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Progress in Clinical and Basic Research of Buzhong Yiqi Decoction in Treating Lung Cancer

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Abstract: ***Lung cancer is the leading cause of cancer-related death in the world, and its hidden onset is a difficult problem in clinical practice. Conventional western medicine treatment, including surgery, chemoradiotherapy, targeted therapy, has achieved a certain effect, but there are obvious side effects, poor compliance, high recurrence rate, affecting the prognosis. Buzhong Yiqi Decoction comes from Li Dongyuan's "on the Differentiation of Internal and External Injuries". It has the function of tonifying lung and invigorating spleen and regulating qi and blood. Clinical studies have found that Buzhong Yiqi decoction can promote lung cancer postoperative recovery, adjuvant chemotherapy, combined targeted therapy, reduce adverse reactions, improve cancer-related fatigue, improve patients' quality of life; Basic studies have shown that Buzhong Yiqi Decoction plays its anti-tumor role by inducing apoptosis of cancer cells, anti-tumor angiogenesis, enhancing immune function and reversing drug resistance. This paper discusses the treatment of lung cancer by Buzhong Yiqi Decoction from three aspects: prescription and syndrome analysis, clinical research and basic research, aiming to further study the new progress of Buzhong Yiqi decoction in the treatment of lung cancer, in order to provide a broader idea for clinical diagnosis and treatment.***

Keywords: Buzhong Yiqi Decoction, Lung cancer, Clinical effect, Basic research**.**

1. Introduction

Lung cancer is the most common primary malignant tumor of the lung, which originates from the trachea, bronchial mucosa or glands. According to statistics, lung cancer is the leading cause of cancer-related death in the world [1]. Although in addition to conventional treatment, some emerging treatment methods have gradually made progress, but its five-year survival rate is still less than 20% [2]. Based on the theory of "strengthening health and eliminating pathogenic factors", traditional Chinese medicine (TCM) enhances the body's anti-cancer immunity, inhibits the growth, proliferation, invasion and migration of tumor cells [3], and shows significant advantages in reducing toxic and side effects, relieving clinical symptoms, preventing tumor recurrence and metastasis, and prolonging the survival time of patients [4].

The classic prescription Buzhong Yiqi Decoction is derived from Li Dongyuan's Treatise on Internal and External Injury Discrimination and puzzling. Experimental studies have shown that it has anti-tumor, anti-inflammatory and immunomodulatory effects, and has achieved good clinical effect on lung cancer [5,6]. Modern Chinese medicine scientists have carried out a lot of clinical and basic research on BuzhongYiqi decoction in the treatment of lung cancer. Therefore, this paper reviews the clinical and basic research progress of BuzhongYiqi decoction in the treatment of lung cancer by combing the domestic and foreign literature reports, in order to provide reference for the subsequent in-depth experimental research and further clinical application and promotion of BuzhongYiqi decoction.

2. The Basic Prescription of Buzhong Yiqi Decoction in the Treatment of Lung Cancer

Although there is no specific disease name of lung cancer in traditional medicine, according to its common clinical manifestations such as cough, expectoration and hemoptysis, it can be classified into the disease categories of "lung accumulation", "pulmonary mass" and "lung stasis" [7]. Buzhong Yiqi Decoction was first recorded in Li Dongyuan's Treatise on Discrimination and Confusion on Internal and External Injuries, and also in Spleen and Stomach. It was formulated according to the meaning of "the labor is warm" and "the damage is beneficial" in Huangdi Neijing [8], and it is one of Li Dongyuan's famous prescriptions for ancient times.

Traditional Chinese medicine believes that the fundamental cause of lung cancer is the deficiency of qi and the dysfunction of the five zang-fu organs, which leads to the entry of pathogens and poisons and their retention in the zang-fu organs and meridians, forming accumulation over time [9,10]. The basic pathogenesis is the deficiency of the original and the excess of the standard. The original deficiency is the deficiency of qi, blood and Yin and Yang, while the standard deficiency is mainly qi stagnation and blood stasis, phlegm turbidity and toxic accumulation [11]. "Plain Questions" cloud: "evil together, its qi will be deficient". In the book of Miraculous Pivot, Hundred Diseases First Birth, it is said, "There is no disease in the strong people, but there is deficiency." In the Bao Jian of Hygiene, it is recorded that "Nourishing Zhengji is self-dividing". The above discussion shows that the key to the occurrence and development of lung cancer is whether the body's healthy qi can overcome the evil qi, and the key to support the body's healthy qi is to invigorate the spleen and qi, which is also consistent with Professor Jiao Zhonghua's idea of "strengthening the spleen and stomach first when treating tumor". Buzhong Yiqi decoction is a representative formula

for invigorating spleen and qi. In the formula, Astragalus membranaceus is used as the main ingredient to replenish the vital qi, strengthen the spleen and stomach, and assist the lung qi to strengthen the surface qi. The subjects are supplemented with Codonopsis ginseng, Atractylodes rhizoma, and licorice to replenish the spleen and qi. The combination of all the drugs, the body's qi gradually strengthened, and the healthy qi gradually recovered.

3. Buzhongyiqi Decoction in the Treatment of Lung Cancer

3.1 To Promote Postoperative Recovery and Improve the Quality of Life

Surgical resection plays an important role in the treatment of early lung cancer [12]. Surgical treatment can completely remove tumors and related local tissues, and can also better understand the situation of regional lymph node metastasis [4]. However, common adverse reactions such as local trauma, inflammation, surgical site infection and atelectasis after surgery [13] lead to lung function damage, decreased immunity, intolerance to subsequent radiotherapy and chemotherapy, and even death of patients [14]. Buzhongyiqi decoction combined with western medicine for patients with lung cancer after operation can promote the recovery of overall function of patients and improve the tolerance of follow-up treatment. Liu Xiaoxiong et al. [15] showed that Buzhongyiqi decoction combined with radiotherapy and chemotherapy for postoperative patients with lung cancer can effectively relieve clinical symptoms, enhance immune function, improve the quality of life of patients, and help improve the prognosis of patients. Lang Zhenyi [16] confirmed that compared with postoperative radiotherapy and chemotherapy alone, Jiawei Buzhong Yiqi decoction was more effective in adjuvant treatment of lung cancer patients during postoperative radiotherapy and chemotherapy, and its incidence of adverse reactions was also lower. Li Xiaohai et al. [17] found that the scores of patients with Jiawei Buzhong Yiqi decoction on the basis of postoperative radiotherapy and chemotherapy increased in the dimensions of function, symptoms and overall health, and the increase was higher than that of the control group($P<0.05$).

3.2 Combined Chemotherapy can Reduce Toxicity and Increase Efficacy

Due to the lack of characteristic manifestations in patients with early lung cancer, many patients have developed to middle and advanced stages once diagnosed, and have lost the opportunity of surgical treatment [18]. For patients with advanced disease or those who cannot tolerate surgery, chemotherapy is still the best choice [19]. Chemotherapy is a kind of cytotoxic therapy, which can destroy tumor cells while also causing damage to normal cells [20]. There are many adverse reactions, such as decreased immune function, gastrointestinal reaction and bone marrow suppression. Buzhongyiqi decoction combined with chemotherapy can effectively reduce the adverse reactions of chemotherapy drugs, improve the compliance of patients, and is conducive to the long-term prognosis of patients. Tan Gang [21] found that Buzhong Yiqi decoction combined with Shashen Maidong decoction combined with adjuvant chemotherapy in the treatment of non-small cell lung cancer can effectively enhance the control effect of tumors, reduce the level of serum tumor markers, and enhance immune function. Wang Caixia [22] showed that the incidence of bone marrow suppression, gastrointestinal reaction and granulocytopenia in the BuzhongYiqi decoction combined with chemotherapy group was lower than that in the control group with chemotherapy alone, and the clinical treatment effect was better than that in the control group. Dana [23] confirmed that Buzhong Yiqi decoction combined with chemotherapy in the treatment of non-small cell lung cancer can significantly improve the quality of life of patients, alleviate the side effects caused by chemotherapy, and help to improve the clinical symptoms of TCM.

3.3 Adjuvant Targeted Therapy to Reduce Adverse Reactions

Targeted drugs can interact with specific targets that play a role in tumor cell growth and metastasis, so that tumor cells die specifically, with little damage to normal cells and good therapeutic effect. However, drug resistance caused by long-term drug use has brought great obstacles to targeted therapy for lung cancer patients [24]. Clinical application of BuzhongYiqi decoction combined with targeted therapy can effectively control the mutation of cancer cells. Ge Shan [25] found that Buzhong Yiqi decoction combined with molecular targeted drugs can effectively control the disease of lung adenocarcinoma, delay gene T790M mutation, so as to delay the emergence of drug resistance in patients, with fewer adverse reactions and better clinical efficacy. In addition, adverse reactions such as rash often occur in the process of targeted therapy, which affects the overall therapeutic effect [26]. Dermatological toxicity is not life-threatening, but severe cases can lead to drug withdrawal. Beom-Joon Lee et al. [27] treated patients with advanced non-small cell lung cancer with Buzhong Yiqi decoction combined with gefitinib, and found that Buzhong Yiqi decoction could effectively alleviate adverse reactions such as rash, anorexia and fatigue caused by targeted drugs, and effectively prolong the survival time of patients.

3.4 To Treat Cancer-related Fatigue and Improve Clinical Symptoms

Cancer-related fatigue (CRF) refers to the persistent, subjective feeling of physical, emotional and/or cognitive fatigue related to cancer or cancer treatment, which is out of proportion to the amount of recent activity and interferes with the normal function of the body [28]. About half of lung cancer patients receiving chemotherapy will experience CRF [29]. At present, western medicine mainly treats CRF with drugs, but the safety and efficacy are not satisfactory [30]. Traditional Chinese medicine believes that the key to the pathogenesis of CRF is spleen deficiency and qi depression. Clinically, the use of Buzhong Yiqi decoction to replenish spleen and qi can effectively improve the clinical symptoms such as fatigue and shortness of breath. Ning Bobiao et al. [31] found that Jiawei Buzhong Yiqi decoction in the treatment of CRF patients with weak temper after non-small cell lung cancer surgery can significantly relieve the fatigue symptoms of CRF patients, improve their quality of life, and promote the recovery of blood routine and liver function of patients. Fang

Tai et al. [32] showed that Buzhong Yiqi decoction combined with basic treatment intervention can effectively improve the clinical symptoms, hormone levels and fatigue state of CRF patients during lung cancer rehabilitation, and then improve their sleep and quality of life. Jiang Aiping et al. [33] also confirmed that Buzhongyiqi decoction on the basis of conventional treatment in the treatment of CRF of lung cancer during the rehabilitation period could significantly improve the sleep quality and fatigue symptoms of patients, and regulate the dysfunction of hypothalamic - pituitary - adrenocortical axis and hypothalamic-pituitary-thyroid axis.

4. Buzhong Yiqi Decoction in the Treatment of Lung Cancer

4.1 Mechanism of Action

4.1.1 Induction of apoptosis in cancer cells

Apoptosis is an autonomous regulation of cell death program, which is the most common homeostatic mechanism, and the occurrence and development of cancer are inseparable from it [34]. Wnt/β-catenin signaling pathway is a complex protein network that regulates cell proliferation and differentiation [35]. Relevant studies have found that abnormal Wnt/β-catenin signaling pathway can promote cancer stem cell renewal and lead to cancer progression [36]. Li He et al. [37] showed that Buzhongyiqi decoction intervention or interference with β-catenin could down-regulate the expression of β-catenin and Survivin protein, reduce the IC50 of cisplatin, and increase the total apoptosis rate induced by cisplatin. Zou Changpeng et al. [38] treated lung adenocarcinoma cells (A549 and A549/DDP) with quercetin or cisplatin alone or in combination and found that quercetin, the active ingredient of BuzhongYiqi decoction, could enhance the anti-tumor activity of cisplatin on A549/DDP cells by inhibiting cell viability and inducing apoptosis. Mu Qirui et al. [39] showed that BuzhongYiqi decoction could enhance the sensitivity of A549/DDP cells to cisplatin by inhibiting Nrf2/ROS pathway to induce apoptosis through mitochondrial pathway. In conclusion, BuzhongYiqi decoction can induce apoptosis of lung cancer cells by regulating the expression of related proteins, Nrf2/ROS pathway and other multiple targets, and exert its anti-tumor effect.

4.1.2 Anti-tumor angiogenesis

Angiogenesis promotes lung cancer progression by stimulating tumor growth, enhancing tumor invasion, promoting metastasis, and changing the immune system response in the tumor microenvironment, while vascular endothelial growth factor (VEGF) is a key growth factor that stimulates existing blood vessels to form new blood vessels [40]. Luo Wen et al. [41] used modified Buzhong Yiqi decoction to treat patients with non-small cell lung cancer undergoing postoperative chemotherapy, and found that VEGF in the observation group was significantly lower than that in the control group after treatment($p<0.05$), indicating that modified Buzhong Yiqi decoction had a good effect on blocking tumor angiogenesis. However, in addition to classical angiogenesis, there is another angiogenic mode, vasculogenic mimicry (VM), which is an important form of neovascularization in highly aggressive tumors, including lung cancer, and is usually associated with treatment resistance and poor patient prognosis [42]. VM production of related proteins (MMP2, MMP9, VEGFA, etc.) and the occurrence of epithelial-mesenchymal transition process are considered to be important drivers of VM formation and tumor development and metastasis [43]. In the treatment of lung cancer, inhibition of VM can break through the limitations of traditional anti-angiogenic therapy. According to the research results of Tian Fang et al. [44], Buzhongyiqi decoction can inhibit the mRNA and protein expression of MMP2 and MMP9 in a dose-dependent manner, thus inhibiting VM. The mechanism may be related to the regulation of JNK/ERK1/2 signaling pathway. In conclusion, BuZHong-Yiqi decoction can block the formation of tumor neovascularization by reducing the level of VEGF and inhibiting the expression of MMP2 and MMP9, and exert its significant anti-tumor activity.

4.1.3 Enhance the body's immune function

Tumor immunotherapy refers to achieve long-term anti-tumor effect by improving the ability of the patient's own immune system, providing a new treatment strategy and powerful assistance for those who have failed to respond to traditional anti-tumor therapy [45]. T lymphocytes and natural killer (NK) cells play an important role in mobilizing the body's immune function [46]. Liu Xiaoxiong et al. [15] randomly divided 88 patients with lung cancer after surgery into two groups, the control group was treated with radiotherapy and chemotherapy alone, and the observation group was treated with Buzhongyiqi decoction combined with radiotherapy and chemotherapy. The results showed that after treatment, CD4+ and CD4+/CD8+ in the observation group were higher than those in the control group, and CD8+ was lower than that in the control group, with statistically significant differences($P<0.05$). The scores of Functional Assessment of Cancer therapy-G(FACT-G) were higher than those of the control group. Wang Siyuan et al. [47] studied the regulatory effect of Buzhong Yiqi decoction on NK cells in immunosuppressed mice. The results showed that compared with the model group, the Buzhong Yiqi decoction group could effectively improve the immune organ index, the proportion and activity of NK cells in mice ($P<0.01$ or $P<0.05$), and the correction effect of the medium-dose group was the most significant, indicating that Buzhong Yiqi decoction could improve the immunosuppressed state. Enhance the immune function of NK cells. In conclusion, BuzhongYiqi decoction can exert its good anti-tumor effect by enhancing the immune function of the body.

4.1.4 Reversal of drug resistance

At present, chemotherapy is still the most common treatment for lung cancer [48]. However, with the progress of treatment, the problem of chemoresistance has begun to plague clinical practice. Studies have shown that 63% of patients with non-small cell lung cancer will progress to cisplatin resistance [49]; therefore, therapeutic strategies to reverse resistance need to be developed urgently. Wang Ying, Song Fei-fei and Liu Chun-ying et al. showed that Buzhong-Yiqi decoction had a significant improvement effect on cisplatin resistance of lung adenocarcinoma, and the mechanism of reversing drug

resistance mainly included that Buzhong-Yiqi decoction inhibited the activation of PI3K/AKT signaling pathway by TGF-β1 in adenocarcinoma cells, and then inhibited epithelial-mesenchymal transition (EMT) [50]. Buzhongyiqi decoction can down-regulate the expression of p-GSK-3βser9 and increase the active expression of GSK-3β in cytoplasm to improve the cisplatin resistance of lung adenocarcinoma [51]. Buzhongyiqi decoction can improve the cisplatin resistance of A549/DDP cells by inhibiting Nrf2/ROS pathway [39]. Buzhongyiqi Decoction has the effect of transient transfection of siβ-catenin [37]. Overexpression of multidrug resistance-related genes MRP1 and ERCC1 in tumor tissues can lead to tumor drug resistance. Wang Jie et al. [52] found that BuzhongYiqi decoction combined with cisplatin could effectively reduce the protein expression of MRP1 and ERCC1, thereby reversing cisplatin-induced multi-drug resistance of Lewis lung cancer cells in tumor-bearing nude mice and improving the drug resistance of drug-resistant cells. In conclusion, BuzhongYiqi decoction can improve and reverse the multidrug resistance of tumor cells through multiple pathways and multiple genes.

4.2 Pharmacological Action Studies

Buzhongyiqi Decoction is composed of eight drugs: Astragali astragali, Atractylodes rhizoma, Tangerine peel, cohosh, Bupleurum, ginseng, licorice and Angelica sinensis. There are many extracted ingredients in this prescription, and the main anti-tumor ingredients confirmed by modern pharmacological research are quercetin, kaolin, β-sitosterol, naringenin and formononetin [53].

Studies have found that quercetin induces apoptosis through Bax, Bcl-2 and caspase3, and has an inhibitory effect on the proliferation of lung cancer cells [54]. In addition, a recent study showed that quercetin could bind to the overexpressed protein lysine deacylase (SIRT5) to inhibit PI3K/AKT signaling and induce apoptosis of lung cancer cells [55]. While kaempferol promotes the treatment of non-small cell lung cancer by targeting EGFR, IGF1R, PIK3R1 and Akt1 to regulate EGFR/PI3K/AKT and IGF1R/PI3K/AKT signaling pathways [56]. Yu Qiquan et al. [57] found that β-sitosterol combined with quercetin had an inhibitory effect on A549 cells under the intervention of estradiol, and its mechanism may be the promotion of cell apoptosis through the PI3K/Akt/mTOR pathway. Zhang Yue et al. [58] found that naringenin inhibited proliferation and promoted apoptosis of A549 cells by activating ROS/P38-MAPK signaling pathway. Lin Xing et al. [59] showed that formononetin could up-regulate the ratio of intracellular bax/bcl-2, increase the expression of PTEN protein in A549 cells, and reduce the expression of p-AKT protein, thereby inducing the apoptosis of A549 cells and inhibiting the proliferation.

5. Conclusion and Prospect

In conclusion, Buzhongyiqi decoction has good effect in the treatment of lung cancer. It can not only promote postoperative recovery, but also assist chemotherapy and targeted therapy to relieve cancer-related fatigue. Its mechanism is related to inducing cancer cell apoptosis, inhibiting cancer cell proliferation and metastasis, anti-tumor angiogenesis, enhancing immune function and reversing drug resistance. Therefore, BuzhongYiqi decoction can be used as an effective adjuvant drug for lung cancer in clinical practice. However, the current research also has shortcomings. In terms of clinical research, there are few clinical trials of BuzhongYiqi decoction combined with immunotherapy, and in terms of basic research, the network pharmacology study of BuzhongYiqi decoction in the treatment of lung cancer is not enough, and the specific effective ingredients of BuzhongYiqi decoction cannot be fully understood. Therefore, relevant clinical trials and pharmacological studies can be carried out in the future to highlight the advantages of BuzhongYiqi decoction in the treatment of lung cancer with multiple components and multiple pathways, and to provide further scientific basis for the clinical application of BuzhongYiqi decoction in the treatment of lung cancer.

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