

# Discussion on the Treatment of Hepatic Fibrosis based on the Theory of “Nourishing Kidney to Produce Marrow and Form Liver”

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**Abstract:** *Hepatic fibrosis is actually a state of imbalance between the generation and degradation of extracellular matrix within liver tissue, It is a stage that various chronic liver diseases inevitably go through as they progress towards cirrhosis, Therefore, in the treatment of liver disease, early treatment plays a crucial role in inhibiting the occurrence and development of liver fibrosis. Clinical studies have shown that traditional Chinese medicine has unique advantages in improving hepatic fibrosis, in recent years, significant results have been achieved in the treatment of hepatic fibrosis based on the theory of “nourishing kidney to produce marrow and form liver” in clinical practice. The method of nourishing kidney to produce marrow and form liver has become a promising traditional Chinese medicine treatment plan. This article will summarize and analyze this from three aspects: theoretical origins, mechanism of action, and clinical prescription and medication selection, To provide reference for the clinical application of treating hepatic fibrosis based on the theory of “nourishing kidney to produce marrow and form liver”.*

**Keywords:** Nourishing kidney to produce marrow and form liver, Hepatic fibrosis.

## 1. Introduction

Hepatic fibrosis is the common pathological process of many chronic liver diseases, But the mechanism of its occurrence is still unclear, Chronic damage caused by factors such as viral hepatitis, alcohol, and drugs can damage liver cells [1]. The key factor is the activation of hepatic stellate cells (HSC), This type of injury can cause HSCs to transform into myofibroblasts after being subjected to various physical and chemical stimuli, Secretes a large amount of extracellular matrix (ECM), ECM production and degradation imbalance [2], Causing excessive accumulation of ECM, Thereby disrupting the normal structure and function of the liver [3,4]. Inflammation and oxidative stress play important roles in the activation of HSC, HSC apoptosis is beneficial to the regression of hepatic fibrosis [5]. In addition, Hepatic fibrosis is a key link from liver injury to Cirrhosis and even hepatic cellular cancer (HCC) [6]. Serious harm to human health, Liver transplantation is the most effective method to treat end-stage Cirrhosis, But it is expensive and may be accompanied by various complications, Therefore, Before hepatic fibrosis has progressed to Cirrhosis or hepatic cellular cancer(HCC), It is very important to take effective preventive and therapeutic measures to deal with hepatic fibrosis.

## 2. Theoretical Origins

The theory of “nourishing kidney to produce marrow and form liver” inherits the “vital energy theory” of traditional Chinese medicine [7], It is a treatment principle aimed at the etiology and pathogenesis of liver diseases such as “hepatic agenesis” and “marrow agenesis”, Due to the interference of various factors in the process of liver regeneration during the progression of chronic liver disease, it is often unable to fully regenerate and repair, resulting in abnormal liver regeneration, inflammation, and induction of fibrosis [8]. As early as in the “Su Wen · Yin Yang Ying Xiang Da Lun”, it is recorded that

“the kidney produces bone marrow, and the marrow produces the liver.” The “Ling Shu · Jing Mai Di Shi” records: “The kidney is short of yin veins... Its straightness runs through the liver from the kidney.” Zhang Jiebin’s “Lei Jing · Guo Xiang Lei” records: “The liver and kidney are the mother and child, and their qi is connected.” The “Jing Yue Quan Shu” records: “When the five organs are injured, they must reach the kidney, lightly injuring the kidney qi and seriously injuring the kidney yang.” Zhang Xichun’s “Medical Zhong Shen Xi Lu” believes that “human vitality is based on the kidney, and sprouts in the liver.” In summary, the theory of liver and kidney homology includes the relationship between liver and kidney essence and blood. The mother child relationship between the liver and kidney, the coexistence of the liver and kidney in the lower burner, and the interconnection of the liver and kidney meridians.

Traditional Chinese medicine is widely used in the treatment of acute and chronic liver diseases, and its mechanism of action may lie in regulating the process of liver regeneration through multiple pathways, levels, systems, targets, and time limits. A comprehensive, systematic, and in-depth study of the regulation of liver regeneration by traditional Chinese medicine can help improve clinical efficacy and achieve innovation and development in traditional Chinese medicine theory [9]. Professor Li Hanmin takes “liver and kidney homology” as the starting point. We have conducted in-depth research on the scientific connotation of “the kidney generates bone and marrow, and the marrow generates the liver” in the Neijing, and believe that “marrow” (“marrow generates the liver”) is the key central link of “liver and kidney homology”. The biological basis of the essence of “marrow” is stem cells and their tissue microenvironment, while the biological basis of “liver stores essence” is liver stem cells and their tissue microenvironment [10]. Acute and chronic development of liver disease, the core pathogenic and pathological mechanism of ‘marrow loss induced liver’, Xiang Junxi [11]. Research has found that in vivo transplantation of bone

marrow mesenchymal stem cells (BM-MSCs) induced by hepatic differentiation can alleviate the degree of fibrosis in chronic liver fibrosis rats and improve liver function [12]. When treating liver disease through “marrow” therapy, especially through the “kidney tonifying” method to promote “marrow generated liver formation”, it plays a crucial role as a common pathway or “core target”. One of the therapeutic mechanisms of traditional Chinese medicine’s “generating marrow” treatment is achieved by regulating stem cells and the tissue microenvironment in which they are located. The liver has a unique and powerful regenerative ability, but it becomes imbalanced under the influence of various pathological factors, resulting in the pathological manifestation of “myelodysplastic liver”. The activation of HSCs leads to their transformation into myofibroblasts, which secrete a large amount of ECM. The imbalance and accumulation of ECM production and degradation disrupt the normal structure and function of the liver. Therefore, improving the microenvironment of liver regeneration is one of the key links in preventing and treating liver diseases [13].

Understanding and cognition of hepatic fibrosis in traditional Chinese medicine: no records directly corresponding to hepatic fibrosis, a modern medical term, were found after consulting ancient books of traditional Chinese medicine. In the field of traditional Chinese medicine, hepatic fibrosis is generally regarded as the final stage of its pathological progress - a precursor or related state of Cirrhosis, and in the process of diagnosis and treatment, the TCM theory is used for reference to the discussion and treatment methods of “symptom accumulation”, “liver accumulation”, “hypochondriac pain”, and “jaundice” and other diseases and syndromes to treat according to the syndrome differentiation [14].

### 3. Mechanism of Action

“Nourishing kidney to produce marrow and form liver” can regulate liver regeneration through at least three ways or mechanisms: (1) Regulating liver regeneration by affecting the hypothalamic pituitary hepatic axis and the neuroendocrine immune network; (2) Regulating liver regeneration by influencing the transformation of bone marrow stem cells into liver cells; (3) Regulating liver regeneration by influencing the hepatic environment (including cytokines regulating liver regeneration, hepatic stem/progenitor cells, etc.) or humoral cytokines [15-18].

“Nourishing kidney to produce marrow and form liver” affects liver regeneration by regulating signal pathways. The gene chip and Western Blot were used to study the effect of “nourishing kidney to produce marrow and form liver” on gene expression of liver tissue related signal pathways in cross sex bone marrow transplantation mice. The results show that “nourishing kidney to produce marrow and form liver” affects Wnt, MAPK, TGF  $\beta$ , Jak STATA, Toll like receptors and other signal pathways related to liver regeneration [19,20]. These signal transduction pathways regulated by the “nourishing kidney to produce marrow and form liver” theory are closely related to the microenvironment of liver regeneration during the occurrence and development of liver cancer, indicating that optimizing the microenvironment of liver regeneration may be prevention and It is an important

mechanism for the treatment of liver fibrosis.

The key proteins of “nourishing kidney to produce marrow and form liver” include at least 14-3-3 protein, glucose regulated protein 78, histone H4 and various enzymes of liver cells. The yeast two hybrid system and immune co precipitation technology were used to study the interaction of key proteins. The results showed that the interaction mechanism of key proteins of “nourishing kidney to produce marrow and form liver” might be the coordination of key proteins and other proteins in the process of transforming bone marrow stem cells into hepatocytes [21].

Based on the theoretical connotation of traditional Chinese medicine, “the liver and kidney have the same origin, and the essence and blood are transformed into each other”, hepatic fibrosis is mostly due to chronic disease that consumes the essence of the kidney, kidney deficiency is weak, liver stagnation and qi stagnation, blood flow is impeded, blood stasis and phlegm are cemented in the liver collateral, leading to the loss of moistening of the liver, forming the syndrome of “deficiency of origin and excess of essence”, and ultimately leading to the formation of hepatic fibrosis. In addition, the clinical symptoms of patients often include dull complexion, sore waist and knees, dull hypochondriac pain, red tongue with less fur, thin pulse or astringency, etc., and hepatic fibrosis can be improved by tonifying the kidney to generate marrow and marrow to generate liver.

### 4. The Theoretical Meaning of “Nourishing Kidney to Produce Marrow and Form Liver”

The meaning of “tonifying the kidney”: The meaning of “tonifying the kidney” here is different from the usual “tonifying the kidney”. The commonly said “tonifying the kidney” may unilaterally emphasize the use of “pure tonifying” drugs, while the “tonifying the kidney” in the theory of “nourishing kidney to produce marrow and form liver” is based on a new understanding of the essence of deficiency syndrome, that is, the biological basis of the essence of deficiency syndrome is the imbalance between pathological damage and regeneration and repair, and the imbalance between liver damage and liver regeneration for liver diseases and syndromes. Therefore, the treatment of “kidney tonifying” emphasizes the simultaneous consideration of both liver injury and liver regeneration. The compatibility rule is to open up the source and reduce the flow, and to apply both tonifying and purging. Reducing damage is the kidney tonifying method of “throttling”, while promoting regeneration is the kidney tonifying method of “opening up”. The two complement each other and work together to restore the pathological state of liver injury and liver regeneration imbalance to a balanced and coordinated physiological state, achieving complete regeneration and repair of liver tissue structure and function.

The meaning of “generating marrow”: “generating marrow” means “making marrow grow”, that is, keeping marrow in a normal physiological state. Regeneration and repair cannot be separated from stem cells and the tissue microenvironment in which they are located. To promote the proliferation and differentiation of stem cells, it is necessary to maintain a

normal physiological state in their microenvironment. Therefore, “marrow regeneration” actually means maintaining the stem cells and their tissue microenvironment in a normal physiological state, ensuring that the regeneration and repair mechanism is developing positively and preventing the deterioration of the liver regeneration microenvironment.

The meaning of “liver formation” is to “make the liver form”. After the liver is subjected to pathological damage from various reasons, its tissue structure will be destroyed, and its function will be impaired or lost. By regulating the regeneration and repair mechanism through the method of “tonifying the kidney and generating marrow”, the damaged liver can be completely regenerated and repaired again, restoring its normal tissue structure and function.

## 5. Clinical Prescription Medication

Prescription selection under the guidance of nourishing kidney to produce marrow and form liver, and the use of Diwu Yanggan Capsule, Antitoxic Ruanjian Capsule, Zuogui Pill (Zuogui Yin), turmeric capsule and its related preparations (decoction, granules, etc. ), which embody the therapeutic principle of “nourishing kidney to produce marrow and form liver”, improve the microenvironment of liver regeneration by regulating the “imbalance between normal liver regeneration and repair and abnormal liver regeneration”. Modern pharmacological research shows that Zuogui Pill is related to the decline of neural endocrine immune network function [22], and experimental research in vivo and vitro carried out by Gao Xiang et al [23]. found that Zuogui Pill has the ability to promote the transformation of bone marrow stem cells into liver cells, and can participate in Regeneration and repair of liver tissue. It effectively reduces the degree of liver tissue damage and optimizes the regeneration process of liver cells through diversified methods and pathways. In addition, Professor Li Hanmin developed Diwu liver nourishing traditional Chinese medicine prescription based on the theory of “nourishing kidney to produce marrow and form liver”, which has anti-inflammatory, liver protective and regulating liver regeneration effects [24]. Li Hanmin believes that “the kidney generates the marrow, and the marrow generates the liver” is an important step in “liver kidney homology”. For chronic liver disease, harmonizing the regulatory system of the liver’s generation and the kidney’s conservation through kidney treatment is an important part of its treatment approach [25].

From the theory of “nourishing kidney to produce marrow and form liver”, it is necessary to give consideration to the constitution and individual treatment in the treatment of liver fibrosis. Qi deficiency can be combined with products such as Codonopsis pilosula, Astragalus membranaceus, stir fried *Atractylodes macrocephala*, and *Gynostemma pentaphyllum* to nourish qi and invigorate the spleen; For those with yin deficiency, it can be combined with nourishing yin and moistening dryness products such as ginseng, *Ophiopogon japonicus*, *Dendrobium officinale*, and *Asparagus japonicus*; Yang deficiency constitution can be combined with warming and dispelling cold products such as dried ginger, aconite, sorghum, cinnamon, etc; Phlegm dampness can be combined with products such as Huoxiang, Peilan, and Coix seed to remove dampness and phlegm; Blood stasis substance can be

combined with blood activating and stasis removing products such as Danshen, Sanqi, Taoren, Honghua, etc; Qi stagnation quality can be combined with products such as Chaihu, Chuanzhenzi, Xiangchuan, Foshou, Xiangfu, etc. that can soothe the liver and relieve depression, regulate qi and relieve depression; When treating liver fibrosis from the theory of “nourishing kidney to produce marrow and form liver”, attention should be paid to the combination of sex, taste and ginseng, reasonable compatibility, combined with pharmacology, and appropriate addition and subtraction.

## 6. Conclusion

The theory of “nourishing kidney to produce marrow and form liver” provides a new idea of “treating the liver from the kidney” for the treatment of hepatic fibrosis. It can improve the microenvironment in the liver by tonifying the kidney and essence, and at the same time, it can eliminate pathological products in combination with promoting blood circulation and removing blood stasis, reflecting the characteristics of “treating diseases and seeking the root” of traditional Chinese medicine. In the future, further multi omics research is needed to reveal the molecular mechanism of “kidney marrow liver” transformation, promote the modernization of traditional Chinese medicine theory, and provide a theoretical basis for the treatment of liver fibrosis.

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