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Current Research on the Application of Xuefu Zhuyu Decoction and Its Modifications in the Treatment of Lung Cancer

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Abstract: ***Xuefu Zhuyu Decoction is a representative formula for treating "blood stasis syndrome" established by Wang Qingren in the Qing Dynasty. The formula consists of peach kernel, safflower, angelica, rehmannia, achyranthes, ligusticum, platycodon, red peony root, bitter orange, licorice, and bupleurum. Its primary therapeutic effects include activating blood circulation, resolving blood stasis, promoting qi flow, and alleviating pain. Xuefu Zhuyu Decoction and its modified versions have been widely used in modern clinical practice. This article summarizes and analyzes recent research on the application of Xuefu Zhuyu Decoction and its modifications in the treatment of lung cancer and related diseases. The review focuses on the mechanisms of action and clinical efficacy of Xuefu Zhuyu Decoction and its modifications in treating lung cancer and associated conditions.***

Keywords: Xuefu Zhuyu Decoction, Lung cancer, Mechanisms of action, Tumor mass, Review**.**

1. Introduction

Primary bronchial lung cancer, commonly referred to as lung cancer, is one of the most prevalent malignant tumors worldwide. Recent reports indicate that in China, lung cancer leads in both the incidence and mortality rates among all types of malignant cancers [1]. By the time lung cancer patients seek medical attention, many are already at intermediate or advanced stages, which significantly increases the difficulty of treatment. At present, aside from early-stage and some stage III lung cancers that may be treated with surgery, the majority of patients still rely on chemotherapy as the primary treatment modality. However, chemotherapy often causes a range of adverse effects, including bone marrow suppression, gastrointestinal disturbances, cardiotoxicity, drug-induced liver injury, and peripheral neuropathy. These side effects not only increase patient suffering but also limit the therapeutic efficacy.

Currently, traditional Chinese medicine (TCM) has gained some recognition in the field of adjunctive treatment for malignant tumors. A review of the relevant literature reveals that Xuefu Zhuyu Decoction, as a representative formula for activating blood circulation and resolving blood stasis, has been extensively applied in the treatment of malignant tumors. This paper reviews research conducted in the past decade on the use of Xuefu Zhuyu Decoction in the treatment of lung cancer and related diseases. It preliminarily explores its mechanisms of action and clinical efficacy, aiming to provide clinical reference and offer insights for future research.

2. The Traditional Chinese Medicine Understanding of Lung Cancer

Primary bronchial lung cancer, or simply lung cancer, is characterized by clinical manifestations such as cough, sputum production, hemoptysis, wheezing, and chest tightness. Although Traditional Chinese Medicine (TCM) does not specifically categorize lung cancer, its symptoms are similar to conditions like "lung accumulation" and "xibi," both of which fall under the broader category of "tumor accumulation" or "zhengji" in TCM. The *Nan Jing* (Classic of Difficulties) records that "the accumulation of the lung, called ‘xibi,’ is located below the right rib, large like a cup. If not treated for a long time, it causes chills, fever, wheezing, cough, and blockage of the lung".

Regarding the etiology and pathogenesis of lung cancer, the prevailing view is that it is caused by a deficiency of the body's vital qi (Zheng Qi) combined with the presence of pathogenic factors. The *Yi Zong Bi Du* states: "The formation of accumulation is due to insufficient vital qi, which allows evil forces to take hold". The lungs are considered a delicate organ, opening to the nose and communicating with the outside world, making them vulnerable to invasion by external pathogens. When the body’s vital qi is insufficient, the ability to resist these pathogens is weakened, allowing them to invade the body. In addition, the deficiency of vital qi leads to stagnation of the pathogenic factors, preventing their expulsion and causing a blockage in the chest. This results in dysfunction of the lung’s ability to diffuse and descend qi, poor distribution of fluids, and the formation of phlegm. As qi and blood flow becomes obstructed, the stagnation of both phlegm and blood leads to the development of toxicity and accumulation.

Pang Dacheng and others believe that "Yang transforms into qi, and Yin forms the material body," which is a succinct summary of the development of malignant tumors in the *Nei Jing* (Inner Canon), with cold evils being a key factor in the formation of tumors [2]. The imbalance between Yin and Yang usually begins with the Yang deficiency, as Yang transforms into qi and the material form follows. As the body's Yang is impaired, Yin fluid stagnates, leading to the accumulation of phlegm and blood, which further exacerbates the condition. Professor Liu Jiaxiang similarly posits that the occurrence of tumors is closely related to the deficiency of

vital qi and the imbalance between the body's internal forces [3]. As the body ages, qi, blood, Yin, and Yang gradually become deficient, leading to weakened vital qi and an inability to resist external pathogens, as well as an inability to promote the movement of qi and blood. This stagnation results in the production of pathological substances such as phlegm, blood stasis, and toxins.

Other views suggest that the primary pathogenesis of lung cancer is characterized by deficiency of vital qi, combined with phlegm, damp-heat toxicity, and Yin deficiency. Professor Zhang Daizhao believes that the key to the development of lung cancer lies in the stagnation of qi and blood stasis. When vital qi is insufficient, it is unable to promote the movement of qi and blood, leading to the gradual formation of blood stasis. This causes the lung to lose its nourishment from blood and Yin, while external heat damages the lung's Yin, leading to a deficiency of lung Yin. The heat from both internal and external sources further damages the body's fluids and promotes the formation of phlegm. The prolonged condition results in phlegm and blood stasis that obstruct the lung, damaging its Yin fluid. Post-surgical and post-chemotherapy lung cancer patients suffer even more severe depletion of Yin, blood, and body fluids, making lung Yin deficiency inevitable [4].

Professor Lu Zhizheng also believes that lung cancer is caused by a deficiency of vital qi leading to blood stasis. The most common patterns in lung cancer are Yin deficiency and a combination of Qi and Yin deficiency. The basic principles of treatment are tonifying Qi, nourishing Yin, regulating Qi, transforming phlegm, eliminating blood stasis, resolving masses, and detoxifying to combat cancer. Based on these principles, he developed the *Yi Lung Hua Ji Decoction* [5].

Some scholars suggest that the occurrence of lung cancer is related to constitution. Chen Shixian et al. [6] propose that lung cancer arises from changes in body constitution, with different constitutions influencing the pathogenic factors, susceptibility, pattern differentiation, and the transformation and prognosis of the disease. Deficiency of vital qi and blood stasis are considered major causes of lung cancer metastasis and recurrence. They also suggest that individuals with a Qi-deficient, Yin-deficient, or blood stasis constitution are more prone to developing lung cancer.

The discussions on the etiology and pathogenesis of lung cancer in TCM mainly focus on three factors: "vital qi deficiency," "Yin fluid deficiency," and "phlegm, blood stasis, and toxins." Vital qi deficiency underlies the entire progression of lung cancer. As the lungs control the body’s qi, and the spleen is the source of qi and blood production, both organs are involved. On one hand, external pathogens obstruct the lung’s channels, causing dysfunction of the respiratory function, disrupted qi and fluid circulation, and depletion of vital qi. On the other hand, the lung, as the "child" of the spleen, is affected by the spleen's dysfunction over time, resulting in a deficiency of both organs' qi, impairing fluid metabolism and leading to dampness and phlegm accumulation. This accumulation gradually leads to blood stasis. Moreover, because the lungs are the "mother" of the kidneys, long-term illness can also affect the kidneys, leading to Qi stagnation and imbalance in fluid metabolism, ultimately contributing to phlegm, blood stasis, and depletion of lung Yin.

In conclusion, the fundamental pathogenesis of lung cancer in TCM is vital qi deficiency, with a pathological process that involves Qi deficiency, Yin deficiency, and a combination of both. The main affected organs are the lung, spleen, and kidney, and the pathological products are commonly phlegm, blood stasis, and toxins.

3. Analysis of the Original Formula of Xuefu Zhuyu Decoction

Xuefu Zhuyu Decoction was created by Wang Qingren during the Qing Dynasty. Wang Qingren believed that "Xuefu" referred to the lowest part of the diaphragm and the area where the two sides of the rib cage meet. In Yilin Gai Cuo, he noted that this formula was primarily used to treat symptoms such as "headache, chest pain, chest tightness or heaviness, sweating at dawn, food regurgitating from the right side of the chest, heart palpitations, restless nights, commonly known as liver Qi disorder, dry retching, and intermittent heat in the evening" [7]. Wang Tao and others categorized these 19 symptoms into conditions such as discomfort in the precordial area caused by coronary heart disease, somatic disorders resulting from anxiety and depression, cerebrovascular diseases, and insomnia.

The original formula combines Taohong Siwu Decoction and Si Ni San, with the addition of Platycodon (Jiegeng) and Achyranthes (Niuxi). In this formula, Peach Kernel (Taoren) and Safflower (Honghua) are the chief ingredients, primarily functioning to activate blood circulation and resolve blood stasis. Ligusticum (Chuanxiong), Red Peony Root (Chishao), and Achyranthes (Niuxi) act as assistant ingredients to support the chief herbs in activating blood and resolving stasis, with Niuxi also guiding the blood downward to ensure smooth blood flow. Rehmannia (Shengdi) and Angelica (Danggui) are used to nourish the Yin and blood, preventing the blood-moving action from damaging the Yin. Shengdi also clears heat, eliminating the heat generated by the stagnation of blood. Platycodon (Jiegeng) and Bitter Orange (Zhike) work in tandem with Bupleurum (Chaihu) to regulate Qi and relieve chest congestion. These four herbs serve as the adjuncts, enhancing the overall formula. Jiegeng carries the medicinal effects upward, while Niuxi guides the blood downward, allowing the Qi to flow smoothly and ensuring that the blood moves freely. The entire formula works synergistically to activate blood, promote Qi circulation, and nourish the blood. It resolves stasis, facilitates blood flow, and harmonizes the Qi, thereby allowing the Qi and blood to circulate unobstructedly. Li Qingmeng and others [8] suggest that the formula incorporates a balance of warm, cool, and neutral properties. It addresses internal stagnation with warming and dispersing properties, supplemented by a slight cooling effect to balance and harmonize the treatment.

4. Clinical Efficacy of Xuefu Zhuyu Decoction in the Treatment of Lung Cancer

Traditional Chinese Medicine (TCM) views lung cancer as a condition characterized by both a deficiency of the root and

excess of the manifestation, with phlegm, blood stasis, and toxicity being the primary pathological products. Among these, "blood stasis" is believed to not only play a key role in the development and progression of lung cancer but also to be one of the main factors contributing to its onset. Studies have shown that the severity of blood stasis is directly related to the stage of the tumor advanced stages tend to present with more pronounced blood stasis, which in turn increases the likelihood of tumor metastasis and recurrence [9-10].

Additionally, chemotherapy drugs, which are often characterized by their heat-toxicity properties, are known to damage the body's Qi and Yin [11]. The resulting Qi deficiency impairs blood circulation, while Yin deficiency leads to the depletion of vital fluids, further aggravating Qi stagnation and blood stasis. Therefore, the mainstream clinical approach to treating lung cancer focuses on activating blood circulation and resolving blood stasis as the primary treatment, with supplementary strategies aimed at tonifying the body's Qi and supporting Yin. This approach also addresses the dual deficiency of Qi and Yin, as well as phlegm-damp accumulation obstructing the lungs.

4.1 Clinical Efficacy of Xuefu Zhuyu Decoction in the Treatment of Lung Cancer

Qiao Xinmei [12] applied a modified Xuefu Zhuyu Decoction combined with the EP chemotherapy regimen to treat small cell lung cancer (SCLC) with blood stasis in the lung collaterals. The clinical efficacy was significant, with an overall response rate of 85% in the treatment group compared to 62.5% in the control group ($P<0.05$), and it notably improved the patients' quality of life. The study concluded that the blood-activating and stasis-dispelling method can inhibit tumor cell growth, suppress the synthesis of tumor oncogenes and DNA, and enhance the patients' immune function, thereby improving the efficacy of chemotherapy and radiotherapy. Dong Qiang et al. [13] found that the modified Xuefu Zhuyu Decoction combined with the EP chemotherapy regimen achieved significant clinical efficacy in treating advanced-stage SCLC, with post-treatment blood rheology indicators in the treatment group showing a significant decline compared to the control group ($P<0.05$). The study suggested that Xuefu Zhuyu Decoction reduces capillary permeability and inhibits platelet aggregation. Zhang Xifeng [14] also used Xuefu Zhuyu Decoction combined with the EP chemotherapy regimen in SCLC treatment and found that it significantly improved short-term clinical efficacy and lung function in SCLC patients. Xu Junming [15] and Yao Heng [16] similarly confirmed through clinical studies that Xuefu Zhuyu Decoction combined with the TP chemotherapy regimen significantly improved blood rheology indicators, enhanced patients' quality of life, reduced chemotherapy-related adverse reactions, and improved patients' tolerance to chemotherapy.

4.2 Clinical Efficacy of Xuefu Zhuyu Decoction in the Treatment of Lung Cancer Complications

Chemotherapy drugs are typically administered via a peripherally inserted central catheter (PICC), with venous thrombosis being the most severe complication of PICC. Due to coagulation dysfunction in advanced lung cancer patients, PICC-related venous thrombosis is highly likely. Gu Xiaoyan et al. [17] conducted a study that found Xuefu Zhuyu Capsules could improve the hypercoagulable state in patients, reduce blood viscosity, and significantly lower the incidence of PICC-related venous thrombosis (1.32% in the observation group vs. 13.16% in the control group, $P<0.01$). Besides chemotherapy, radiotherapy is also a common treatment for lung cancer. According to the "Chinese Society of Clinical Oncology Guidelines for Lung Cancer Diagnosis and Treatment (2023 edition)," radiotherapy is recommended for early-stage non-small cell lung cancer (NSCLC) patients who are unsuitable for or refuse surgery [1]. However, chest radiotherapy can cause lung tissue damage, and in advanced stages, pulmonary fibrosis may develop, which is difficult to reverse once it occurs [18]. Early intervention to reduce radiation-induced lung injury is crucial. Sun Fangchu et al. [19] found that at the end of radiotherapy and three months after radiotherapy, the increase in plasma transforming growth factor-beta 1 (TGF-β1) was significantly lower in the observation group than in the control group ($P<0.05$). This study confirmed that Xuefu Zhuyu Capsules can suppress TGF-β1 levels, thereby reducing the incidence of radiation-induced lung injury. Wu Qiong et al. [20] demonstrated that Xuefu Zhuyu Decoction can improve radiation-induced lung injury and fibrosis, enhancing overall quality of life in patients. The study concluded that the blood-activating and stasis-dispelling method downregulates the expression of various inflammatory factors, promotes blood circulation, and aids in inflammation clearance. On the one hand, it inhibits tumor growth and metastasis, and on the other hand, it promotes the repair of tissues damaged by radiotherapy.

4.3 Clinical Efficacy of Xuefu Zhuyu Decoction in the Treatment of Cancer-related Pain in Lung Cancer

Cancer-related pain is a common complication in advanced lung cancer patients, severely affecting their quality of life. Zheng Qiao et al. [21] applied Xuefu Zhuyu Decoction combined with opioid analgesics to treat cancer pain caused by blood stasis in advanced lung cancer. Compared to pre-treatment levels, the post-treatment equivalent oral morphine dosage significantly decreased in both the treatment and control groups ($P<0.01$), with the treatment group showing a markedly lower equivalent oral morphine dosage than the control group ($P<0.05$). The pain relief rate in the treatment group was 94.8%, which was significantly higher than the control group's 86.7% ($P<0.05$). This study provides evidence for the clinical use of Xuefu Zhuyu Decoction in treating cancer pain, demonstrating its ability to alleviate adverse reactions to a certain extent and improve the patients' quality of life.

5. Mechanisms of Action of Xuefu Zhuyu Decoction in the Treatment of Lung Cancer

A review of the literature reveals that a substantial number of clinical studies have shown that modified Xuefu Zhuyu Decoction can improve clinical symptoms in lung cancer patients, alleviate hypercoagulable states, reduce pain, enhance the patients' quality of life, and boost their confidence in treatment. However, the precise mechanisms underlying the therapeutic effects of Xuefu Zhuyu Decoction in treating

lung cancer and related diseases remain unclear. The prevailing view suggests that the inhibition of tumor growth by Xuefu Zhuyu Decoction is related to its multiple pharmacological effects, including promoting angiogenesis, inhibiting vascular remodeling, anti-inflammatory and antioxidant activities, and anti-fibrosis effects.

Tian Lin et al. [22] conducted a study and found that the active ingredients of Xuefu Zhuyu Decoction primarily interact with processes such as reactive oxygen species (ROS) responses, nutritional metabolism, and steroid hormone metabolism. The treatment of non-small cell lung cancer (NSCLC) by Xuefu Zhuyu Decoction occurs through pathways such as the bladder cancer signaling pathway, the AGE-RAGE signaling pathway involved in diabetic complications, and the tumor necrosis factor (TNF) signaling pathway. These findings suggest that the effects of Xuefu Zhuyu Decoction on NSCLC are mediated through specific proteins and signaling pathways, providing insights for further research into its mechanisms of action in treating NSCLC. Xu Xu et al. [23] proposed that the anti-tumor and anti-metastatic effects of Xuefu Zhuyu Decoction may primarily occur through targets such as the TP53 gene, B-cell lymphoma-2, and epidermal growth factor receptor (EGFR), and are mediated via various signaling pathways including PPAR and vascular endothelial growth factor (VEGF) pathways. Wang Lihui et al. [24] found that Xuefu Zhuyu Decoction inhibited the proliferation of human lung cancer PC9 cells in a dose- and time-dependent manner. The research team further demonstrated that Xuefu Zhuyu Decoction could effectively inhibit tumor growth in NSCLC-bearing mice [25], and that high-dose Xuefu Zhuyu Decoction suppressed the activation of the Wnt/β-catenin signaling pathway. This was achieved by downregulating the expression of Wnt3α and β-catenin proteins, while upregulating P-GSK-3β protein expression, which helped overcome tyrosine kinase inhibitor (TKI) resistance [26], thereby improving the clinical efficacy of molecular-targeted therapies.

Currently, there is limited research on the specific mechanisms of action of Xuefu Zhuyu Decoction in the treatment of lung cancer and related diseases. However, its significant clinical efficacy highlights the need for further studies focusing on its modern pharmacological mechanisms. Such research would provide more evidence for the clinical application of traditional Chinese medicine in the treatment of lung cancer.

6. Conclusion

This review summarizes the current research on the clinical efficacy and mechanisms of action of Xuefu Zhuyu Decoction in the treatment of lung cancer. The following discussions address the gaps and limitations in the existing studies:

1) Limitations of Clinical Studies: Most clinical studies adopt a prospective randomized controlled trial (RCT) design. However, due to small sample sizes, single-center studies, and controversial blind settings, the authenticity of their conclusions has been limited.

2) Variability in Treatment Regimens: Some studies use different modifications of Xuefu Zhuyu Decoction and chemotherapy regimens across groups, which introduces bias in the evaluation of its clinical efficacy. Given the holistic approach and individualized treatment concept in Traditional Chinese Medicine (TCM), there is a pressing need to standardize patient selection and design appropriate treatment protocols.

3) Limitations of Outcome Measures: Most studies evaluate the efficacy of Xuefu Zhuyu Decoction using TCM syndrome scores and the Karnofsky Performance Status (KPS) scale, which may not fully and objectively reflect clinical efficacy. The use of more specific and objective indicators, as well as reliable and valid assessment tools, may enhance the credibility of the findings.

4) Limited Research on Mechanisms: Research on the mechanisms of Xuefu Zhuyu Decoction in treating lung cancer is still limited. While TCM theory supports Xuefu Zhuyu Decoction as a representative blood-activating and stasis-dispelling formula for treating lung cancer, some scholars argue that blood-activating and stasis-dispelling therapies may accelerate tumor metastasis and recurrence. Therefore, comprehensive modern pharmacological studies are crucial to promote the clinical application of Xuefu Zhuyu Decoction and advance the modernization of TCM. In conclusion, further research is needed to address these issues and provide more robust evidence for the clinical use of Xuefu Zhuyu Decoction in lung cancer treatment.

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