Basic Research Progress of Promoting Blood Circulation and Removing Blood Stasis Jingfang on Diabetic Nephropathy

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Abstract. Clinical studies have demonstrated that Jingfang can effectively reduce urine protein and delay the process of DN. Jingfang of promoting blood circulation and removing blood stasis which has a long history in the treatment of diabetic nephropathy. It has many effects such as anti-oxidation, lipid-lowering, and hypoglycemic effect. To this end, this article reviews the basic research progress of the prevention and treatment of DN about Jingfang of promoting blood circulation and removing blood stasis.

1. Introduction
Diabetic nephropathy (DN) is not only one of the most serious complications of diabetes but also the leading cause of death in type 1 diabetes. Besides, in type 2 diabetes, it is second only to cardiovascular and cerebrovascular diseases in endpoint events.

DN patients have obvious glycolipid metabolism disorder, and the degree of disorder is consistent with the degree of renal dysfunction, systemic and local inflammatory response [1]. Proteinuria, edema and progressive renal decline are the principal clinical manifestations of DN. According to traditional medicine, obstruction of collaterals by blood stasis is considered as the core pathogenesis of DN. The drugs of promoting blood circulation to eliminate blood stasis and dredging collateral are the basic medicine for the treatment. Composing prescriptions for dispersing blood stasis and dredging collateral have been used frequently for the treatment of DN. Its curative effect is definite, which has been shown in a large number of clinical and basic experiments [2]. In recent years, the author has
2. References analysis

Frequency analysis of clinical research on DN-related PBCRBS syndrome: 43 relevant high-quality pieces of literature are selected by keywords such as “diabetic nephropathy”, “promote blood circulation and remove blood stasis”, “Jingfang”, “clinical research” and “basic research” for frequency statistics, and are reviewed by four other researchers in the research group.

The results show that there are 22 clinical studies and 21 basic studies on diabetic nephropathy, and the frequency of the two is quite similar. This shows that the basic research and clinical research on DN are currently comparable. This article will focus on basic research. In the clinical study of DN, there are 13 studies related to the method of promoting blood circulation to remove blood stasis, and 1 case of Non-Jingfang, the treatment effect is all ideal (Tab 1). In the study of the Jingfang, there are 3 studies on Danggui Shaoyao San (DSS), 3 studies on Guizhi Fuling Pill (GFP), 4 studies on Taohe Chengqi Decoction (TCD), 2 studies on Dahuang Zhechong Pill (DZP) and 1 study on Didang Decoction (DD). Among them, DSS, GFP, TCD have been studied more, and the study of DZP is less and DD is the least (Fig 1).

| References                  | Basic Jing Fang of the treatment group | The control group | The result of Basic Jing Fang |
|-----------------------------|---------------------------------------|-------------------|------------------------------|
| Wang Lihua, Liu Liqi. 2016  | DSS                                   | 4-PBA group and citric acid buffer solution group | The expression of GRP78 and Caspase-12 ↓, the levels of 24-hour urinary protein excretion, glycosylated hemoglobin, and Scr ↓ |
| Zhang Lizhen, Zhao Yunfang, et al. 2011 | DSS                                   | Captopril suspension gavage group and saline group | Serum SOD, Ccr ↑, Serum MDA, uALB and β2-MG ↓ |
| Wang Deng. 2015             | DSS                                   | Melatonin group and saline group | HPA Axis hormone CRH, ACTH, and CORT ↓, INS, HOMA-IR ↓, ISI ↑ renal function improved |
| Gao Shirong. 2016.          | GFP                                   | Saline group      | renal function improved      |
| Su Peiyong, Wang Jian. 2015.| GFP                                   | Aminoguanidine group, captopril group and 2-t-Butyl-p-cresol group | renal function improved |
| Nakagawa T. 2003.           | GFP                                   | Saline group      | The expression of NF-κB, MCP-1, and VCAM-1 of the thoracic aorta ↓, Serum IL-6, TNF-α ↓ |
| Deng Xiaofeng. 2016.        | TCD                                   | Metformin group   | The expression of PI3K (p85), Akt protein of thoracic aorta ↓, Blood glucose, blood lipid ↓ |
| Gu Yumei, Zhu Zhangzhi. 2017.| TCD                                   | Metformin group   | The expression of TLR-2, TLR-4, TGF-β1 ↓, IGF-1 ↑ |
| Xu Yang, Wang Jun. 2017.    | TCD                                   | Saline group      | Urinary Scr, Bun, 24h urinary protein, β2-MG, NAG, and RBP ↓ Hb, RBC ↑, Serum CRP, TNF-α and IL-6 ↓, ALB ↑, The levels of CHO, TG ↓, TP, ALB ↑, The levels of BUN, Scr ↓ |
| Su Meiling. 2016.           | TCD                                   | Niaoduqing granule gavage group | The levels of t-PA, 6-KetoPGF1α ↑, PAI ↓ |
| Sun Wei, Zhu Xuanxuan, et al. 2006. | DZP                                   | Tripterygium glycosides group | The expression of PEDF protein ↑, The expression of IL-1β protein ↓ |
| Wang Guoxian. 2015.         | DZP                                   | Danshen group     |                              |
| Chang Bai, Li Chunshen, et al. 2016. | DD                                   | Metformin group and simvastatin group |                              |
reduce the free radicals accumulated in rats in the early stage. Its results showed that Modified Danggui Shaoyao San could significantly delay the progression of DN well [9]. Zhang Liyi et al. used Modified Danggui Shaoyao San to treat DN rats and found that it could effectively reduce the levels of serum SOD content and increased the levels of Ccr. Additionally, the levels of serum MDA, a marker of oxidative stress, were also decreased.

4. Effect of promoting blood circulation and removing blood stasis prescription on inflammatory state

4.1. Danggui Shaoyao San

Wang Lihua et al. studied the effects of Qutan Tongluo Decoction, which is based on Danggui Shaoyao San (DSS), on diabetic nephropathy and found that it could effectively reduce the accumulation of free radicals and oxidative status in rats with diabetic nephropathy by increasing the levels of serum SOD content and Ccr. Moreover, the levels of serum MDA, GRP78 protein, and the content of uALB and uβ2-MG were also decreased. The research proved the effect of DSS in delaying the progress of DN well [9]. Zhang Liyi et al. used Modified Danggui Shaoyao San to treat DN rats in the early stage and found that it could significantly reduce the free radical production caused by hyperglycemia as well as the excretion of urinary...
microalbumin and β2-microglobulin, improving the endogenous creatinine clearance rate of rats through anti-oxidation [10]. Wang Deng's study showed that DSS could regulate blood glucose and lipid metabolism and HPA axis hormone level. Compared with the control group, the DSS group rats' fasting glucose level was reduced. And glucose tolerance and insulin resistance were much ameliorated. Meanwhile, it could also reduce the levels of TG and LDL-c, on the contrary, there was up-regulation on the level of HDL-c, the content of liver glycogen and muscle glycogen [11].

4.2. Guizhi Fuling pill
Gao Shirong et al. have observed that the Guizhi Fuling pill could reduce the deposition of AGEs in renal tissues, improving urinary protein excretion and serum creatinine to delay the advance of DN [12]. Su Peiyong's pharmacological studies on the Guizhi Fuling pill have demonstrated that it can reduce urinary protein excretion and serum creatinine and improve the kidney-related pathological state. These effects inhibit the development of DN [13]. Some scholars have shown that Guizhi Fuling pill can inhibit the development of DN and reduce the accumulation of AGES as well as the quality of peroxidative lipid in renal tissue [14].

4.3. Taohe Chengqi Decoction
Clinical basic research indicates that Taohe Chengqi Decoction can act on multiple signaling pathways, affecting the expression of inflammatory factor gene levels. Deng Xiaofeng reported that Taohe Chengqi Decoction could reduce the levels of serum inflammatory factors IL-6 and TNF-α by inhibiting the activation of NF-Kbp65 and the expression of MCP-1 mRNA and VCAM-1 mRNA [15]. Gu Yumei et al. have observed that Modified Taohe Chengqi Decoction has a preventive effect on the macrovascular disease in DN. It can also decrease blood sugar and blood lipid. The mechanism may be linked to inhibition of PI3K/Akt signaling pathway and reduction of PI3K/Akt mRNA expression [16]. Xu Yang et al. have observed that Modified Taohe Chengqi Decoction could improve micro inflammatory state and delays the development of CRF by decreasing the levels of serum CRP, TNF-α and IL-6, correcting the anemia and improving glomerular and tubular dysfunction [18].

4.4. Dahuang Zhechong Pill
Modern pharmacological studies have confirmed that Dahuang Zhechong Pill (DZP) have shown good effects on animal models of diabetic nephropathy. Treatment groups were divided into high-dose and low-dose group, and Tripterygium willordii was used as the positive control group, Sunwei et al. showed that DZP could delay the progression of chronic glomerular diseases, significantly reduce the urinary protein in the diabetic rats, and the high-dose group could reduce the blood urea nitrogen (BUN). In treatment groups, the inflammatory cell infiltration of the renal pathological tissues, the inhibition of the proliferation of the mesangial cells and the reduction of the interstitial fibrosis were inhibited, and the improvement effect of the high-dose group was more obvious [19]. Wang Guoxian's study showed that DZP could prevent the generation of blood stasis by inhibiting platelet activation and decreasing whole blood viscosity. Meanwhile, DZP can maintain the dynamic balance between coagulation and fibrolysis system, increasing the level of t-PA, 6-KetoPGF1α and decreasing the value of PAI [20].

4.5. Didang Decoction
Didang Decoction is mainly composed of leeches to breaking stagnant and eliminating blood stasis. It was noted that Didang Decoction could improve renal damage in DN rats and effectively reduce the expression level of IL-1β protein and gene in diabetic rats [21].
5. Evaluation and Outlook

In conclusion, modern medicine considers the influencing factors of DN mainly include glucose and lipid metabolism disorder, hemodynamic abnormalities, oxidation, inflammatory medium, cytokine, signal path activation and so on, among which the degree of the inflammatory response and oxidative stress is a reliable means for early diagnosis and treatment of DN.

Therefore, actively looking for drugs to prevent the activation and expression of inflammatory factors is expected to delay the progress of diabetic nephropathy and better prevent and treat DN. Chinese medicine has an advantage in the treatment of DN. And there are more clinical studies and less basic research. Currently, in terms of basic research, we tend to investigate single traditional Chinese medicine, while the Jingfang compound is difficult to study due to its complex composition. The basic research on Jingfang or traditional Chinese medical compound, which has relatively few researches on diabetic nephropathy, mainly focuses on the observation of inflammatory cytokines and other phenomena, and there are few reports on more in-depth research on signal pathways. Future research on the mechanism of Jingfang of Promoting Blood Circulation and Removing Blood Stasis in the treatment of DN from the cellular, molecular and gene levels will open up a new path for the clinical prevention and treatment of diabetic nephropathy and the development of proprietary Chinese medicine.

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References

[1] Li Lan, Li Jianwei. Glucose and lipid metabolism of diabetic nephropathy patients and their relationship with renal function, inflammation [J]. Journal of Hainan Medical College, 2017, 23(10):1341-1343.
[2] Chen Zhiqiang, Fang Jing, Xu Jing, et al. Effect of Huayu Tongluo Traditional Chinese Medicine on skeleton protein in podocytes of rats with diabetic nephropathy [J]. Natural product research and development. 2016, 28:1540-1544, 1584.
[3] Huang Jie, Cui Yunzhu. Research on the treatment of diabetic nephropathy by JingFang [J]. Shaanxi Journal of Traditional Chinese Medicine, 2014, 35(6):768-769.
[4] Nan Zheng. A brief explanation of the mechanism of diabetic nephropathy by kidney-collaterals impaired by toxin [J]. Jilin Traditional Chinese Medicine, 2007, 27(1):8-10.
[5] Nan Zheng. A brief explanation of the mechanism of diabetic nephropathy by kidney-collaterals impaired by toxin [J]. Jilin Traditional Chinese Medicine, 2007, 27(2):10-12.
[6] Wu Yiling, Wei Cong, Jia Zhenhua, et al. Discussion on the pathogenesis of diabetic nephropathy from collateral disease theory [J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine, 2007, 13(9):659-660.
[7] Liu Shangjian, Wang Cui, Wang Yaoxian, et al. Theory exploration of Micro Mass in Kidney Channel [J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine, 2009, 15(09):649-650.
[8] He Yuhua, Zhao Liangbin, Li Mingquan. A new theory on the pathogenesis of "three times of differentiation of pure substance from turbid one" in diabetic nephropathy. New Chinese Medicine, 2013, 45(9):6-8.
[9] Wang Lihua, Liu Liju, Yang Pengpeng, et al. Effect of Qutan Tongluo Decoction on protein expression of endoplasmic reticulum stress in renal of diabetic nephropathy rats [J]. Chinese medicine emergency, 2016, 25(9):1667-1670.
[10] Zhang Lizhen, Zhao Yunfang, Wang Yihua, et al. Study on the mechanism of protection of JDSS on the early diabetic nephropathy [J]. Practical Journal of Internal Medicine, 2011, 25(1):26-28.

[11] Wang Deng. Effects of Neu-p11 and Danggui-Shaoyao-San on glucose and lipid metabolism and the mechanism mediated by the HPA axis in chronic stress rats with high-fat diet [D]. Gansu University of Traditional Chinese Medicine. 2015.

[12] Gao Shirong. Review of pharmacological function and clinical application of Cinnamon and Poria Pill [J]. Henan Traditional Chinese Medicine, 2016, 36(2):358-359.

[13] Su Peiyong, Wang Jian. Research progress of Guizhi Fuling Pills [J]. Pharmacology and Clinics of Chinese Medicine, 2015, 31(1):356-357.

[14] Nakagawa T. Effect of Guizhi Fuling Pill on diabetic nephropathy [J]. Trad Med, 2002, 19(6):200-208.

[15] Deng Xiaofeng. Effect of modified Taohe Chengqi Decoction on prevention diabetic macroangiopathy in mice based on the NF-κB pathway [D]. Guangzhou University of Traditional Chinese Medicine, 2016.

[16] Gu Yumei, Zhu Zhangzhi, Xu Shuai, et al. Effects of Modified Taohe Chengqi Decoction on blood glucose, blood lipid and macrovascular lesions in diabetic rats [J]. Chinese Journal of New Drugs and Clinical Pharmacology, 2017, 28(5):86-90.

[17] Xu Yang, Wang Jun. The effect of Taohe Chengqi Decoction on the vascular expression of Toll-like Receptor in Rats with Diabetes [J]. Chinese Journal of Integrated Traditional and Western Medicine, 2017, 23(1):60-64.

[18] Su Meiling. Effect of Taohe Chengqi Decoction on the micro-inflammation state of chronic renal failure rats [D]. Fujian University of Traditional Chinese Medicine: 2016.

[19] Sun Wei, Zhu Xuanxuan, et al. Protective effect of Dahuang Zhechong pills on the improved adriamycin nephropathy mouse models [J]. Chinese Traditional Patent Medicine. 2006, 28(1):81-85.

[20] Wang Guoxian. The effects of Dahuang Zhechong Pill on the activation of blood stasis type rat platelet and the correlation factors [D]. Hebei Medical University. 2015.

[21] Chang Bai, Li Chunshen, Tan Junzhen, et al. Effect of early intervention with didang decoction on the expression of PEDF and IL-1β in the retina of diabetic rats [J]. Journal of Practical Diabetes, 2016, 12(6):53-55.