

# Research progress in the treatment of idiopathic membranous nephropathy using traditional Chinese medicine

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## ABSTRACT

This article reviews the most significant literature of the recent years on the treatment of idiopathic membranous nephropathy (IMN) with traditional Chinese medicine (TCM). One major goal of the article is to classify and summarize the research on the clinical aspects and the associated mechanisms of the use of Chinese herbal compounds and single drugs to treat IMN. It was found that TCM treats IMN via two major approaches: by benefiting qi, activating blood circulation and eliminating dampness, or by benefiting qi and nourishing yin. The method of benefiting qi, to activate blood circulation and eliminate dampness for dredging channels, is the most popular. The commonly used drugs in this approach include Huang Qi (astragalus), Dang Shen (codonopsis root), Bai Zhu (white atractylodes rhizome), Fu Ling (poria cocos), Dang Gui (angelica sinensis), and so on. Several randomized, controlled, clinical trials are reviewed in the article, including a multicenter one.

**Key words:** idiopathic membranous nephropathy, traditional Chinese medicine, Chinese herbal compounds, research progress.

## INTRODUCTION

Idiopathic membranous nephropathy (IMN) is a common pathological type of primary glomerular disease in adults. Of all patients with a renal biopsy, IMN accounts for 24.1% of the cases of primary glomerular disease,<sup>[1]</sup> ranking second in terms of incidence after IgA nephropathy. Although the spontaneous remission rate of IMN is 31.7%,<sup>[2]</sup> it will progress to end-stage renal disease in approximately one-third of the patients.<sup>[3]</sup>

Although the etiology and pathogenesis of IMN remain unidentified, most experts believe it to be primarily related to abnormal immune mechanisms. With the discovery of two autoantigens, M-type phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A), our understanding of IMN has entered a new stage, because these two autoantigens are both macromolecular transmembrane glycoproteins expressed in the podocytes. The

fact that they can induce humoral immune responses led by IgG4 makes them suitable for the diagnosis and monitoring of IMN. In addition, the pathological changes introduced by these two antigens are consistent. In the blood of patients with IMN, the rate of positivity to PLA2R antibody is more than 70%.<sup>[4]</sup> About 5–10% of the patients with negative PLA2R antibody expression test positive for THSD7A autoantibodies in the circulation.<sup>[5]</sup>

Hormones combined with either cyclophosphamide (CTX) or calcineurin inhibitors (CNIs) are the main treatment approaches recommended by the KDIGO Clinical Practice Guideline for IMN.<sup>[6]</sup> However, they face the challenges of compromised clinical response rates, high recurrence rates, as well as side effects, such as infection<sup>[7]</sup> and renal impairment,<sup>[8]</sup> often causing patients to be hospitalized repeatedly and even risk their lives. In the recent years, with the continuous progress of theoretical and clinical studies on the use of traditional Chinese medicine (TCM)

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### Access this article online

**Website:**

www.intern-med.com

**DOI:**

10.2478/jtim-2020-0002

**Quick Response Code:**



to manage IMN, the advantages of this approach to the treatment of IMN have been gradually discovered. In addition to a comparable clinical response rate, TCM can better alleviate symptoms such as edema and fatigue by increasing the serum albumin level more rapidly, while introducing fewer adverse reactions when compared with Western medicine.<sup>[9]</sup> According to the TCM, the pathogenesis of this disease is based on qi deficiency of spleen and kidney, the deficiency of both qi and Yin, yang deficiency of spleen and kidney, yin deficiency of liver and kidney, as well as dampness and turbidity, blood stasis, and damp heat.<sup>[10]</sup> This article reviews and summarizes the major Chinese herbal compounds and Chinese patent medicines used in the treatment of IMN.

## LEADING CLINICAL STUDIES ON TREATING IMN WITH TCM

### *Chinese herbal compounds focusing on benefiting qi, activating blood circulation, and eliminating dampness*

The typical clinical manifestations of IMN include edema and proteinuria. On this basis, TCM classifies the disease into the “Edema,” “Fluid Retention Disease,” and “Renal Wind Syndrome” categories. The TCM pathogenesis of IMN is mainly spleen–kidney qi deficiency accompanied with damp-heat and blood stasis. Chen *et al.* conducted a prospective, randomized, controlled, multicenter clinical trial on the use of a comprehensive TCM scheme based on Shenqi Moshen granules (Huang Qi [astragalus], Cang Zhu [black atractylodes rhizome], Bai Zhu [white atractylodes rhizome], Dang Gui [angelica sinensis], Ban Zhi Lian [barbat skullcap], etc.) in the treatment of IMN syndromes. The control group of the trial was treated with hormones + CTX. There were 63 and 69 cases in the treatment and control groups, respectively. After 48 weeks of treatment, the total rate of effectiveness in the treatment group was 73%, consistent with that of the control group. In addition, of the 11 cases with severe adverse reactions 10 were from the control group and only 1 was from the treatment group. This study verified that the adopted comprehensive TCM scheme could effectively reduce urine protein and increase plasma albumin in patients with IMN. It also demonstrated higher safety while improving the patients’ renal functions.<sup>[9]</sup> Another study performed by the group of Renhuan Yu applied the “Jianpi Qushi Heluo” formula (raw Huang Qi [astragalus], stir-fried Bai Zhu [white atractylodes rhizome], Han Fang Ji [stephania root], Dang Gui [angelica sinensis], He Ye [lotus leaf], etc.) for treating 15 refractory IMN cases and followed up the patients for 12 months. Their results indicated that the clinical response rate reached 80%.<sup>[11]</sup>

In a randomized controlled trial that used the Qiling Tongluo formula (Huang Qi [astragalus], stir-fried Bai Zhu [white atractylodes rhizome], Fu Ling [poria cocos], Gui Ban [turtle shell], Chan Tui [cicada moulting], Wu Shao She [black-striped snake], Jiang Can [body of sick silkworm], Di Long [earthworm], Tu Bie Chong [wingless cockroach], Shui Zhi [leech], Quan Xie [scorpion], Qing Feng Teng [*Sinomenium acutum*], Deng Zhan Hua [*Erigeron breviscapus*], Jin Que Gen [Chinese peashrub root], Ling Zhi [reishi mushroom], etc.), 96 low-risk patients with IMN were divided into a Western medicine group (30 cases), an integrated TCM and Western medicine group (33 cases), and a TCM group (33 cases), who were administered valsartan, the combined use of TCM formula and Western medicines, and the Qiling Tongluo formula, respectively. After a 6-month follow-up, the clinical response rate of both the TCM group and the integrated group was more than 80%, whereas that of the Western medicine group was merely 57%. Therefore, the study concluded that both the TCM scheme and the integrated TCM and Western medicine scheme were effective in treating low-risk patients with IMN and were capable of alleviating the patients’ clinical symptoms, reducing urine protein while protecting renal functions.<sup>[12]</sup> In another study, to treat 80 high-risk patients with IMN, the Qiling Tongluo formula was combined with methylprednisolone and CTX. The patients were divided equally into a treatment group (40 cases) and a control group (40 cases), the latter being treated with methylprednisolone and CTX only. After a 6-month follow-up, the clinical response rate of the treatment group was 85%, whereas that of the control group was 60%. In addition, only two cases in the treatment group developed adverse reactions, compared with eight in the control group. The study suggested that the integrated TCM and Western medicine scheme was both more effective and safer than Western medicine alone in treating high-risk patients with IMN.<sup>[13]</sup>

### *Chinese herbal compounds focusing on benefiting qi and nourishing yin*

A single-center trial adopted the Shenqi Dihuang Decoction (Dang Shen [codonopsis root], raw Huang Qi [astragalus], Shu Di Huang [steamed Chinese foxglove root], Shan Yao [Chinese ram rhizome], Fu Ling [poria cocos], Ze Xie [water plantain rhizome], Mu Dan Pi [cortex of the peony tree root], Shan Yu Rou [Asiatic cornelian cherry fruit]) as the main formula to treat 32 qi-yin-deficient patients with IMN. While the 28 cases in the control group were treated with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), the patients in the experimental group were treated with the Shenqi

Dihuang Decoction as the main formula in addition to ACEI/ARB. After 24 weeks of treatment, the total clinical response rate of the experimental group reached 81%, whereas that of the control group was 54%. In addition, although 24-h urine protein quantification and serum albumin level were enhanced after treatment in both groups, the degree of improvement was better in the experimental group.<sup>[14]</sup>

### ***Glycosides of *Tripterygium wilfordii****

Glycosides of *Tripterygium wilfordii* (GTW) is a Chinese herbal extract commonly used for the treatment of nephrotic syndromes. Owing to its anti-inflammatory, anti-immune, antiproliferative, and pro-apoptotic effects, GTW is widely used in the management of a variety of autoimmune and inflammatory diseases. Meta-analysis of the efficacy and safety of GTW in treating IMN indicated that for patients with IMN whose 24-h urine protein quantification was <4.0 g, although GTW was effective, the onset of the effect was slow. Alternatively, for patients with IMN whose 24-h urine protein quantification was >3.5 g, GTW not only exhibited a clinical response equivalent to that of CNI but also demonstrated a lower recurrence rate. Combined treatment of GTW with CNI can correspondingly reduce the dosage of CNI, but it should be noted that GTW may lead to liver impairment, and, therefore, its prescription in women of childbearing age should be approached with great caution.<sup>[15]</sup> Previous clinical trials on the use of GTW to treat IMN showed that GTW could effectively reduce proteinuria in patients with membranous nephropathy (MN).<sup>[16]</sup> Lastly, a study combined GTW with angiotensin II receptor antagonists to treat patients with IMN whose 24-h urine protein quantification was <3.5 g. In the study, the control group was administered losartan potassium tablets once a day at a dosage of 50 mg. After 12 months of treatment, the total response rate of the treatment group was 75%, which was superior to that of the control group. Therefore, the study concluded that the combined treatment of GTW with ARBs could significantly reduce proteinuria in patients with IMN with non-nephrotic syndromes, as well as alleviate adverse reactions.<sup>[17]</sup>

## **STUDIES ON THE MECHANISMS INVOLVED IN THE TREATMENT OF IMN WITH TCM**

### ***Chinese herbal compounds focusing on benefiting qi, activating blood circulation and eliminating dampness***

The Shenqi Moshen granules, which serve to benefit qi, activate blood circulation, and eliminate dampness, function by upregulating the mRNA expression levels

of podocin, podocalyxin, and so on. On this basis, the medication can alleviate pathological damage, including podocyte foot process fusion and GBM thickening in rats with passive Heymann nephritis, and reduce their 24-h urine protein quantification, thereby protecting the podocytes.<sup>[18]</sup>

Alternatively, *in vitro* experiments on podocytes in the serum containing the Jianpi Qushi Heluo formula suggested that by increasing the expressions of marker proteins such as nephrin and podocalyxin in injured podocytes, the medication could reduce the damage to the glomerular filtration barrier. In addition, by inhibiting mTOR activation in injured podocytes, decreasing the synthesis of P-P70S6K and P-4EBP1, and upregulating the expression of LC3-II, it can restore the autophagy levels of the injured cells, thus repairing the injured podocytes. The mechanism by which the Jianpi Qushi Heluo formula reduces urine protein in patients with IMN is related to the protection of the glomerular podocytes.<sup>[19]</sup>

### ***Chinese herbal compounds focusing on benefiting qi and activating blood circulation***

The Yishen Tongluo formula (Huang Qi [astragalus], Dang Shen [codonopsis root], stir-fried Bai Zhu [white atractylodes rhizome], Xian Ling Pi [aerial parts of epimedium], Jiaogulan [*Gynostemma pentaphyllum*], Dang Gui [angelica sinensis], E Zhu [zedoary rhizome], Di Long [earthworm], and Shui Zhi [leech]) has been proven capable of substantially decreasing urine proteins, increasing plasma proteins, and improving blood lipid metabolism in a rat model of MN induced by cationic bovine serum albumin (C-BSA). In addition, it can inhibit the expression of PAI-1, TGF- $\beta$ 1, and ColIV mRNA and that of Hpa, in the renal tissue,<sup>[20-22]</sup> the deposition of immune complexes on the glomerular basement membrane, and the thickening of the basement membrane while upregulating the expressions of nephrin and podocin mRNAs in the renal tissue of rats with MN.<sup>[23]</sup> On this basis, the Yishen Tongluo formula can facilitate the repair of damaged glomerular basement membranes and reduce podocyte fusion, thereby minimizing renal impairment. Its effective mechanism may also be related to preventing the degradation of podocyte cytoskeletal proteins, such as ezrin and synaptopodin, and maintaining the structural integrity of the podocyte cytoskeleton and the foot process.<sup>[24]</sup>

The Shenqi Zhilong decoction (Huang Qi [astragalus], Dang Shen [codonopsis root], Dang Gui [angelica sinensis], Chuan Xiong [Szechuan lovage root], Shui Zhi [leech], Di Long [earthworm], Jiang Can [body of sick silkworm], Hu Zhang [bushy knotweed root and rhizome], Yin Yang Huo [astral parts of epimedium],

Feng Wei Cao [herba pteridis multifidae]) has the effect of reducing urine protein and increasing serum total protein as well as albumin in rats with MN induced by C-BSA.<sup>[25]</sup> Its therapeutic effect on this rat model of MN is exerted by regulating IL-2 and TNF- $\alpha$  levels in the serum, decreasing the weight and index of immune organs, and enhancing changes in the glomerular ultrastructure.<sup>[26]</sup>

The Sanqi Oral Solution (Huang Qi [astragalus] and San Qi [notoginseng root]) exhibits multiple functions, including reducing proteinuria, increasing serum albumin, alleviating renal pathological damage, decreasing the depositions of glomerular C3 and IgG, increasing the expressions of podocin and synaptopodin, and inhibiting the activation of the nuclear factor-kappa B (NF- $\kappa$ B) signaling pathway in rats with MN. Its mechanism of action may be related to the inhibition of the NF- $\kappa$ B pathway.<sup>[27]</sup>

### **Chinese herbal compounds focusing on benefiting qi and nourishing yin**

A single-center trial adopted the Shenqi Dihuang Decoction (Dang Shen [codonopsis root], raw Huang Qi [astragalus], Shu Di Huang [steamed Chinese foxglove root], Shan Yao [Chinese ram rhizome], Fu Ling [poria cocos], Ze Xie [water plantain rhizome], Mu Dan Pi [cortex of the peony tree root], Shan Yu Rou [Asiatic cornelian cherry fruit]) as the main formula to treat 32 qi-yin-deficient patients with IMN who were positive for serum anti-PLA2R antibody. While the 28 cases in the control group were treated with ACEI/ARB, the patients in the experimental group were treated with the Shenqi Dihuang Decoction as the main formula in addition to ACEI/ARB. The titer of anti-PLA2R antibody in the experimental group were  $181.57 \pm 126.3$  ru/mL before treatment and  $75.27 \pm 252.13$  ru/mL after treatment; the titer of anti-PLA2R antibody in the control group was  $223.28 \pm 140.84$  ru/mL before treatment and  $143.51 \pm 386.09$  ru/mL after treatment. The improvement of anti-PLA2R antibody titer was more obvious in the experimental group.<sup>[14]</sup>

### **Single Chinese medicine focusing on activating blood circulation and dispelling blood stasis**

In the recent years, there have been few studies on the application of a single Chinese medicine for activating blood circulation and dispelling blood stasis in the treatment of MN. The two medications that have been mostly studied are salvianolate and safflower yellow injection. The renal protective effect of the former in rats with MN may be associated with the upregulation of CD2AP expression, the downregulation of desmin expression, the inhibition of podocyte injury, and the protection of the integrity of the glomerular filtration barrier.<sup>[28]</sup> Furthermore, it has been shown that salvianolate can alleviate the renal damage in rats with MN by inhibiting the expressions of Ctsd

and chymase and, consequently, the activation of RAS.<sup>[29]</sup> Alternatively, safflower yellow injection protects the kidneys of rats with MN possibly by downregulating the expression of TIMP-1 and upregulating that of MMP-9.<sup>[30]</sup>

### **Chinese herbal compounds focusing on benefiting Qi and dispelling wind**

The Fuzheng Qifeng formula (Huang Qi [astragalus], Chuan Shan Long [*Dioscorea nipponica*], Xi Xian Cao [siegesbeckia], and Niu Xi [*Achyranthes bidentate*]) can effectively improve proteinuria, increase plasma albumin levels, and regulate the expression of nephrin and TGF- $\beta$ 1 in the renal tissue of a rat model of MN induced by C-BSA, thereby alleviating renal pathological damage and delaying the progression of MN.<sup>[31,32]</sup>

### **Chinese herbal compounds focusing on warming yang and promoting diuresis**

Water extracts from the Wenyang Lishui formula (Huang Qi [astragalus], Zhi Fu Zi [processed aconite root], Bai Zhu [white atractylodes rhizome], Bai Shao [white peony root], Fu Ling [poria cocos], and Sheng Jiang [ginger]) can facilitate the rearrangement of damaged podocyte cytoskeletal protein F-actin in mice with spleen-kidney yang deficiency induced by the serum of patients with IMN. Its role in alleviating podocyte injury in mice with MN is possibly effected by inhibiting the expression of caspase-3 mRNA, thereby exerting an anti-apoptotic effect.<sup>[33]</sup>

## **CONCLUSIONS**

Treatment of IMN via TCM is realized mainly via Chinese herbal compounds, the primary treatment approaches including those focusing on benefiting qi, activating blood circulation, and eliminating dampness and those focusing on benefiting qi and nourishing yin. Chinese herbal medicines used to treat IMN clinically, which have been relatively well studied, include the Shenqi Moshen granules, the Jianpi Qushi Heluo formula, the Qiling Tongluo formula, and the Shenqi Dihuang Decoction. Despite the different names, they all have similar prescription principles and drug composition, which mainly consist of Huang Qi (astragalus), Bai Zhu (white atractylodes rhizome), Dang Gui (angelica sinensis), Fu Ling (poria cocos), and Chuan Shan Long (*D. nipponica*). Among them, Huang Qi (astragalus) improves protein and lipid metabolism, facilitates urination and detumescence, regulates immunity, and plays an antifibrotic role.<sup>[34]</sup> Dang Gui (angelica sinensis) exhibits antithrombotic, antioxidant, and immune-regulating effects, among others.<sup>[35]</sup> The primary active ingredients of the “Huang Qi–Dang Gui” drug pair participate in multiple biological processes, such as signal transduction and anti-apoptotic and anti-

inflammatory responses, by regulating immunity and inflammation.<sup>[36]</sup> Alternatively, Bai Zhu (white atractylodes rhizome) inhibits the production of inflammatory factors, regulates immunity, and so on.<sup>[37]</sup> Poria exhibits diuretic, anti-inflammatory, and immune-regulating effects.<sup>[38]</sup> Lastly, the main ingredient of Fang Ji (stephania root), tetrandrine, demonstrates antipyretic, analgesic, anti-inflammatory, and diuretic effects.<sup>[39]</sup> Therefore, all the abovementioned Chinese medicine compounds share a similar effective mechanism by exerting immune-regulating, protein-metabolism-promoting, anti-inflammatory, antioxidation, diuretic, and other effects.

A growing number of clinical trials have indicated that Chinese herbal compounds demonstrate superior clinical efficacy in managing IMN, especially in aspects such as improving serum albumin levels, alleviating symptoms such as edema and fatigue, and protecting renal functions. In addition, it is associated with minor adverse reactions and is, therefore, highly safe.

TCM plays an important role in the treatment of IMN through the mechanisms of benefiting qi, activating blood circulation and eliminating dampness, benefiting qi and activating blood circulation, benefiting qi and nourishing yin, activating blood circulation and dispelling blood stasis, benefiting Qi and dispelling wind, warming yang, and promoting diuresis. Despite the recent progress in the application of TCM to the treatment of IMN, the number of multicenter, large-sample, randomized, controlled, clinical trials on this topic is still insufficient. Moreover, the multi-target mechanisms explaining the efficacy of TCM on MN have not been fully clarified. Therefore, the adoption of modern scientific methods to analyze the key links of the treatment of MN with TCM and the establishment of unified syndrome differentiation criteria and an efficacy evaluation system are of great significance for future investigations on the treatment of MN with TCM.

## Source of Foundation

This study was supported by the Major Project of Xiyuan Hospital, China Academy of Chinese Medical Sciences (2019XYMP—17); National Key R&D Plan of China (2019YFC1708500).

## Acknowledgments

We acknowledge the important contribution of the staff of Nephrology Department at Xiyuan Hospital in China, to the conduction of the study.

## Conflict of Interests

The authors declare that they have no competing interests.

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**How to cite this article:** Lang R, Wang X, Liang Y, Yan L, Shi B, Yu R. Research progress in the treatment of idiopathic membranous nephropathy using traditional Chinese medicine. *J Transl Int Med* 2020; 8: 3-8.