

Pharmacological Study of Liver Accumulation Formula in the Treatment of Hepatic Carcinoma

Shiqing Zhou

College of Pharmacy Harbin Medical University, Harbin, Heilongjiang, 150081, China

Keywords: Primary hepatic carcinoma; Traditional Chinese Medicine; Treatment

Abstract: Primary hepatocellular carcinoma (PHC) is one of the common malignant tumors in clinic, which has the characteristics of occult onset, rapid progress, high malignancy, easy metastasis and recurrence, difficult treatment and short survival period. At present, surgical treatment of PHC still occupies the main position, but it can not be widely carried out because of its strict selection of indications, high technical requirements, high cost, low success rate and long-term survival rate. Traditional Chinese Medicine (TCM) is not only effective in treating this disease, but also of great significance in controlling the development of the patient's condition, improving the quality of life and prolonging the survival period. In this paper, the mechanism of TCM and its active components in inhibiting the proliferation of hepatocellular carcinoma cells, promoting the apoptosis and focal death of hepatocellular carcinoma cells, inhibiting the invasion and metastasis of hepatocellular carcinoma, and inhibiting the angiogenesis of hepatocellular carcinoma tissues are reviewed, so as to bring inspiration to the study of the mechanism of Liver accumulation recipe on PHC and provide stronger theoretical support for TCM anti-hepatocellular carcinoma treatment.

1. Introduction

PHC is one of the main malignant tumors that harm people's health. Hepatic carcinoma is a malignant tumor, and the initial symptoms of patients are not obvious. In the later stage, the main manifestations are fatigue, liver pain, weight loss, ascites, and other symptoms [1]. In clinical practice, patients are generally treated with Western medicine surgery, radiotherapy, and chemotherapy. However, due to the spread of cancer cells in the late stage, the probability of patient death is very high [2]. Therefore, in clinical practice, it is necessary to achieve early detection and timely treatment of hepatic carcinoma. Surgical treatment has a good effect on early hepatic carcinoma, but it is not effective for hepatic carcinoma that has already metastasized in the middle and late stages. TCM has a positive effect on alleviating the condition of cancer patients and prolonging their survival time [3]. Hepatic carcinoma is often difficult to detect, develops rapidly, and has a poor prognosis. When symptoms appear, most patients are already in the advanced stage and have lost the opportunity for surgery. Moreover, the recurrence and metastasis rate after surgery is high, and chemotherapy has significant toxic side effects, posing a great threat to the health and life of patients [4]. TCM has a history of treating hepatic carcinoma in China for hundreds of years, and TCM and its active components can play a role in treating hepatic carcinoma by participating in various mechanisms [5].

TCM has significant advantages in preventing and treating hepatic carcinoma recurrence, metastasis, improving symptoms in mid to late stage patients, improving quality of life, and prolonging survival. It is one of the indispensable means in the comprehensive treatment of PHC [6]. It is often flexibly applied in various stages of tumor onset and has been throughout the treatment process of hepatic carcinoma, even serving as a separate treatment method for some mid to late stage hepatic carcinoma [7]. Liver accumulation recipe is a prescription developed by the Oncology Department of Longhua Hospital affiliated with Shanghai TCM University, led by veteran Chinese medicine Qiu Jiixin. It has good clinical therapeutic effects on hepatic carcinoma, and can be used alone or in combination with targeted drugs to inhibit the growth and metastasis of hepatic carcinoma, improve patient symptoms and quality of life. Clinical trials have shown that the 1-year survival rate of patients treated with Liver accumulation recipe alone for advanced PHC is 31%

(18/58), compared to 4.5% (1/22) in the control group [8]. In order to improve the symptoms of patients and improve their survival rate and quality of life, this article reviews the mechanisms and mechanisms of TCM and its active ingredients in inhibiting hepatic carcinoma cell proliferation, promoting hepatic carcinoma cell apoptosis and necrosis, inhibiting hepatic carcinoma invasion and metastasis, and inhibiting hepatic carcinoma tissue angiogenesis. The aim is to provide inspiration for the study of the mechanism of Liver accumulation recipe on PHC and provide stronger theoretical support for TCM anti hepatic carcinoma treatment.

2. Treatment principles for hepatic carcinoma

At present, it is believed that the occurrence of hepatic carcinoma is the result of a long-term comprehensive effect of multiple factors, not caused by day and night. Among them, external factors such as invasion of the human body by exogenous dampness and turbid epidemic toxins, improper or inappropriate diet, excessive or insufficient emotions, various liver diseases, insufficient innate endowment, acquired spleen and stomach weakness, etc., all have a significant impact on the occurrence of hepatic carcinoma [9]. Under the interaction of various internal and external causes, pathological products such as qi stagnation, blood stasis, phlegm coagulation, dampness and turbidity, phlegm fire, and stagnation toxin are formed, resulting in the formation of "cancer toxin". Over time, it damages the normal qi and involves multiple organs. Hepatic carcinoma belongs to the categories of liver accumulation, swelling, jaundice, etc. in traditional Chinese medicine. The pathogenesis of this disease is mostly internal injury, seven emotions, fatigue, external six exogenous factors, epidemics, deficiency and damage of the viscera, disharmony of qi and blood in the meridians, resulting in qi stagnation and blood stasis, toxin stasis, and accumulation over time, belonging to the category of positive deficiency and evil excess. Figure 1 is a pathological image of primary hepatic carcinoma.

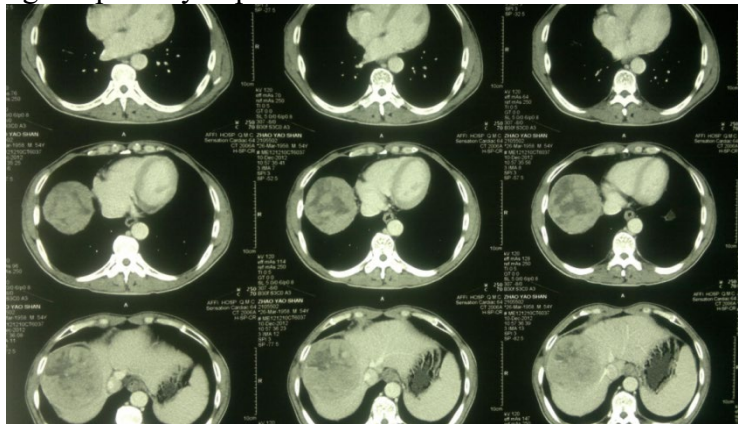


Figure 1 Pathological images of primary hepatic carcinoma.

As far as hepatic carcinoma itself is concerned, proper differentiation of symptoms and treatment methods can significantly alleviate clinical symptoms and prolong patient survival. In fact, the advantages of TCM syndrome differentiation and treatment are not only reflected in the treatment and rehabilitation after the diagnosis is completely clear, but also in both syndrome and disease differentiation. Because hepatic carcinoma is often asymptomatic in the early stages, some cases are only discovered during physical examinations such as alpha fetoprotein and B-ultrasound, which are currently unlicensed and can only be treated through disease differentiation. At different stages of hepatic carcinoma formation and progression, it is necessary to seize the powerful opportunity to dispel pathogenic factors and promote health. Hepatic carcinoma is in its early stage, with an early onset of disease and a lack of vitality. It is characterized by excessive accumulation and stasis, and treatment should focus on eliminating pathogenic factors while also supporting the body; In the middle stage of hepatic carcinoma, the cancer further develops, depleting some of the body's vital energy, causing excessive and deficiency of pathogenic factors. Therefore, it is advisable to use a combination of dispelling pathogenic factors and supporting the right; In the late stage of hepatic

carcinoma, the vital energy is severely damaged and the body is weak. The treatment mainly focuses on tonifying deficiency and strengthening the body, while also eliminating pathogenic factors and anticancer drugs. On the basis of protecting the patient and enhancing the body's resistance, appropriate application of anticancer drugs and eliminating pathogenic factors can delay the dissipation of cancer toxins, and even inhibit tumor development [10].

3. Mechanism of TCM treatment for PHC

The occurrence of tumors is not only manifested as an increase in cell proliferation rate, but also related to a decrease in cell death rate. Some effective components of TCM can upregulate certain molecules related to apoptosis, thereby inducing apoptosis in hepatic carcinoma cells. Jiang Hao and others observed the inhibitory effect of ginsenoside Rh2 on the growth of Be-17404 cells in vitro, the changes of apoptotic cells and cell cycle, and the expression of p53, Bax, and Bc-12 proteins related to apoptosis before and after drug treatment, indicating that ginsenoside Rh2 can inhibit the proliferation of Be-17404 cells in vitro and induce apoptosis by up regulating the expression of Bax, down regulating the expression of mutant p53, and blocking cells in G1 phase [11]. Ray et al. grape seed extract (GSPE) proanthocyanidins modify metabolic cascade reactions and regulate the cell death program of multi-level tumor occurrence, reducing the rate of dimethylnitrosamine (DMN) induced hepatic carcinoma formation and mortality in B6C3F1 mice, and reducing the number of tumor bearing mice [12]. Sikewei et al. treated HepG2 hepatic carcinoma cells with a certain concentration of matrine and found that it inhibited the malignant proliferation of HepG2 at both metabolic and genetic levels [13]. DengX et al reported that brucine has the strongest cytotoxic effect in human hepatic carcinoma cells, which can cause HepG2 programmed cell death, caspase-9 enzymatic hydrolysis, and depolarization of HepG2 cell mitochondrial membrane, playing a central regulatory role [14].

Abnormal cell differentiation plays an important role in the pathogenesis of malignant tumors, and tumor induced differentiation therapy is a new approach and method for tumor treatment. TCM active ingredients have shown significant advantages in the field of tumor prevention and treatment, with characteristics such as low dosage and relatively safety. Huang Wei et al. found that glycyrrhetic acid and glycyrrhetic acid can significantly inhibit the proliferation of Be-17402 cells established from adult PHC, and induce differentiation reversal, including a decrease in cell proliferation rate and a significant decrease in the nuclear cytoplasmic ratio, a morphological quantitative indicator of hepatic carcinoma cell differentiation [15]. Deng Xukun et al. found that brucine has a significant anti-tumor effect on solid tumors in H22 and S180 mice, and can effectively inhibit tumor growth in transplanted hepatic carcinoma model bearing mice. In the short term, brucine has no significant toxicity to animal hematopoiesis, immune system, liver and kidney [16]. Ba Yi et al. isolated sulfated polysaccharide Gepsin from Shougong and observed its effect on the growth and differentiation of human hepatic carcinoma Bel-7402 cells. They found that Gepsin can significantly inhibit the growth of hepatic carcinoma Bel-7402 cells [17]. Telomere is a special structure of chromosome terminations in eukaryotic cells. It is composed of 6 base repeats of TTAGGG. It has stable chromosomal functions and participates in DNA replication. The repeat sequence of telomeres is shortened after each cell division. When the length of telomeres is shortened to a certain extent, the cell stops dividing and enters senescence. Tumor cells can break away from the aging phenotype and become immortal, often accompanied by activation or upregulation of telomerase function.

Meng Zhiqiang et al. used the TRAP method to observe the changes in telomerase activity of mouse H22 hepatic carcinoma and human hepatic carcinoma SMMC-7721 cells in vitro after treatment with Jianpi Liqi TCM. They found that telomerase activity measurement showed that SMMC-7721 cells were almost completely inhibited after treatment with Jianpi Liqi TCM at a concentration of 40mg/mt for the 5th day, and there was a certain degree of recovery after drug removal [18]. Chen Guihua et al. found in their study of telomerase changes in hepatic carcinoma cell apoptosis induced by oridonin that a decrease in telomerase HTERT mRNA expression level and telomerase activity were accompanied by a decrease in Bc-12 protein expression and

upregulation of Bax protein, indicating that oridonin has a wide range of anti-tumor effects [19]. Wang Qinggao observed that both the high, medium, and low doses of Aitongxiao Capsules and Kangsaidi Capsules had significant anti-tumor effects. Positive staining for VEGF, p53, and p21ras was observed in hepatic carcinoma cells of all animal models. The high-dose group of Aitongxiao Capsules and Kangsaidi Capsules both significantly reduced the positive expression of VEGF, p53, and p21ras in hepatic carcinoma cells [20].

4. Conclusion

China has a history of using TCM to treat cancer for thousands of years, and traditional Chinese medicine also has its unique advantages in the treatment of tumors; Moreover, the price of Chinese herbal medicine is relatively low compared to Western chemical therapy, and patient compliance is good. The liver is a disease with very complex clinical manifestations, and many other diseases are related to the liver. The treatment methods listed above should be combined with clinical syndrome differentiation and flexibly applied to achieve ideal therapeutic effects. A tumor is a malignant transformation of a small number of cells in the body, which is autonomous and irreversible. Therefore, it is necessary to eliminate or kill the cancerous cells as much as possible. Currently, the most effective treatments include surgery, radiation therapy, and chemotherapy. Years of clinical practice have shown that these methods can achieve good results for early tumors, significantly improve patient symptoms, and even cure some tumors. Modern TCM treatment of hepatic carcinoma emphasizes the differentiation of symptoms and treatment, as well as the treatment of both symptoms and symptoms. At the same time, with the continuous deepening of research on etiology, pathogenesis, and TCM pharmacology, the level of TCM anti hepatic carcinoma treatment has risen to a new level. Signal pathways are communication channels for information transmission between cells and between cells and extracellular factors. The biggest advantage of TCM is its ability to intervene in various signal transduction pathways between hepatic carcinoma cells to block information transmission between hepatic carcinoma cells and inhibit the generation and development of hepatic carcinoma.

Simple TCM treatment and single target TCM treatment have obvious limitations. How to combine Western medicine targeted treatment drugs and find a common target for anti hepatic carcinoma treatment combining Chinese and Western medicine is the future development trend. The evaluation system for the effectiveness of TCM in treating hepatic carcinoma is not perfect enough, and further clarification and refinement are needed. Only by forming a comprehensive and in-depth therapeutic evaluation mechanism can scientific feedback information be provided for the future development of TCM in treating hepatic carcinoma. For tumors in the middle and late stages, especially those that have already metastasized or frequently recurred, radiotherapy and chemotherapy are widely used due to the inability of local surgical methods to completely eliminate cancer cells. However, they can only temporarily or to some extent inhibit the growth of tumor cells, and have a great damage and destruction effect on normal cells, resulting in a sharp decline in the body's immune capacity. Therefore, the application of Chinese herbal medicines such as Liver accumulation recipe to treat patients has a positive effect on improving their condition and improving their survival rate.

References

- [1] You Liping, Kong Xiaoni, Gao Yueqiu, et al. Literature-based analysis of experimental research on the treatment of hepatic carcinoma with traditional Chinese medicine [J]. Journal of traditional chinese medicine, 2023, 64(1):6.
- [2] Zhao Tong, Yin Zifei. Research progress on the effect of traditional Chinese medicine on hepatic carcinoma stem cells [J]. Journal of traditional chinese medicine, Liaoning, 2020, 47(7):3.
- [3] Zhang Cheng, Sun Jianguang, Xie Guanyue. Meta-analysis of TCM decoction combined with TACE in the treatment of primary hepatic carcinoma [J]. Journal of traditional chinese medicine,

Hunan, 2018, 34(12):5.

[4] Ma Xing, Xia Wei. Research progress on signal pathway of anti-proliferation and apoptosis of hepatocellular carcinoma cells induced by traditional Chinese medicine [J]. Shanghai Journal of Traditional Chinese Medicine, 2018, 52(8):98-101.

[5] Zheng Yuanyuan, Li Liangsong, Zhao Biao. Clinical study of Peiyuan Kangai decoction combined with acupuncture in the treatment of qi deficiency and blood stasis syndrome in advanced hepatic carcinoma [J]. International Journal of Traditional Chinese Medicine, 2023, 45(00):1-6.

[6] Zang Hongyu. Analysis of the influence of traditional Chinese medicine on the therapeutic effect and complications of hepatic carcinoma [J]. Prescription drugs in China, 2018, 16(5):2.

[7] Dai Xincan, Liu Shuang, Lv Wenliang. Lv Wenliang's experience in treating hepatic carcinoma with traditional Chinese medicine [J]. Jilin Traditional Chinese Medicine, 2023, 43(1):4.

[8] Jia Yanhui, Yang Jinzu, Gao Feng, et al. A case of lung metastasis of primary hepatic carcinoma treated by Chinese herbal compound with spleen as the main ingredient [J]. Western Traditional Chinese Medicine, 2012, 25(4):3.

[9] Zhang Bin, Xu Chunjiang, Cha Fangfang, et al. Effects of traditional Chinese medicine for invigorating spleen and detoxifying on proliferation and expression of PI3K and AKT in hepatocellular carcinoma HepG2 cells [J]. Journal of Traditional Chinese Medicine, 2019, 47(3):4.

[10] Zhang Yi, Zhang Yufeng, Qi Yating. Research progress of traditional Chinese medicine in treating hepatic carcinoma based on PI3K/AKT signaling pathway [J]. Journal of traditional Chinese medicine, Shandong, 2022, 41(5):583-589.

[11] Jiang Hao, Fan Guanghua. Effects of ginsenoside -Rh2 on proliferation and apoptosis of human hepatocellular carcinoma Be- 1 7404 cells [J]. Chinese journal of clinical oncology and rehabilitation, 2004, 11(4): 289- 292.

[12] Ray SD, Parikh H, Bagchi D. Proanthocyanidin exposure to B6C3F1 mice significantly attenuates dimethylnitrosamine - induced liver tumor induction and mortality by differentially modulating programmed and unprogrammed cell deaths [J]. Mutat Res, 2005, 579 (1- 2):81- 106.

[13] Si Kewei, Li Peng, Yao Jie. Effects of Matrine on the Metabolic Level and Gene Level of HepG2 Cells [J]. Journal of third military medical university, 2002, 24(11):1346- 1349.

[14] Deng X, Yin F, Lu X, et al. The apoptotic Effect of Brucine from the Seed of Strychnos nuxvomica on Human Hepatoma Cells is Mediated via Bcl- 2 and Ca²⁺ Involved Mitochondrial Pathway [J]. Toxicol Sci, 2006, 1:27.

[15] Huang Wei, Huang Jiqun, Zhang Dongfang, et al. Study on differentiation and apoptosis of human hepatocellular carcinoma cells induced by glycyrrhetic acid and glycyrrhizic acid [J]. Journal of Hepatology of Integrated Traditional Chinese and Western Medicine, 2003, 13(3):148-150.

[16] Deng Xukun, Cai Baochang, Wu Yan, et al. Inhibitory effect of brucine on tumor in mice [J]. chinese journal of natural medicines, 2005, 3(6):392.

[17] Ba Yi, Wu Xiongzhi, Xie Guangru, et al. Effects of sulfated polysaccharides from Shougong on proliferation and differentiation of human hepatocellular carcinoma cells [A]. Proceedings of the 4th China Cancer Society and the 5th Cross-Strait Cancer Society [C], Tianjin, 2006: 135.

[18] Meng Zhiqiang, Yu Erxin, Song Mingzhi, et al. Effect of traditional Chinese medicine for invigorating spleen and regulating qi on telomerase activity of hepatocellular carcinoma [J]. China Journal of Traditional Chinese Medicine, 2000; 6(1):23- 26.

[19] Chen Jihua, Zhang Junfeng, Lu Minqiang, et al. Study on the changes of Bc- 1 2 and telomerase in the apoptosis of hepatocellular carcinoma cells induced by oridonin [J]. China Journal of Traditional Chinese Medicine, 2006; 31(21) :1811-1813.

[20] Wang Qinggao, Wei Ailing, Xu Zhixin. Experimental study on Aitongxiao capsule regulating the expression of VEGF, p53 and p21ras in H22 transplanted hepatic carcinoma cells in mice [J]. Guangxi Traditional Chinese Medicine, 2005, 28(2):45-48.