

# *Study on the mechanism of shejianlian compound regulating the transformation of viral hepatitis, inflammation and cancer based on PI3K Akt / WT1*

Zhuoran Ji<sup>1</sup>, Man Wang<sup>2</sup>, Mingxia Hao<sup>2</sup>, Xiaoni Kou<sup>2,\*</sup>

<sup>1</sup>*Shaanxi University of traditional Chinese medicine, Shaanxi Xianyang 712000, China*

<sup>2</sup>*Affiliated Hospital of Shaanxi University of traditional Chinese Medicine, Shaanxi Xianyang 712000, China*

*\*Corresponding author*

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**Abstract:** Chronic hepatitis B is a systemic infectious disease caused by hepatitis B virus infection. Hepatitis B patients with hepatitis B in the world develop to cirrhosis or even liver cancer. In the process of inflammatory transformation, liver fibrosis is reversible, but the time of reversal is too slow. At present, there is no approved drug for the treatment of liver fibrosis, so the advantage of Chinese medicine in the prevention of liver fibrosis is particularly prominent. 20%-30% Shejianlian compound is composed of Hedyotis diffusa, Shijianchuan and Scutellaria barbata. Based on PI3K Akt / WT1, it can effectively prevent the transformation of viral hepatitis to liver cirrhosis and liver cancer. This paper discusses the mechanism of shejianlian compound regulating inflammatory and cancer transformation through PI3K Akt / WT1.

## 1. Introduction

Chronic viral hepatitis type B is a chronic infectious disease caused by DNA hepatitis virus and mainly manifested by liver damage. According to world Epidemiology, about 30% of the global population is currently or in the past infected with HEPATITIS B virus <sup>[1]</sup>. Hepatitis B has become a public health problem in the world and aroused widespread concern worldwide. In the infection process of CHRONIC hepatitis B, the continuous inflammatory reaction of the liver will activate the liver fibrosis, cause liver fibrosis and even cirrhosis, and eventually lead to liver cancer. Research expresses, the annual occurrence rate that chronic hepatitis b virus sex develops cirrhosis is 2%-10%. Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and one of the causes of cancer-related deaths worldwide <sup>[2]</sup>. The prevalence of HCC increased with increasing HBV viral load, duration of HBV infection, and severity of liver damage. Liver fibrosis is the manifestation of hepatic inflammation and cancer transformation, which is a reaction of wound healing. When infected with hepatitis B virus, the liver produces an inflammatory response, resulting in excessive deposition of extracellular matrix (ECM) in the liver tissue, resulting in changes in the morphology and structure of the liver tissue, and thus affecting the normal physiological functions of the liver <sup>[3]</sup>.

Liver fibrosis is a key factor affecting the prognosis of liver disease and the risk of hepatocellular carcinoma. Although it is an immune response, persistent liver injury, chronic hepatitis, and progressive liver fibrosis are driven by an interrelated vicious cycle. The initial stage of cirrhosis is liver fibrosis, which is a reversible process. Active intervention to reverse or delay the development of liver fibrosis can prevent the transformation of the disease to the direction of liver cancer, effectively improve the quality of life of patients and improve the prognosis of the disease<sup>[4]</sup>. However, the reversal of liver fibrosis occurs too slowly<sup>[5]</sup>, and there is no clinically approved effective treatment for human anti-liver fibrosis<sup>[6]</sup>. Therefore, the use of TRADITIONAL Chinese medicine to intervene in the transformation process of viral hepatitis B cancer is particularly prominent.

Viral hepatitis, liver fibrosis, cirrhosis and liver cancer are modern medical concepts. There is no specific name corresponding to them in Traditional Chinese medicine, but many doctors now name them as "hypochondriac pain" and "accumulation" according to their clinical manifestations and characteristics at different stages. The main etiology and pathogenesis of this disease is the liver heat and dampness accumulate for a long time into poison. Compound Snake jianlian is a Traditional Chinese medicine compound composed of hedyotis diffusa, Shi Jianchuan and Chinese herb. These three herbs all belong to heat-clearing and detoxifying drugs. From the perspective of traditional Chinese medicine, they are consistent with the etiology and pathogenesis of liver diseases that become toxic after a long time of dampness and heat. Clinically, Shejianlian compound has a significant effect on the prevention and treatment of cancer transformation of viral hepatitis B. The mechanism of pi3K-Akt /WT1 based prevention and treatment of inflammatory cancer transformation is discussed.

## **2. The transformation mechanism of HBV inflammatory cancer**

### **2.1 The transformation of HBV inflammatory cancer is based on the mechanism of PI3K/Akt signaling pathway**

There are multiple signaling pathways involved in cell proliferation, apoptosis, invasion and migration, including phosphatidyl inositol 3 kinase/protein kinase B (PI3K/Akt) is one of the important pathway, it can deliver important signals inside the cell, the ability to connect that inside and outside the cell<sup>[7]</sup>, in the process of formation of liver fibrosis, it also plays an irreplaceable role. Hepatic fibrosis is caused by chronic liver injury, which leads to excessive deposition of extracellular matrix (EMC). Hepatic stellate cell (HSC) is the main effector cell of hepatic fibrosis. The PI3K/Akt signaling pathway can participate in the formation of liver fibrosis from many aspects, and it can regulate the degradation of EMC, the activation of HSC, and the capillarization of hepatic sinuses<sup>[8]</sup>. A number of studies have shown that many anti-fibrosis and anti-tumor therapies achieve their goals by inhibiting the PI3K/Akt signaling pathway. Liwen Wei et al.<sup>[9]</sup> found that the phosphorylation levels of AKT, mTOR and P70S6K in rats with liver fibrosis were significantly reduced after treatment with aoxalic acid (AA) compared with the model group, indicating that AA protects liver from liver fibrosis through the PI3K/ AKT signaling pathway. Shahad W. Kattan et al.<sup>[10]</sup> proved through experiments that the anticancer drug-steroidal heterocyclic compounds play an anti-tumor role by inhibiting the PI3K/Akt signaling pathway, and its mechanism of mediating cell apoptosis is the inhibition of the PI3K/Akt/mTOR pathway. Gao Juncha<sup>[11]</sup> et al. in their experiments on the anti-liver cancer mechanism of sorafenib, found that sorafenib can inhibit the activation of HSC and the phosphorylation of ERK and Akt in rats with fibrosis, and achieve the purpose of anti-liver cancer by inhibiting the ERK/MAPK and PI3K/Akt signaling pathways. Anyhow, hot liver cancer is a very complicated process, it involves multiple signaling pathways, a variety of cells and cytokines<sup>[12]</sup>, the PI3K/Akt signaling pathway is one of the important pathways, further study of the role of this pathway in inflammatory carcinoma transformation mechanism, clarify for liver fibrosis mechanism, seek treatment of liver fibrosis, Prevention and treatment of inflammatory cancer transformation has

a positive significance.

## **2.2 HBV inflammatory cancer transformation is based on the mechanism of WT1 gene expression**

Wilms tumor 1 gene (WT1) plays multiple roles in cell development, tissue homeostasis and disease<sup>[13]</sup>. It can regulate transcription, participate in RNA metabolism and translation, and play carcinogenic and anticancer roles<sup>[14]</sup>. Martin Mžik et al.<sup>[15]</sup> found that WT1 is not found in the livers of healthy adults, but can be detected in the livers of patients with severe chronic hepatitis and fibrosis, and high levels of WT1 can be detected in liver cirrhosis and liver cancer. Long Lv et al.<sup>[16]</sup> confirmed that the expression of WT1 was up-regulated in HCC tumors, thus revealing the carcinogenic effect of WT1, which can promote the proliferation of HCC cells and inhibit the apoptosis of HCC cells. This study also found a negative correlation between WT1-AS and WT1 in tumor gene expression in HCC patients. Wt1-as can down-regulate the expression of WT1 in HCC and play a tumor suppressive role in HCC by reversing the carcinogenic effect of WT1. Timothy James Kendall et al.<sup>[17]</sup> also examined liver fibrosis tissues in a series of injury models, in which a large number of WT1-positive cells existed in liver fibrosis tissues. In conclusion, WT1 gene expression plays an important role in viral hepatitis cancer transformation, but the mechanism of WT1 in inflammatory cancer transformation is worthy of further investigation, which will provide new ideas and methods for clinical diagnosis and treatment of HCC.

## **3. Mechanism of Shejianlian compound on the transformation of hepatoinflammation and cancer**

Snake jianlian compound is a compound composed of hedyotis diffusa, Shi Jianchuan and Chinese herb. These three herbs are heat-clearing and detoxifying drugs, which have unique advantages in anti-inflammatory and anti-tumor aspects. This paper discusses the mechanism of pI3K-Akt/WT1 by regulating pI3K-Akt/WT1 to intervene in the transformation of viral liver inflammation, providing new ideas for the treatment of reversing liver fibrosis and regulating the transformation of inflammatory cancer.

### **3.1 Mechanism of HEdyotis diffustidis on cancer transformation based on PI3K/Akt signaling pathway**

Hedyotis diffusa Wild (Hedyotis diffusa Wild) is a plant of the rubiaceae family. It is also known as Lupulus scandens, Humulus scandens, Lupulus scandens, and Lupulus scandens. This product has the effect of clearing heat and detoxification, eliminating carbuncle, dispersing swelling, diuresis and dehumidification. In recent years, the anticancer effects of HEdyotis diffusers have attracted extensive attention from scholars at home and abroad, and more and more studies have been conducted on it. It has been found that some compounds in anthraquinones, flavonoids, terpenoids and steroids in HEdyotis diffusers are antitumor active ingredients. These anticancer active ingredients play an anti-tumor role by regulating immune function, inhibiting the formation of tumor cells, tissue blood vessels and lymphatic vessels, inducing apoptosis of cancer cells, regulating related signal pathways, and anti-oxidation<sup>[18]</sup>. As a traditional Chinese medicine, Hedyotis diffusa has been clinically applied in multi-system diseases such as digestive system tumors, lung cancer, glioma, cervical cancer and leukemia. It can inhibit the proliferation of tumor cells and induce their apoptosis by regulating the expression of different signal pathways and target genes<sup>[19]</sup>. Rong Zhang<sup>[20]</sup> found that the PI3K/Akt signaling pathway can promote tumor necrosis factor-induced endothelial cell migration and regulate tumor angiogenesis. Zhang Y Q<sup>[21]</sup> et al. Intra-gastric administration of Hedyotis diffusa in a nude

mouse model of hepatocellular carcinoma HepG2 cells transplanted subcutaneously to observe the tumor inhibition rate of *Hedyotis diffusa* and its effects on the expression of PI3K, Akt and phosphorylated Akt proteins in tumor bearing mice. The results showed that: *Hedyotis diffusa* can significantly inhibit the tumor growth of tumor-bearing mice, and the expression of PI3K, Akt and P-Akt in the cytoplasm of the model group is strong, while the expression of PI3K, Akt and P-Akt in the administration group is weakened. In conclusion, *Hedyotis diffusa* can significantly inhibit the protein expression levels of PI3K, Akt and P-Akt, and inhibit the expression of vascular endothelial growth factor by regulating the PI3K/Akt signaling pathway, thus achieving the anti-angiogenesis effect of hepatic malignant tumor. Wang Xin et al. [22] also showed that kahenol, the active ingredient in *Hedyotis diffusa*, could inhibit tumor cell proliferation by regulating PI3K/Akt signaling pathway and down-regulating iNOS and COX2 downstream inflammatory factors to significantly suppress inflammatory response. In conclusion, *Hedyotis diffusa* can play anti-inflammatory, anticancer and interventional roles in inflammatory and cancer transformation through PI3K/Akt signaling pathway.

### **3.2 Mechanism of Action on cancer transformation of viral liver inflammation based on PI3K/Akt signaling pathway of *Scutellaria chinensis***

*Scutellaria barbata* D. Don, also known as driving mountain rhizome and thin *Scutellaria baicalensis*, is spicy, bitter and cold, and has the functions of reducing swelling and relieving pain, clearing heat and detoxifying, protecting liver and diuresis. Modern pharmacological studies have shown that the main active components in *Scutellaria chinensis* include flavonoids, diterpenoids, polysaccharides and volatile oils [23]. In clinical practice, *Baritellia sinensis* can be used to treat malignant tumors, including primary liver cancer. The main mechanisms include: Inhibit the proliferation of HCC cells, induce apoptosis of HCC cells inhibit the invasion and metastasis of HCC cells, inhibit angiogenesis of stem cells, through the immune adjustment inhibit the occurrence and progress of hepatocellular carcinoma (HCC), but also increase in the clinical treatment of liver tumor curative effect, increasing the drug sensitivity, reduce the toxic effects of drugs. Chen [24] melanoma tumor-burdened mice model through experiment, the main observation of PI3K/Akt/mTOR pathway marker protein phosphorylation levels, study of these components - the molecular mechanism of autophagy induced cells, total flavonoids found in these flavonoids can effectively inhibiting the production of a tumor-burdened mice melanoma, reduced tumor size and increase the inhibitory rate, It significantly increased the apoptosis index of tumor cells and inhibited the protein expression levels of P-PI3K and P-Akt. It can be concluded from these experiments that total flavonoids of *Scutellaria chinensis* can inhibit the growth of melanoma, and its mechanism is related to the inhibition of PI3K/Akt/mTOR pathway, autophagy induction and apoptosis. Yang Yang [25] investigated the mechanism of compound Banzhilian granule in treating rat liver fibrosis by observing the effect of compound Banzhilian granule on MAPK/ERK-PI3K/Akt absorption pathway in liver fibrosis. The results indicated that compound Banzhilian granules could block the conduction of MAPK/ERK-PI3K/Akt signaling pathway, inhibit the activation of HSC, and promote the apoptosis of HSC, thus reducing the degree of liver fibrosis in rats with liver fibrosis model and improving liver fibrosis in rats. However, there are many components in *Scutellaria chinensis*, and its mechanism is complicated. Further research and discussion on its anti-liver fibrosis mechanism are needed in order to better apply it to clinical practice.

### **3.3 *Shijianchuan* is based on the role of WT1 gene in the transformation of viral liver inflammation**

*Salvia chinensis* Benth., also known as purple ginseng, *Salvia miltiorrhiza*, huoxue grass, is the whole grass of *Salvia* in the labiaceae. It was first recorded in Compendium of Materia Medica.

Gynecology and other diseases. Its active ingredients mainly include salvianolic acid, protocatechualdehyde, saccharide, shihuanolic acid, amino acid and so on. Its anti-tumor mechanisms include inducing tumor cell apoptosis, inhibiting tumor cell migration and invasion, anti-tumor angiogenesis, and increasing the sensitivity of tumor cells to chemotherapy drugs [26]. Study [27] found that in Kunming mice with H22 ascites liver cancer, administration of Shijian Chuan Zhong polysaccharides (PSCC) could significantly inhibit the in vitro proliferation of H22 cells. Ning Wang et al. [28] studied the anti-tumor effects of several Chinese herbs on human liver cancer cells and found that WT1 was overexpressed in liver cancer tissues, which promoted the proliferation and invasion of liver cancer cells and participated in the activation of Wnt, and was negatively correlated with the survival rate of patients. Inhibition of liver cancer in situ studies show nude mice model of the Chinese sage treatment inhibits tumor growth of liver cancer in situ and mice with pulmonary metastasis of liver cancer was completely cut off, the results show that the Chinese sage hepatocellular carcinoma cells in vitro, obvious inhibition, inhibit the growth of liver cancer in situ in mice liver, and can restrain the pulmonary metastasis of tumor cells, It was also found that protocatechualdehyde (PCA) may be the active ingredient of Shijianchuan, and PCA in Shijianchuan can be used as a lead compound targeting WT1 in the discovery of liver cancer drugs. However, so far, there are few experimental and clinical studies on the treatment of liver cirrhosis and liver cancer and the intervention of inflammatory cancer transformation by Shijianchuan. Further research and discussion are needed to explore the mechanism of its clinical treatment of liver disease and develop new drugs and new treatments to reverse inflammatory cancer transformation.

#### 4. Conclusion

At present, although the number of patients infected with the hepatitis B virus is gradually decreasing, but in some areas, chronic hepatitis B has not been taken seriously, so that the disease worsens further, from the initial hepatitis to fibrosis to cirrhosis to liver cancer, and finally life-threatening. So early intervention and treatment are key to preventing further deterioration. Inflammatory carcinoma in the intervention of traditional Chinese medicine has outstanding advantages in the process of transformation, but the research is not enough in-depth, participate in the transformation of viral hot liver cancer related pathways and related factors are many, in this paper the snake see lotus compound by regulating the PI3K/Akt WT1 affect viral hot liver cancer transformation mechanism are discussed in this paper, in order to develop effective drugs of liver fibrosis, Improve the quality of life of patients with hepatitis and cirrhosis.

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