

# Feasibility Study of Yuejuwan as an Adjuvant Therapy for Primary Liver Cancer

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**Abstract:** *Primary liver cancer is one of the common malignant tumours of the digestive system in clinical practice, and in the modern healthcare system, the therapeutic efficacy of primary liver cancer and the quality of patients' survival have always been the focus of medical research. In the face of this challenge, traditional Chinese medicine (TCM) offers unique perspectives and potential solutions, among which Yuejuwan, as a traditional Chinese medicine prescription with a long history, has attracted widespread attention for its application value in the treatment of primary liver cancer. This paper discusses and analyses the treatment of primary liver cancer in terms of the etiology and pathogenesis of liver cancer, the types of evidence, as well as the rationale and prescription of Yuejuwan, and the study of its pharmacological effects, aiming at exploring the feasibility of Yuejuwan as an adjuvant therapy in the treatment of primary liver cancer and its mechanism of action. It provides a new understanding of the identification and treatment of primary liver cancer, in order to improve the clinical efficacy of primary liver cancer, and to achieve the purpose of alleviating the pain of patients and improving the quality of their survival.*

**Keywords:** Yuejuwan, Primary liver cancer, Traditional Chinese medicine, Malignant tumour, Adjuvant therapy.

## 1. Introduction

As one of the malignant tumours with high incidence rate and high mortality rate in China, according to the latest data from National Cancer Centre based on tumor registration and follow-up monitoring, liver cancer is the fifth most common malignant tumour in China, while the mortality rate is the second most common malignant tumour in China, second only to lung cancer, and primary liver cancer includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and mixed HCC-ICC type of liver cancer. HCC accounts for about 90% of the primary liver cancers, which has insidious symptoms, rapid development, easy metastasis, and because the liver is the only organ in the human body without pain nerves, most of the patients are in the middle or late stage of the disease when they are diagnosed, and they have lost the opportunity of early radical surgical treatment, and most of the patients are accompanied by hepatitis B and cirrhosis, and have a high rate of postoperative recurrence, and the recurrence and metastasis rate of tumors within 5 years after liver cancer resection is as high as 50% - 70%. [1]. In exploring the therapeutic field of primary liver cancer (PLC), the integration of TCM and modern medicine presents new therapeutic strategies, and TCM makes important contributions to the prevention and treatment of PLC by prolonging the survival time, delaying tumour recurrence and metastasis, improving the quality of life, and alleviating the symptoms, truly achieving 'survival with tumour' [2]. Among them, Yuejuwan, as a traditional Chinese medicine compound with a long history, has shown potential value in the adjuvant treatment of PLC in recent years. In view of the fact that patients with primary liver cancer are often accompanied by the symptoms of qi stagnation and blood stasis in clinical treatment, Yuejuwan, with its properties of activating blood circulation, removing blood stasis and detoxifying the liver, theoretically can provide the possibility of adjuvant treatment for such patients. In this paper, we will explore the feasibility of Yuejuwan as an adjuvant treatment for PLC, and illustrate its application

prospect in PLC treatment by analysing its pharmacological mechanism, clinical findings and comparison with traditional treatment methods.

## 2. Current Status of Domestic Research

In exploring the feasibility of Yuejuwan as an adjuvant treatment for primary liver cancer, the current status of research at home and abroad presents an attitude of active exploration. Despite the remarkable progress made by modern medicine in the field of tumour treatment, there is still an urgent need to improve the quality of patients' survival and reduce the side effects of drugs. In this context, traditional Chinese medicine, with its unique therapeutic concepts and means, provides new perspectives and possibilities for the comprehensive treatment of liver cancer.

The attention of domestic researchers on Yuejuwan is mainly focused on its antidepressant effect and its potential to improve the quality of life of primary liver cancer patients. Yuejuwan, as a classic traditional Chinese medicine prescription, has been proven to be effective in regulating mood and alleviating depressive symptoms by several studies. This antidepressant property of Yuejuwan is particularly important considering that liver cancer patients are often accompanied by depressed mood and reduced quality of life. As shown in a study of patients with tumour-associated depression of the liver-depression and qi stagnation type, treatment with the addition and subtraction of the 16-flavour Liuqi Drink significantly improved the patients' depressive symptoms and quality of life [3]. This further confirms the uniqueness of traditional Chinese medicine in regulating mood and improving quality of life.

However, the application of Yuejuwan in the treatment of primary liver cancer is not without challenges. How to scientifically quantify its therapeutic effect, clarify its applicability in patients with different stages of liver cancer, and how to synergise with modern medical treatments are all

issues that need to be thoroughly explored in the current study. Meanwhile, considering the complexity of traditional Chinese medicine compounding, how to ensure the stability and reliability of its efficacy is also a part that cannot be ignored in the process of promoting the application of Yuejuwan.

In conclusion, although the domestic research on Yuejuwan as an adjuvant treatment for primary liver cancer has achieved certain results, more high-quality clinical trials and in-depth mechanism studies are still needed to comprehensively assess its efficacy and application prospects. Through these efforts, it is expected that a more comprehensive and personalised treatment plan will be provided to patients with primary liver cancer, thus improving their quality of life and prolonging their survival.

### 3. Current Status of Foreign Research

Yuejuwan, a time-honoured traditional Chinese medicine formula, has attracted much international attention in recent years, particularly in exploring its potential as an adjuvant treatment for primary liver cancer. The complexity and therapeutic difficulty of primary liver cancer as a global health problem have prompted researchers to seek more diverse treatment strategies. In this context, traditional Chinese medicine (TCM) provides a rich pool of resources, and Yuejuwan has attracted much attention due to its unique pharmacological effects.

Overseas studies have mainly focused on analysing the main bioactive components in Yuejuwan and its mechanism of influence on hepatocellular carcinoma cells. Through in-depth analysis of the chemical composition of the volatile oil of Yuejuwan, researchers have identified a variety of compounds with potential antitumour activity, mainly including monoterpenes and sesquiterpenes [4]. These compounds showed inhibitory effects on the growth of hepatocellular carcinoma cells in in vitro experiments, revealing their possible mechanisms of action at the molecular level, such as regulating the cell cycle and inducing apoptosis in cancer cells.

Further studies verified the antidepressant effect of Yuejuwan extract through animal models, a finding that is particularly important. Depression often accompanies the long-term treatment process of hepatocellular carcinoma patients, which seriously affects their quality of life and therapeutic effects. The positive effect of Yuejuwan in improving the behavioural performance of chronic unpredictable mild stress (CUMS) mice provides a new perspective for its application in the comprehensive treatment of hepatocellular carcinoma. Specifically, Yuejuwan demonstrated its potential in improving depression-related cerebral blood flow and optimising nerve conduction pathways by modulating neurotransmitter and protein expression. In addition, Yuejuwan showed significant effects on improving the balance of neurotransmitters in depressed patients, especially in increasing ERK/AKT-mediated GLT-1 expression to clear glutamate.

However, the safety and efficacy of Yuejuwan in clinical applications still require further rigorous evaluation. Although preliminary toxicological evaluations suggest that Yuejuwan

has low acute toxicity, long-term efficacy observation and monitoring of potential side effects remain indispensable. In addition, more systematic and in-depth studies are needed on its synergistic effects with existing liver cancer treatment regimens, as well as variable responses in different individuals.

In summary, the current status of foreign studies suggests that the scientific value and medical potential of Yuejuwan as a potential adjuvant therapy for primary liver cancer is gradually being explored. Future studies need to further explore its specific pharmacological mechanism, optimize the drug formulation, and conduct large-scale clinical trials to ensure its safety and efficacy, so as to better serve the comprehensive treatment needs of liver cancer patients.

### 4. Primary Liver Cancer from the Perspective of Traditional Chinese Medicine

The liver likes to be organised and is not depressed, and 'Su Wen - Ling Lan Secret Canon' says: 'The liver is the official of the general, and it is the source of planning and thinking.' One of the most important physiological functions of the liver is that the liver is the master of detachment, which means that the liver has the ability to unclog and unimpeded the qi of the whole body, thus regulating the operation of essence, blood and fluid, the lifting and lowering of the qi of the spleen and stomach, the secretion and excretion of bile, as well as the role of emotional and spiritual activities. Liver loss of detachment is mainly manifested in three aspects: one for the liver qi stagnation, detachment failure. Mostly due to depression, anger and injury to the liver. Secondly, the liver qi hyper-reversal, too much excretion. Mostly due to anger and injury to the liver, or qi depression for a long time, resulting in fire. 'Su wen - regulating the theory of 'said:' blood and gas and go on, then for the big syncope, syncope is violent death, gas back (return) is born, not against is dead.' Thirdly, liver qi is weak, not as good as the excretion, rise and rise, showing a series of clinical manifestations due to deficiency and stagnation. 'The Spiritual Pivot - Ben Shen' says: 'Liver qi deficiency leads to fear.' 'Su wen - Tibetan gas law theory' said: 'the virtual is the eye Wan Wan dirty no see, ear no hear.' Liver main drainage, it can also be on the distribution of fluid also has a regulatory role, if the liver qi stagnation, drainage dereliction of duty, gas stagnation and fluid stop, breeding phlegm, water and wet and other pathological products, the development of wet and phlegm depression. Therefore, the loss of liver detachment, qi dysregulation can directly lead to the production of six depression [5]. Primary liver cancer is mainly caused by emotional depression, dietary injury, post-disease weakness, jaundice, etc., so that the liver and spleen are damaged, viscera and bowels are out of harmony, qi stagnation, stagnation of silt and blood, coagulation for a long period of time, and accumulation of lumps. As the 'medical must read' said: 'the accumulation of also, the positive gas is not enough and then the evil gas in the house.' There is no specific name of 'liver cancer' in the classics of Chinese medicine, but in modern medicine, it can be categorised as 'liver accumulation', 'accumulation' according to the symptoms and signs of patients, 'Jaundice'. For example, 'Yellow Emperor's Classic of Internal Medicine': 'Drowning yellow and red, lying down peacefully, jaundice..... eye yellow is said to be jaundice', 'The face is

slightly yellow, the teeth scale is yellow, the claws and nails are yellow, jaundice is also jaundice, lying down peacefully, urination is yellow and red.' [6]. In the early stage of liver cancer, it is often caused by emotional disorders. At this time, the body's qi is not smooth, and the phenomenon of liver depression and qi stagnation is highlighted. Liver depression and qi stagnation then leads to abnormal blood movement, and the state of qi stagnation and blood stasis gradually becomes established. Blood stasis continues to accumulate, blocking the veins and channels, and eventually accumulates under the dermatome, resulting in liver stagnation.

## 5. Pharmacological Actions of Yueju Pills

### 5.1 Regulation of Emotion and Nervous System

Yuejuwan has antidepressant effects, and its mechanism of action may be achieved by increasing the expression of pituitary adenylate cyclase-activating polypeptide (PACAP) and its receptor PAC1-R, which in turn regulates the expression of brain-derived neurotrophic factor (BDNF) [7]. By regulating the function of the nervous system and improving the psychological state of patients, it helps to maintain the overall balance of the organism. As revealed in the literature [4], the active ingredients in the volatile oil of Yuejuwan can effectively remove glutamate, thereby alleviating depressive symptoms and improving the quality of life of patients, which provides a new way of thinking about the treatment of PLC patients from both physiological and psychological perspectives. From the perspective of pharmacological composition, the main active ingredients in the volatile oil of Yuejuwan, including monoterpenes and sesquiterpenes, as well as a small number of aromatic and aliphatic compounds, provide a basis for understanding its efficacy. In particular, five of the endemic compounds, whose unique presence in YJVO suggests that the composite formula may have a synergistic effect beyond that of the herbs alone. This synergistic effect may act as an antidepressant by enhancing ERK/AKT-mediated GLT-1 expression to scavenge glutamate. Although this mechanism was revealed in a model of depression, it provides clues to explore the possible bioactivity of Yuejuwan in tumour therapy. Disturbed glutamate metabolism in the tumour microenvironment is closely related to tumour growth and invasiveness, and modulation of this pathway may have an inhibitory effect on tumour development.

### 5.2 Improvement of Digestive System Function

Cangzhu, Shenzhu and other ingredients help to improve the function of the digestive system. It can promote gastrointestinal peristalsis, enhance the secretion of digestive juices, improve appetite, and help patients better absorb nutrients [8]. It can improve the structure of duodenal villi, which helps to improve the absorption of nutrients in the duodenum and maintain the normal physiological function of the intestinal tract. Meanwhile, Yuejuwan can reduce the levels of serum inflammatory factors IL-6 and TNF- $\alpha$  [7], which indicates that Yuejuwan has an anti-inflammatory effect, which can reduce the inflammatory response of the intestinal tract and alleviate the symptoms of dyspepsia caused by inflammation. In addition, increasing gastrointestinal motility can promote the digestion and

emptying of food in the gastrointestinal tract and reduce food retention, thus improving the symptoms of abdominal distension, abdominal pain, and loss of appetite in patients with functional dyspepsia. In conclusion, Yueju Pills provide an effective option for the treatment of functional dyspepsia. It has a certain alleviating effect on the symptoms of dyspepsia and loss of appetite which are often seen in patients with liver cancer.

### 5.3 Regulating the Operation of Qi and Blood

Chuanxiong and other ingredients have the effect of activating blood circulation and removing blood stasis, which can improve the state of abnormal blood circulation. It promotes blood circulation, reduces the formation of blood stasis and prevents stagnation of the veins. It helps to improve the blood supply to the liver and reduce the symptoms of blood stasis in the liver, and has a certain regulating effect on the pathological changes caused by qi stagnation and blood stasis in the early stage of liver cancer.

### 5.4 Anti-tumour and Regulating Immune Function

The pharmacodynamic components of Yuejuwan are complex, including a variety of natural compounds with antitumor activity, such as cyclic enol ether terpene glycosides in gardenia with antitumor and hepatoprotective effects [9]; Fang Guoying [10]. et al. learnt that, among the various extracts of *Fragrance adenophora*, the petroleum ether extract showed a better antitumor effect; Chuanxiong ligusticum, one of the main components of Chuanxiong ligusticum, can have antitumor effects on liver cancer cells through a variety of pathways, and it can also regulate immunity function. One of the main components of *Ligusticum chuanxiong*, Chuanxiongizine, can inhibit the proliferation of various types of tumour cells, such as hepatocellular carcinoma cells, lung carcinoma cells, breast carcinoma cells, glioma cells, and melanoma cells, through a variety of pathways [11]. It may also have a certain regulatory effect on the immune function of the organism. By enhancing the body's immunity and improving the patient's resistance to the tumour, it helps to control the development of hepatocellular carcinoma, and at the same time reduces the state of immunosuppression brought about by the tumour and treatment.

In conclusion, through multifaceted pharmacological effects, Yueju Pill has a certain regulating and improving effect on pathological changes in the early stage of liver cancer due to emotional and emotional disorders, poor qi, liver depression and qi stagnation, abnormal blood transport, qi stagnation and blood stasis, and so on.

## 6. Relationship between Liver and Yuejuwan for Treating Six Depressions

Yue Ju Wan is a classic formula for the treatment of the six depressions (Qi, Blood, Phlegm, Fire, Dampness, and Food) from Zhu Dan Xi's *Dan Xi Xin Fa* (The Heart Method of Dan Xi), which was written by Zhu Dan Xi, a medical practitioner of the Yuan Dynasty. From the viewpoint of Chinese medicine theory, the occurrence of depressions is mostly due to emotional disorders and stagnation of qi, while the operation of qi in the human body is closely related to the

liver's function of detoxification.

### 6.1 Association of the Liver with the Six Depressions

1) Qi stagnation and the liver: the liver is the main regulator of Qi. If liver qi is stagnant, the qi of the whole body will not be smooth, resulting in qi depression. Qi depression is a key factor in the formation of the six depressions, and is often the basis for other depressions.

2) Blood depression and the liver: The liver hides blood and is the main regulator. Liver qi stagnation can affect the operation of blood, leading to blood stagnation due to poor blood circulation.

3) Phlegm Depression and Liver: Liver-Qi stagnation and Qi dysfunction can affect the transmission and distribution of fluids, which may accumulate into phlegm and form Phlegm Depression. At the same time, Liver depression transforms fire and refines fluid into phlegm, which can also aggravate phlegm depression.

4) Fire Depression and Liver: If the liver is depressed for a long time, it will easily turn into fire, forming fire depression. Liver fire inflammation, headache, red eyes, bitter mouth and other symptoms. 5.

5) Dampness and the liver: the liver is the main excretory, which helps the spleen's function of transporting and transforming water and dampness. If liver qi stagnation, can affect the spleen's transport, resulting in water-dampness internal storage, the formation of dampness.

6) Depression of food and the liver: The liver is the main regulator of excretion, which promotes the digestive function of the spleen and stomach. Liver qi stagnation may affect the transport and digestion of the spleen and stomach, leading to stagnation of food and drink and formation of food stagnation.

### 6.2 Effects of Yuejuwan on the Liver

In Yue Ju Pill, Xiang Fu moves qi and relieves depression to treat qi depression, and is the monarch drug, which has the efficacy of dredging the liver and regulating the emotions and moods. It can relieve the state of liver depression and stagnation of qi caused by emotional disorders, and reduce anxiety, depression and other adverse emotions. Rhizoma Chuanxiong activates blood circulation and dispels blood stasis to treat blood depression, Rhizoma Atractylodis Macrocephalae dries dampness and transports the spleen to treat dampness and depression, Gardenia jasminoides clears heat and laxes fire to treat fire depression, and Divine Quatre subdues food and channels stagnation to treat food depression. The whole formula regulates the excretory function of the liver to relieve qi depression, which in turn has a positive therapeutic effect on the other five depressions.

In conclusion, in Chinese medicine theory, the dysfunction of the liver is closely related to the formation of depression, and the liver plays an important role in the formation and development of six depressions, and Yueju Pills from the perspective of Chinese medicine through regulating the functions of the liver and related organs to achieve the

purpose of solving six depressions, to solve the 'six depressions', and has a better effect on the various depressions caused by dysfunction of the liver. It has better therapeutic effects on various depression symptoms caused by liver dysfunction.

## 7. Limitations of the Study

In exploring the feasibility study of Yue Ju Wan as an adjuvant treatment for primary liver cancer, we need to pay attention to the trend of its development, which involves the integration of new insights into traditional Chinese medicine formulations with modern medical research. Yue Ju Wan, a long-established Chinese medicine compound formula, works mainly by regulating Qi stagnation in the body and resolving blood stasis. In modern medicine, the potential value of this drug lies in its potential to intervene in the process of liver cancer development through a multi-pathway, multi-targeted approach.

Despite the long history of use of Yuejuwan in traditional Chinese medicine theory, its integration into the modern medical system still faces many challenges. Most studies have small sample sizes and lack multi-centre, large-sample randomised controlled trials; its mechanism of action is complex and variable, leading to difficulties in standardisation and batch production. Furthermore, as the ingredients of TCM compound formulas are diverse, in-depth investigation is required to determine the active ingredients and their optimal ratio, as well as to assess long-term efficacy and safety. From the design of clinical trials to regulatory approvals, every step of the process requires scientific methodology and strict standards to ensure patient safety and drug efficacy. Moreover, the mechanism of efficacy of Yueju Pills is not yet fully understood. Although existing studies suggest that it may work by modulating certain biomarkers, most of these findings are based on in vitro experiments or animal models. Therefore, it is questionable whether these results can be directly generalised to humans. In addition, liver cancer itself is a highly complex disease involving alterations in multiple genes and signalling pathways, making it difficult for a single drug to achieve a comprehensive therapeutic effect.

It should also be noted that Yueju Pills, as a Chinese medicine compound, the standardisation of its production and quality control is another issue that should not be ignored. The quality of Chinese herbal medicines is affected by a variety of factors such as origin, collection and processing, which may lead to differences in the efficacy of the finished product. Therefore, ensuring the consistency and reliability of each batch of Yueju Pills is a prerequisite for realising its clinical application. In summary, the feasibility study of Yueju Pills as an adjuvant therapy for PLC is still in its infancy and needs to be supported by more in-depth clinical trials and mechanistic studies. As with all drug studies, the safety assessment of Yuejuwan is an indispensable part before promoting its application. Although existing studies have shown no significant adverse effects of Yueju Pills, the long-term effects and side effects still need further scientific verification.

## 8. Summary

In this article, we explored the feasibility of Yuejuwan as an adjuvant treatment for primary liver cancer, and through in-depth analyses of the literature and the results of relevant clinical trials, a series of illuminating conclusions were drawn.

Firstly, it is worth focusing on the fact that Yuejuwan has been remarkably effective in alleviating depressive symptoms. This was fully evidenced in a clinical study on the treatment of patients with tumour-associated depression of the liver-depression and qi stagnation type with the addition and subtraction of 16-flavour Liuqi Drink. The study showed that the KPS score, SDS score and HAMD-17 score of the patients showed significant improvement after the treatment with the addition of Shiliwei Liuqi Drink, and the difference was statistically significant compared with that of the control group ( $P < 0.05$ ) [3]. This result not only confirmed the excellent efficacy of Yuejuwan in improving depressed mood, but also implied its potential value in enhancing patients' quality of life.

Further, the role of Yuejuwan in regulating qi and blood and dredging the Sanjiao should not be overlooked. As described by Zhang Mengmeng et al, the treatment of cancer pain can be approached from the perspective of San Jiao therapy [12], in which the pathological changes of the 'three stasis' (i.e., qi stagnation, blood stasis, and phlegm stasis) are regarded as the core pathomechanism of cancer pain. As a traditional Chinese medicine formula capable of activating blood stasis and relieving liver stasis, Yuejuwan has a promising application in this field. In addition, the compounds in the volatile oil of Yuejuwan also show potential antidepressant effects on the regulation of neurotransmitters and protein expression, as evidenced by the study of Bike Z et al. They found that Yuejuwan volatile oil was able to exert antidepressant effects by upregulating ERK/AKT-mediated GLT-1 expression to clear glutamate [4].

In summary, the feasibility of Yuejuwan as an adjuvant treatment for primary liver cancer is not only reflected in its improvement of depressive symptoms, but also in its unique advantages in regulating qi and blood and improving the overall condition of patients. Although existing studies have preliminarily confirmed the efficacy and application potential of Yuejuwan, future studies need to further explore its applicability and mechanism of action in patients with different types of tumours, with a view to providing more clinical basis and therapeutic options for the comprehensive treatment of primary liver cancer.

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