

Research progress of Chinese medicine in the treatment of primary liver cancer

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Abstract. Primary liver cancer is a refractory tumor with a high recurrence rate and low quality of life. Traditional Chinese medicine, especially Chinese patent medicines, has shown positive therapeutic prospects in improving symptoms and quality of life. This study summarizes the potential efficacy of various Chinese patent medicines for primary liver cancer through a literature review, and describes their mechanism of action through multiple pathways, such as regulating the tumor immune microenvironment, modulating metabolic patterns, and inhibiting tumor cell growth and proliferation. Despite considerable advancements in the clinical utilization of Chinese patent medicines, existing research exhibits limitations, including the necessity to enhance the comprehensiveness of clinical data and the profundity of mechanistic investigations. Future research trajectories should encompass broadening the scope of clinical studies, intensifying the exploration of the mechanisms underlying Chinese patent medicines, and fostering the standardization and personalization of treatment protocols.

Keywords: primary liver cancer, Chinese patent medicines, tumor immune microenvironment, tumor cell apoptosis

1. Introduction

Primary liver cancer ranks among the foremost causes of cancer-related mortality globally, particularly in Asia. Data from 2024 indicates approximately 431,000 new liver cancer cases and around 203,000 fatalities year worldwide, with China representing 45.3% of cases and 47.1% of deaths [1]. Primary liver cancer has a high incidence and is difficult to diagnose early. Once diagnosed, patients are often in the middle or late stages, with a poor prognosis. Although existing Western medical treatments such as surgical resection, radiotherapy and chemotherapy have a certain effect in prolonging patients' survival, these methods are often accompanied by significant side effects, drug resistance issues and a high recurrence rate. Therefore, there is an urgent need to explore new treatment strategies [2]. In recent years, Chinese patent medicines have gradually become an important research direction in the field of liver cancer treatment through their multi-pathway mechanisms of action, such as regulating the tumor immune microenvironment and inhibiting tumor cell growth and metabolism [3]. This study aimed to carefully analyze the current status and mechanisms of action of Chinese patent medicines in treating primary liver cancer, as well as to identify the bottlenecks and issues in existing research. A literature analysis was performed to investigate the mechanisms by which Chinese patent medicines modulate the tumor immune microenvironment, induce apoptosis in tumor cells, and suppress tumor metabolism, while also evaluating their efficacy and safety in clinical applications. A systematic investigation into the application and mechanism of action of Chinese patent medicines for the treatment of primary liver cancer holds substantial clinical significance and research value.

2. Theoretical basis for the treatment of primary liver cancer with Chinese patent medicine

The pathogenesis of primary liver cancer is intricate and encompasses multiple pathological processes, including chronic inflammation, fibrosis, and cirrhosis resulting from chronic liver disorders including hepatitis B and hepatitis C. Traditional Chinese medicine theory believes that the occurrence of liver cancer is closely related to the “toxic evil” in the body, and the pathogenesis is mainly related to pathological factors such as Qi stagnation and blood stasis, internal heat and dampness, and condensation of phlegm-dampness. In traditional Chinese medicine theory, Qi stagnation and blood stasis means that the flow of Qi and blood is not smooth, leading to blood stasis. This stasis may form “lumps” or tumors. Damp-heat retention refers to the accumulation of damp-heat evil energy in the body, which over time damages the internal organs and forms the basis of the disease.

Phlegm-damp accumulation refers to the accumulation of phlegm-damp in the body, which further blocks the meridians and Qi and blood, leading to the formation and development of tumors. These pathological factors work together to disrupt the normal function of the body, impairing the liver's metabolic and detoxification functions, and ultimately leading to the development of tumors. Chinese patent medicines can effectively inhibit the growth and spread of tumors through methods such as clearing away heat and toxins, promoting blood circulation and resolving blood stasis, and softening hard lumps and dispersing knots [4]. The anti-tumor mechanism of Chinese patent medicines not only directly acts on the tumor itself, but more importantly, enhances the patient's overall anti-tumor ability by regulating their overall function.

3. Clinical application and efficacy of proprietary Chinese medicines

3.1. Overview of clinical research

As a classic proprietary Chinese medicine prescription, the kidney-tonifying and phlegm-transforming formula is based on the above TCM theory and is widely used in the treatment of liver cancer. This formula's primary components, including astragalus, epimedium, and wolfberry, can significantly bolster the patient's immune response, inhibit tumor cell proliferation, and facilitate tumor cell apoptosis. This formula mainly regulates the internal environment of the body through the effects of tonifying the kidney and strengthening yang, resolving phlegm and softening hard lumps. The specific manifestations are tonifying the kidney to enhance the patient's overall immune function and restore and enhance the positive energy [1].

In a clinical study, researchers followed up patients with primary liver cancer who had been treated with the kidney-tonifying and phlegm-transforming formula for six months. The results showed that tumor markers such as Alpha-Fetoprotein (AFP) levels decreased by an average of 40%, and about 60% of patients showed tumor shrinkage or stabilization on imaging studies without further tumor progression. This study suggests that the kidney-tonifying and phlegm-transforming formula plays an important role in the treatment of liver cancer, especially when used as part of an integrated treatment regimen. The kidney-tonifying and phlegm-resolving formula is often used in combination with conventional Western treatments such as surgery, radiotherapy or chemotherapy to enhance the overall efficacy and reduce side effects [5].

Heat-clearing and detoxifying Chinese medicines such as Qinggan Jiangjie Wan and Huanglian Jiedu Tang are also widely used in the treatment of liver cancer. The main mechanism of action of heat-clearing and detoxifying Chinese medicines is to clear damp-heat toxins from the body, improve the inflammatory response of the liver, and thereby inhibit tumor growth. In a randomized controlled trial, Qinggan Jiangjie Wan was combined with conventional treatment (including surgery, radiotherapy or chemotherapy) for patients with liver cancer. The results showed that compared with patients who received conventional treatment alone, those who received combined Qinggan Sanjie Pill treatment had significantly improved liver function indicators, such as a 30% and 25% reduction in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) levels, respectively. In addition, the tumor shrinkage rate in the combined treatment group increased by 20%, and 60% of patients had their tumors shrink or stabilize [6].

3.2. Clinical research on the efficacy evaluation of Chinese patent medicines

The efficacy evaluation of Chinese patent medicines in clinical practice involves multiple aspects, including improvement of symptoms, prolongation of survival, changes in tumor marker levels, imaging assessments, and patients' quality of life.

Improvement of symptoms is an important aspect of the efficacy evaluation of Chinese patent medicines. For example, in a clinical study of a kidney-tonifying and phlegm-transforming formula, researchers followed up with patients with intermediate and advanced liver cancer who received treatment with the formula for 3 months. The background to the investigation was understood: the kidney-strengthening and phlegm-transforming formula has the theoretical effect of tonifying the kidney and strengthening yang, resolving phlegm and softening hard lumps in traditional Chinese medicine, and can achieve an anti-tumor effect by enhancing the body's immune function and improving the internal environment. The results of the study showed that the patient's symptoms such as fatigue, abdominal distension and loss of appetite improved significantly after treatment, with more than 70% of patients reporting a reduction in symptoms. At the same time, the patient's overall quality of life score improved by more than 30% compared to before treatment [7].

Prolonged survival is one of the most clinically meaningful indicators in the efficacy evaluation of Chinese patent medicines. A number of studies have shown that Chinese patent medicines can prolong the survival of liver cancer patients through various mechanisms. These mechanisms include regulating the tumor immune microenvironment, inhibiting tumor cell proliferation and metastasis, inducing tumor cell apoptosis, and improving the overall physical condition of patients. Through these combined effects, Chinese patent medicines are not only effective in locally controlling tumor growth, but also enhance the patient's ability to fight the disease and improve their tolerance of treatment.

Changes in tumor marker levels are another commonly used indicator of efficacy. Alpha-fetoprotein (AFP) is one of the most commonly used tumor markers for liver cancer, and changes in its level often reflect tumor activity. Many studies have shown that Chinese patent medicines can significantly reduce AFP levels, suggesting their potential to inhibit tumor activity. In a study using Chinese patent medicine for treatment, the researchers found that the tumor volume had significantly shrunk using imaging

methods, and that tumor necrosis had occurred in some patients, which further verified the anti-tumor effect of Chinese patent medicine. Imaging assessment provides objective evidence of the efficacy of Chinese patent medicine.

4. Experimental studies on the mechanism of action of Chinese patent medicines

4.1. Mechanism of regulation of Chinese patent medicines in the tumor immune microenvironment

Alterations in the tumor immunological microenvironment can profoundly influence tumor development, metastasis, and therapeutic response. Research on primary liver cancer has revealed immunosuppression within the tumor immune microenvironment, primarily characterized by the augmented activity of pro-tumor immune cells. These cells can suppress anti-tumor immune responses, facilitate immunological evasion, and diminish the body's immune monitoring of malignancies.

Traditional Chinese medicine (TCM) has increasingly emerged as a significant area of research for liver cancer treatment by modulating the immune microenvironment and demonstrating anti-tumor effects through several mechanisms. Traditional Chinese Medicine (TCM) can suppress the activity of regulatory T cells and tumor-associated macrophages, diminish their immunosuppressive effects, and augment the anti-tumor efficacy of effector T cells and Natural Killer (NK) cells, thereby reinstating the body's immune surveillance capabilities and enhancing the effectiveness of anti-tumor immune responses. This multifaceted regulatory influence provides TCM with a distinctive edge in the management of liver cancer.

4.1.1. *Regulating the function of tumor-infiltrating immune cells*

Traditional Chinese medicine can improve the tumor immune microenvironment by regulating the number and function of tumor-infiltrating immune cells. For example, Astragalus membranaceus, Atractylodes macrocephala, and other traditional Chinese medicine ingredients have been widely studied and found to promote the migration and aggregation of Tumor-Infiltrating Lymphocytes (TILs), increase the number and activity of these cells in the tumor microenvironment, and significantly enhance the body's anti-tumor immune surveillance function. Astragalus membranaceus has been found to significantly increase the number and function of T cells, Natural Killer (NK) cells and Dendritic Cells (DCs), and promote the anti-tumor role of immune cells in the tumor microenvironment [8].

4.1.2. *Inhibit the activity of immunosuppressive cells*

Tumor-Associated Macrophages (TAMs) are important immunosuppressive cells in the tumor immune microenvironment. They are usually polarized in the M2 type, which has the effect of promoting tumor growth and suppressing immune responses. They mainly support tumor progression by secreting anti-inflammatory cytokines and promoting tissue repair. Traditional Chinese medicine can inhibit the M2 polarization of TAMs by regulating their polarization state, promoting the transformation of these macrophages to the M1 phenotype. M1 macrophages are an anti-tumor phenotype with pro-inflammatory effects, capable of secreting large amounts of pro-inflammatory cytokines such as TNF- α and IL-1 β . These factors can activate other immune cells, enhance the anti-tumor immune response, and directly attack and kill tumor cells.

4.1.3. *Regulate immune escape-related pathways*

Traditional Chinese Medicine (TCM) has shown unique advantages in regulating the PD-1/PD-L1 pathway. For example, matrine and baicalin have been found to effectively inhibit PD-L1 expression, relieve the suppression of T cells, and enhance the anti-tumor activity of T cells. By inhibiting immune escape-related pathways, Chinese patent medicines can restore and enhance the body's anti-tumor immune function, so that the immune system can more effectively recognize and attack tumor cells. This not only helps to inhibit tumor growth, but also further improves the patient's response rate to immunotherapy, thereby significantly improving the overall treatment effect.

4.2. Influence of Chinese patent medicine on tumor cell metabolism

Abnormal tumor cell metabolism is an important feature of tumor development. Chinese patent medicine can inhibit tumor cell proliferation, migration and invasion by regulating tumor cell metabolic pathways, thereby exerting an anti-tumor effect.

4.2.1. *Inhibit the glycolytic pathway of tumor cells*

Glycolysis serves as a crucial energy source for neoplastic cells. Numerous tumor cells preferentially derive energy via glycolysis, even in the presence of oxygen, a phenomenon referred to as the "Warburg effect".

Glycolysis not only provides energy for tumor cells, but also produces a variety of metabolites, such as lactic acid and pyruvate. These metabolites can promote tumor growth and metastasis by acidifying the tumor microenvironment and promoting

angiogenesis. Chinese patent medicines have shown significant effects in inhibiting glycolysis. For example, matrine has been found to significantly inhibit the activity of key glycolytic enzymes in tumor cells, such as Hexokinase (HK) and Lactate Dehydrogenase (LDH), thereby reducing the energy supply of tumor cells and inhibiting their proliferation [9]. However, considering that glycolysis is not only active in tumor cells, but normal cells (such as red blood cells) also rely on glycolysis for energy, the side effects of this therapy require special attention.

4.2.2. Regulate lipid metabolism

Tumor cells usually exhibit enhanced lipid metabolism to maintain the synthesis of membrane lipids required for rapid proliferation. Alterations in lipid metabolism not only provide structural materials for tumor cells, but also participate in regulating tumor growth and invasion through signal molecules. Chinese patent medicines have also shown significant anti-tumor effects in regulating lipid metabolism. Studies have found that some traditional Chinese medicines such as *Hedyotis diffusa* Willd. and *Isatis tinctoria* L. can inhibit the activity of Fatty Acid Synthase (FASN), reduce the synthesis of tumor cell membrane lipids, and thus inhibit tumor growth and spread.

5. Research outlook

Future research should focus on the following areas:

Basic research: In-depth exploration of the molecular mechanisms of action of Chinese patent medicine ingredients, especially their role in regulating the tumor immune microenvironment and tumor metabolism, is one of the important directions of future research. Existing studies have shown that Chinese patent medicines such as astragalus and salvia have played a significant role in anti-tumor therapy through multi-targeted and multi-pathway mechanisms. Future basic research should further explore the specific molecular mechanisms of these Chinese medicine ingredients and clarify how they regulate tumor immune responses and metabolic pathways at the cellular and molecular levels. This will not only help to understand the anti-tumor mechanism of Chinese medicine, but also provide a scientific basis for the development of new and more effective Chinese medicine treatment regimens. In addition, exploring the mechanism of the combined action of Chinese medicine's multi-target, such as how to simultaneously regulate immune responses and metabolic processes to achieve better anti-tumor effects, is also an important direction for basic research.

Clinical trials: Execute extensive, multi-center clinical trials to validate the clinical efficacy and safety of Chinese patent medicines, thereby enhancing the reliability of evidence.

Integrative medicine: Integrative medicine has shown unique advantages in the treatment of tumors. Future research should explore the combination strategies of Chinese patent medicines and modern medical methods (such as targeted therapy and immunotherapy) to achieve synergistic therapeutic effects. For example, in the treatment of liver cancer, modern medicine's targeted therapy and immunotherapy can precisely attack tumor cells and inhibit their growth and metastasis, but are often accompanied by large side effects, such as immune-related Adverse Reactions (irAEs) and drug resistance. Traditional Chinese medicine can alleviate these side effects and enhance the therapeutic effect through its multi-target regulatory effect. In addition, the holistic conditioning effect of traditional Chinese medicine can improve patient tolerance and reduce adverse reactions caused by targeted therapy and immunotherapy. This strategy of combining Chinese and Western medicine not only prolongs patients' survival time, but also improves their quality of life and provides a more personalized and comprehensive treatment plan.

6. Conclusion

This study systematically explored the multifaceted role of Chinese patent medicines in the treatment of primary liver cancer, revealing their molecular mechanisms by regulating the immune microenvironment, affecting tumor cell metabolism, inhibiting tumor proliferation and metastasis, and inducing tumor cell apoptosis. The results of this study show that Chinese patent medicines have significant therapeutic potential and can provide new treatment options for liver cancer patients, and may synergize with traditional treatments to improve treatment outcomes. Although this study has revealed the role of some Chinese patent medicines in regulating the immune microenvironment and tumor metabolism, the multi-target molecular mechanism of Chinese patent medicines still needs to be further elucidated. Future research should use more refined molecular biology techniques, such as genome editing and single-cell sequencing, to explore in depth how Chinese patent medicines precisely regulate multiple biological processes of tumors at the molecular level.

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