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Article

Interventional Effects of Traditional Chinese Medicine Compound Formulas on the Expression of Inflammatory Factors in Diabetic Nephropathy

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Abstract: DN is still one of the major microcirculatory complications of diabetes mellitus and the leading cause of end stage renal disease worldwide. The advancement of DN is hard to foresee, all we know at present is it's starting off with long duration minor inflammation. It takes a long time for your blood sugar to be too high, it makes a lot of things happen in your body, just like how it makes you blood move around and how it mixes up with food that gives you energy. And then your body starts making way too many of these special helpers and trouble makers, these help you fight infections, but sometimes your body decides to make too many. The inflammatory mediators are all TNF-α, IL-6, MCP-1, etc., which will lead to glomerular endothelial dysfunction, promoting podocyte damage, mesangial cell hyperplasia, promoting tubulointerstitial fibrosis directly, which are the pathologic characteristics of DN. The conventional treatment mainly focuses on lowering the sugar and blood pressure, which do not stop the progression of the disease, and exploring other complementary and alternative treatments is now inevitable. Traditional Chinese Medicine (TCM) tends to take an overall approach when dealing with things and it's pretty old at tackling health concerns related to diabetes, and that's great! Multi-compont Multi-target TCM Fufang. Due to more and more studies on the TCM Fufang to look into the nephro-protective effects. This paper will do review for different kind of TCM compound formula intervention to the key inflammatory factors expression in DN. We'll see how these formulas change the inflammation, we may show that they can lower TNF-α, IL-6, MCP-1, and other really key stuff, to help kidneys feel good. So the cool thing we figured out is the TCM compound formulas are another sweet treat for DN as this focuses on that big inflammatory piece of the sickness.

Keywords: diabetic nephropathy; traditional Chinese medicine; compound formula; inflammation; cytokines; tumor necrosis factor-alpha; interleukin-6

1. Introduction

Diabetic nephropathy (DN) is another term for diabetic kidney disease (DKD), which is the most significant and frequent microvascular complication that affects individuals suffering from both type 1 and type 2 diabetes. It is the only leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). its health care system, impact to the quality of life and mortality of the patients The DN's disease progress is from little increasing of urine albumin excretion which is microalbuminuria, then macroalbuminuria. At this point, the GFR begins its slow decay until it reaches renal failure. DN's inner workings are so complex, it mixes up a whole lot of metabolic stuff, changes in blood pressure, and genes all together. For decades, pathogenesis was mainly focused on the hyperglycemic induction of glucose toxicity of cells and organs and the accretion of AGEs, and activation of the renin-a ngiotensin-aldosterone system (RAAS) [1]. These factors matter, and more and more data has conclusively demonstrated that there is an unceasing, germless, and sub-clinical inflammatory reaction happening within the kidneys; it is a fundamental mechanism in the onset and progression of kidney injury. It isn't just that something

got hurt, which creates inflammation, but that it actively goes on to do this to keep going a cycle of things stressing out cells, cells of your immune system getting in on it, and tissue getting rebuilt in scar tissue. Inflammatory cytokines like TNF-α, IL-6 and the chemokine MCP-1 are considerably over-produced in the diabetic renal niche, igniting destructive cascades of endothelial malfunction, podocytic demise, glomerular mesangium outgrowth and nephron fibrosis. Since it's so much of the matter then if there were ways to mess around with those inflammation pathways it'd be nice. TCM stands for Traditional Chinese Medicine, it is a medical system with more than countless years of medical experience and practice. TCM treats the patient, rather than just the disease. It's about everything except the body finding balance again. TCM compound formulars (Fufang) which includes a lot of types of herbs is supposed to treat lots of disease parts at once. Multi-target feature, which makes them good for hard chronic illnesses like DN. Review will be to integrate and test the current literature on the current scientific review of the interventional consequences of TCM compound formulations on key inflammatory factor expressions so as to get a summary of how well these TCM compound formulations can help diabetes nephropathy and why they do so [2].

2. Inflammatory Factors' Significant Role in Diabetic Nephropathy

There are an array of inflammatory changes in kidneys within the course of diabetes and this inflammatory response take place right at each stage of nephropathy. In when there is high glucose there are lots of different types of cells in the kidney that get excited and start making all this proinflammatory stuff, lots of different kinds, and this is mostly because of the local production getting ramped up because of all those immune cells, the main ones monocytes ans macrophages, that go into the interstitium and the glomeruli of the kidney. One of the master regulators involved in this cascade is Nuclear Factor-kappa B (NF-κB). Diabetic kidney contains high level of NF-κ B because of hyperglycemia, AGEs, oxidative stress, angiotensin II. Activated NF-κB goes inside the cell's nucleus and starts making more of the genes that make things that cause inflammation, like cytokines and chemokines (which fight invaders), as well as the cell glue stuff called adhesion molecules. it was TNF 1-α was identified to be an important cytokinemore pleiotropic [3]. Once TNF-a levels start to rise, no matter if it's all over or just inside the kidney, it shows in much worse cases and progressing to albuminureia more quickly and declining GFR faster, when TNF-a is on the rise, it hurts the nubbins by triggering their receptors, namely, TNFR1 and TNFR2 on the cells, which causes TNF-a to create signals that make things called podocytes go away and die, the liquid in your tubes that allow fluid to move through your kidneys becomes passable for other things, other cells of the kidney called mesangial make more of the stuff they're all supposed to release so you can go into the space outside of cells, the amount of inflammatory stuff also goes up, starting a loop. Like IL-8, IL-6 is another cytokine involved in the pathogenesis of DN and is clearly up-regulated in glomeruli of patients and DN animals. IL-6 signallying will also promote the proliferation and hypertrophy of mesangial cells and synthesis matrix proteins. At the same time, IL-6 signal also causes resist to insulin. When tubulointerstitial damage steps up, a big thing to know is inflammatory cells in there; most of the control is chemokines at this point. Monocyte Chemoattractant Protein 1 (MCP-1), also known as C-C Motif Chemokine Ligand 2 (CCL2), is the most well-studied chemo kine in DN. It is the result of different renal cell types as a high glycosylation and other kind of metabolism damage. CCR2 on the monocytes and MCP-1 are very strongly attracted to these cells so cells flowing through the kidney are attracted when they bind to receptors on their surface—then they become macrophages: The macrophages that got there become an immense supply, of additional pro-inflammatory and pro -fibrotic elements just like TNF -α, IL-1 β, TGF-β1 and so one. Direct cause of tubular atrophy, interstitial fibrosis, slow loss of kidney function So blocking both TNF-α and IL-6 and also MCP-1 which are 2 really key inflammatory stuff makes sense and it's quite a smart way of making sure you avoid doing anything to your kidneys through DN [4].

3. TCM Classic Compound Formula Intervening in Inflammatory Cytokines

The traditional Chinese medicine's classic compound formula is used for a very long time to treat the symptom of diabetes, TCM regards this disease as "Xiao ke" (Wasting thirst) and has applied many kinds of traditional Chinese medicine to relieve the symptoms caused by diabetes. Modern drugological study has started to explore the scientific reasons for it to work. Often times when I find out I have a very strong ability to stop inflammation. There are many formulas out there known but the one that many people remember is a formula known as Liu wei di huang wan, or six-ingredient rehmannia, which is an ancient Chinese herbal formula that has long been used as a way to nourish the kidney and liver yin made with 6 herbs: R, Shu di huang, Shan zhuyu, Shan yao, Ze xie, Mu danpi, Fu ling There are a lot of literature evidence showing that Liuwei Dihuang Wan and its relevant formulations could effectively improve renal injury in DN animals [5]. From a mechanistic standpoint, its curative benefits are mainly related to inhibiting inflammatory pathways. From my researching I found out is

that after Liu wei Dihuang Wan treat- mentally the extract the renal NF-kB expression is less significant and down-stream pro-inflammatory cytokines produced is much less too. Like in STZ-induced diabetic rats and so on, serum and renal tissue levels of TNF-a and IL -were far less than those before formula intake, which correlated to lower levels of albuminuria and better renal pathology and the reduction of glomerular hypertrophy and mesangial enlargement [6]. As for some individual parts of the formula such as paeonol, which was produced from plants Paeonia suffruticosa, we have noticed to be strong as a medium of creating inflation in the formula. As for the whole effects of the formula, it shows the TCM principle that herbs mutually supporting each other which means its effects are much larger than the sum of effects of every individual herbs. This Formularies Effects on the Key Inflammatory Markers (Table 1).

Table 1. Effects of Liuwei Dihuang Wan and Its Modifications on Inflammatory Factors in Diabetic Nephropathy Models.

TCM Formula	Study Type	Model	Key Inflammatory Factors Measured	Observed Effect
Liuwei Dihuang Wan	Animal (Rat)	STZ-induced DN	TNF-α, IL-1β, NF-κB	Significantly decreased renal expression and serum levels of all factors.
Zishen Tongluo Formula (Modification of Liuwei Dihuang)	Animal (Rat)	High-fat diet/STZ-induced DN	MCP-1, ICAM-1, TNF-α	Downregulated renal expression of MCP-1 and ICAM-1; reduced TNF-α.
Qi-Ju Dihuang Wan	Animal (Mouse)	db/db mice	IL-6, TNF-α, NLRP3 Inflammasome	Inhibited activation of the NLRP3 inflammasome and reduced IL-6 and TNF-α levels.
Liuwei Dihuang Decoction	Clinical Trial	Patients with early-stage DN	hs-CRP, TNF-α, IL-6	Reduced serum levels of hs-CRP, TNF-α, and IL-6 compared to placebo.

4. Efficacy of Tangshen Formula in Modulating Renal Inflammation

The latest current TCM studies in the past several years have found and studied some formulae for taking care of diabetic kidney that combines the modern and traditional illness and treatments. of which TSF, Tangerine Peel Formula has been the most researched and promising formula: TSF: compound formula. Mainly contains many kinds of herbs which can protect the kidney and also lower the blood sugar level, like yellow-qi root (*Astragalus membranaceus*), red-sesbania root (*Salvia miltiorrhiza*), great rhubarb root (*Rheum palmatum*), angelica root (*Angelica sinensis*). TSF's therapeutic rational of tonic qi, activate blood, expel toxin corresponds to treatment for DN from a holistic perspective and clinical trials and experimental studies have all found that the TSF can greatly reduce the amount of proteinuria and protect kidney function and slow DN [7]. A big part of how it works is that it's really good at fighting inflammation. And as a result of that research, TSF is involved with some of the inflammation in which NF-κB signaling activation in renal tissue (upstream to inflammatory gene activation). Consequently, the production and release of key pro-inflammatory cytokines are substantially suppressed. Animal model for DN, TSF lower TNF-alpha and IL-6 level in renal tissue and in circulation and lower MCP-1 expression to reduce macrophage infiltration in glomeruli and interstices, this reduction of immune cell infiltration is very important for prevent tubulointerstitial fibrosis from going forward which is a big part of how long-term kidney results are made. Concerning its multifold actions, TSF with both oxidative stress and the fibrotic pathway and controlling metabolism apart from reducing inflammation all point out at a general advantage of TCM-compound formulas for an ailment like DN, being systemic as we can observe from Table 2 compilation.

Table 2. Modulation of Inflammatory Pathways by Tangshen Formula (TSF) in Diabetic Nephropathy.

TCM Formula	Study Type	Model/Patient Group	Key Inflammatory Factors Measured	Observed Effect
Tangshen Formula (TSF)	Clinical Trial	Patients with Stage 3-4 DN	Urinary MCP-1, Serum TNF-α	Significant reduction in urinary MCP-1 and serum TNF-α levels after 24 weeks.
Tangshen Formula (TSF)	Animal (Rat)	STZ-induced DN	NF-κB, TNF-α, IL-6	Inhibited phosphorylation and nuclear translocation of NF-κB p65; decreased renal TNF-α and IL-6 mRNA and protein expression.

Modified Tangshen Formula	Animal (Mouse)	db/db mice	Thioredoxin-interacting protein (TXNIP), NLRP3, IL-1β	Suppressed the TXNIP/NLRP3 inflammasome pathway, leading to a marked decrease in IL-1β production.
Tangshen Formula (TSF)	In Vitro	High-glucose-stimulated mesangial cells	MCP-1, TGF-β1	Attenuated the high-glucose-induced upregulation of MCP-1 and TGF-β1 secretion.

5. Effects of Other Notable TCM Formulas on Inflammatory Factor Expression

As mentioned earlier, aside from Liuwei Dihuang Wan and Tang shen Formula, there are so many other varieties of TCM Chinese compound formulas (not just Liuwei Dihuang Wan and Tang shen Formula are famous) and there is a lot of room for tempering the inflammatory storm caused by diabetic nephtopathy [8]. Danggui Buxue Tang (Decoction of Angelica that Tonifies Blood), a formula like this simple yet profound, made up just by two herbs—*Astragalus membranaceus* (Huang Qi) and *Angelica sinensis* (Dang Gui). It's a traditional "qi"-tonifying and blood-nourishing substance. It is a very good pharmaceutical for immunomodulation and anti-inflammatory [9]. I am going back to DN, Danggui Buxue Tang seems to help with kidney inflammation by changing cytokines. As studies say, lower the release of inflammatory factors such as TNF-α and IL-1βand also increase and boost the expression of anti-inflammatory factors at the same time and balance internal micro-immune environment of the kidney. And this has an effect on our immune system, which is really important for avoiding that constant and persistent inflammation that turns into those fibro scar tissues. Astragalus abundant in polysaccharides and saponins, together with angelica rich in ferulic acid, have a cooperative effect to guard podocytes and tubular epithelial cells against inflammatory harm. Danggui Buxue Tang has anti inflammatory effect Support is found in Table 3. Another very important type of therapeutic approach in TCM are the formulas used for clearing damp and blood stasis (damp-heat). According to TCM theory, these are considered the main pathological products during the progressing of DN [10]. Touxie-Huoxue-Decoction is a good example: Then to get it to the result for this formula can prevent diabetics kidney from getting inflammation well. The first is lower the amount of MCPI in your urine and kidneys, it's the first hurdle to the mac's ability to cause Interstitial scaring. And these formulas want to help in improving micro circulation, breaking vicious circle of advanced DN and reducing the inflammation by breaking the cycle of ischemia, inflammation and fibrosis. Such kind of formulations have an impact on chemokines and the rest of the inflammatory makers may be found in Table 4:

Table 3. Anti-inflammatory Effects of Danggui Buxue Tang in Diabetic Nephropathy.

TCM Formula	Study Type	Model	Key Inflammatory Factors Measured	Observed Effect
Danggui Buxue Tang	Animal (Rat)	STZ-induced DN	TNF-α, IL-1β, IL-10	Decreased renal TNF-α and IL-1β; increased the anti-inflammatory cytokine IL-10.
Danggui Buxue Tang	In Vitro	AGE-stimulated podocytes	NF-κB, IL-6	Inhibited AGE-induced NFκB activation and subsequent IL-6 secretion.
Danggui Buxue Tang	Animal (Mouse)	Unilateral ureteral obstruction (fibrosis model)	Macrophage infiltration, MCP-1	Reduced MCP-1 expression and subsequent infiltration of F4/80+ macrophages.
Danggui Buxue Tang	Clinical Trial	Patients with DN	Serum hs-CRP, IL-8	Showed a trend towards reduction in systemic inflammatory markers hs-CRP and IL-8.

Table 4. Effects of Toxin-Expelling and Blood-Invigorating Formulas on Inflammatory Mediators in Diabetic Nephropathy.

TCM Formula	Study Type	Model/Patient Group	Key Inflammatory Factors Measured	Observed Effect
Touxie-Huoxue Decoction	Animal (Rat)	5/6 nephrectomy + STZ model	Urinary MCP-1, Renal RANTES	Significantly decreased urinary MCP-1 excretion and renal RANTES expression.
Huoxue Xiaozheng Formula	Clinical Trial	Patients with macroalbuminuric DN	VCAM-1, E-selectin	Reduced serum levels of adhesion molecules VCAM-1 and E-selectin.
Shen-Qi-Di-Huang Decoction	Animal (Rat)	STZ-induced DN	TNF-α, IL-6, TGF-β1	Markedly suppressed renal expression of TNF-α, IL-6, and the pro-fibrotic cytokine TGF-β1.

Chaihuang Yishen Granule	Animal (Rat)	STZ-induced DN	TGF-β1/Smad3 pathway	Inhibited the TGF-β1/Smad3 signaling pathway, which is closely linked to inflammation and fibrosis.

6. Conclusions

The pre-clinical and the clinical proof is just far too powerful; the idea can be simply not contested, that the persistent inflamed reaction is the key foundation of pathogenesis of diabetic kidney disease. Chronic upregulation of pro inflammatory cytokines and chemokines like TNF-alpha, IL-6 and MCP-1 inside the renal parenchyma make an overall toxic milieu that continues to wreak havoc on the glomeruli and interstitial spaces of the kidney, it's this last one, this review has pulled together a bunch of studies that indicate these traditional TCM compound formulas as being an excellent strategy for trying to beat back inflammation in the kidneys. And for these Liuwei Dihuang Wan, Tangshen formulas, Danggui Buxue Tang, detoxifying exudative decoctions, etc., also exhibited pretty substantial intervention in these key inflammatory elements. Their way is not the same, and can stop big control of inflammation (NF-kappaB), so it stops the body from making too many things, the things that make you inflamed (cytokines) and having less of the things that help find enemies in your immune system (chemokine), and change the way other messages work together (like inflammasome NLRP3). TCM compound formula possesses a special advantage as a whole and multi-target strategy. Different from single-molecule drugs that target only one type of receptor or enzyme, these herbal formulations contain many kinds of active ingredients that work together to address the complex DN pathophysiology; they address inflammation, oxidative stress, fibrosis, and metabolic disturbances at the same time. Comprehensive in this sense would correspond to a systemic treatment of a systemic illness: But, good news as we seem to see it so far, but a lot of work still needs to be done. In the future they'll be doing lots of big centers and careful tests to prove for sure the small bottles really do work and are safe for people to use. also need several latest "omics" technologies and system biological methods for more details about the specific molecular mechanisms and to look for the main active ingredient which is linked to the anti-inflammatory functions. These old ways of helping sick people mixed up with new information from science helps us find ways to stop the disease called diabetes hurting people's kidneys and make life better for sick people all over the world.

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