Research Progress on the Mechanism Exploration and Clinical Application of Traditional Chinese Medicine in Treating Non-Small Cell Lung Cancer

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Abstract. Lung cancer is the malignant tumor with the highest incidence and mortality in China, among which non-small cell lung cancer (NSCLC) occupies a dominant position. Traditional therapies such as chemotherapy, radiotherapy and targeted therapy have limitations including drug resistance, systemic toxicity and poor selectivity. However, traditional Chinese medicine (TCM) has shown unique advantages in NSCLC treatment through a multi-target synergistic mechanism: active ingredients of TCM (such as polysaccharides, alkaloids, flavonoids) can block the tumor cell cycle, induce apoptosis and inhibit angiogenesis; compound preparations regulate immune function and inhibit metastasis and recurrence through syndrome differentiation and treatment. In the field of combined therapy, the combination of TCM and chemotherapy can enhance the tumor suppressive effect, reduce bone marrow suppression and digestive tract reactions, and significantly improve patients' quality of life; the combination with radiotherapy can sensitize the anti-tumor effect while alleviating adverse reactions such as radiation-induced lung injury and dermatitis; the combination with targeted drugs can delay the occurrence of drug resistance and reduce toxic and side effects. In summary, TCM, through multi-channel intervention in the tumor microenvironment and signaling pathways, has the dual value of enhancing efficacy and reducing toxicity in direct anti-tumor and auxiliary traditional therapies, providing a new strategy for the comprehensive treatment of NSCLC. In the future, it is necessary to deeply explore its molecular mechanisms and promote standardized clinical research. According to the 2022 Global Cancer Statistics Report jointly released by the International Agency for Research on Cancer and the National Cancer Center of China, lung cancer ranks first in the incidence of malignant tumors in China with 106.06 thousand new cases, accounting for 42.7% of the total number of lung cancer cases worldwide. Meanwhile, its number of fatal cases (51.9 cases per 100,000 people) also ranks first in the spectrum of cancer deaths in China. It is mainly divided into two categories: small cell lung cancer and non-small cell lung cancer. NSCLC accounts for 80%-85% of lung cancer cases and is further subdivided into four subtypes: lung adenocarcinoma, lung squamous cell carcinoma, large cell carcinoma and bronchial carcinoid. Among them, lung adenocarcinoma is the most common subtype of NSCLC, accounting for more than 40% of all lung cancer cases. In traditional lung cancer treatment research, methods such as chemotherapy, radiotherapy and targeted therapy are often used in combination with first-line drugs to treat non-small cell lung cancer. However, radiotherapy has the defect of multiple adverse reactions such as increased dosage causing physical discomfort; chemotherapy also has the defect of no selectivity, which can also eliminate normal cells; patients receiving targeted therapy often develop drug resistance. Therefore, we are in urgent need of new methods for the treatment of non-small cell lung cancer. TCM has unique advantages in the prevention and treatment of NSCLC, with definite efficacy and few side effects in the treatment of lung cancer. It exerts synergistic effects through multiple targets and multiple pathways, which can make up for the deficiencies in drug resistance of first-line drugs such as targeted chemotherapy, and has significant efficacy in reducing the high metastasis and recurrence rate of NSCLC, improving patients' clinical symptoms and radiotherapy side effects. In recent years, under the new model of advocating multi-disciplinary combined diagnosis and treatment of malignant tumors, a large number of clinical studies on the combined application of TCM and chemotherapy in non-small cell lung cancer have been initiated. This article reviews the relevant studies on TCM active ingredient monomers and TCM compound preparations in the treatment of NSCLC in recent years, and provides a reference for the research and clinical application of TCM against NSCLC.

Keywords: Non-Small Cell Lung Cancer; Traditional Chinese Medicine; Mechanism Exploration and Clinical Application.

1. Direct Anti-Tumor Effect of Traditional Chinese medicine

Pure TCM treatment, as one of the TCM treatment modes for malignant tumors, is especially suitable for patients who are not suitable for or do not accept surgery, radiotherapy, chemotherapy, or molecular targeted therapy. It has more advantages in maintenance treatment in improving clinical symptoms, enhancing quality of life, and prolonging progression-free survival.

1.1 The Role of Active Ingredients of Traditional Chinese Medicine in the Treatment of NSCLC

The mechanisms of TCM in treating NSCLC mainly include arresting the cell cycle, inhibiting angiogenesis, regulating immune function, and promoting cell apoptosis. Components such as polysaccharides, alkaloids, and flavonoids contained in TCM can exert anti-tumor effects by inhibiting DNA synthesis of tumor cells, arresting the cell cycle, and slowing down the growth rate of tumor cells [3]. In recent years, many active ingredients derived from TCM have been verified to have extensive pharmacological effects, such as anti-oxidation, anti-tumor, anti-inflammation, and immune regulation. Monomers of anti-NSCLC active ingredients from TCM are also constantly being discovered, such as astragalus polysaccharides, paclitaxel, and tanshinone, which can act on multiple targets and affect various signaling pathways to achieve anti-NSCLC effects. See Table 1.

Table 1. Active monomer components of TCM against NSCLC

Name	Source of Traditional Chinese Medicine	Type	Cell Model	Mechanism of Action	Literature
Astragalus Polysaccharide	Astragalus membranaceus	Polysaccharide	A549	MAPK/NF-κB	[4]
Paclitaxel	Taxus chinensis	Diterpene Alkaloid	A549 A549 H446	MEG3-P53 Wnt/β-catenin MAPK/PKC	[5] [6] [7]
Tanshinone IIA	Salvia miltiorrhiza	Diterpene	A549 A549 & H1975 HCC827	PI3K/Akt/mTOR AURKA/PLK1 VEGFR/Akt	[8] [9] [10]
Matrine	Sophora flavescens	Alkaloid	A549 A549 & H299 H1975	PI3K/AKT/mTOR Akt/GSK-3β IL-6/JAK1/STAT3	[11] [12] [13]
Puerarin	Pueraria lobata	Isoflavone	A549	miR-342/CCDN1 PI3K/Akt MAPK/Erk1/2	[14] [15] [16]
Paeonol	Paeonia suffruticosa	Phenol	A549 & H299 A549	miR-126-5p/ZEB2 STAT3/NF-κB	[17] [18]

1.2 Anti-NSCLC Effects of Traditional Chinese Medicine Compound Prescriptions

Traditional Chinese medicine (TCM) compound prescriptions possess the diagnostic and therapeutic characteristics of TCM syndrome differentiation and treatment. The prescriptions are flexible and efficient in medication use, eliminating pathogenic factors while also supporting healthy qi. The research on the anti-cancer mechanisms of TCM prescriptions is mainly manifested in the inhibitory effects on the proliferation, migration, and invasion of tumor cells during tumorigenesis. TCM prescriptions contain a variety of active ingredients, and each ingredient has multiple targets in the body. Many TCM prescriptions have been proven to have good anti-cancer efficacy in clinical practice [19].

Fuzheng Quji Decoction is composed of Chinese medicinal materials such as North and South Adenophora, Radix Pseudostellariae, Ophiopogon japonicus, Asparagus cochinchinensis, fresh

Dendrobium, processed Pinellia ternata, Zhejiang Fritillaria, Coix seed, Radish seed, Curcuma zedoaria, Cat's Claw Herb, Scutellaria baicalensis, Houttuynia cordata, and Wild Buckwheat Root. It has the effects of replenishing qi and nourishing yin, resolving phlegm and removing blood stasis. Zhao Tongwei [20] et al. formed transplanted tumors by subcutaneously injecting A549 cells into the armpits of nude mice to construct a mouse lung cancer transplanted tumor model. Compared with the expression level of cleaved Caspase-3 protein in the model group, the expression level of Cleaved caspase-3 protein in the Fuzheng Quji Decoction combined with Icotinib group increased. TUNEL fluorescence staining was used to detect cell apoptosis, and it was found that compared with the apoptosis rate of the model group, the apoptosis rate of the Fuzheng Quji Decoction combined with Icotinib group was significantly increased. It is suggested that Fuzheng Quji Decoction can enhance the tumor-inhibitory effect of Icotinib on the transplanted tumor of lung cancer A549 cells in nude mice. The synergistic tumor-inhibitory mechanism may be related to enhancing the exogenous death receptor pathway and the endogenous mitochondrial pathway, and jointly activating Caspase-3 to cause an increase in cell apoptosis.

Yangyin Fuzheng Prescription is composed of Codonopsis pilosula, Adenophora stricta, Astragalus membranaceus, Asparagus cochinchinensis, Ophiopogon japonicus, raw Atractylodes macrocephala, Chinese yam, Hedyotis diffusa, Poria cocos, Gynostemma pentaphyllum, Bistorta officinalis, and Curcuma zedoaria. It has the effects of resolving phlegm and unblocking collaterals, replenishing qi and nourishing yin, dissipating blood stasis and detoxifying. Sun Xiyuan et al. established a transplanted tumor model of Lewis lung cancer and Lewis lung cancer C57BL/6 mice with programmed death-ligand 1. The results showed that in PD-L1+Lewis lung cancer, compared with the relative expression levels of Bcl-2 and Bax proteins in the control group 1, the relative expression level of Bcl-2 protein in the Yangyin Fuzheng Prescription group decreased, and the relative expression level of Bax protein increased; in Lewis lung cancer, compared with the relative expression levels of Bcl-2 and Bax proteins in the control group 2, the relative expression level of Bcl-2 protein in the Yangyin Fuzheng Prescription group decreased, and the relative expression level of Bax protein increased. This suggests that Yangyin Fuzheng Prescription can promote the apoptosis of PD-L1+Lewis lung cancer cells and Lewis lung cancer cells by regulating the expression of Bax and Bcl-2 proteins [21].

Chen Chao et al. divided Fuzheng Sanjie Prescription into four groups of Chinese medicines: resolving phlegm and dissipating masses, replenishing qi and supporting healthy qi, clearing heat and detoxifying, and promoting blood circulation and removing blood stasis. It was found that each group of Chinese medicines could inhibit the growth of Lewis lung cancer transplanted tumors. The mechanism might be to inhibit the vascular endothelial growth factor (VEGF), up-regulate the expression levels of angiostatin (AS) and endostatin (ES), thus inhibiting tumor angiogenesis [22]. Deficiency of healthy qi is a key factor in the onset and development of lung cancer, and TCM can improve the body's immune function, mainly manifested in the regulation of cellular immune functions, such as natural killer cells, T-cell subsets, interleukin-4, interleukin-13, interferon-γ, transforming growth factor-β, tumor-associated macrophages, etc., so as to achieve the goals of anti-recurrence and metastasis, and prolonging survival time [23].

2. Traditional Chinese Medicine Combined with Chemotherapy in the Treatment of NSCLC

Generally, traditional chemotherapy directly kills tumor cells, inhibits their growth, and promotes their differentiation, but it lacks specificity. Chemotherapy for lung cancer includes simple chemotherapy and combined chemotherapy. Chemotherapy combined with anti-angiogenic therapy can inhibit the neovascularization of tumors, block the nutritional supply to tumors, thereby achieving the goal of "starving" the cells. Chemotherapy is generally a systemic treatment, i.e., a non-local treatment method. For stage I NSCLC patients, treatment is mainly based on surgical resection, combined with adjuvant chemotherapy after surgery. Adjuvant chemotherapy refers to chemotherapy

administered after tumor surgery or radiotherapy to kill residual tumor cells. For stage IIIA patients, neoadjuvant therapy (i.e., chemotherapy before surgery) is mostly used. When it is difficult to surgically resect tumors near important organs or large blood vessels, neoadjuvant therapy can reduce the tumor volume, creating opportunities for subsequent surgery. For stage IV patients, palliative chemotherapy is the main approach, which is used for advanced lung cancer patients to reduce or stabilize the tumor, improve their symptoms and quality of life, and prolong survival time. Unlike early-stage patients who undergo surgical treatment, advanced-stage patients have low postoperative survival rates and high recurrence rates, so chemotherapy is generally used as the main treatment to control the disease progression and prolong survival. Although chemotherapy has a relatively good therapeutic effect, it can induce toxic and side effects of varying degrees, which may seriously affect patients' quality of life and treatment compliance. Given this situation, the application of traditional Chinese medicine (TCM) combined with chemotherapy in the treatment of lung cancer has become increasingly widespread. Clinical practice has found that TCM combined with chemotherapy can not only enhance patients' immune function, prolong survival, reduce cancer metastasis, and improve quality of life, but also effectively reduce and alleviate some toxic and side effects of chemotherapy, thereby improving the efficacy of chemotherapy from multiple dimensions.

2.1 Improving Clinical Symptoms and Quality of Life

Ye Xuanting [24] et al. used Fuzheng Jiedu Granules combined with chemotherapy for postoperative NSCLC patients at stages IB-IIIA. The results showed that in the treatment group, scores of physical function, health status, and emotional function significantly increased, while scores of cognitive function, cough, fatigue, and insomnia decreased; in the control group, only the physical function score increased and the cognitive function score decreased, and the health status score of the treatment group was better than that of the control group. Liu Dongbo [25] et al. applied Fuzheng Huatan Guben Decoction combined with chemotherapy for early postoperative NSCLC patients. The results showed that in the observation group, scores of TCM syndromes (such as chest distension and pain, cough with phlegm, shortness of breath and reluctance to speak, and fatigue) were reduced and lower than those in the control group; the effective rate of symptom improvement in the observation group (91.43%) was significantly higher than that in the control group (71.43%); scores of KPS and QLQ-C30 (including physical, cognitive, role, emotional, and social functions) in the observation group increased and were higher than those in the control group. The above research results indicate that the combination of qi-tonifying and healthy-qi-supporting TCM with heat-clearing and detoxifying, cough-relieving and phlegm-resolving, yin-nourishing and lung-moistening TCM in postoperative NSCLC treatment can improve patients' clinical symptoms and quality of life, with a better effective rate than purely western medicine treatment.

2.2 Regulating Immune Function

Chemotherapy is a main treatment for NSCLC, but while exerting its therapeutic effect, it can cause certain damage to the body's immune function, reduce patients' immune function, and affect the progress and clinical efficacy of chemotherapy. Therefore, correcting immune dysfunction is helpful for the treatment of NSCLC. Experimental studies have proven that TCM can regulate the body's immune function and inhibit the immune escape of tumor cells, thereby exerting anti-lung cancer effects. Clinical studies have also shown that TCM can improve the immune function of postoperative NSCLC patients receiving chemotherapy.

In the body's anti-tumor immune response, T lymphocyte subsets (CD3+, CD4+, CD8+, CD4+/CD8+) play a crucial regulatory role. Generally, the relative proportions of various subsets in T cells are maintained at specific levels. Once the proportion of T cell subsets is imbalanced, i.e., abnormalities in CD4+/CD8+, CD3+, CD4+, and CD8+ occur, it indicates that the body's cellular immune function is low, and the anti-tumor effect cannot be effectively exerted. Cui Bixian et al. [26] used Bufei Huayu Decoction as an adjuvant treatment for elderly postoperative NSCLC patients. The results showed that levels of CD3+, CD4+, and CD4+/CD8+ in the observation group increased and

were higher than those in the control group, while levels of CD3+, CD4+, and CD4+/CD8+ in the control group decreased. Zhang Sufang [38] observed the effect of Fuzheng Quxie Decoction on the immune function of patients after radical resection of early NSCLC. The results showed that levels of peripheral blood CD3+, immunoglobulin A (IgA), and IgM in the treatment group were significantly higher than those in the control group, while levels of regulatory T cells and myeloid-derived suppressor cells were significantly lower than those in the control group. Luo Wen et al. [27] used modified Buzhong Yiqi Decoction as an adjuvant treatment for postoperative NSCLC patients receiving chemotherapy (with lung-spleen qi deficiency syndrome). The results showed that levels of serum CD4+/CD8+, CD4+ cells, and immunoglobulin G (IgG) in the combined treatment group were significantly higher than those in the chemotherapy group. Li Jian et al. [28] observed the effect of Jianpi Yiqi Decoction combined with chemotherapy on the immune function of postoperative NSCLC patients. The results showed that levels of CD3+, CD4+, and CD4+/CD8+ in the combined medication group increased, CD8+ decreased, and all indicators were better than those in the control group; levels of IgG and IgM in the combined medication group were significantly higher than those in the control group. The above research results indicate that TCM for supplementing middle qi and strengthening healthy qi to eliminate pathogenic factors can regulate cellular and humoral immune functions in postoperative NSCLC patients receiving chemotherapy.

2.3 Preventing Cancer Recurrence and Metastasis

For patients with stage I, II, and some resectable stage IIIA NSCLC, surgical radical resection is the best choice, but 30%-55% of patients will still experience recurrence and metastasis after surgery, leading to treatment failure [45]. Postoperative NSCLC patients can receive adjuvant chemotherapy or targeted therapy to kill residual cancer cells, which helps prevent recurrence and metastasis, but the effect is not ideal. TCM has a certain effect on preventing recurrence and metastasis of NSCLC after treatment.

Li Hua et al. [29] used Yiqi Yangyin Huayu Decoction as an adjuvant treatment for postoperative NSCLC patients. The results showed that after 12 months, the recurrence rate and metastasis rate in the combined medication group were 4.55% and 22.73%, respectively, while those in the simple chemotherapy group were 6.82% and 27.27%. The recurrence rate and metastasis rate in the combined medication group were lower than those in the chemotherapy group, indicating that Yiqi Yangyin Huayu Decoction can reduce the postoperative recurrence and metastasis rates of NSCLC patients. Wang Suzhen et al. [30] observed the effect of Shenzhu Ercao Decoction in preventing recurrence in high-risk postoperative NSCLC patients. The results showed that after 6 months, the recurrence rate in the conventional chemotherapy group was 23.26%, while that in the TCM combined with chemotherapy group was 3.92%. Zheng Fengchang et al. [31] used Weimaining Capsules combined with radiotherapy and chemotherapy to treat postoperative NSCLC patients. The results showed that after one year, the total recurrence rates in the observation group and the control group were 3.19% and 14.89%, respectively, with the observation group significantly lower than the control group. The above research results indicate that TCM used in postoperative NSCLC patients receiving chemotherapy can reduce their recurrence and metastasis rates, which has positive clinical significance for prolonging survival.

2.4 Improving Patient Survival

Improving patients' long-term survival is the ultimate goal of lung cancer treatment. Surgery is the first choice for stage I-II and some stage IIIA NSCLC, but the long-term postoperative survival rate of patients is still not high. The 5-year survival rate after surgery for stage IA patients is 77%, while that for stage IIIA patients is only 23% [32]. Therefore, how to adopt effective treatments to improve the long-term postoperative survival rate of NSCLC patients has become an important content of clinical research. Studies have found that adjuvant TCM treatment for postoperative NSCLC patients can improve their prognosis and disease-free survival [33].

Guan Sisi et al. [32] conducted a cohort study to retrospectively evaluate the effect of TCM on disease-free survival of stage IIIA NSCLC patients who received chemotherapy after complete resection. The results showed that the median disease-free survival in the simple chemotherapy group and the TCM combined with chemotherapy group was 33.60 months and 40.83 months, respectively. The 1-year, 2-year, and 3-year disease-free survival rates in the simple chemotherapy group and the TCM combined with chemotherapy group were 87.9%, 66.4%, 45.6% and 88.6%, 72.9%, 54.6%, respectively, indicating that TCM treatment can prolong the disease-free survival of stage IIIA NSCLC patients who received chemotherapy after complete resection. Zhang Li et al. [34] used Elemene Injection as an adjuvant treatment for postoperative NSCLC patients. After a two-year follow-up, the results showed that the total survival rate, 1-year survival rate, and median disease-free survival in the observation group were 37.5%, 67.5%, and 19.5 months, respectively, while those in the control group were 18.2%, 42.4%, and 9.2 months, with the observation group significantly higher than the control group.

Huang Mingyu [35] retrospectively evaluated the effect of Fuzheng Quxie Decoction combined with chemotherapy on the disease-free survival of postoperative NSCLC patients. The results showed that the median DFS in the treatment group was 27.80 months, which was significantly longer than 18.60 months in the control group. Zhang Ren [36] conducted a prospective, multi-center randomized controlled study to observe the efficacy of Jinfukang Oral Liquid combined with chemotherapy in treating postoperative NSCLC patients at stages I-IIB. The results showed that the expected average DFS in the treatment group (Jinfukang Oral Liquid combined with chemotherapy) was 36 months, and that in the control group (simple chemotherapy) was 33 months, with the treatment group higher than the control group, but the difference was not statistically significant. The above research results indicate that TCM intervention after surgery for NSCLC patients can prolong their survival, improve disease-free survival rate, and improve prognosis.

2.5 Reducing and Alleviating Some Toxic and Side Effects of Chemotherapy

Chemotherapy is a main adjuvant treatment for postoperative NSCLC patients, but it often causes severe adverse reactions, mainly including myelosuppression, digestive system reactions, nervous system reactions, and damage to organs such as the heart, liver, and kidneys, which seriously affect patients' quality of life and clinical efficacy. Clinical studies have shown that TCM can alleviate the adverse reactions caused by chemotherapy in NSCLC patients [37].

2.5.1 Alleviating Myelosuppression

NSCLC patients often experience various severe adverse reactions during chemotherapy, among which myelosuppression is the most common and serious one, which can cause reductions in red blood cells, hemoglobin, white blood cells, and platelets, easily induce infections, and in severe cases, may lead to the inability to complete the chemotherapy course, affecting the efficacy of chemotherapy [38]. Studies have shown that TCM has a prominent effect in preventing and treating myelosuppression caused by chemotherapy in NSCLC [39]. Han Xu et al. [40] conducted a retrospective study to analyze the bone marrow protective effect of Diyu Shengbai Tablets in postoperative chemotherapy for stage II NSCLC. Patients who took Diyu Shengbai Tablets orally during 4 cycles of chemotherapy were in the prevention group, and those who did not take the tablets were in the control group. The results showed that the dosage of recombinant human granulocyte colony-stimulating factor in the prevention group was significantly lower than that in the control group; in the 4th cycle of chemotherapy, the incidence of grade II or higher myelosuppression in the prevention group was 74.1%, and that in the control group was 92.8%, with the prevention group significantly lower than the control group, indicating that Diyu Shengbai Tablets have a bone marrow protective effect. Luo Wen et al. [27] used modified Buzhong Yiqi Decoction for postoperative NSCLC patients receiving chemotherapy. The results showed that the incidence of myelosuppression in the observation group was 20.83%, and that in the control group was 39.58%, with the observation group lower than the control group. Shen Jia et al. [41] used Jiedu Yangyin Qingfei Decoction combined with chemotherapy to treat postoperative NSCLC patients. The results showed that the

incidence of leukopenia in the combined medication group was 53.1%, while that in the control group was 62.5%, indicating that Jiedu Yangyin Qingfei Decoction can reduce myelosuppression caused by chemotherapy. The above research results indicate that TCM can alleviate myelosuppression caused by postoperative chemotherapy in NSCLC patients, reduce the degree and incidence of myelosuppression after chemotherapy, and improve blood routine levels.

2.5.2 Alleviating Digestive System Reactions

Postoperative NSCLC patients often experience digestive system symptoms such as nausea, vomiting, abdominal pain, diarrhea, constipation, and loss of appetite after chemotherapy, which affect their quality of life and clinical efficacy. Studies have shown that TCM has a good effect on digestive system adverse reactions caused by chemotherapy for lung cancer [42].

Shi Huimin et al. [43] observed the efficacy of Sun Guangrong Jianzhong Hewei Decoction in treating chemotherapy-related nausea and vomiting in postoperative NSCLC patients. The control group was given Western medicine treatment. The results showed that after treatment, the nausea and vomiting scores in the experimental group were significantly lower than those in the control group, and the TCM syndrome scores and quality of life scores were better than those in the control group. Liu Xuejing et al. [43] used Xuanfu Daizhe Decoction to prevent adverse reactions such as nausea and vomiting in lung cancer patients after postoperative chemotherapy. The results showed that scores of the nausea, vomiting, and retching symptom assessment scale in the combined group (Xuanfu Daizhe Decoction+conventional treatment) were lower than those in the conventional group, and scores of the comfort status scale and other quality of life scores were higher than those in the conventional group. In addition, Yang Dongjie et al. [44] used acupoint massage therapy, sequentially kneading and pressing Dazhui, Feishu, Dachangshu, Zhongwan, Tianshu, Guanyuan, Neiguan, Lieque, Zusanli, and Sanyinjiao acupoints. The results showed that acupoint massage therapy can significantly improve chemotherapy-related digestive tract reactions such as nausea, vomiting, diarrhea, and constipation in postoperative NSCLC patients. In summary, TCM has a good effect on digestive system adverse reactions caused by postoperative chemotherapy in NSCLC patients, and can reduce the incidence and severity of reactions such as nausea, vomiting, retching, and constipation in patients.

3. Treatment of NSCLC with Traditional Chinese Medicine Combined with Radiotherapy

Radiotherapy is one of the important means for treating non-small cell lung cancer (NSCLC). Radiotherapy is mostly a local treatment, using high-energy radiation to kill tumor cells. It is also the most commonly used local treatment option besides surgery. It can be used alone or in combination with chemotherapy and surgery. If patients cannot undergo surgical treatment due to physical reasons, radiotherapy can also be used for radical treatment of patients with early-stage NSCLC, that is, to achieve the goal of radical cure through radiotherapy. At the same time, radiotherapy can also be used as an adjuvant treatment before and after surgery for patients. However, radiotherapy also brings many problems. The radiotherapy cycle often causes fatigue, skin reactions, hair loss, poor appetite, and emotional reactions such as depression and fear. At the same time, during radiotherapy, the range and marks need to be determined, and these cannot be washed off. Patients also need to keep their bodies still during radiotherapy and keep their skin clean. At the same time, some physiological reactions may occur. Due to the existence of radiation resistance and the adverse events caused by radiotherapy, the effect and progress of radiotherapy are seriously affected. More and more evidence shows that the combination of traditional Chinese medicine (TCM) and radiotherapy in the treatment of NSCLC has the advantages of synergistically enhancing efficacy and reducing toxicity, and has the effects of improving the anti-tumor effect and reducing treatment-related adverse reactions.

3.1 The Efficacy-Enhancing Effect of TCM on NSCLC Radiotherapy

The existence of radiation resistance not only affects the curative effect of tumors, but is also the main reason why patients cannot tolerate radiotherapy in the later stage. Radiotherapy causes direct damage by inducing single-strand and double-strand breaks of tumor cell DNA within the irradiation field. At the same time, it acts on other atoms or molecules (especially water molecules) in the cells, generating reactive oxygen species (ROS) that can highly bind to deoxyribonucleic acid, proteins, and lipids, causing indirect damage, and inducing tumor cells to undergo apoptosis, mitotic death, ferroptosis, and autophagic cell death, etc. [45]. Radiotherapy can induce tumor cells to release and present a large number of tumor-related antigens in a short time, promoting anti-tumor immune responses. However, due to factors such as the DNA damage repair system, cell cycle arrest, and changes in the tumor microenvironment, tumor cells develop radiation resistance. Wang Yong et al. [46] found that the TCM extract liquiritigenin can enhance radiotherapy sensitivity by regulating the expression of wild-type p53-induced gene 1. WANG et al. [47] found that quercetin can increase the expression of miR-16-5p and reduce the expression of serine/threonine protein kinase I, thereby reversing the radiation resistance of NSCLC. Jin Lei et al. [48] found that tetrandrine can reduce the expression of hypoxia-inducible factor-1α at the protein expression level, reduce the VEGF expression of hypoxic-induced lung cancer cells, and the drug can also significantly enhance the radiotherapy sensitivity of p53-deficient NSCLC cells. The influence of TCM on the radiotherapy sensitivity of tumor cells may be related to its regulation of biological processes such as the cell cycle, apoptosis, and signal transduction.

3.2 The Toxicity-Reducing Effect of TCM on NSCLC Radiotherapy

3.2.1 TCM Improves Radiation-Induced Lung Injury

Radiation-induced lung injury is the most common adverse reaction in NSCLC patients after chest radiotherapy, and it is also one of the important factors that hinder the radiotherapy dose and reduce the tumor control rate [49]. Many studies on TCM compounds, monomers, and monomer extracts have found that inhibiting the release of inflammatory mediators such as IL-1β, IL-6, and TNF-α, regulating Th1/Th2 imbalance, reducing oxidative stress reactions, and regulating related pathways can reduce the occurrence of radiation-induced lung injury (RILI) [50]. Chen Yanyan et al. [51] found that the extract of Salvia miltiorrhiza can reduce the levels of IL-6, TNF-α, and TGF-β1 in RILI rats, increase the level of serum superoxide dismutase, reduce the level of malondialdehyde (MDA) in lung tissue and the expression of NF-κBp65, inhibit lung inflammation, and prevent pulmonary fibrosis. In the early stage of radiation pneumonitis, Th1 secretes IL-2, interferon-γ, TNF-α, etc. to initiate the inflammatory response, manifested as Th1 inhibition and Th2 upregulation. In the stage of radiation-induced pulmonary fibrosis, it is the opposite. Th2 cells promote pulmonary fibrosis by inducing collagen synthesis [52]. Yin-nourishing and qi-tonifying TCMs such as Glehnia littoralis, Ophiopogon japonicus, Rehmannia glutinosa, and Codonopsis pilosula have been proven to improve Th1/Th2 imbalance. The Sangxing Hufei Granules composed of these drugs with appropriate modifications can improve RILI in rats and have a dose-dependent lung protection effect [53]. NF-κ is a classic pathway related to inflammatory mediators and is easily activated by radiation. The classic TCM prescription Danggui Buxue Decoction (Astragalus membranaceus and Angelica sinensis) can play a radioprotective role by inhibiting this pathway [54]. The phosphatidylinositol-3-kinase/protein kinase B pathway is an important signaling pathway mediating pulmonary fibrosis. The Dabu Pi Tang from Dunhuang medical ancient prescriptions, using the method of nourishing the spleen to generate lung qi, can inhibit the phosphorylation of PI3K and AKT, thereby playing a role in resisting RILI [55]. TGF-β/Smads is considered a key pathway in the occurrence and development of RILI, especially extremely important in the process of pulmonary fibrosis. The Compound Kushen Injection is extracted and processed from Sophora flavescens and Smilax glabra, and has the effects of clearing heat and detoxifying, and eliminating dampness and resolving masses. After acting on RILI mice, it was found that it can activate the TGF-β1/Smads and Wnt/β-catenin signaling pathways, regulate

epithelial-mesenchymal transition, and reduce the degree of lung inflammation and fibrosis [56]. These studies provide a scientific basis for TCM to effectively improve RILI caused by radiotherapy.

3.2.2 TCM Improves Radiation Dermatitis

During the radiotherapy process of NSCLC patients, it is inevitable to have radiation dermatitis caused by radiation. In mild cases, erythema and desquamation may occur and heal spontaneously in a short time. In severe cases, moderate to severe skin damage, ulcer formation, and skin necrosis may occur, which are difficult to heal and may cause interruption of radiotherapy, affecting the patient's radiotherapy process. TCM treats radiation dermatitis (RD) through internal and external treatment methods such as oral administration or external application of ointments and powders. Its function is mainly to accelerate the neovascularization of the wound surface to promote blood circulation, promote the proliferation of fibroblasts, and thus promote wound healing [57, 58]. Some scholars have summarized from the literature that the commonly used TCMs for treating RD mainly include heat-clearing and detoxifying Chinese herbal medicines such as Arnebiae root, Coptis chinensis, Phellodendron amurense, and Scutellaria baicalensis [59]. Arnebiae root oil is a commonly used external medicine in TCM. The chemical components contained in Arnebiae root have modern pharmacological activities such as antibacterial, anti-inflammatory, antiviral, antioxidant, and anti-tumor [60]. Multiple studies have shown that Arnebiae root oil can promote the formation of new blood vessels, increase the collagen content, thereby promoting the proliferation of granulation tissue, and effectively control RD [61]. In addition to oils, TCMs for clearing heat, detoxifying, and drying dampness such as Coptis chinensis, Phellodendron amurense, Lonicera japonica, and Forsythia suspensa are often made into external water agents, which are mostly used after ulceration of sores. Due to the variety and low price of external TCM treatment methods, they have the advantages of quickly promoting wound healing and wound surface repair, and can be flexibly formulated according to different stages of the wound surface in the treatment of RD, and have received more and more attention in relevant studies after radiotherapy.

3.2.3 TCM Improves Myelosuppression Caused by Radiotherapy

During the radiotherapy process, some patients experience myelosuppression. Common clinical manifestations include various symptoms such as fatigue, dizziness, shortness of breath, palpitations, and low fever. According to its symptoms, in TCM theory, it is a kind of deficiency syndrome, especially mainly kidney deficiency. Therefore, when treating myelosuppression, TCMs for tonifying the kidney and replenishing the marrow, and strengthening the spleen and replenishing qi are often used to tonify the root of the congenital and acquired, and TCMs for nourishing blood and softening the liver are used to prevent liver hyperactivity from damaging the spleen. Studies have found that some TCMs for tonifying the kidney to generate marrow, strengthening the spleen and nourishing the liver, and replenishing qi and blood can increase the levels of white blood cells, red blood cells, hemoglobin, platelets, granulocyte-macrophage colony-stimulating factor, and granulocyte colony-stimulating factor in the peripheral blood, and improve the degree of myelosuppression [62]. Astragalus membranaceus is a qi-tonifying medicine, which can benefit essence and fill the marrow. Among them, astragalus polysaccharide can increase hematopoietic progenitor cells, reduce apoptosis, and promote the repair of hematopoietic function, thereby alleviating myelosuppression [63]. Angelica sinensis can tonify blood and activate blood circulation. Angelica polysaccharide can promote the proliferation and differentiation of hematopoietic stem cells, accelerate the differentiation and maturation of blood cells, and has an improving effect on myelosuppression caused by radiotherapy [64]. Modern research shows that Danggui Buxue Decoction can resist the apoptosis of megakaryocyte Meg-01 cells, regulate the proliferation and differentiation of megakaryocyte progenitor cells in the body, promote the formation of hematopoietic cell colonies, activate the PI3K/AKT pathway, and upregulate miRNA to promote cell proliferation and inhibit cell apoptosis [65]. Diyu Shengbai Tablets and Qijiao Shengbai Capsules are Chinese patent medicines that are effective for leukopenia after radiotherapy and chemotherapy in clinical practice. They can promote the proliferation of hematopoietic stem cells and the bone marrow hematopoietic

microcirculation, thereby increasing the content of white blood cells in the peripheral blood [66, 67]. More and more clinical practices show that TCM has a definite curative effect in improving and treating myelosuppression caused by radiotherapy, and the adverse reactions are relatively small. Its mechanisms mainly include promoting the proliferation and differentiation of hematopoietic stem cells, regulating the body's immunity, reducing the damage of radiotherapy to bone marrow tissue, and promoting bone marrow repair.

3.2.4 TCM Improves Cardiac Injury Caused by Radiotherapy

The radiotherapy area for NSCLC generally includes the lungs and mediastinal lymph nodes, and its anatomical position is close to the heart, so the heart will inevitably be damaged by radiation. Radiation-induced heart injury may appear in the forms of pericarditis, cardiomyopathy, myocardial fibrosis, pericardial effusion, and arrhythmia. Vascular endothelial cell injury is an important cause of radiation-induced heart disease (RIHD) [68]. In TCM theory, RIHD belongs to the categories of "palpitation" and "chest stuffiness and pain". Due to qi and blood deficiency, pathogenic heat disturbing the heart, or blood stasis blocking the meridians, leading to "pain due to obstruction" and "pain due to malnourishment", the treatment principle of eliminating pathogenic factors and tonifying deficiency is often adopted. The mechanisms by which TCM improves RIHD mainly include anti-oxidation, anti-inflammation, and promoting myocardial repair. After exposing rats to radiation, KOLIVAND et al. found that the expression of IL-4 and IL-13 cytokines and the infiltration of lymphocytes and macrophages increased, and curcumin can reduce the expression of these inflammatory mediators and the infiltration of inflammatory cells. Duan Yifan et al. [69] used Huangqi Shengmai Yin, which is composed of adding Astragalus membranaceus to Shengmai San, to treat RIHD rats. It can reduce the early inflammatory response, inhibit the expression of fibrosis molecules such as TGF-β1, type I collagen (Collagen Type I, Col1), and Col3, and can effectively protect the heart and delay its fibrosis process. Commonly used TCM types in clinical practice include tonifying TCMs (such as Astragalus membranaceus and Panax ginseng), blood-activating and stasis-removing TCMs (such as Salvia miltiorrhiza and Carthamus tinctorius), and heat-clearing and detoxifying TCMs (such as Coptis chinensis and Isatis indigotica), which can reduce symptoms such as palpitations and chest tightness in radiotherapy patients, improve cardiac function indicators, and enhance patients' quality of life.

4. Treatment of NSCLC with Traditional Chinese Medicine Combined with Targeted Drugs

Targeted therapy is a treatment method that inhibits the growth of lung cancer or even kills cancer cells by targeting the oncogenic sites of tumors (specific gene mutations that cause lung cancer). This treatment method has significant advantages such as strong specificity, high effectiveness, few toxic and side effects, and good patient tolerance. Generally speaking, targeted therapy is the first choice for patients with advanced (stage 4) non-small cell lung cancer with positive driver gene mutations. Driver genes include EGFR, ALK, ROS1, MET, RET, KRAS, BRAF, and NTRK. In general, targeted drugs do not act on specific targets; they can only inhibit one pathway of tumor formation. When this pathway is inhibited, tumor cells will continuously seek other pathways to obtain substances needed for their own growth. After obtaining other pathways, drug resistance is likely to occur. Drug resistance is divided into local resistance and extensive resistance. Local resistance refers to tumor metastasis to the brain or other single part, while extensive resistance refers to tumor metastasis to the whole body or multiple part. After drug resistance occurs, tumor growth cannot be controlled, the tumor enlarges, metastasizes to other part through lymphatic and hematogenous metastasis, and new symptoms such as cough, asthma, dizziness, and headache may appear. At this time, after drug resistance to targeted drugs, genetic testing should be performed again to determine the mechanism of drug resistance, and then the corresponding treatment plan should be selected based on the mechanism. The drug resistance mechanism of first- and second-generation EGFR and TKI drugs is mainly t790 secondary mutation, and the method is to use third-generation drugs for

subsequent treatment. The drug resistance mechanism of third-generation EGFR and TKI drugs is mainly c797s mutation and MET amplification.

4.1 Improving the Therapeutic Effect of Targeted Drugs

The combined use of traditional Chinese medicine (TCM) and targeted drugs has a synergistic effect, and TCM can enhance the efficacy of targeted drugs. Yu Pan et al. [32] concluded from a comparative experiment that after treatment with TCM combined with targeted drugs, the levels of serum carcinoembryonic antigen (CEA), CYFRA21-1, and S100B protein in patients decreased, and the control rate of solid tumors was higher than that in the group treated with targeted drugs alone. This suggests that the therapeutic effect of combined medication is higher to a certain extent. The treatment of NSCLC with TCM can control the growth of cancer cells, kill cancer cells to the maximum extent, and prevent the proliferation of cancer cells. Tao Zhihui et al. [70] used pemetrexed disodium combined with cisplatin injection, and then used Xiangsha Liujunzi Decoction combined with Xuanfu Daizhe Decoction. In the first week, Xiangsha Liujunzi Decoction was used to invigorate the spleen and improve digestive tract reactions, and in weeks 2-4, it was used to strengthen healthy qi and consolidate the root, as well as clear heat and detoxify to resist tumors. After 4 cycles, the clinical benefit rate of the observation group (80.43%) was higher than that of the control group. Wu Yaqin [71] et al. pointed out in their analysis that the application of Chinese patent medicines such as Shenyi Capsule and Kang'ai Injection combined with targeted drugs can improve the therapeutic effect of NSCLC, protect immune function, and have high safety, indicating that TCM combined with targeted drugs in the treatment of NSCLC has a synergistic effect.

4.2 Management of Toxic and Side Effects of Targeted Drugs

Although targeted drugs have high efficacy and safety in the treatment of NSCLC, their toxic and side effects cannot be ignored. Clinical application of targeted drugs may cause hand-foot skin reactions, which generally manifest as abnormal sensation, redness, swelling, itching, swelling and pain of the hands or feet, gastrointestinal reactions such as nausea, vomiting, and diarrhea, as well as rare interstitial pneumonia, liver and kidney function damage, etc. Once these adverse reactions occur, if not handled in time, they will seriously threaten the patient's life safety. For the skin side effects of patients, wind-dispelling, heat-clearing and detoxifying prescriptions can be used for treatment. Some scholars believe that Xiaozhen Powder can effectively treat skin reactions in NSCLC patients after taking targeted drugs [72]. This prescription is composed of cicada slough, borneol, asarum, etc. In the prescription, cicada slough and windproof dispel wind and relieve itching; borneol detoxifies and relieves itching; asarum dispels wind and dissipates pathogens. This prescription has no impact on the normal efficacy. In the study by Zhang Yami et al. [73], Fuzheng Huayu Decoction combined with chemotherapy had a 90% effective rate in treating gastrointestinal reactions in advanced NSCLC patients.

4.3 Prevention of Drug Resistance to Targeted Drugs

Targeted drugs have obvious efficacy in patients with advanced NSCLC and can prolong the survival time of tumor patients. However, drug resistance occurs in all patients who initially use targeted drugs. TCM can effectively prevent drug resistance to targeted drugs, providing a new direction for the clinical treatment of NSCLC and the prevention of drug resistance. To further explore the drug resistance mechanism of targeted drugs, some scholars found that related TCM can reverse cisplatin resistance in lung cancer by inhibiting the Akt/Foxo pathway and activating the endogenous apoptotic pathway [74]. Another research team has made new progress in the study of using Yiqi Chutan Decoction to intervene in acquired drug resistance to targeted drugs. Subsequent cell-level and animal-level experiments showed that Yiqi Chutan Decoction can inhibit the PI3K pathway and promote the expression of autophagy proteins, thereby intervening in acquired drug resistance to targeted drugs [75].

4.4 Improving Immunity and Quality of Life

Patients with advanced NSCLC take chemotherapy or radiotherapy drugs for a long time, leading to the gradual decline of various organ functions and reduced immunity. Therefore, modern scientific treatment attaches great importance to improving the quality of life of patients. Although targeted drugs can effectively reduce the occurrence of clinical symptoms, inhibit tumor growth, and improve patient survival rate, long-term use of these drugs may cause certain toxic and side effects. The qi-tonifying and healthy-qi-strengthening prescriptions of TCM can enhance the body's healthy qi, relieve symptoms caused by toxic and side effects without changing the effect of chemotherapy drugs, and have a significant effect in improving survival rate. Yu Hui et al. [76] pointed out in their research analysis that TCM combined with targeted drug therapy can improve the objective remission rate, therapeutic effect, and quality of life. TCM believes that lung cancer is caused by the decline of the body's healthy qi and internal accumulation of pathogenic toxins. The prescriptions mainly focus on replenishing qi and blood and restoring the body's healthy qi, such as ginseng and astragalus. Shenyi Capsule and other Chinese patent medicines are representative of qi-strengthening and healthy-qi-strengthening preparations, which can promote the recovery of the body, improve disease resistance, prolong survival time, and improve quality of life.

5. Conclusions and Outlook

Traditional Chinese medicine (TCM) has attracted much attention from researchers due to its advantages such as strong pharmacological activity, few toxic and side effects, and multi-target combined treatment of tumors. Currently, the studied anti-NSCLC active ingredients of TCM mainly include alkaloids, saponins, terpenes, polysaccharides, etc., all of which show proliferation-inhibiting effects on NSCLC. Whether it is monomer therapy or compound therapy, the combination with radiotherapy and chemotherapy can effectively reduce the recurrence and metastasis rates, reverse multi-drug resistance, improve treatment efficiency, significantly improve patients' clinical symptoms, enhance quality of life and immune function, prolong survival time, and reduce tumor recurrence and metastasis rates. The combination with targeted drugs is mainly reflected in the synergistic effect with targeted drugs, which can enhance efficacy, reduce the toxic and side effects caused by targeted drugs, prevent and reduce drug resistance to targeted drugs, thus having a good application prospect.

In recent years, although research on TCM in anti-NSCLC has made many positive progress, there are still many deficiencies at the current stage. Moreover, the understanding of the mechanism of TCM active ingredients in anti-NSCLC and clinical research are very limited, with insufficient sample size as data support. Therefore, in the future, we should formulate scientific diagnosis and treatment standards in line with TCM theory, deeply clarify the molecular mechanism of TCM in treating NSCLC, carry out large-sample, multi-center clinical studies, and use modern information technology to follow up patients, so as to provide more sufficient basis for TCM treatment of NSCLC.

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