

# *The Mechanism and Research Progress of Angelica Sinensis in Preventing and Treating Diabetes Nephropathy*

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**Abstract:** Diabetes nephropathy is the most important microvascular complication of diabetes, which can eventually progress to end-stage renal disease and affect the quality of life of patients. Traditional Chinese medicine has irreplaceable advantages in the treatment of diabetes and its complications. In recent years, more and more studies have found that angelica sinensis can play a certain role in the prevention and treatment of diabetic nephropathy. The active ingredients of Angelica sinensis can reduce the kidney damage of diabetic nephropathy patients through antiinflammatory, immune enhancement and other functions. It can also play the role of antioxidation, antitissue fibrosis and clearing white group in the local tissue, reduce the changes of kidney hemodynamics and thus reduce the damage caused by hypoxia to kidney tissue. This article reviews the active ingredients of single drug Angelica sinensis, the mechanism of action of Angelica sinensis pair and Angelica sinensis compound in the treatment of diabetes nephropathy and the current research progress, so as to open up new ideas for the treatment of diabetes nephropathy by traditional Chinese medicine.

Diabetes Nephropathy (DN) is a renal injury caused by long-term hyperglycemia, which can involve the glomerulus, renal tubules, renal interstitium, and even affect the whole kidney, and may eventually progress to ESRD, which is one of the main causes of death in diabetes patients<sup>[1]</sup>. DN has a hidden onset and rapid development, and its mechanism has not yet been fully revealed. Traditional Chinese medicine treats diabetes nephropathy in an all-round and multi-target way with the principle of overall regulation, the treatment based on syndrome differentiation, and the treatment based on both symptoms and symptoms, and has achieved certain results. In recent years, the research on the treatment of diabetes nephropathy with angelica sinensis and its compound is being carried out in depth. This article will make a Systematic review on the mechanism of angelica sinensis and its compound in the treatment of diabetes nephropathy and the current research progress.

Angelica sinensis, also known as Gangui, Horsetail Angelica, is the dry root of the Apiaceae perennial herb Angelica sinensis. It has a long medicinal history. It is listed as the middle grade in the Shennong Ben Cao Jing. Its nature is warm, its taste is spicy, and its taste is sweet. Its heart, liver, and spleen meridians <sup>[2]</sup>. Danggui is a commonly used ingredient in the compatibility of traditional Chinese medicine, known as the "Ten Medicines and Nine Gui". In recent years, a large number of

scholars found that *Angelica sinensis* and its compound play an increasingly important role in the treatment of kidney damage caused by diabetes through experimental research and clinical observation. Studies have shown that *Angelica sinensis* can alleviate renal damage in DN patients through anti-inflammatory and immune enhancement functions, delay disease progression, and also exert antioxidant, anti-fibrosis, and free radical scavenging effects in local tissues, alleviating changes in renal hemodynamics, thereby reducing the damage caused by hypoxia to tissues and delaying renal damage<sup>[3]</sup>.

## 1. Single medicine *Angelica sinensis*

The active ingredient of single medicine *Angelica sinensis* mainly include volatile oil, organic acid, polysaccharide, flavonoids, alkaloids and other components, of which Ferulic acid and *Angelica sinensis* polysaccharide play an important role in the treatment of diabetes and the kidney damage caused by it<sup>[4]</sup>.

### 1.1 Ferulic Acid

Ferulic acid is an early active ingredient isolated from *Angelica sinensis*, which has anti-inflammatory, analgesic and other effects. Due to its special molecular structure, there were few early studies on Ferulic acid in the treatment of diabetes nephropathy, and more studies focused on Ferulic acid derivatives Ferulic acid sodium and Ferulic acid piperazine. As early as 2005, Zheng Fengming and others found through clinical observation that sodium Ferulic acid can reduce UAER and BUN in patients with early DN and clinical DN, and its mechanism may be related to reducing the production of ET-1 or antagonizing the binding of ET-1 to its receptor<sup>[5]</sup>. Zhao Tongfeng and his team learned through research that sodium Ferulic acid can inhibit the expression of TGF-1 and RAGE mRNA in the kidney, inhibit the activation of PKC, increase the antioxidant capacity and eliminate free radicals, thus protecting the renal function of diabetes rats<sup>[6]</sup>. Piperazine ferulate is a piperazine salt derivative synthesized by structural modification of ferulate acid, an active component of *angelica sinensis*<sup>[7]</sup>. Zhuang Fuchun and others confirmed through clinical randomized Scientific control that PF can reduce blood sugar, blood pressure and blood lipid in patients with end-stage diabetes nephropathy, improve renal function of patients, reduce renal damage, and has high safety<sup>[8]</sup>. In recent years, many scholars have found through animal experiments that Ferulic acid can also improve kidney damage caused by diabetes. Zhou Bin et al found that Ferulic acid regulates TGF in kidney tissue- $\beta 1$ . The expression of MMP-9, nephrin and podocin protein can reduce renal fibrosis, maintain the structure of Podocyte, reduce BUN, Cr, 24h UP and other indicators of DN rats, and protect renal tissue<sup>[9]</sup>. Ma et al. found that Ferulic acid can reduce the body weight and Glucose test#Fasting blood sugar of DN mice, and can reduce the level of Blood urea nitrogen in urine and blood and 24-hour urinary protein excretion after feeding DN model rats with high sugar/high-fat diet<sup>[10]</sup>.

### 1.2 *Angelica* Polysaccharides

*Angelica* polysaccharide is another important active component of *Angelica*. Research has found that *Angelica* polysaccharides can regulate the generation and degradation of extracellular matrix components, and can act on renal tubular epithelial cells, hinder their transformation to fibroblasts, and inhibit the fibrogenic signaling pathway TGF-  $\beta$  1/Smads signal transduction activity plays a role in protecting the kidney from diabetes nephropathy and effectively delaying the development of renal interstitial fibrosis<sup>[11]</sup>. Another study has shown that *Angelicae* polysaccharide can effectively inhibit the expression of TLR4, MyD88, NF- $\kappa$ B proteins and genes in the TLR4/ NF- $\kappa$ B signaling pathway,

reduce the release of MCP-1, TNF- $\alpha$ , IL-1 and other inflammatory factors, thus delaying the progression of the disease<sup>[12]</sup>. Wang Jiangxia et al. studied the effect of Angelica polysaccharide on the AMPK signaling pathway activated by adenosine phosphate and mitochondrial autophagy in the kidney of KK Ay mice with diabetes nephropathy through animal experiments. They found that Angelica polysaccharide can improve the kidney damage of DN mice and delay the disease of DN by inhibiting mitochondrial autophagy mediated by AMPK signaling pathway. However, how angelica polysaccharide regulates mitochondrial autophagy and how mitochondrial autophagy promotes diabetes nephropathy remains to be further studied<sup>[13]</sup>.

### 1.3 Angelica volatile oil

In the treatment of diabetic nephropathy, prevention and treatment of hypertension is also a very important part. Research has found that the volatile oil of Angelica sinensis can significantly reduce the systolic blood pressure of spontaneously hypertensive rats. YI Lin et al. conducted a long-term in-depth study on the volatile oil of Angelica sinensis and found that it can reduce blood pressure through the following aspects: ① Angelica sinensis volatile oil reduces blood pressure by improving the expression of insulin signaling pathway and Vascular endothelial growth factor (VEGF) signaling pathway miRNA<sup>[14]</sup>. ② Angelica sinensis volatile oil exerts antihypertensive effects by antagonizing the ACE system through the ACE2/[Ang (1-7)]/Maas receptor axis ③ Angelica sinensis volatile oil reduces blood pressure by reducing serum renin and angiotensin II levels. ④ Angelica sinensis volatile oil reduces blood pressure by reducing the abundance of intestinal proteus and ferritobacter. ⑤ Angelica sinensis volatile oil improves blood pressure by regulating the PI3K/Akt/eNOS signaling pathway<sup>[15]</sup>.

## 2. Medicine pairs of Angelica

### 2.1 Angelica - Astragalus

Modern research shows that angelica astragalus drugs can reduce renal damage and delay the progress of diabetes nephropathy by reducing urinary protein, resisting oxidative stress, and inhibiting renal inflammatory reaction<sup>[16]</sup>. Kongchang et al. found through experimental research that angelica astragalus medicine can improve kidney damage in type 2 diabetes nephropathy mice by reducing Glucose test#Fasting blood sugar, reducing Proteinuria, improving renal function, reducing oxidative stress, inflammation and fibrosis damage, and the angelica astragalus 1:1 group has the best effect<sup>[17]</sup>. Zhou Ji et al. found through clinical observation that Qigui medicine can regulate oxidative stress by increasing SOD and CAT activities to treat diabetes nephropathy of qi deficiency and blood stasis type. When the ratio of angelica and astragalus is 2: 3, it can reduce 8-iso-PGF2 in DN patients  $\alpha$  Equal oxidative stress products achieve the effect of improving DN<sup>[18]</sup>. Dong Youzi et al. found that the combination of Angelica sinensis and Astragalus membranaceus can utilize TGF- $\beta$ / Smads pathway regulates Smad7 and TGF in renal tissue of DN rats-  $\beta$ 1 expression to treat renal fibrosis in diabetes<sup>[19]</sup>.

### 2.2 Angelica—Hongqi

Hongqi is the dry root of the leguminous plant Astragalus membranaceus. with the continuous deepening of research on the two, it has gradually been discovered that Hongqi and Astragalus membranaceus are not the same traditional Chinese medicine. In the 1985 edition of the Chinese Pharmacopoeia, the two drugs were used separately<sup>[20]</sup>. Through animal experiments, a team found

that *Angelica sinensis* and Hongqi ultrafiltration membrane extract can treat diabetes nephropathy by improving inflammation, reducing blood sugar, improving blood lipids, and protecting kidney function. Wan Shengfang and his research team found that the extract of *Angelica sinensis* and Hongqi ultrafiltration membrane can improve the general situation of DN rats, such as reducing Glucose test#Fasting blood sugar, triglyceride, cholesterol, 24-hour urine protein, blood creatinine and Blood urea nitrogen levels of DN rats, and play a protective role in the kidneys of DN rats<sup>[21]</sup>. Its mechanism may be related to downregulating the inflammatory factor NF in the renal tissue of DN rats-  $\kappa$  B. TNF-  $\alpha$  Protein and mRNA expression, improving inflammatory status, protecting renal tissue<sup>[22]</sup>, may be related to inhibiting the expression of NF-KB and TNF- $\alpha$  genes and proteins in renal tissue<sup>[23]</sup>.

### 3. *Angelica* classic prescription

#### 3.1 Danggui Shaoyao San

Danggui Shaoyao San is derived from the "Synopsis of the Golden Chamber" and consists of Danggui, Shaoyao, Fuling, Zexie, Baizhu, and Chuanxiong as the basic formulas. The author has consulted relevant literature and found that Danggui Shaoyao San can treat renal injury in rats with diabetes nephropathy at different stages. Li Xiaobing and others studied the effect of Danggui Shaoyao Powder on early diabetes nephropathy through animal experiments, and found that Danggui Shaoyao Powder can significantly reduce Glucose test#Fasting blood sugar, 24h urinary protein, TC, LDL-C levels in DN rats, and can increase HDL-C levels in rats. Compared with the control group, the Danggui Shaoyao Powder group showed a significant increase in GSH-Px and CAT, while the MDA level decreased significantly. It is concluded that the mechanism of Danggui Shaoyao Powder in treating early diabetes nephropathy rats is to regulate the oxidative stress of the body<sup>[24]</sup>. Based on NF- $\kappa$ B signaling pathway, Xia Zhenzhong et al. studied the drug effect of Danggui Shaoyao San on early diabetic nephrotic model rats. Danggui Shaoyao San can reduce the expression of NF- $\kappa$ B in kidney tissues, reduce the release of TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and other cytokines, and protect renal function in DN rats<sup>[25]</sup>. Wang Liulin et al. used a clinical randomized Scientific control to explore the clinical efficacy of Danggui Shaoyao San in patients with stage IV DN. They added Danggui Shaoyao San to the general treatment and found that it can better alleviate the general symptoms of stage IV DN patients, and the blood lipid metabolism in the treatment group was also significantly improved compared with the control group, indicating that Danggui Shaoyao San can play a therapeutic role in diabetes nephropathy by improving kidney function and blood lipid<sup>[26]</sup>.

#### 3.2 Danggui Buxue Decoction

Danggui Buxue Tang was first recorded in the ancient book "On the Differentiation of Internal and External Injuries" and was created by Li Dongyuan, one of the four great masters of the Jin and Yuan dynasties. The compatibility ratio of Huangqi and Danggui in the formula is 5:1. Modern research has found that this compatibility ratio can fully exert its various pharmacological effects. Ding Xin et al. found that Danggui Buxue Decoction may activate AMPK and PGC-1 $\alpha$ , Improve the oxidative stress of DN rats, reduce the degree of renal pathological damage, reduce Proteinuria, so as to effectively protect the kidney and alleviate the progress of DN<sup>[27]</sup>. By establishing a rat model of diabetic nephropathy, Zhang Manling et al found that the protective effect of Danggui Buxue Decoction on the kidney of DN rats may be related to the regulation of the expression of glucose regulated protein 78 (GRP78), a stress related factor of Endoplasmic reticulum, and the inhibition of Endoplasmic reticulum stress response<sup>[28]</sup>. Jin Hechao and others found through animal experiments that Danggui Buxue Decoction can improve the mitochondrial function of Podocyte in DN rats, regulate inflammatory reaction, reduce oxidative stress, and protect renal function<sup>[29]</sup>. Wang Yifan and

others observed the effect of modified Danggui Buxue Decoction on the micro inflammatory state of the body in the treatment of type 2 diabetes nephropathy. After treatment, two groups of inflammatory factors, TGF- $\beta$  1. The levels of CTGF, VEGF, 24hpro, and UAER decreased compared to before treatment, and the levels of hs CRP, MCP-1, sICAM-1, and IL-18 in the Danggui Buxue Tang group were lower than those in the conventional group. Conclusion: Danggui Buxue Decoction can treat diabetes nephropathy by regulating the micro inflammatory state<sup>[30]</sup>.

### 3.3 Angelica Liuhuang Decoction

Danggui Liuhuang Decoction is derived from the "Orchid Room Secret Collection" and is another classic prescription of Li Dongyuan. It is composed of Danggui, raw Rehmannia glutinosa, cooked Rehmannia glutinosa, Huangqin, Huanglian, Huangbai, and Huangqi. It is mainly used to treat diabetes nephropathy with deficiency of both qi and yin, and it is mostly used for diabetes nephropathy in Phase III-IV. Through clinical randomized controlled experiments, Jia Yanli et al. added Angelica Liuhuang Decoction on the basis of Western medicine to treat diabetic nephropathy (stage III-IV) (Qi and Yin deficiency, stasis and heat intercombination syndrome), and found that compared with conventional Western medicine treatment alone, Angelica Liuhuang decoction could improve patients' traditional Chinese medicine symptoms, blood pressure, coagulation function, and urinary protein status<sup>[31]</sup>. Yu Jiali et al. randomly divided 126 patients with type 2 DN (stage III) into a control group and a treatment group, with 63 patients in each group. Both groups were given routine treatment to control blood lipid and blood sugar. The control group was added with Irbesartan, and the treatment group was added with Danggui Liuhuang Decoction. After 12 weeks, the three renal function indicators in the treatment group were lower than those in the control group, and the syndrome scores in the treatment group were lower than those in the control group. It shows that the modified Danggui Liuhuang Decoction combined with Irbesartan can further improve the renal function and TCM syndromes of patients, and improve the clinical effect. However, at present, there is no study on Danggui Liuhuang Decoction alone in treating diabetes nephropathy, and the mechanism of its treatment of diabetes nephropathy has not yet been revealed.

### 3.4 Self drafted Danggui Fang

Some scholars, through long-term clinical experience, have developed an empirical formula of Angelica sinensis to treat diabetes nephropathy. Wang Shihui<sup>[32]</sup> et al. used self-prepared Yiqi Huayu formula (Astragalus sinensis, Angelica sinensis, Saltiorrhiza, Chinese herb, Radix Sculariae, safflower, pueraria root, atractylodes, Delong and Radix Rehmannia) to treat patients with diabetic nephropathy stage (III), and took Angelica sinensis and Radix Astragalus as the main drugs. Serum levels of IL-6, TNF- $\alpha$ , SCr, BUN and CysC in the treatment group were lower than those in the reference group ( $P < 0.05$ ). Conclusion: Yiqi Huayu formula has a good effect on diabetic nephropathy (III) patients. Song Yuping and others jointly used the self-made Yiqi Huoxue Jiangtang decoction (20g safflower, 20g astragalus, 15g angelica and red peony, 10g chuanxiong, earthworm and peach kernel) for patients with type 2 diabetes nephropathy on the basis of controlling blood sugar. With angelica and red peony as their courtiers, they found that the prescription can reduce Proteinuria, delay the progress of DN, and has high clinical safety<sup>[33]</sup>.

## 4. Conclusion

The number of patients with diabetes nephropathy has increased year by year, and has not yet been cured. Therefore, it is very important to improve the quality of life of patients and delay the progress of the disease. Diabetes nephropathy belongs to "Diabetes Mellitus", "Guan Ge" and "Edema" in

traditional Chinese medicine. Traditional Chinese medicine believes that diabetes nephropathy is caused by long-term onset of diabetes, deficiency of qi and yin, and intersection of dampness, phlegm and blood stasis. Western medicine believes that the pathogenesis of diabetes nephropathy is related to abnormal glucose and lipid metabolism, changes in renal hemodynamics, cytokines, inflammatory reaction, and increased oxidative stress. The study found that the renal vascular disease of diabetes began to appear as early as the early stage of the disease. Therefore, effective intervention of related pathological changes after the diagnosis of diabetes is of great significance for the treatment of diabetes nephropathy. As a commonly used traditional Chinese medicine in clinical compatibility, *Angelica sinensis* can resist oxidation and renal tissue fibrosis, thereby improving blood flow perfusion, reducing renal tissue hypoxia, and alleviating renal microvascular disease. The effective active ingredients of *Angelica sinensis* are effective in treating diabetes nephropathy, but their compound ingredients are complex, so the mechanism of action in treating diabetes nephropathy is not completely clear. Further research is needed in the future to further explore the mechanism of action of *Angelica sinensis* and its compound in treating diabetes nephropathy.

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