showed that APS significantly inhibits inflammatory responses and the proliferation of glomerular podocytes by reducing the expression of inflammatory cytokines IL-1β, IL-6, and MCP-1 and suppressing the activity of the TLR4/NF-κB pathway in DN rats, thereby improving renal injury. Sclareol, a natural diterpenoid compound, has beneficial effects against inflammation. Han [21] et al. found that a mixture of MAPKs inhibitors can suppress the NF-κB pathway and the release of inflammatory cytokines involved in sclareol activity, preventing HG-induced fibrosis and inflammatory responses, and significantly alleviating renal dysfunction, fibrosis, and inflammatory cytokine levels in diabetic mice. Angelica decursiva is a plant of the Apiaceae family. Its root, known as Qianhu, is used as an antipyretic, antitussive, and expectorant. Umbelliferone (Umb) possesses various properties, including antidepressant, antioxidant, and anti-inflammatory effects. Wang [22] et al. investigated the effects of Umb in an STZ-induced DN rat model and found that it significantly reduces the levels of downstream inflammatory molecules (TNF-α, IL-6, IL-1β) by inhibiting TLR2, TLR4, MyD88 expression, and NF-κB activation, thereby improving renal function through modulation of the inflammatory TLR/NF-κB pathway.

Geniposide (GE) is an iridoid glycoside extracted from gardenia flowers. It has functions such as lowering blood sugar, reducing weight, anti-inflammatory, anti-tumor, neuroprotective, and alleviating myocardial ischemia-reperfusion injury. Fengtao Li [23] et al. found that GE effectively blocks oxidative stress and the inflammatory response associated with pyroptosis, thereby inhibiting the development of DN, possibly through the AMPK/SIRT1/NF-κB pathway. Ginsenoside Rg2 (Rg2) is an important active component in Ginseng, with potent inhibitory effects on adipogenesis and hepatic glucose production. Ke Li [24] et al. discovered that Rg2 reduces the phosphorylation levels of IKKβ, IκBα, and NF-κB p65, inhibits NLRP3 inflammasome activation, and suppresses the release of inflammatory factors. Rg2 prevents the progression of DN by inhibiting the activation of the pyroptosis-related NF-κB/NLRP3 signaling pathway both in vivo and in vitro. Akebia Saponin D (ASD) is a bioactive triterpenoid saponin isolated from the rhizome of Dipsaci Radix, used as an anti-osteoporosis drug. Lu [25] et al. found that ASD prevents renal injury in DN mice by activating the NRF2/HO-1 pathway and inhibiting the NF-κB pathway, improving renal function and inflammatory responses, ameliorating oxidative stress, and inhibiting renal tubular cell apoptosis.

A protein polysaccharide extracted from Ganoderma lucidum, named Fudan-Yueyang Ganoderma lucidum (FYGL), is a water-soluble hyperbranched proteoglycan found to protect pancreatic tissue from oxidative stress damage. Pan [26] et al. discovered that FYGL significantly inhibits HG/palmitic acid (PA)-induced HBZY-1 cell proliferation, ROS production, MDA generation, promotes SOD activity, and suppresses the expression of NOX1, NOX4, MAPK, NF-κB, and pro-fibrotic proteins. Furthermore, FYGL significantly alleviates blood glucose levels, enhances antioxidant activity and lipid metabolism, improves renal function, and mitigates renal histopathological abnormalities, particularly renal fibrosis. Breviscapine (Bre), a flavonoid extract from Erigeron breviscapus, has renal protective effects in diabetic rats. Sun [27] et al. found that Bre effectively enhances podocyte viability and inhibits HG-induced apoptosis by suppressing NF-κB/NLRP3-mediated pyroptosis. Isoliquiritigenin (ISL), the main physiological active component in licorice root, is a flavonoid with a chalcone structure. It exhibits various biological activities, including anti-tumor, anti-free radical, antioxidant, and anti-lipid peroxidation effects. Yanhong Wang [28] et al. found that ISL improves renal pathological damage and restores renal function in diabetic mice. The potential mechanism involves inhibiting oxidative stress, reducing ROS levels, and suppressing the activation of NF-κB and the NLRP3 inflammasome, as well as the occurrence of pyroptosis. Curcumin (CUR) is a natural active substance found in the rhizome of the Curcuma longa plant, with anti-inflammatory, antioxidant, and anti-fibrotic properties. Zamanian [29] et al. demonstrated that CUR's ability to reduce oxidative stress, inflammation, and improve vascular function is attributed to its modulation of key signaling pathways such as CaMKII, PPAR-γ, NF-κB, and TGF-β1. Berberine (BBR) is an isoquinoline alkaloid isolated from Coptidis rhizome, Cortex phellodendri, and Berberis vulgaris. It has broad pharmacological activities, such as anti-oxidative stress, anti-inflammatory, anti-tumor, antibacterial, and anti-fibrotic effects. Zhu [30] et al. found that BBR improves DN by alleviating STZ-induced renal injury, inflammatory responses, and HG-induced podocyte apoptosis through inactivation of the TLR4/NF-κB pathway.

4.3 Chinese Herbal Compound Formulations

Sanziguben Formula (SZGB) consists of Rosae laevigatae Michx (Rosaceae), Phyllanthus emblica L. (Phyllanthaceae), Schisandra chinensis (Turcz) Baill. (Schisandraceae), and Gynostemma pentaphyllum (Thunb.) Makino (Cucurbitaceae). It is an empirical prescription clinically used for treating DN and protecting against kidney injury. Fan Wang [31] et al. found that SZGB significantly reduces 24-hour urinary albumin, insulin resistance index, serum creatinine, and blood urea nitrogen levels in DN mice. It also decreases the

abundance of Gram-negative bacteria and lipopolysaccharide levels. Furthermore, SZGB inhibits the expression levels of TLR4, phosphorylated NF-κB p65, NLRP3 protein, as well as interleukin (IL)-18 and IL-1β, thereby alleviating DN. DanZhi JiangTang Capsule (DJC) is primarily composed of Pswudostellariae Radix, Rehmanniae Radix, Moutan Cortex, Alismatis Rhizoma, Cuscutae Semen, and Hirudo. It functions to strengthening qi, nourishing yin and activating the blood. It is used for type II diabetes and its chronic complications characterized by qi deficiency, yin depletion, and blood stasis. XIE [32] et al. demonstrated that DJC-mediated protection against renal injury is associated with the reduction of the TLR4/NF-κB signaling pathway and apoptosis in diabetic rats. Huangqi Decoction is derived from Volume 17 of Renzhai Zhizhi Fang Lun by Yang Shiying of the Southern Song Dynasty. It has the effects of strengthening qi, nourishing yin, and promoting fluid production. Li [33] found that Huangqi Decoction can improve general indicators, renal function, and proteinuria in diabetic nephropathy rats and LPS-induced diabetic nephropathy rats. By reducing the expression of TLR4, it further decreases the phosphorylation of IKK and NF-κB, thereby inhibiting the TLR4/NF-κB signaling pathway. This leads to reduced expression levels of downstream inflammatory factors such as IL-6, TNF-α, and IL-1β, alleviating inflammatory responses, improving renal pathological indicators, and reducing renal fibrosis levels. Gualou Qumai Decoction is formulated based on Gualou Qumai Pill with the addition of Cinnamomum cassia, Prunus persica, and Leonurus japonicus. Gualou Qumai Pill functions to Moisturizing Dryness, Producing Fluid, warming yang to promote diuresis. Sun [34] found that Gualou Qumai Decoction can intervene in the activation of the upstream immune system, inhibit the release of pro-inflammatory factors, regulate the TLR4/MyD88 signaling pathway, and reduce kidney damage caused by diabetes mellitus.

In addition, many other Chinese herbal compound formulations, such as Yishen Tongluo Formula [35], Yitangkang [36], have been proven to inhibit renal cell pyroptosis by regulating the TLR4/NF-κB signaling pathway, thereby reducing renal tubulointerstitial injury in diabetic nephropathy mice and exerting renal protective effects.

5. Discussion

Today, diabetic nephropathy (DN) poses a significant challenge to human health due to its complex immunological and molecular mechanisms, exerting a substantial negative impact on global health. The TLR4/NF-κB signaling pathway plays a crucial role in the progression of DN, and it is hoped that in the near future, this pathway will become a novel approach for the prevention and treatment of DN. With numerous research achievements in the prevention and treatment of DN using TCM, TCM has demonstrated significant advantages in this field. Targeting the regulation of the TLR4/NF-κB signaling pathway in DN to halt disease progression has gradually emerged as a new research direction. This article summarizes recent studies on TCM-mediated regulation of the TLR4/NF-κB signaling pathway for DN treatment: active components of Chinese herbs and TCM compound formulations can specifically inhibit the TLR4/NF-κB signaling pathway, exerting anti-inflammatory, antioxidant, apoptosis-regulating, and anti-proliferative effects, thereby alleviating renal injury and delaying the progression of nephropathy.

Although many foundational studies on TCM for DN prevention and treatment have been conducted, providing a certain objective basis for new drug development and TCM therapy, there are still limitations. First, clinical research is significantly insufficient. Current studies primarily remain at the level of animal experiments and cellular models, and there is a need for large-sample, multi-level clinical research. Second, the pharmacodynamic substances of TCM compound formulations are extremely complex, and research on their molecular mechanisms is relatively lacking. Further in-depth exploration of specific active components is required. Third, the key specific targets of intervening in the TLR4/NF-κB signaling pathway for DN treatment remain unclear. It is challenging to systematically determine the extent of this pathway's involvement in DN, and the crosstalk with other signaling pathways has not yet been elucidated. Future research should further deepen the understanding of the mechanism of TLR4/NF-κB in DN. Fourth, using the TLR4/NF-κB signaling pathway as a potential target for DN treatment, combined with the traditional TCM theory of syndrome differentiation and treatment, unifying drug molecular targets with TCM syndrome types, and innovating and optimizing prescription combinations are worthy of in-depth exploration.

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