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REVIEW

Research Progress of Baihe Gujin Decoction in the Treatment of Lung Cancer

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Abstract: Baihe Gujin decoction is one of the most commonly used decoction in traditional Chinese medicine for the treatment of lung cancer. It can nourish yin and moisten the lung as well as prevent phlegm from forming and stop coughing. On the one hand, Baihe Gujin decoction is characterized with extensive application, proven efficacy, a long history, and high safety. On the other hand, Baihe Gujin decoction can induce apoptosis of tumor cells, improve immune function and inhibit inflammation. The main anti-tumor components of this include kaempferol, quercetin, isorhamnetin, glycyrrhizin and β-sitosterol. Clinically, Baihe Gujin decoction can improve the adverse reactions caused by radiotherapy, chemotherapy and immunotherapy for lung cancer, enhance the quality of life of patients, and prolong their survival time. At present, there are a large number of clinical and basic researches on the treatment of lung cancer with Baihe Gujin decoction. In this paper, we mainly discussed the treatment of lung cancer with Baihe Gujin decoction through analyzing basic and clinical researches at home and abroad in the past 20 years. Through the discussion, we aimed to probe deeper into Baihe Gujin decoction for the treatment of lung cancer, thereby providing a broader idea for clinical diagnosis and treatment of lung cancer.

Keywords: Baihe Gujin decoction, lung cancer, traditional Chinese medicine, basic research, clinical study

Introduction

Lung cancer is one of the most common malignancies,[1] with the incidence and mortality rates at the forefront among all malignant tumors. According to the latest statistics from the International Agency for Research on Cancer (IARC), lung cancer deaths make up approximately 18% of all cancer deaths worldwide.[2,3] Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two primary subtypes of lung cancer.[3,4] The incidence of NSCLC accounts for about 85% of all lung cancers,[5] whereas SCLC for only 13% to 15%.[2,6] The modern medical treatment of lung cancer mainly constitutes a comprehensive therapy, involving various means such surgery, radiotherapy, and targeted therapy. However, the overall prognosis of lung cancer patients after these therapies is not optimistic.[2,7]

Traditional Chinese Medicine (TCM) has been a repository of ancient Chinese wisdom and cultural knowledge, constituting a life science handed down through the ages. TCM plays a crucial role in the regulation and management of lung cancers.[8] In TCM theory, the body's well-being is governed by "healthy qi", and maintaining its balanced flow is crucial for health. Disruptions, often attributed to "evil qi", can result from environmental factors and internal imbalances. Optimal blood circulation plays a vital role in delivering nutrients, eliminating waste, and sustaining overall well-being. The Zang Fu concept pertains to the internal organs, categorized into Zang and Fu. Zang organs, recognized as the solid or yin organs (heart, liver, spleen, lung, and kidney), are able to store and regulate vital substances like qi (energy) and blood. Besides, Fu organs, considered as hollow or yang organs (small intestine, large intestine, gallbladder, bladder, and stomach), are responsible for processes such as digestion. In the concept of TCM, these organs form an integral part of a holistic system where their functions are interconnected. Imbalances in a single organ can impact the overall harmony of the entire body.[9] The Yin-Yang concept, highlighting opposing yet complementary forces, along with the Five Phases (Wood, Fire, Earth, Metal, Water), forms the foundational philosophy. Briefly, Yin represents depletion of

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qi and qualities like darkness, passivity, receptivity, and coolness; while Yang represents repletion of qi and embodies characteristics such as light, activity, assertiveness, and warmth.[10] The Five Phases describe the cyclic transformation of qi and vital substances through distinct stages. The perpetual interplay and dance of harmonization between yin and yang follow a predictable pattern (Figure 1). Heat is viewed as an imbalance marked by excess Yang or Yin deficiency, disrupting vital harmony for optimal health. Elevated heat levels can lead to hyperactivity, resulting in symptoms such as fever, thirst, restlessness, and irritability.[11] TCM addresses heat and fire imbalances characterized by symptoms from excessive internal heat. Influenced by factors like diet and emotions, TCM employs interventions like dietary changes, herbal remedies, acupuncture, and lifestyle adjustments to restore balance.[12]

"Lung cancer" is described as "Feiji", "Xiben", "Feiyong", etc. in ancient Chinese medical literature.[13] Patients with lung cancer cannot resist evil qi due to the deficiency of healthy qi. The blood flow fails to be promoted because of qi deficiency and stagnant movement of qi. The stagnation of blood flow results in blood stasis, followed by phlegm-dampness. Over time, heat is formed, and the combination of heat and dampness prevents the release of toxin.[14] The stasis of toxin in the lungs causes mass formation and finally develops into lung cancer.[15] Deficiency of lung yin is one of the key pathogenic mechanisms of lung cancer. At present, there is no clear unification of the syndrome type of lung cancer. Modern medical practitioners have classified deficiency of lung yin as one of the common syndrome types of lung cancer.[16,17] Based on analysis of the symptoms and signs of 388 lung cancer cases in terms of single syndrome, Wang et al[17] classified lung cancer into five major syndrome types, ie, lung yin deficiency, lung qi deficiency, spleen qi deficiency, phlegm stagnation and blood stasis, and lung yin deficiency and fire hyperactivity. Feng[18] used statistical methods including cluster analysis to observe the differences in bronchoscopic manifestations of different syndrome types, and then classified lung cancer into following four types: yin deficiency, qi stagnation and blood stasis combined with damp obstruction, qi deficiency and phlegm-dampness, and deficiency of both qi and yin.

Baihe Gujin decoction was firstly published in *Shenzhai Yishu* (Volume VII, Part Yin Deficiency) compiled by Zhou Zhiqian (a medical practitioner in Ming Dynasty). Clinically, Baihe Gujin decoction is applicable to the lung yin deficiency syndrome,[19] with the composition of three qian each of *Radix Rehmanniae Praeparata, Radix Rehmanniae* and *Angelica sinensis*, one qian each of *Radix Paeoniae Alba* and *Licorice Root*, eight fen each of *Radix Platycodonis* and *Radix Scrophulariae*, one and a half qian each of *Fritillaria cirrhosa, Radix Ophiopogonis*, and *Lily*[20] (Figure 2). Moreover, Baihe Gujin decoction is effective for nourishing the lungs and kidneys as well as relieving cough and

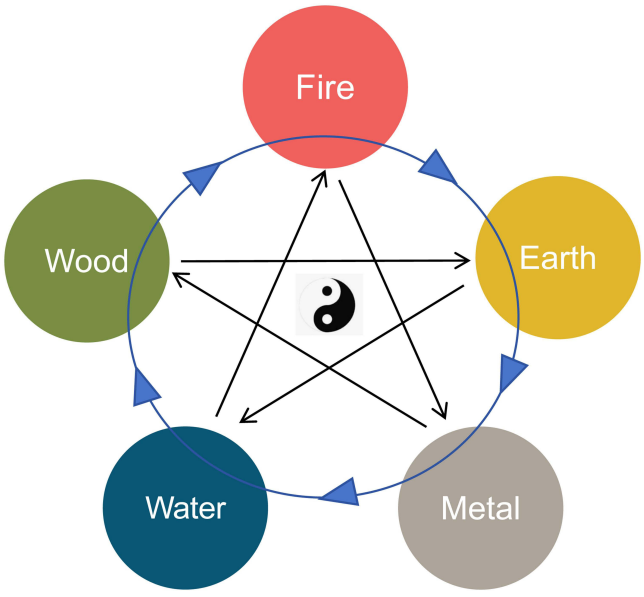

Figure 1 Illustration of the concept of the five phases and yin-yang. The generative cycle was depicted with arrows moving clockwise, whereas the destructive cycle was indicated by star-shaped arrows on the inside, also following a clockwise direction. Five phases, literally translating to "moving star", delineated the cyclical transformation of the five types of qi (vital substances) through various stages. In an incessant dance of harmonization, yin and yang continually adjusted and transformed in a predictable pattern.

Figure 2 Pharmaceutical composition of Baihe Gujin decoction. Baihe Gujin decoction was a traditional Chinese herbal formula. The pharmaceutical composition typically included a combination of various herbs carefully selected for their synergistic effects. Baihe Gujin decoction often consisted of the following key ingredients: *Lily* (12g), *Radix Ophiopogonis* (12g), *Fritillaria cirrhosa* (12g), *Radix Rehmanniae* (9g), *Radix Rehmanniae Praeparata* (9g), *Angelica sinensis* (9g), *Radix Scrophulariae* (3g), *Licorice Root* (3g), *Radix Platycodonis* (3g), *Radix Paeoniae Alba* (3g).

resolving phlegm.[21] A similar description was also found in *Yi Fang Ji Jie* (*Wang Ang's Collected and Analyzed Medical Formulas*) compiled by physician Wang Ang from Qing Dynasty that the above medicinal materials could be combined for improving lung-related diseases such as cough, phlegm and blood. In addition to improving these symptoms, Baihe Gujin decoction can also be used for the treatment of lung cancer.[22] Therefore, Baihe Gujin decoction is available for treating lung cancer with deficiency of lung yin. Concerning the components of this decoction, *Radix Rehmanniae Praeparata* and *Radix Rehmanniae* can benefit kidney essence as well as cool blood and promote hemostasis; *Lily* protects the lungs and soothes the nerves; *Radix Ophiopogonis* can clear heat and moisten dryness; *Fritillaria cirrhosa* nourish yin and moisten lung; *Radix Scrophulariae* promote *Radix Rehmanniae Praeparata* and *Radix Rehmanniae to* produce body fluid, thereby playing a role in nourishing yin and cooling blood, clearing the lungs and reducing heat; *Angelica sinensis* and *Radix Paeoniae Alba* are able to nourish the blood and calm the liver; *Radix Platycodonis* can dispel phlegm and arrest cough, *Licorice Root* can clear the lungs, and the two are used as channel-guiding drugs to introduce the above herbs into the lungs. The interaction of these herbs aids in the mutual promotion between lung and kidney. All in all, Baihe Gujin decoction has the function of nourishing yin and clearing heat, moistening the lungs and arresting cough, as well as cooling the blood and promoting hemostasis.[20]

There has already been numerous clinical and basic research on the use of Baihe Gujin decoction for the treatment of lung cancer. In order to provide reference for the subsequent in-depth experimental study and further clinical application and promotion of Baihe Gujin decoction, the Chinese and English literature on Baihe Gujin decoction for the treatment of

lung cancer was searched from Pub Med, VIP database, SinoMed, Wanfang Data, and Chinese National Knowledge Infrastructure (CNKI) from the the establishment time of database to April 2023. Overall, this paper provided a review for the progress of clinical and basic research on the application of Baihe Gujin decoction in the treatment of lung cancer.

Basic Research on the Role of Baihe Gujin Decoction in Treating Lung Cancer

Research on Mechanism of Action (Figure 3)

Induction of Apoptosis of Tumor Cells

Baihe Gujin decoction can induce cancer cell differentiation and apoptosis to different degrees. Apoptosis is a form of non-inflammatory cell death that happens when cells naturally self-destruct or die. It maintains homeostasis in vivo and has a close correlation with the development of tumors. Mechanically, apoptosis is activated by two pathways: exogenous death receptor signaling pathway and endogenous mitochondrial signaling pathway.[23] Tumor is a disease of abnormal cell proliferation and apoptosis. To date, a large number of experiments have confirmed the deep connection of apoptosis with the unrestricted growth and metastasis of tumor cells. One study[24] demonstrated that Baihe Gujin decoction not only induced significant cell cycle arrest through down-regulation of CDK4 and cell cycle protein D1 in the G0/G1 phase, but

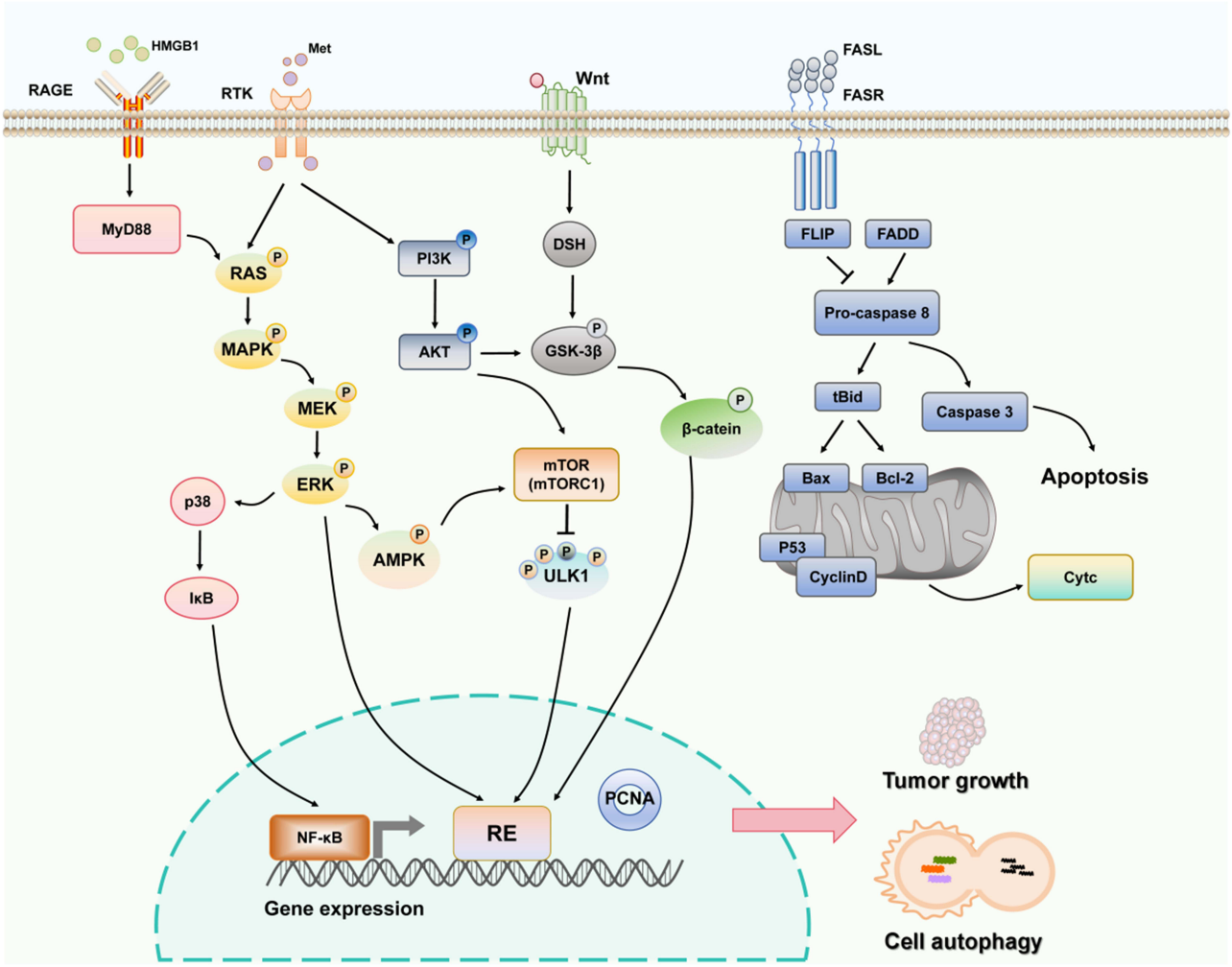

Figure 3 The potential mechanism of Baihe Gujin decoction for treating lung cancers. Baihe Gujin decoction could regulate the balance between yin and yang, nourish yin, hydrate the lungs, and alleviate heat in TCM theory. Baihe Gujin decoction was thought to induce cancer cell autophagy by affecting regulators like CDK4, Cyclin D1, cleaved caspase 3/9, the BCL-2 family, the AKT/GSK3β/β-catenin pathways, the AMPK/mTORC1/ULK1 pathway and so on.
Abbreviation: TCM, Traditional Chinese Medicine.

also promoted mitochondria-dependent apoptosis through the AKT/GSK3β/ β-catenin signaling pathway. After the successful establishment of a Lewis lung cancer nude mouse model, Lv[25] observed that modified Baihe Gujin decoction combined with radiotherapy inhibited the growth of transplanted tumors and promoted the apoptosis of tumor cells in the mice, and that the mechanism may lie in the down-regulation of the expression of hypoxia-inducible factor-1α (HIF-1α), P53, and survivin mRNA and protein. Zhou[26] et al used CCK-8 and EdU assays to examine the killing effect of Baihe Gujin decoction on NSCLC cells. They discovered that Baihe Gujin decoction could slow down the growth of tumor, weaken the ability of in vitro clone formation, and induce cycle arrest and apoptosis of tumor cells in the G0/G1 phase.

Improvement of Immune Function

Immunotherapy is in line with "strengthening vital qi", a treatment concept in TCM.[27] The theory of "when there is sufficient vital-qi inside, evil-qi cannot invade human body" comes from *Suwen Yipian· Cifa Lun*. Mobilizing the body's immune system is the most important part of tumor immunotherapy,[28] in which interleukin (IL), T lymphocytes, tumour necrosis factor (TNF)-α and natural killer (NK) cells play a key role.[29] Many modern medical scientists believe that the internal cause of lung cancer is the deficiency of vital qi in the body.[30] After the formation of lung cancer, the body continues to consume qi and blood, which further weakens the vital qi. Lily is the sovereign drug in Baihe Gujin decoction. The water-soluble polysaccharide BHP in lily can effectively regulate the immune function in mice.[31,32] Modern research[23] also revealed that TCM could improve immune function in lung cancer patients through regulating immune cells such as T lymphocyte subpopulations, NK cells, and macrophages. Briefly, TCM controls and removes the tumor cells via improving anti-tumor immunity. Clinical studies by He et al[33] reported that Baihe Gujin decoction could improve immune function to a certain extent. Mechanically, this decoction may affect the expression of cytokine products of T lymphocytes, such as CD3+, CD4+, CD4+/CD8+, IL-2 and interferon (IFN)-γ, through regulating the anti-tumor immune response of T lymphocytes. Li[34] discovered that Baihe Gujin decoction in combination with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) could significantly improve the immune function and effectively reduce the toxic side effects of the drug in the treatment of advanced NSCLC in the elderly. According to the study of Liang et al,[35] the combination of Shengmai decoction and Baihe Gujin decoction could lower the levels of cyclase-associated protein 1 (CAP1) and intercellular adhesion molecule-1 (ICAM-1), thereby obviously enhancing efficacy and reducing toxicity in advanced lung cancer with qi-yin deficiency syndrome.

Anti-Inflammation

The co-existence of cancer and infection is not only a non-negligible issue in cancer treatment, but also a contributor to the death of cancer patients. Pathogenic bacteria can promote the development of tumors at different stages to different degrees; especially during chronic infection, the toxic factors released by pathogens can affect normal tissues, which is reflected on several aspects,[36] like hyperthermia, elevated leukocytes and microcirculatory failure.[37] Modified Herbal Compound Formula of Baihe Gujin decoction can reduce TNF-α and IL-10 levels and inhibit excessive inflammatory response in cancer patients with infection.[38] Wu et al[39] uncovered that Baihe Gujin decoction could significantly inhibit the increase in capillary permeability and leukocyte rolling. Such finding further confirmed the significant phlegm-relieving, antimicrobial and anti-inflammatory effects of Baihe Gujin decoction.[40] Liu et al[15] discovered good therapeutic effect of Shengmai Powder combined with Baihe Gujin decoction plus or minus in the treatment of qi and yin deficiency lung cancer. Specifically, the clinical symptoms of patients were relieved, the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and fibrinogen-to-albumin ratio were decreased, the inflammation was controlled, and the recovery of the prognosis was improved. In regard to the findings of Zhu et al,[41] the active ingredients of Baihe Gujin decoction could reduce the levels of C-reaction protein (CRP), procalcitonin (PCT), TNF-α, transforming growth factor (TGF)-β and other inflammatory factors, thereby exerting significant antibacterial and anti-inflammatory effects. Li et al[42] disclosed that Baihe Gujin decoction could enhance the immune responses of CD4+ and CD4+/CD8+, lower the levels of CD8+, CA125, carcinoembryonic antigen (CEA), CYFRA21-1, nuclear factor (NF)-κB, matrix metalloproteinase (MMP)-2 and MMP-9, further strengthen the anti-infective ability of phagocytes, and finally inhibit inflammatory response.

Research on Pharmacological Effects

Baihe Gujin decoction is composed of 10 herbs, including Lily, Radix Rehmanniae Praeparata, Radix Rehmanniae, Angelica sinensis, Radix Paeoniae Alba, Licorice Root, Radix Platycodonis, Radix Scrophulariae, Fritillaria cirrhosa, and Radix Ophiopogonis. There are a large number of extracted constituents in this decoction, and the main anti-tumor constituents confirmed by modern pharmacological research include kaempferol, quercetin, isorhamnetin, glycyrrhizin, and β-sitosterol, etc.[43] Most of these components belong to flavonoids. Flavonoids are natural products that can reverse the immunosuppressive microenvironment of tumors.[43] As reported by a related study, kaempferol can induce apoptosis in NSCLC cells through down-regulating Nrf2 mRNA, thereby inhibiting cancer cell proliferation.[44] Also, kaempferol can slow down cancer progression via inhibiting TGF-β1-induced epithelial-mesenchymal transition, migration and invasion of NSCLC cells.[45] As for quercetin, it exhibits significant cytotoxicity against the viability and growth of human NSCLC cells[46] and shows superior anticancer activity in NSCLC cells.[47] Apart from the ability to inhibit the migration and invasion of NSCLC cells,[48] isorhamnetin also serves as a natural radiosensitizer that enhances the radiosensitivity of NSCLC cells.[49] Yu et al[50] found that the inhibitory effect of glycyrrhizin on migration of human lung adenocarcinoma cells was achieved through the down-regulation of proMMP-2 and the PI3K/AKT signaling pathway. In addition, β-sitosterol, a predominant phytosterol, has a preventive effect on a variety of tumors, including NSCLC.[51] It has been reported that β-sitosterol can exert a significant inhibitory effect on human lung adenocarcinoma cells but not damage normal lung tissue cells.[23] Moreover, β-sitosterol is able to achieve its anticancer effects by interfering with a variety of cellular signaling pathways such as cell cycle, apoptosis, proliferation, survival, invasion, angiogenesis, metastasis, and inflammation.[52] Besides, β-sitosterol was shown to be effective in preventing the growth of human lung adenocarcinoma cells through down-regulating the cell cycle in human lung adenocarcinoma cells.[53] Vundru et al[54] disclosed that β-sitosterol could result in cell cycle arrest at G0/G1 phase by down-regulating the expression levels of cyclin-dependent kinase CDK4 and cell cycle protein D1, thereby inducing apoptosis in human lung adenocarcinoma cells.

Potential Mechanisms of Baihe Gujin Decoction on Lung Cancer

Baihe Gujin decoction is a traditional Chinese herbal formula in TCM for lung-related disorders. Although this decoction has historical use and anecdotal evidence, its mechanisms and effectiveness, especially in complex diseases like lung cancer, may not be fully understood. As Table 1 shown, we briefly summarized the potential underlying molecule pathways on Baihe Gujin decoction or its active components that exerted inhibitory effects on lung cancer in vivo.[24,55–59] According to TCM principles, Baihe Gujin decoction is thought to nourish Yin, hydrate the lungs, and alleviate heat. Besides, the components of this decoction are believed to possess properties that promote lung health by addressing imbalances in the body's Yin and Yang.[60] In western medicine, as mentioned above, Baihe Gujin decoction hinders lung cancer cell proliferation in a dose-dependent manner, thereby inhibiting in vivo tumor growth. Also, it induces cell cycle arrest and apoptosis by affecting regulators like CDK4, Cyclin D1, cleaved caspase 3/9, and the BCL-2 family. The AKT/

Table 1 The Key Mechanisms of Action of Baihe Gujin Decoction on Lung Cancers

Therapies	Test System	Biological Effects	References
Baihe Gujin decoction	Subcutaneous xenograft A549 cell mouse model	Inhibits tumor growth by AKT/GSK3β/β-catenin and MPK/mTORC1/ULK1 signaling pathways	[24]
Flavonoids	A549 BALB/c nude mice of A549	Inhibited tumor growth via the COX-2-Wnt/β-catenin signaling pathway	[55]
Kaempferol	BALB/c nude mice of A549	Promoting NSCLC cell autophagy by affecting Met-and its downstream PI3K/AKT/mTOR signaling	[56]
Quercetin	Athymic nude mice of A549	Suppresses cancer growth by inhibiting aurora B kinase activity	[57]
Isorhamnetin	Lewis lung carcinoma cell mice	Induces cancer cell apoptosis by increased expression of Bax, Caspase-3 and P53, and decreased expression of Bcl-2, cyclinD1 and PCNA protein	[58]
Glycyrrhizin	Nude mice of Human NSCLC cell line HCC827	Suppresses the tumor growth by declining HMGB1 level.	[59]

GSK3β/β-catenin pathways contribute to Baihe Gujin decoction-induced apoptosis. Moreover, Baihe Gujin decoction also triggers autophagy through the AMPK/mTORC1/ULK1 pathway, and blocking autophagy enhances Baihe Gujin decoction's efficacy in lung cancer cells.[24] Furthermore, Baihe Gujin decoction enhances immune responses by boosting the anti-tumor effects of T lymphocytes, NK cells, and macrophages. Notably, the anti-inflammatory properties of Baihe Gujin decoction play a crucial role in reducing various cytokines and inflammatory factors, contributing to its effectiveness in combating lung cancers. More importantly, through network pharmacology and molecular docking, Baihe Gujin decoction, containing active compounds such as kaempferol, quercetin, luteolin, isorhamnetin, beta-sitosterol, stigmasterol, mairin, and liquiritigenin, along with hub targets like AKR1B10 and AKR1C2, exhibited therapeutic potential against NSCLC. GO analysis emphasized the influence of this decoction on apoptosis. Kyoto Encyclopedia of Genes and Genomes pathway analysis revealed three modules linked to endocrine, inflammation, hypoxia, and other cancer pathways, shedding light on Baihe Gujin decoction's biological mechanisms. Molecular docking validated a significant binding of AKR1B10 and AKR1C2 to the eight key compounds in NSCLC.[43] In addition to these aspects, the immunomodulatory and anti-inflammatory effects triggered by Baihe Gujin decoction are also crucial for demonstrating its potential in combating tumors.

Clinical Study of Baihe Gujin Decoction in the Treatment of Lung Cancer

Improvement of Radiation Pneumonitis

Radiotherapy is prone to radiation pneumonitis (RP). At present, the clinical symptoms of RP can only be alleviated by hormones, anti-inflammatory and antibacterial drugs. However, overuse of these drugs can induce side effects such as imbalance of human bacterial flora, elevation of inflammatory factors, and decrease of immunity.[23] Radiation can be reckoned as heat toxin and evil qi, which are most likely to consume the vital qi and blood of the body. The deficiency of vital qi results in the excess of evil qi, and the blood deficiency leads to the difficulty in moistening and nourishing veins. Accordingly, heat accumulation and lung yin deficiency are presented in the lung lobe located in the upper jiao. On the basis of the vital qi deficiency, the tumor patients are more likely to suffer lung collateral damage and lung yin depletion as a result of the evil heat produced by radiotherapy.[53] The congestion of heat toxin not only prevents qi movement but also impairs yin and stagnates blood. Next, the lungs fail to be moistened and lose control of dispersion due to the combination of heat congestion and blood stagnation, and then RP is consequently formed.[61] According to the pathogenic mechanism, the treatment of RP should focus on expelling heat and detoxifying, promoting blood circulation and removing blood stasis, as well as tonifying qi and nourishing yin. Baihe Gujin decoction can enrich yin gradually, promote essence and blood generation, and purge the deficient fire. Not only does it remove the heat toxin and evil qi from the lungs, but also it improves the pathological changes of the lungs in a systematic way.[53,62] Through clinical research, Fang et al[62] pointed out that Baihe Gujin decoction could reduce TGF-β1 level, alleviate interstitial lung fibrosis, and improve the survival quality of lung cancer patients. Hence, they concluded that Baihe Gujin decoction could be used as a routine medication for the prevention of RP in clinical practice. Zhu et al[41] divided 82 lung cancer patients into a control group (radiotherapy) and an observation group (Baihe Gujin decoction combined with radiotherapy) by a random number table They observed that the serum CRP, PCT, TNF-α, and transforming growth factor (TGF)-β levels of the observation group were lower than those of the control group. Such finding indicated that Baihe Gujin decoction could reduce inflammatory responses and improve immunity of lung cancer patients. As described in the clinical study of Lv,[25] the modified Baihe Gujin decoction enhanced the efficacy of radiotherapy on the treatment of NSCLC and alleviated the clinical symptoms of RP; the imaging results also revealed clear efficacy of Baihe Gujin decoction.

Increasing the therapeutic effect of chemotherapy and reducing toxicity

In recent years, despite emerging various new drugs for the treatment of lung cancer, chemotherapy still is an important therapeutic means in the era of precision medicine.[63] Nonetheless, chemotherapy is limited by some practical problems such as serious side effects and poor long-term efficacy. It has been reported that the combination treatment of TCM and chemotherapy can significantly increase the efficacy and weaken the toxicity, so as to improve the patient's adherence to chemotherapy.[30] TCM believes that chemotherapy is a kind of heat toxin invasion for the human body that can injure lung collaterals and deplete body fluids. Usually, the deficiency symptoms of the

lungs and kidneys, such as weakness, dry throat and bitter mouth, waist and knee pain and weakness, red tongue, less moss and weak pulse, follow chemotherapy. Hence, clinical treatment should be based on nourishing yin and clearing heat. Owing to the efficacy of clearing heat and removing toxins, nourishing yin and moisturizing the lungs, Baihe Gujin decoction is the main treatment for lung and kidney yin deficiency.[33,64] The combination of Baihe Gujin decoction with chemotherapy has been revealed to improve the benefit of lung cancer patients. For instance, Baihe Gujin decoction with vinorelbine/cisplatin (NP) chemotherapy can significantly improve the clinical symptoms, reduce the toxic side effects, and improve the quality of life of patients with advanced NSCLC.[65] Liang et al[35] observed that the combination of Shengmai Decoction and Baihe Gujin Tang could enhance efficacy and reduce toxicity in advanced lung cancer with qi-yin deficiency syndrome via down-regulating the serum CAP1 and ICAM-1 levels, which is worthy of clinical promotion and application. Gui et al[66] made a retrospective study on 100 patients with advanced NSCLC. They found that on the basis of conventional treatment, the modified Baihe Gujin decoction could increase the total efficacy, improve the symptoms of TCM and assist the successful completion of chemotherapy.

Improving Gastrointestinal Reactions Caused by Chemotherapy

After undergoing chemotherapy, lung cancer patients often have poor spleen and stomach transportation and digestion. If the patient does not focus on the maintenance of the spleen and stomach, the treatment effect will be poor. Even, spleen and stomach diseases, such as nausea and vomiting, bloating and belching, anorexia, will develop,[67] which in turns affects the treatment progress.[68] The main mechanism of these diseases is that chemotherapeutic drugs damage the spleen and kidney, resulting in gastrointestinal dysfunction, spleen and stomach disharmony, and deficiency of qi, blood, yin and yang. Therefore, regulating the spleen and stomach as well as tonifying qi and yin should be the treatment target. Baihe Gujin decoction can strengthen the spleen and stomach, nourish yin and promote body fluid generation.[69,70] Fang et al[71] retrospectively analyzed 60 cases of locally advanced NSCLC treated with Baihe Gujin decoction combined with cisplatin. They claimed that the incidence of nausea and vomiting in the treatment group and the control group were 63.33% and 86.67%, respectively, and the incidence of adverse reactions in the treatment group was significantly lower than that in the control group. These findings suggested that Baihe Gujin decoction could significantly reduce the toxic side effects of chemotherapeutic drugs on the digestive tract of the human body. Using the Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13), Wang et al[72] examined the effect of modified Baihe Gujin decoction on the quality of life of lung cancer patients. The examination results revealed that the scores of nausea and vomiting, loss of appetite, and diarrhea of patients treated with modified Baihe Gujin decoction much lower than those treated with single western medicine. Such results indicated that Baihe Gujin decoction could improve the quality of life of lung cancer patients and had superior efficacy to the single western medicine treatment.

Improving Hemoptysis Caused by Chemotherapy

Hemoptysis is a common complication of lung cancer and sometimes can be the first symptom. It is mostly caused by bronchial vascular rupture due to the tumor invasion.[73] Medication and surgery are the common clinical treatments for hemoptysis, but their therapeutic effects are not satisfactory. In the view of TCM, hemoptysis after chemotherapy is fundamentally attributed to yin deficiency and blood heat. Furthermore, lung and kidney yin deficiency along with lung loss of purification and descending leads to cough, which is the causative factor for the occurrence and aggravation of hemoptysis. In the Ming Dynasty, Luo Zhouyan explained in *Yi Zong Cui Yan* that if the innate yin of the lungs is weakened that it cannot control the fire, which leads to the flaring up of the deficient fire, while Baihe Gujin decoction can serve as the main regimen. Consequently, Baihe Gujin decoction can be used for the treatment of hemoptysis caused by the deficiency of lung yin.[74] Chen et al[73] treated 50 lung cancer patients with hemoptysis using Baihe Gujin decoction together with conventional western medicine. They observed that compared with simple western medicine, the treatment of Baihe Gujin decoction exhibited better improvement effect on hemoptysis, indicating the outstanding therapeutic effect of this decoction on hemoptysis in lung cancer. In the study on 84 lung cancer patients with hemoptysis by Wang,[75] modified Baihe Gujin decoction was able to relieve hemoptysis.

Improving Myelosuppression Caused by Radiotherapy and Chemotherapy

Radiotherapy is one of the main treatments for lung cancer, and the application of 3-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) has brought it into the precision medicine era. Specifically, 3D-CRT and IMRT can irradiate the tumor more accurately and improve the local control rate, but the accompanying adverse reactions cannot be completely avoided. For example, they may induce myelosuppression, which is mainly manifested as a reduction in leukocytes and hemogram.[76] Baihe Gujin decoction has anticancer efficacy and can effectively prevent leukopenia. Therefore, the used of Baihe Gujin decoction during radiation therapy can significantly enhance the resistance of patients to the toxic and side effects of radiation therapy as well as the tolerance of patients to radiotherapy.[77] Zhang et al[78] selected 91 lung cancer patients and found that based on WHO standards, the incidence of adverse reactions in the treatment group (combined with Baihe Gujin decoction) was much lower than that in the control group (with radiotherapy only). This finding indicated that Baihe Gujin decoction could reduce the adverse reactions caused by radiotherapy for lung cancer and effectively improve the myelosuppression in patients. Similarly, Chen et al[79] divided 116 lung cancer patients into two groups. The control group was treated with radiation therapy, while the treatment group with Baihe Gujin decoction on the basis of radiotherapy. They discovered that the probability of myelosuppression of patients in the treatment group was significantly lower than that of patients in the control group, suggesting that Baihe Gujin decoction could effectively reduce the adverse reactions induced by radiotherapy.

Chemotherapy is an important means of lung cancer treatment, but it also brings a series of side effects, including myelosuppression. Myelosuppression caused by chemotherapy is often the result of internal invasion of evils, which damages the internal organs such as liver, spleen, and kidney, depletes qi, blood, and fluid, and finally leads to the imbalance between yin and yang. TCM can improve the clinical symptoms of patients with myelosuppression by reinforcing qi and enriching blood, and nourishing the liver and kidney.[80] Zhang et al[81] evaluated the effect of etoposide and cisplatin chemotherapy combined with modified Baihe Gujin decoction in the treatment of SCLC based on WHO standards. As a result, the severity of myelosuppression in the treatment group was notably smaller than that in the control group, which indicated that the combination of TCM and chemotherapy in the treatment of SCLC was more clinically effective than chemotherapy alone. According to the retrospective analysis on 60 cases of NSCLC performed by Fang et al,[71] the incidence of leukopenia in treatment group and control group was 46.67% and 76.67%, respectively; besides, the control group exhibited a much higher incidence of adverse reactions than the treatment group. Such findings implied that Baihe Gujin decoction could significantly reduce the toxic and side effects of chemotherapeutic drugs on the blood system and weaken the adverse effects of myelosuppression on lung cancer patients.

Improving Toxic and Side Effects of Molecular Targeted Therapeutic Drugs in the Treatment of Non-Small Cell Lung Cancer

Molecular targeted therapeutic drugs provide new treatment means for patients with advanced NSCLC, which are beneficial to individualized treatment.[82] The long-term use of targeted therapeutic drugs may deplete yin essence gradually, and even impair kidneys over time. Due to the lack of kidney essence, the deficient fire will attack the lung. More seriously, a prolonged cough exacerbates the depletion of lung yin. Hence, the patients with long-term use of targeted therapeutic drugs often present with deficiency of both lungs and kidneys. Baihe Gujin decoction is good at supplementing the qi and yin and purging deficient fire, so it can be used for treating the deficiency of lung and kidney yin, calming the lung and regulating the qi.[26] Qu [83] treated 68 NSCLC patients with modified Baihe Gujin decoction combined with tyrosine kinase inhibitor. He discovered that the incidence of adverse reactions in the study group was lower than that in the control group, while the 1-year survival rate was higher than that in the control group. His finding uncovered that Baihe Gujin decoction could effectively alleviate clinical symptoms, regulate immune function, and improve the survival rate of lung cancer patients. A clinical study by Wang[84] revealed remarkable efficacy of Mai Men Dong Tang+Baihe Gujin decoction combined with gefitinib in treating elderly patients with advanced NSCLC. The combined treatment improved the syndrome, immune function, and the quality of life, and reduced the adverse reactions of patients. Wang et al[85] retrospectively analyzed 86 advanced NSCLC elderly patients with negative driver gene whose second-line treatment failed. They found that anlotinib had a certain degree of clinical efficacy as a third-line

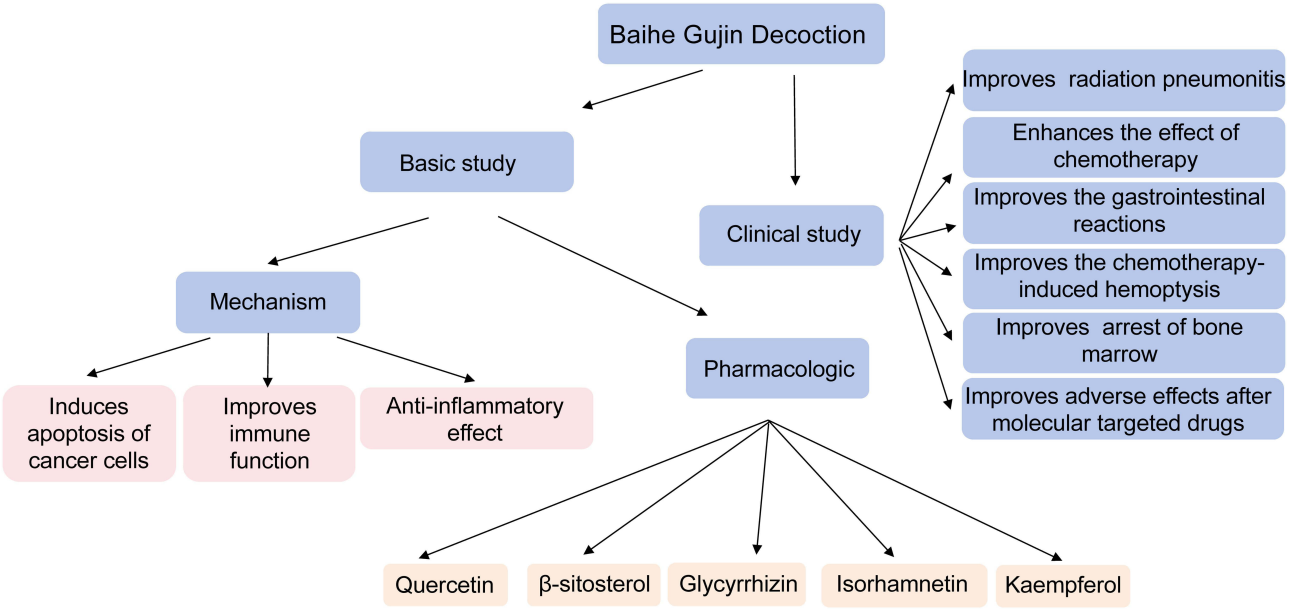

Figure 4 The summary of Baihe Gujin decoction in both preclinical and clinical studies. The pharmacological mechanisms of Baihe Gujin decoction for treating lung cancers included induction of cancer cell apoptosis, improvement of immune function, and anti-inflammatory effect. Quercetin, β-sitosterol, glycyrrhizin, isorhamnetin, and kaempferol were thought to be key pharmacological components. Regarding clinical studies, the main findings of Baihe Gujin decoction potency in treatment of lung cancers were composed of improvement of radiation pneumonitis, GI reactions, chemotherapy-induced hemoptysis, and AE after molecular targeted drugs and enhancement of chemotherapy effect.
Abbreviations: AE, adverse effect; GI, gastrointestinal.

treatment in the treatment of those patients. Moreover, after the oral intake of Si Jun Zi Tang+Baihe Gujin decoction, the patients exhibited lower incidence of treatment-related toxic side effects and prolonged survival time.

Conclusion and Prospect

This paper summarized the basic and clinical studies of Baihe Gujin decoction (Figure 4). Baihe Gujin decoction has been shown to be effective in treating lung cancer either alone or in combination with chemoradiotherapy. However, there are still some urgent problems to be solved. In terms of clinical research, there is a lack of literature on the improvement of adverse effects of Baihe Gujin decoction in postoperative rehabilitation of lung cancer. Besides, more in-depth studies are needed in conjunction with changes in the course of lung cancer treatment. Although immune checkpoint inhibitor is a hot research topic in the field of tumor treatment, there are few reports on the combination of immune checkpoint inhibitors with Baihe Gujin decoction in the treatment of lung cancer. Hopefully, this direction can be delved into deeper in the future. In the aspect of basic research, as the components of Baihe Gujin decoction are diversified, further exploring its mechanism of action is of great significance for the development of multi-target and multi-level effects on lung cancer cells and the inhibition to the proliferation and metastasis of lung cancer. To sum up, the efficacy of TCM+western medicine in the treatment of lung cancer is very remarkable. More thorough and in-depth clinical and basic researches, including molecular and cellular researches, are expected to be carried out on Baihe Gujin decoction in the future, with the hope of providing greater survival benefits and improving the quality of life of patients.

Data Sharing Statement

The data used to support the findings of this study are included within the article.

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Disclosure

The authors declare that they have no competing interests.

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