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Research Progress on Regulation of Nrf2/Keap1 Signaling Pathway by Traditional Chinese Medicine in the Treatment of Diabetic Nephropathy

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Abstract: ***Diabetic kidney disease (DKD) is one of the more common microvascular diseases in diabetes, and its pathogenesis has not been fully revealed. Oxidative stress and inflammatory reaction play an important role in its pathogenesis. Studies have proved that the nuclear factor E2 related factor2(Nrf2)/Kelch like epichlorohydrin related protein-1 (Keap1) pathway is a signal pathway closely related to the occurrence and development of DKD, participating in the antioxidant stress and inflammatory response of the body, and is one of the important targets in the treatment of diabetes nephropathy. Some traditional Chinese medicine and related compound formulas can regulate the Nrf2/Keap1 signaling pathway to resist oxidative stress and anti-inflammatory effects, thereby improving renal function and delaying renal fibrosis, such as Tripterygium wilfordii glycosides, berberine, baicalin IV, icariin, resveratrol, emodin, curcumin, asiatica acid, tangshenning, compound asiatica, etc. Therefore, focusing on the composition and activation of the Nrf2/Keap1 signaling pathway, this paper summarizes the mechanism and current research progress of traditional Chinese medicine intervention in the treatment of DKD through the Nrf2/Keap1 signaling pathway, in order to provide new theoretical references for the prevention and treatment of DKD with traditional Chinese medicine and the development of new drugs.***

Keywords: Diabetic nephropathy, Nrf2/Keap1, Oxidative stress, Inflammatory response, Traditional Chinese medicine monomer, Traditional chinese medicine decoction**.**

1. Introduction

Diabetic Kidney Disease (DKD) is one of the most prevalent microvascular complications of diabetes mellitus, and has now become the leading cause of End-stage renal disease (ESRD) worldwide1.It is predicted that about 50% of diabetic patients will develop diabetic nephropathy after having diabetes mellitus for more than 20 years 2.The pathology of DKD is characterized by glomerulosclerosis, basement membrane thickening, glomerular thylakoid stroma and thylakoid cell hyperplasia, tubular epithelial cell fibrosis and vacuolated lesions, which triggers persistent albuminuria and progressive glomerular filtration rate (GFR) decline, which leads to the progression of end-stage renal disease3.The pathogenesis of DKD is associated with disorders of glycolipid metabolism, The development of DKD is associated with disorders of glucose and lipid metabolism, inflammation, oxidative stress, hemodynamic changes, and genetics. Among them, oxidative stress and inflammatory response have a key role in the pathogenesis of DKD, and oxidative stress can be activated by activation of the polyol pathway, accumulation of advanced glycation end products (AGEs), and a variety of cytokines, leading to exacerbation of renal microangiopathy and subsequent kidney injury4. Approximately 20% of patients with diabetic renal failure progress to the need for dialysis without treatment by a nephrologist5, affecting the patient's quality of life. In recent years, Chinese medicine has made some progress in the treatment of diabetic nephropathy through the Nrf2/Keap1 signaling pathway. Many scholars, by studying the relationship between the Nrf2/Keap1 signaling pathway and oxidative stress and inflammatory response, have discovered the mechanism of a variety of Chinese medicine single drugs and compound formulas in treating diabetic nephropathy through this pathway, which expands a new way of thinking for the treatment of diabetic nephropathy.

1.1 Overview of Nrf2/Keap1 Signaling Pathway

Nuclearfactorerythroid2 -related factor2 (Nrf2) is a basic Leucine Zipper transcription factor that is a product of the Red blood cell derived nuclear factor 2 like protein 2 (NFE2L2) gene. factor 2 like protein 2 (NFE2L2) gene, Nrf2 has a basic leucine zipper DNA-binding motif and is primarily responsible for the maintenance of cellular homeostasis6.Nrf2 is a seven highly conserved structural domains (Neh 1-7) 66KDa cap "n" collar (CNC) transcription factor proteins, and the Neh2 structural domain located at the n-terminal end of Nrf2 is thought to be a regulatory structural domain that responds to oxidative stress7. Neh2 interacts with kelch-like ECH-associated protein 1 (KEAP1) through two motifs, DLG and ETGE, to negatively control Nrf2 function.Neh2 negatively controls Nrf2 function by interacting with kelch-like ECH-associated protein 1 (KEAP1) through both DLG and ETGE motifs.Keap1 is a substrate-converting protein of the cul3-e3 ligase complex and a cysteine (Cys)-rich sensor of redox damage8.Human Keap1 contains 27 cysteine residues, of which Cys151, Cys226, Cys273, Cys288, Cys434, and Cys613 are critical for Nrf2 activation9. Under resting conditions, intracellular cytoplasmic Nrf2 binds directly to kelch-like ech-related protein 1 (Keap1) and contributes to Nrf2 proteasomal degradation. Under stress conditions, reactive oxygen species (ROS) or electrophilic substances lead to modification of cysteine residues (Cys273, Cys288) in the IVR structural domain of Keap1 by affecting the intracellular redox state, which results in a change in the conformation of Keap110. The cysteine residues of Keap1 are modified to form molecular and intramolecular disulfide

bonds, and the modified Keap1 loses its negative regulatory function for Nrf2, which escapes keap1-mediated inhibition and translocates to the nucleus, where it binds to the small myofascial fibrosarcoma protein (sMaf) dimer.Nrf2 regulates the expression of a wide range of antioxidants, and its target genes include a group of enzymes involved in drug metabolism and deposition, such as glutathione S-transferase (GST), NADPH: quinone oxidoreductase 1, and cytochrome P450CYP2A5, and genes encoding enzymes and proteins involved in antioxidant defenses and oxidative signaling, such as heme oxygenase 1 (HO-1), superoxide dismutase 3 (SOD3), and peroxiredoxin-1 (Prx-1) and human glutathione peroxidase 2 (GPx2)11. The activated Nrf2-sMaf heterodimer binds to the antioxidant response element (ARE) DNA sequence in the promoter of the antioxidant genes described above, which is described as a cis-acting enhancer in the promoter region upstream of its target genes 12-13 to induce the expression of the target genes for antioxidant action, thereby controlling cellular protection from oxidative stress and xenobiotics.

1.2 Role of the Nrf2/Keap1 Signaling Pathway in Diabetic Nephropathy

1.2.1 Nrf2/Keap1 prevents diabetic nephropathy by resisting oxidative stress

Studies have shown that the Nrf2/Keap1 signaling pathway is closely related to diabetic nephropathy14, and the accumulation of AGEs in vivo in a high-glucose environment is a major causative factor for diabetic nephropathy. AGEs can initiate the accumulation of oxidative stress, act as signaling factors mediating the cascade response of multiple intracellular signaling pathways, and, by promoting lipid peroxidation, DNA damage, mitochondrial dysfunction, and renal mesangial impairment of cell or endothelial cell function15 induces chronic inflammation, fibrosis, OS, and apoptosis in renal tissues, leading to DKD16. Oxidative stress activates the Nrf2/Keap1 pathway, and the Nrf2 transcription factor has been described as a "master regulator" of the antioxidant response, which is a defense factor against some diabetic complications. It regulates the expression of a large number of genes, including not only those controlling antioxidant enzymes, but also those controlling immune and inflammatory responses17.Under the stimulation of oxidative stress, the conjugate Keap1-Nrf2 dissociates, and subsequently Nrf2 enters the nucleus, binds to ARE, initiates the transcription of related genes, activates its antioxidant target genes to play their roles18, such as heme oxygenase 1 (HO-1), superoxide dismutase (SOD), and quinone oxidoreductase 1 (NQO1)19, reduces the production of fibronectin (FN) and intercellular adhesion molecule-1 (ICAM-1) overproduction and resist oxidative stress, thus protecting cells from excessive oxidative stress damage, exerting cytoprotective and detoxifying effects, and delaying the onset and progression of DKD kidney injury20.

1.2.2 Nrf2/Keap1 prevents diabetic nephropathy by inhibiting inflammatory response

Nrf2/Keap1 and NF-κB are key pathways that regulate intracellular redox and inflammatory responses, and they can interact with each other.NF-κB can regulate the transcription and activity of Nrf2 22, and the deletion of Nrf2 may lead to the enhancement of NF-κB activity thus promoting cytokine production, and keap1 plays a critical roles in both pathways23.P65, a subunit of NF-κB, binds the histidine deacetylase HDAC3 to MafK and prevents the formation of Nrf2 heterodimers, which in turn negatively regulates ARE-mediated expression of related genes24.The target gene of Nrf2, p62, enhances Nrf2 activity by mediating the autophagic degradation of keap1 and is able to potentiate the NF-κB pathway mediated by the nerve growth factor NGF. Oxidative stress Nrf2 binds to HO-1, which inhibits the renal inflammatory response by inhibiting IκB phosphorylation and its subsequent degradation, leading to NF-κB translocation and its downstream inflammatory gene transcription25.The application of pharmacologic anti-inflammatory effects may also demonstrate the relationship between the Nrf2/Keap1 pathway and the inflammatory response. Meng-Chen Lu et al. found through in vivo and in vitro experiments26 that the small molecule Keap1-Nrf2PPI inhibitor (CPUY192018) could activate the Nrf2-dependent antioxidant pathway and inhibit the inflammatory response involved in NF-κB, thus antagonizing LPS-induced chronic kidney inflammation in HK-2 cells and in vivo. Another study found that selegiline can improve insulin resistance and promote pancreatic β-cell insulin by inhibiting the Nrf2-Keap1-ARE system, and the mechanism of action is closely related to its anti-inflammatory effect 27, suggesting that the Nrf2-Keap1 pathway can prevent diabetic nephropathy by inhibiting inflammatory response 21.

2. Traditional Chinese Medicine Improves DKD by Regulating the Nrf2/Keap1 Pathway

Ancient Chinese medicine books on "diabetic nephropathy" this overview is not recorded, the ancient medical practitioners will be recorded as "thirsty diseases" "dissipation of disease" "bottom eliminationf" and so on. The ancient medical practitioners recorded it as "Kidney Cancer", "Diabetes", "Lower Cancer", etc. Among them, the Yellow Emperor's Classic of Internal Medicine-Suwen describes it as, "When thirst-quenching disease lasts for a long time, the kidney qi is injured, and when the kidney qi weakens, the urine is to sweet and creamy." Medical Outline" cloud: 'under the elimination of the person, the scripture is called 'kidney elimination", kidney elimination of the person, drink a ulcer two, its ulcer such as cream oil....."The Ancient and Modern Record of Examination and Recipes recorded: "thirst, the disease has three..... thirst and drinking water can not be more, urination number, yin impotence and weakness, but the legs are swollen, the feet first thin small, this kidney elimination of the disease is also." Chinese medicine believes that thirst disease for a long time, visceral dysfunction, phlegm and dampness, blood stasis, heat and toxins gathered in the collateral veins, resulting in obstruction of the blood flow, so as to send for thirst disease kidney disease.

In recent years, the efficacy of active ingredients of single-flavored traditional Chinese medicines (TCM) and TCM combinations in inhibiting diabetic nephropathy has been remarkable. The treatment of diabetic nephropathy by single-flavored Chinese medicines and Chinese medicinal compounds can exert a multi-session and multi-target

protective effect, and the Nrf2/Keap1 signaling pathway is one of the important therapeutic pathways. At present, the mechanism of diabetic nephropathy treated by single Chinese medicine extracts is initially clear, and the study of the role of Nrf2/Keap1 signaling pathway in the prevention and treatment of diabetic nephropathy by Chinese medicine may provide a useful reference for the study of the mechanism of Chinese medicine intervention in diabetic nephropathy.

2.1 Chinese Herbal Monomer

2.1.1 Tripterygium wilfordii multiglycoside, GTW

Studies have shown that GTW can treat diabetic nephropathy by improving oxidative stress, inhibiting inflammatory factors and related pathways 28. Under normal conditions, the body can express Nrf2 and HO-1 in small amounts, while in the state of diabetic nephropathy, the antioxidant stress state is activated, Nrf2/Keap1 is dissociated, and Nrf2 binds with downstream HO-1 and other substances to resist oxidative stress. As a result, the expression of Nrf2 and HO-1 is reduced, and some studies have found that GTW can inhibit renal fibrosis in diabetic nephropathy by up-regulating the expression of Nrf2 and HO-1, and down-regulating the expression of Keap129.

2.1.2 Berberine

Sheng Dongqin and others found through the experimental research on diabetes nephropathy mice that berberine has a certain delaying effect on diabetes nephropathy by reducing the fasting blood glucose level, reducing the excretion of urinary protein, and reducing the levels of serum urea nitrogen and creatinine. Its mechanism of action is to effectively reduce the expression of Keap1 protein, increase the content of Nrf2 protein, and then effectively inhibit the generation of NADPH oxidase 4 gene (NOX4), inhibit the expression of ROS, promote the synthesis of SOD, and fully alleviate the oxidative stress response 30.

2.1.3 Baicalin

Nrf2 is a target-interacting gene of miR-14231, miR-142 overexpression decreases the expression of the Nrf2 signaling pathway, which induces inflammatory responses. miR-142-5p inhibitors significantly increase the expression of Nrf2, HO-1, SOD2 and quinone oxidoreductase 1 (NQO1)32, and diabetic nephropathy has a miR-142 overexpression situation in diabetic nephropathy, which inhibits Nrf2/Keap1 pathway activation. Peng Fumei et al. confirmed that baicalin acts as a miR-142 inhibitor by reversing the inhibitory effect of miR-142 on the Nrf2/Keap1 signaling pathway, increasing Keap1 and Nrf2 expression, and improving diabetic nephropathy through animal studies.

2.1.4 Icariin

WangKai et al. showed that nuclear translocation, DNA-binding activity and transcriptional activity of Nrf2 were decreased, and the level of fibronectin (FN) was increased in high glucose (HG)-induced human glomerular mesangial cells (HMCs) by animal studies. Icariin was able to up-regulate Nrf2 DNA-binding activity and Nrf2 transcriptional activity in HG-induced HMC, thereby promoting the activity of antioxidant enzymes in HMC under high glucose treatment, implying that Icariin may delay HG-induced oxidative stress and ECM production in HMC by activating the Nrf2 signaling pathway33.

2.1.5 Resveratrol

It has been demonstrated that the activity of antioxidant enzymes is reduced in diabetic kidneys, and oral administration of resveratrol significantly increased the activity of antioxidant enzyme agents, which resulted in a significant normalization of creatinine clearance, C-peptide, renal superoxide anion, hydroxyl radical, nitric oxide, TNF-α, IL-1β, IL-6, NF-κBp65 subunit levels, and end products of advanced glycosylation in diabetic nephropathic rats 34. During hyperglycemia-mediated oxidative stress, the expression of Nrf2 and its down-regulated enzymes γ-GCL, μ-GST, and HO-1 was significantly reduced in kidney tissues of diabetic rats. However, resveratrol significantly regulated the expression of Nrf2 in hyperglycemia-mediated oxidative stress by up-regulating γ-GCL, μ-GST, and HO-1, and normalized the expression of Nrf2/keap1 and its downstream regulatory proteins in diabetic rat kidney. Resveratrol was shown to have a renoprotective effect by reducing oxidative stress markers in diabetic rat kidney tissue 35.

2.1.6 Emodin

Emodin is the main active ingredient extracted from the traditional Chinese medicine rhubarb. Many studies have shown that emodin can effectively reduce diabetes related complications by reducing blood glucose levels, inhibiting inflammation and restoring energy sensing pathways. Ji et al. found that compared with the DM group, the renal function impairment indicators in the emodin treatment group were significantly weakened. The mRNA expression of Nrf2, glutathione peroxidase 4 (GPX4), solute carrier family members (SLC7A11), and ferritin 1 (FTH-1) were upregulated in the emodin treatment group, while the mRNA expression of transferrin receptor 1 (TFR-1) was reduced. In addition, emodin can reduce iron concentration, enhance glutathione expression, and restore the antioxidant capacity of the kidneys 36.

2.1.7 Curcumin

Curcumin has been shown in animal experiments to be a potent Nrf2 activator with reversal ability on suppressed Nrf2 function, H. Yang et al. found through clinical observation that curcumin can reduce the excretion of U-mAlb. DKD patients with supplementation of curcumin showed that the function of Nrf2 antioxidant system in the blood lymphocytes was activated, and inflammatory signals were suppressed, thus preventing DKD 37.

2.1.8 Asiatic acid

Asiatic acid has a protective effect against diabetic nephropathy, significantly reducing albumin levels as well as serum Cr and BUN levels. Ji Yi et al. evaluated the effects of streptozotocin-induced diabetes and AGEs-stimulated HK-2 cell model on renal tubular injury and found that cumaric acid

prevented tubular injury and mitochondrial damage by modulating the Nrf-2 pathway and mitochondrial dynamics 38.

2.2 Traditional Chinese Medicine, TCM

2.2.1 Di Hong Fang

Di Hong Fang was modified from Liu Wei Di Huang Tang and Tao Hong Si Wu Tang. He Weidong et al. found that the mRNA and Keap1 protein expression of Nrf2, HO-1, SOD, CAT, GST, GPX, NQO1, and GCL were significantly elevated in the low-, medium-, and high-dose groups of the Dihong Fang compared with the model group of DKD, and the mRNA and Keap1 protein expression of Nrf2, HO-1, SOD, CAT, GST, GPX, NQO1, and GCL were especially pronounced in the medium-dose group, which suggests that the Dihong Fang may improve oxidative stress injury of DKD vascular endothelial cells by regulating the Keap1/Nrf2 pathway [39]. this pathway to ameliorate oxidative stress injury in DKD vascular endothelial cells39.

2.2.2 Centella Asiatica Component

Centella asiatica component consists of Centella asiatica, Astragalus membranaceus and Tripterygium wilfordii. Qin et al found that after treatment with Centella asiatica component, the ratio of urinary protein/creatinine in diabetes rats decreased, and the kidney pathology of DKD improved, indicating that Centella asiatica component can effectively treat DKD. The levels of Keap1 and total Nrf2 in diabetes rats were lower than those in normal rats, while the expression of Keap1 and the total expression of Nrf2 were increased after the treatment of Centella asiatica complex. In the kidney of DKD nephropathy rats, the expression of MDA was down regulated and the expression of HO-1 was up regulated, suggesting that Centella asiatica component may regulate oxidative stress and improve DKD by activating the Keap1-Nrf2-ARE pathway 40.

2.2.3 Tang Shen Ning

The formula for Tangshenning includes Rehmannia glutinosa, Epimedium, Cornus officinalis, Chinese yam, Stir fried Paeonia lactiflora, Leech, Rhubarb, and Eucommia ulmoides. Liu Yunhua et al. found through immunohistochemistry, Western blot, and RT-PCR experiments that Tangshenning can significantly upregulate Nrf2, HO-1, and GPX4 proteins in the kidneys of DKD rats, downregulate Keap1 protein, protect the renal function of DKD rats, reduce AGEs induced oxidative stress damage to renal tubular epithelial cells, and thus delay the progression of DKD 41.

3. Summary

The Nrf2/Keap1 signaling pathway exhibits an important role in the treatment of DKD by regulating oxidative stress and inflammatory response, therefore, targeting and regulating the Nrf2/Keap1 signaling pathway can be an important strategy for the treatment of DKD. In this paper, through combing the relevant literature, we identified eight single Chinese medicines for the treatment of DKD, as well as three compound components, which could effectively regulate the Nrf2/Keap1 signaling pathway, exert antioxidant and anti-inflammatory effects, and improve the symptoms of DKD and hyperglycemia-induced renal injury. Through multi-targeted intervention, TCM can inhibit oxidative stress and inflammation downstream of Nrf2/Keap1 signaling pathway, and play a systematic and comprehensive therapeutic role. However, there are some limitations in the modulation of Nrf2/Keap1 signaling pathway by TCM in the treatment of DKD: firstly, most of the current studies focus on animal experiments and cellular level, and there is a lack of well-designed, large-sample, multi-center, high-quality studies, and there is a need for more high-level evidence-based medical research evidence. In addition, using Nrf2/Keap1 signaling pathway as a potential target for the treatment of DKD, we need to innovate prescription combinations and combine with the theory of diabetic nephropathy in Chinese medicine, so as to improve the treatment plan.

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