

Research on the Mechanism of Tripterygium Wilfordii in Intervening Diabetic Nephropathy Development

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Abstract. The most prevalent and dangerous microvascular consequence of mellitus diabetes is diabetic nephropathy (DN). DN, the primary cause of end-stage renal disease, can develop in around half of diabetes people. Through anti-oxidative stress, anti-inflammatory response, and anti-fibrosis mechanisms, Tripterygium wilfordii (TW), a traditional Chinese medicine considerably slows the evolution of DN. In this paper, the pathogenesis of DN and the pathway of TW in delaying the progression of DN were described. From the aspects of clinical research and experiment, Tripterygium wilfordii polyglycosides (TG) combined with angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB) can be used in the treatment of DN, and the efficacy is better than ACEI/ARB alone. Nevertheless, its toxic and negative consequences limit its clinical application, and it is necessary to optimize the dose and duration of treatment to balance the risk. Future research should focus on improving the targeting of nano-drug delivery systems, and explore the combination strategy with liver protective drugs to achieve the goal of clinical transformation of enhanced efficacy and attenuated toxicity.

Keywords: Tripterygium Wilfordii, Diabetic Nephropathy, Oxidative Stress, Inflammation

1. Introduction

Currently, there are about 240 million people with Diabetes Mellitus (DM) worldwide, which is expected to climb to 642 million by 2040. As an important disabling and fatal disease, diabetes is a major risk factor for cardiovascular and cerebrovascular diseases, blindness and renal failure, leading to about 1.5 million deaths every year [1]. Among the many complications of diabetes, Diabetic Nephropathy (DN), as a serious microvascular disease, has a high morbidity and mortality. Compared to diabetic individuals without nephropathy, those with DN had an estimated 30-fold higher overall death rate. End-stage renal disease (ESRD) develops 14 times faster than other kidney diseases after the disease reaches the level of obvious proteinuria. It is now the main cause of ESRD in China's middle-aged and older population, so early intervention is very important [2].

Oxidative stress, inflammation, fibrosis, autophagy, mitochondrial damage and other pathways contribute significantly to the pathophysiology of DN. The traditional Chinese medicine (TCM) Tripterygium wilfordii (TW), Its active ingredients, such as Triptolide and tripterygium glycosides (TG), can delay the progression of DN by regulating key signaling pathways, and their multi-target effects (including anti-inflammation, anti-oxidative stress, anti-fibrosis, etc.) have shown significant

potential in delaying the progression of DN and even playing a therapeutic role. Some clinical trials have proved that TW plays a significant role in the treatment of DN and has more advantages than traditional drugs ACEI/ARB. On this basis, some studies showed that the clinical efficacy of TW combined with ACEI/ARB drugs was better than that of traditional ACEI/ARB drugs, which further proved the clinical potential of TW. However, some toxic side effects have been found in the clinical efficacy of TW, and no studies have clearly pointed out the effective methods to avoid the risk of side effects or the means to reduce the severity and probability of the side effects.

Therefore, this article aims to systematically review the molecular mechanism and clinical efficacy of *Tripterygium wilfordii* in the treatment of DN, explore the nanotechnology oriented medication strategy, and provide theoretical basis for promoting its clinical safe transformation.

2. Oxidative stress and inflammation drive kidney injury and fibrosis

Despite the complexity of the DN development, oxidative stress, inflammation, and autophagy are thought to be core driving factors [3]. At the same time, podocyte injury, mitochondrial dysfunction and glucose and lipid metabolism disorders further aggravate the damage of kidney structure and function.

Oxidative stress is widely considered to be one of the core mechanisms of DN, and high glucose environment induces it through multiple pathways [4]. Firstly, the increased aldose reductase activity and the inhibition of sorbitol dehydrogenase activity in the polyol pathway lead to the accumulation of sorbitol in cells, increase the permeability of cell membrane, and trigger the efflux of key intracellular substances like decreased glutathione and inositol, as well as ultimately cause this circumstance. Secondly, advanced glycation end product (AGE) synthesis and the expression of the receptor for AGEs (RAGE) can both be directly accelerated by hyperglycemia. When AGEs bind to RAGE, they can further activate oxidative stress. In addition, excess fructose-6-phosphate (F6P) in the route of glycosamine is transformed into uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), a substrate that mediates the O-linked N-acetylglucosamine (O-GlcNAc) glycosylation modification of proteins. Abnormal elevation of intracellular O-GlcNAc levels can interfere with mitochondrial function and promote the production of reactive oxygen species (ROS). Finally, protein kinase C (PKC) pathway activates a variety of PKC isoforms in high glucose environment, stimulating the production of intracellular ROS and aggravating oxidative stress [4].

In the development of DN, oxidative stress response is dominated by a precise regulatory network. Its core includes pro-injury mechanisms including phosphocarnosine 3-kinase/protein kinase B (PI3K/Akt), nuclear factor kappa B (NF- κ B), transforming growth factor β 1 (TGF- β 1) and Janus kinase (JAK)/signal transducer and activator of transcription 3 (JAK2/STAT3). These pathways jointly promote the pathological process of DN by promoting fibrosis, enhancing inflammatory response and inhibiting autophagy [4]. In contrast, protective pathways such as Nuclear factor erythroid 2-related factor 2/antioxidant response elements (Nrf2/ARE) and Adenosine monophosphate-activated protein kinase (AMPK) combat oxidative stress damage by enhancing antioxidant defense, reducing inflammation, and promoting cytoprotective mechanisms (such as autophagy) [4]. In addition, the activation of endothelin-1 receptors (ETARs) has also been confirmed to induce oxidative stress response and take part in DN's development [5].

In the progression of DN, fibrosis and inflammation promote each other to form a closely related pathological axis. The central hub of this axis lies in the primary factor causing inflammation and tissue fibrosis is the TGF- β 1 signaling pathway. The central role of TGF- β 1 signaling can be driven by oxidative stress, AGEs/ ROS-mediated oxidative stress can significantly up-regulate TGF- β 1 expression, and can also be induced by fibrosis. The activated TGF- β 1 pathway promotes the

expression of various intracellular factors (such as fibrotic cytokines and protein kinases), leading to excessive deposition of extracellular matrix (ECM). In addition, one of the main factors causing the epithelial-mesenchymal transition (EMT) is TGF- β 1, which further aggravates the fibrosis process [4]. TGF- β 1 can also play a role through signal transduction. After binding to its receptor, Tgf- β 1 mainly activates the downstream maternal anti-epidermal growth factor-like domain 2/ maternal anti-epidermal growth factor-like domain 3 (SMAD2/SMAD3) signaling molecules. The traditional method of mediating fibrosis involves phosphorylated SMAD2/3 establishing a complex with SMAD4 and transposing into the nucleus to control the expression of gene targets [5]. Key pro-inflammatory signaling pathways can play a synergistic role, including one important avenue for starting inflammation is the NF- κ B signaling pathway. Toll-like receptors (TLRs) recognize their ligands (such as DAMPs and PAMPs), triggering an innate immune response and activating downstream TLRs signaling and inflammatory effects. This process promotes the polarization and infiltration of M1-type macrophages. It also strongly activates the NF- κ B transcription factor. Activated NF- κ B translocates into the nucleus and induces the production of numerous pro-inflammatory cytokines, including TNF-, IL-1, and IL-6, chemokines, and adhesion molecules, triggering a strong inflammatory cascade that continues to damage renal tissue [4,5]. JAK2/STAT3 signaling pathway can play an amplified role through cytokines. Finally, The PI3K/AKT signaling pathway has a bidirectional regulation, and its activation can be induced by upstream inflammatory signals and participate in the regulation of NF- κ B and other pathways. In addition, the Pi3k/Akt/mTOR signaling pathway is also involved in fibrosis. Studies have shown that high glucose levels can induce reactive oxygen species production in renal tubular epithelial cells NRK-52E, stimulate the synthesis of TGF- β 1 and the activation of Akt, which phosphorylates mTOR. It contributes to NRK-52 E cell EMT and exacerbates diabetes-related renal fibrosis [4].

The excessive production of vascular endothelial growth factor A (VEGF-A) by diabetic podocytes in an environment with reduced endothelial NO is also thought to be the main driving force of DN [6]. Lipotoxicity, hemodynamic abnormalities, mitochondrial dysfunction (mitochondrial DNA damage, mitochondrial respiratory chain damage, mitochondrial dynamics changes, etc.), autophagy dysfunction, pyroptosis and calcium channel abnormalities can cause podocyte injury [7,8]. In addition, hyperglycemia and disorders of glucose and glucose/lipid metabolism homeostasis driven by hyperglycemia gradually promote structural and functional changes in the kidney [5].

3. Multi-target mechanism of action of tripterygium wilfordii

A total of 144 chemical components of TW were evaluated using the TCMSP analytic tool and pharmacology database, of which 51 were active components, mainly alkaloids and terpenoids. Triptolide, triptolide, demethylzelacrylate and celastrol are used for DN treatment [6]. Studies have shown that TW's therapeutic mechanisms for DN are primarily enriched in five areas, including immunological modulation, oxidative strain, the inflammatory process, and anti-vascular disease [6,9].

3.1. Anti-inflammatory effect

TW can regulate many inflammatory factors. Studies have shown that in the model of DN created by unilateral nephrectomy and intraperitoneal streptozotocin (STZ) administration, TW can inhibit the over-expression of TNF- α , IL-1 β and TGF- β 1 in the kidney. In another model, which was brought on by high-fat high-sugar diet and low-dose STZ injection, by decreasing TGF- β 1 activity and the invasion of ED1-positive macrophages in the kidney, triptolide decreased proteinuria and

podocyte damage. According to a different study, it may also prevent macrophage infiltration in the kidney of diabetic rats and harmonize Th1 and Th2. In conclusion, triptolide extract has anti-inflammatory effect, which can not only regulate TNF- α , IL-1 β , TGF- β 1 and other inflammatory factors, but also regulate Th1, Th2, macrophages and other inflammatory cells [6,9].

3.2. Anti-oxidative stress

Triptolide has been shown in earlier research to lessen oxidative stress in the kidneys of db/db mice, which shows up as a decrease in the production of 4-HNE generated by intracellular oxidation of lipids. Triptolide can also effectively reduce superoxide dismutase and oxidative carbonyl protein generation in the kidney of DN rats [6]. A large amount of ROS can not only cause fibrosis, but also induce mitochondrial oxidative stress and lead to mitochondrial abnormalities, which plays a crucial role in the evolution of DN [10]. Therefore, in addition to triptolide, the antioxidant effect of TW extract, kaempferol, celastrol and nobiletin is of great significance in the therapeutic effect of DN [6,9].

3.3. Anti-fibrosis

According to a research, triptolide may lessen diabetic kidney fibrosis via restoring autophagy. Further studies showed that it may induce the up-regulation of PTEN and the down-regulation of Akt and mTOR by inhibiting the suppressing the levels of miR-141-3p. Another study demonstrated that the same TW extract could improve EMT by down-regulating miR-188-5 p followed by inhibiting PI3 K/Akt pathway by increasing PTEN. In addition, recent studies have found that it inhibits PTENK27-polyUb mediated EMT in renal epithelial cells [7,8]. These studies all indicate that triptolide has an anti-fibrotic effect, and its intracellular mechanism is closely related to autophagy, PI3K/Akt pathway, and regulation of PTEN ubiquitination [6,9].

3.4. Anti-glomerulosclerosis

By upregulation of miR-137, triptolide inhibits Notch1 pathway, reduces ECM accumulation in glomerular cells, and regulates mesangial cell hyperplasia through PDK1/Akt/mTOR mechanism. Therefore, TW's ability to prevent glomerulosclerosis may be linked to the p38 MAPK, NF- κ B, Notch 1, and Akt signaling processes [6].

Therefore, the active ingredients of TW in the treatment of DN mainly rely on anti-inflammation, anti-oxidation, anti-fibrosis and anti-glomerulosclerosis. The intracellular and extracellular action pathways involved include Notch1 and AKT pathways, etc., and there is more sufficient evidence that the action pathway of TW is related to the AKT pathway [6,9].

4. The balance of the clinical efficacy and toxicity

In the clinical trial, a small prospective randomized controlled trial (RCT) directly compared the efficacy of TW with the standard-of-care drug valsartan in patients with DN. The results showed that mean urinary protein levels decreased significantly by 34.3% in patients treated with TW (120 mg/d for the first 3 months and 60 mg/d for the second 3 months). In contrast, the standard drug treatment (160 mg/ day for 6 months) resulted in a mean reduction in urinary protein of only 11.7% [6,9]. The results suggest that TW monotherapy may be superior to ARB monotherapy in reducing proteinuria. More intensive studies focused on the combination of tripterygium wilfordii polyglycosides (TG) and traditional cornerstone drugs (ACEI/ARB) for DN and showed better efficacy: TG in

conjunction with ACEI/ARB medication can more effectively lower the 24-hour urine total protein (24h-UTP) level, raise serum albumin, and improve serum creatinine (SCr) levels than ACEI/ARB monotherapy [11]. Specifically, in the study of combined treatment with TG and ARB (such as valsartan), the statistical improvement in reducing 24h-UTP, urinary albumin excretion rate (UAER) and improving SCr level was noticeably greater in the group receiving combination treatment than in the group receiving ARB monotherapy [12]. Another study explored in depth the effects of ARB monotherapy versus irbesartan combined with TW therapy on urinary protein and podocyte-related biomarkers. Studies have found that ARB combined with TW treatment is significantly better than ARB monotherapy in decreasing the excretion of urine protein, urine podocytes, and urine connective tissue growth factor (CTGF) /TGF- β 1 levels [6]. This further supports the superiority of combination therapy in terms of podocyte protection and anti-fibrosis.

Although the above results highlight the therapeutic potential of TW, its clinical application still faces multiple challenges. Damage to the kidneys, gastrointestinal responses, irregular menstruation, and other issues are among the dangers of systemic poisoning [6]. Combined treatment studies revealed that The frequency of negative responses of TG combined with ACEI/ARB regimen was significantly higher than that of monotherapy (especially liver injury) [11,13]. An analysis of DKD treatment showed that 9 out of 10 systematic reviews clearly reported that TG combination therapy increased the risk of adverse reactions [13]. Extreme cases warn that acute renal failure and even death have occasionally been reported with high doses of medication [6]. These evidences suggest that TW's remarkable efficacy coexists with its multisystem toxicity, severely limiting its clinical promotion. In order to balance the efficacy and safety, some countermeasures have been proposed in current studies: precise dose control, following the principle of "stopping the disease when it occurs", and adopting a gradual dose reduction strategy (such as the initial 120 mg/ day and 60 mg/ day after 3 months) [6]; The continuous medication cycle should be controlled within 3 months to avoid the risk of long-term exposure. Compatible with protective drugs, combined with immunomodulators (such as *Cordyceps sinensis*, *Ganoderma lucidum*); Hepatoprotective ingredients (such as extracts of milk thistle and *Polygonum cuspidatum*) are added [14]. In summary, TW has been proved to have great potential in the treatment of DN, but the side effects associated with its application have limited its wide clinical application. With the progress of research, some methods to deal with the side effects have been proposed, which will pave the way for the routine clinical application of TW in the future.

5. Conclusion

It has been found that the development of DN is significantly influenced by oxidative stress, inflammation, fibrosis, as well as podocyte damage. TW and its active ingredient extracts have been shown to be the preferred drugs for multi-target treatment of DN through their anti-inflammatory, anti-oxidative, anti-fibrosis and podocyte repair mechanisms. TW combined with ACEI/ARB can improve the therapeutic effect and delay the progression of DN, which provides a new direction for the treatment of DN in the future years. But because of the adverse effects of treatment, TW's clinical use is restricted. Therefore, future TW drug research can focus on the elucidation of the mechanism of TW toxicity or the development of TW nanoparticles targeting glomerular endothelium for precise delivery of lesions to achieve synergistic improvement in efficacy and safety.

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