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Research Progress on Shengxian Decoction in the Treatment of Non-Small Cell Lung Cancer

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Abstract: ***Lung cancer has the highest incidence and mortality rates among malignant tumors in China, with non-small cell lung cancer (NSCLC) accounting for 80%-85% of lung cancer cases. In recent years, treatment methods such as surgery, radiotherapy, and chemotherapy have advanced significantly; however, issues such as numerous complications, severe side effects, and increased drug resistance remain. Traditional Chinese Medicine (TCM) offers a multi-component, multi-target, and multi-pathway approach for treating NSCLC without these drawbacks, which has attracted considerable attention. The fundamental pathogenesis of NSCLC in TCM is characterized by Qi deficiency and Qi sinking, encapsulated in the saying, "When the righteous Qi is present, evil cannot invade." The great Qi resides in the chest, and its sinking makes one susceptible to cancer toxins. Shengxian Decoction is a representative formula for treating Qi sinking syndrome. Clinical and experimental studies have confirmed that Shengxian Decoction is effective against NSCLC, demonstrating good results in inhibiting tumor proliferation, promoting tumor cell apoptosis, blocking tumor cell invasion and metastasis, reducing inflammation, and preventing tumor cell immune evasion. Research at the levels of network pharmacology and molecular biology has also identified several active components in Shengxian Decoction with anti-lung cancer properties, which exert their effects through multiple targets. Currently, there is a lack of comprehensive literature on the use of Shengxian Decoction for treating NSCLC. This paper reviews the effects of Shengxian Decoction on NSCLC from the perspectives of theoretical origins, material basis, network pharmacology, and experimental and clinical studies, aiming to provide a reference for further research on the pharmacological effects and clinical applications of Shengxian Decoction.***

Keywords: N*on-small cell lung cancer*, Shengxian decoction, Research progress**.**

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. In China, lung cancer has the highest incidence and mortality rates among malignant tumors, accounting for 17.9% of new cancer cases and 23.8% of cancer deaths [1]. Non-small cell lung cancer (NSCLC) comprises 80%-85% of lung cancer cases [2], posing a severe threat to the health of the Chinese population. Currently, the treatment of NSCLC involves a multidisciplinary approach with various treatment modalities, including surgery, immunotherapy, targeted therapy, radiotherapy, and chemotherapy [3]. However, challenges remain, such as postoperative recurrence and metastasis [4], a high incidence of complications [5], significant side effects [6], and increased drug resistance [7]. From the perspective of Traditional Chinese Medicine (TCM), the development and progression of NSCLC is closely related to the conflict between righteous Qi and evil Qi, with the underlying TCM pathogenesis identified as Qi deficiency and Qi sinking. Shengxian Decoction, classified as a classic formula in the "First Batch of Classic Formulas from Ancient Classics," is a representative formula for treating Qi sinking syndrome. Clinical and experimental studies conducted both domestically and internationally have confirmed the efficacy of Shengxian Decoction in treating NSCLC, drawing significant attention to its therapeutic effects on this disease.

2. Theoretical Origins of Shengxian Decoction

The term "Qi sinking" first appeared in the "Yellow Emperor's Classic of Internal Medicine" (Neijing). During the Qing Dynasty, physician Zhang Xichun clearly defined the pathogenesis and treatment principles of Qi sinking based on his clinical experience and understanding of classical texts. The great Qi resides in the chest, "encompassing the lungs and serving as the hub of respiration." It can also circulate through the heart vessels, "acting as the framework for the blood circulation throughout the body," and supports the whole body, energizing the spirit, as well as mental and physical activities, all relying on this Qi. Therefore, the great Qi plays a crucial role in respiration, regulating blood circulation, invigorating the spirit, and governing mental function. When the great Qi is abundant, breathing is even, and blood circulation is smooth; when it sinks, there is insufficient breath, resulting in blood stasis, abnormal fluid transformation, and the production of phlegm and toxins, which can lead to the development of lung cancer. Thus, Qi sinking forms the fundamental pathogenesis for the occurrence and progression of lung cancer.

The representative formula for treating Qi sinking syndrome is Shengxian Decoction, which originates from Zhang Xichun's work "Medical Record of Traditional Chinese and Western Medicine." The formula consists of Huangqi (Astragalus), Zhimu (Anemarrhena), Chaihu (Bupleurum), Jiegeng (Platycodon), and Shengma (Cimicifuga). In this formula, Huangqi tonifies and lifts the Qi, harmonizing with the great Qi in the chest, while Zhimu represents yin, balancing with the yang of Huangqi. Chaihu belongs to the shaoyang category and helps lift the great Qi from the left side, while Shengma, belonging to the yangming category, directs the Qi upward from the right side. Together, they work with Jiegeng to transport medicines upward, elevating the sinking great Qi in the chest. Shengxian Decoction has been widely applied in internal medicine, including in the treatment of respiratory [8-10], and cardiovascular diseases [11, 12]. In oncology, modified Shengxian Decoction can improve the quality of life for patients after surgery for malignant tumors in the chest [13], and it holds particular significance in the

treatment of NSCLC [14, 15].

3. Material Basis and Pharmaceutical Evaluation of Shengxian Decoction in the Treatment of NSCLC

The foundation for the treatment of NSCLC with Shengxian Decoction lies in its effective components. A comprehensive analysis of the literature on the chemical constituents of Shengxian Decoction indicates that its primary chemical components include flavonoids, saponins, polysaccharides, phenolic acids, triterpenoids, and alkaloids [16, 17]. Modern pharmacological studies have demonstrated that the effective components of Shengxian Decoction with anti-lung cancer effects can be categorized by their primary sources: Huangqi (Astragalus) contains elements like isoflavones (e.g. maohuiyihuangton), astragaloside, and soy isoflavones; Zhimu (Anemarrhena) includes zhi mu saponins and mangiferin; Shengma (Cimicifuga) contains ferulic acid; Chaihu (Bupleurum) has compounds such as bupleuroside, isoliquiritigenin, quercetin, puerarin, and shan-nai phenol; and Jiegeng (Platycodon) has jiegeng saponins. These effective components act through different mechanisms to exert anti-cancer effects by inhibiting epithelial-mesenchymal transition of lung cancer cells, suppressing lung cancer cell proliferation, invasion, and migration, and promoting apoptosis of lung cancer cells, thereby showcasing the advantages of traditional Chinese medicine's multi-component, multi-target, and multi-pathway approach to tumor treatment (Table 1).

Table 1: Effective Components of Shengxian Decoction Against NSCLC

Active ingredient	experimental subjects	mechanism of action	target pathway	references
Formononetin	SPC-A1	Induces nuclear shrinkage in lung adenocarcinoma cells, forms apoptotic bodies, induces apoptosis, and inhibits proliferation.	Cyclin D1↓, CDK4↓, CDK6↓	[18]
	A549	Inhibits the proliferation, adhesion, migration, and invasion of lung cancer cells.	PKC-α/ERK1/2↓, E-cad↑, MMP-2↓, MMP-9↓, integrin β1↓	[19]
Mangiferin	A549	Affects the cell cycle, inhibits cell proliferation, and promotes apoptosis.	cyclin E1↓, Bcl-2↓, Bax↑	[20]
	A549, NCI-H23	Induces G1 phase cell cycle arrest in lung cancer cells and promotes apoptosis.	p21↑, cyclin A↓, cyclin D1↓, caspase-3↑, Bcl-2↓, Bax↑, p53↑	[21]
Astragaloside	A549 and H1299 lung cancer cell lines cultured in M2 macrophage conditioned medium	Significantly inhibits tumor growth and reduces the number of metastases in Lewis lung cancer, inhibiting invasion, migration, and angiogenesis of A549 and H1299 cells induced by M2-CM.	AMPKα↓	[22]
Daidzein	H1299	Inhibits the proliferation of lung cancer cells and promotes apoptosis.	CASP9↑, p53↑	[23]
	A549, H1299	Induces apoptosis and autophagy, inhibits the proliferation of lung cancer cells, and significantly reduces the migration and invasion capabilities of lung cancer cells.	Caspase-3↑, LC3 II/I↑	[24]
Glycyrrhizin	A549	Inhibits the proliferation and migration of lung cancer cells.	IL-18↑	[25]
Mangiferin	A549, H460, H1299	Inhibits the proliferation of NSCLC cells.		[26]
	A549	Inhibits the migration and invasion of lung cancer cells, reduces the actin cytoskeleton of cancer cells, and suppresses cancer cell survival.		[27]
Ferulic acid	A549 xenograft tumor in nude mice	Inhibits the growth of lung cancer xenografts.	m TOR↓, Ki-67↓, Caspase-3↑	[28]
	A549	Inhibits the proliferation and metastasis of lung cancer cells.	JAK2/STAT6↓, IL-4↓, PDGF↓, GM-CSF↓	[29]
Bupleurum saponins	A549	Inhibits the proliferation, migration, and invasion of non-small cell lung cancer cells.	VEGF/VEGFR2↓, N-cadheri↓, Vimentin↓, p-MEK↓, p-ERK↓	[30]
	H460	Inhibits the proliferation of lung cancer cells and promotes apoptosis.	IL-10 mRNA↓, p-JAK2/JAK2↓, p-STAT3/STAT3↓, IL-2 mRNA↑	[31]
Isoquercetin	A549	Inhibits the adhesion, invasion, and migration of lung cancer cells; inhibits epithelial-mesenchymal transition.	N-cadherin↓, vimentin↓, snail↓, E-cadherin protein↑, AKT/ERK1/2↓	[32]
	A549, H460	Inhibits the proliferation of lung cancer cells and enhances their radiosensitivity.	NF-κBp65↓, Bcl-2↓, Bax↑IL-13↑	[33]
Quercetin	A549, HCC827	Inhibits the survival, proliferation, migration, and invasion of lung cancer cells, enhances apoptosis, and suppresses tumor growth.	SNHG7↓, miR-34a-5p↑	[34]
	A549, H1975, H441	Inhibits the growth of lung cancer cells.	aurora B↓	[35]
Puerarin	A549	Alters the morphology of lung cancer cells, inhibits their colony formation ability, induces apoptosis in lung cancer cells, and suppresses their proliferation, invasion, and migration.	MMP-2↓, MMP-9↓, p-p65/p65↓, NF-κB↓	[36]
	A549	Inhibits the growth, invasion, and migration of non-small cell lung cancer.	miR- 490↑, E3 (DTL)↓, E-cadherin↑, N-cadherin↓, Vimentin↓	[37]
Kaempferol	A549	Inhibits the proliferation of non-small cell lung cancer cells.	miR21↓, PTEN/AKT↓	[38]
	A549	Reduces the invasion and migration capabilities of lung cancer cells and inhibits epithelial-mesenchymal transition.	N-cadherin↓, Snail-2↓, E-cadherin↑, ER-Ra↓	[39]
Platycodon saponins	H520	Exhibits direct cytotoxic effects, induces apoptosis in lung cancer cells, stimulates immunity, and can control cancer-related cachexia.	IL-6↓, IFN-γ↑, Caspase-3↑, NK↑	[40]
	A549	Exhibits cytotoxic effects and induces apoptosis in lung cancer cells.	Caspase-3↑, Caspase-9↑, Bax↑, Bak↑, Bcl-2↓, Bcl-xl	[41]

4. Mechanism of Action of Shengxian Decoction in the Treatment of NSCLC

4.1 Network Pharmacology Research

Wu Jingyuan [42] and colleagues conducted a network pharmacology study on Shengxian Decoction to screen for active components with a strong association to NSCLC targets. They identified eight compounds: quercetin, kaempferol, acetic acid, daidzein, luteolin, beta-sitosterol, puerarin, and isoliquiritigenin. The potential action targets of Shengxian Decoction in the treatment of NSCLC include AKT1, STAT3, MAPK1, TP53, VEGFA, and EGFR. It may exert anti-cancer effects by intervening in the HIF-1, TNF, IL-17, and PI3K-AKT signaling pathways.

Experiments have confirmed that inhibiting HIF-1 can enhance the response of human NK cells [43], and downregulate the expression of PD-L1, thereby eliminating PD-L1 mediated immune escape [44]. TNF-α in TNF and IL-17 are both pro-inflammatory factors that can act as tumor promoters, affecting cell survival, proliferation, invasion, and angiogenesis [45]. The PI3K-AKT signaling pathway can influence tumor development and progression from multiple aspects, including inflammatory response, apoptosis, and immunity [46]. Experimental studies have also indicated that isoliquiritigenin can exert anti-lung cancer effects by intervening in the Akt/ERK pathway [32], which is consistent with the conclusions of the network pharmacology study. In summary, Shengxian Decoction may exert its therapeutic effects on NSCLC through the HIF-1, TNF, IL-17, and PI3K-AKT signaling pathways.

4.2 Mechanism of Action of Shengxian Decoction in the Treatment of NSCLC

Modern studies have found that Shengxian Decoction can inhibit tumor proliferation, promote tumor cell apoptosis, block tumor cell invasion and metastasis, reduce inflammation, and delay immune evasion of tumor cells through multiple targets and pathways, thereby treating NSCLC from different aspects. Zhao Lianmei [47] and colleagues used human lung cancer A549 cells to investigate the effects of Shengxian Decoction on NSCLC and found that the n-butanol extract of Shengxian Decoction significantly inhibited lung cancer cell proliferation, induced lung cancer cell apoptosis, and suppressed tumor cell migration. These effects were achieved by reducing the activity of the ERK pathway and inhibiting the expression of matrix metalloproteinases MMP2 and MMP9. The ERK pathway promotes tumor cell proliferation, inhibits apoptosis, induces tumor angiogenesis, and facilitates tumor invasion and metastasis [48]. Li Xiaohong [49] conducted experiments using BALB/c nude mice and human lung cancer A549 cells to observe the effects of Shengxian Decoction on NSCLC. The study revealed that Shengxian Decoction significantly inhibited human lung adenocarcinoma A549 cells and the A549 tumor xenografts in nude mice, which was associated with reduced levels of HIF-1α and TNF-α in the serum of the nude mice. It also improved the survival status of the mice, alleviated lung and spleen tissue damage, decreased the growth tendency of the tumors, promoted tumor necrosis, and suppressed the increase in tumor volume, with the best overall effect observed in the dose group of Shengxian Decoction. Kejuan Li [50] and colleagues also utilized human lung cancer A549 cells and BALB/c nude mice to study the effects of Shengxian Decoction, demonstrating its excellent anti-tumor activity. The serum from Shengxian Decoction inhibited the in vitro proliferation of A549 lung cancer cells, delayed tumor progression in vivo, induced tumor necrosis, and reduced levels of HIF-1α and TNF-α in the serum of the mice. These experiments provide strong evidence for the clinical use of Shengxian Decoction in the treatment of NSCLC.

5. Clinical Application of Shengxian Decoction in the Treatment of NSCLC

Currently, there are various treatment options for NSCLC, but the improvement in quality of life for advanced patients is not significant [51, 52]. Clinical studies have confirmed that Shengxian Decoction has the function of uplifting Yang and raising the sinking, demonstrating good clinical efficacy. Su Chunyu [53] and colleagues found that Shengxian Decoction significantly alleviates discomfort symptoms such as shortness of breath and fatigue in NSCLC postoperative patients, improving their quality of life. Zhang Shiwen [54] and others, through clinical research, discovered that a modified version of Shengxian Decoction combined with Siwu Decoction could enhance the clinical efficacy of chemotherapy for NSCLC while reducing adverse reactions, mitigating chemotherapy-induced bone marrow suppression, enhancing immune function, and improving cancer-related fatigue. Other studies have also confirmed that the modified Shengxian Decoction can enhance the clinical efficacy of chemotherapy in NSCLC patients, improve immune function, alleviate patient symptoms, and reduce chemotherapy side effects [14, 55, 56]. Sun Gen [57] found that Shengxian Decoction has definite clinical efficacy for NSCLC patients, without causing abnormal vital signs or liver and kidney function.

The aforementioned experiments demonstrate that Shengxian Decoction can significantly relieve symptoms such as dyspnea, chest tightness, and fatigue in NSCLC patients while enhancing their immune capacity, reducing inflammation levels, improving quality of life, enhancing the clinical efficacy of chemotherapy, and alleviating the side effects of chemotherapy, with added advantages of low side effects and high safety. In the different stages of NSCLC treatment, attention should be paid to benefiting Qi and uplifting the sinking, as the saying goes, “When the accumulation is formed, it is due to deficiency of righteous Qi, allowing evil Qi to take hold.” Therefore, deficiency of righteous Qi is fundamental to the occurrence of NSCLC. The significance of benefiting Qi and uplifting the sinking lies in: (1) Sufficient Qi can resist evil: Modern medicine believes that tumor cells arise from mutations of normal body cells [58]. When the body's defense and clearance functions are normal, it can promptly eliminate mutated cells, maintaining the body's balance. Qi deficiency can lead to an imbalance in immune function [59], allowing mutated tumor cells to proliferate unchecked, ultimately developing into malignant tumors. Sufficient Qi is essential; when the Qi is abundant in the chest, the body can resist cancerous toxins. In contrast, when Qi is deficient and sinks, the body becomes susceptible to

cancerous toxins, leading to the proliferation of tumor cells and ultimately resulting in lung cancer in the area where Qi resides. (2) The formation and progression of cancerous toxins are closely related to Qi deficiency: “Strong individuals do not accumulate, while weak individuals do.” Weakness in the spleen and stomach, along with deficiency in Qi and blood, makes one susceptible to accumulation during seasonal changes. Qi deficiency leads to abnormal transformation and accumulation of phlegm and dampness; it also results in blood stasis, where phlegm and blood congeal, forming cancerous toxins. When Qi is deficient and sinks, the chest is the first to be affected, making it more susceptible to stasis and toxin formation, leading to lung cancer. Over time, with Qi deficiency, cancerous toxins can circulate in the body, potentially causing recurrence and metastasis. (3) Surgery and radiotherapy/chemotherapy can easily cause Qi to sink in the chest: Lung cancer resection damages the normal structure of the chest, directly affecting the Qi in the chest, leading to a loss of its proper place and causing it to sink. Radiotherapy has heat-toxic properties [60]; as the saying goes, “Cold injures form, heat injures Qi.” Heat toxins can damage fluids and deplete Qi, worsening the patient's Qi deficiency and making it difficult for Qi to uplift. Chemotherapy drugs affect the functional dynamics of the spleen and stomach [61], damaging the body's righteous Qi. NSCLC patients already have weak lung Qi, and the use of these treatments can further lead to extreme Qi deficiency, resulting in a state where Qi cannot rise, is trapped, and cannot circulate. Shengxian Decoction can restore the physiological function of Qi, benefiting righteous Qi while uplifting the sinking, allowing the sinking Qi to return to the chest and restoring the weakened righteous Qi to strength. “When Qi flows, blood flows.” The movement of Qi facilitates the distribution of fluids, leading to the resolution of phlegm and dampness. Therefore, Shengxian Decoction can normalize the metabolism of Qi, blood, and body fluids, as well as the functions of the organs and channels, reversing the state of evil overpowering righteous Qi, filling the chest with Qi, dissipating evil Qi, and ultimately delaying the occurrence and progression of NSCLC, improving the symptoms of NSCLC patients.

In clinical applications, Shengxian Decoction has not shown any impact on vital signs or liver and kidney function [57], nor have any adverse reactions been observed [62]. However, there is still a lack of safety evaluations regarding its carcinogenicity, immunotoxicity, and other toxicological aspects. This article utilizes ProTox-II (https://tox-new.charite.de/protox_II/) [63] to evaluate the safety of the chemical components in Shengxian Decoction, with parameters including multiple toxicological endpoints. According to existing research, compounds with acute oral toxicity rated below level 3 and more than three positive toxicity endpoints are considered toxic [64]. Thus, the 13 main chemical components of Shengxian Decoction are non-toxic. Although mangiferin has relatively strong acute oral toxicity, experimental studies have confirmed that its toxicity is moderate when administered orally, and it is safe within a certain dosage range [65]. While this analysis provides some evidence of the safety of Shengxian Decoction, the complexity of its composite ingredients requires further research.

6. Summary and Prospect

This article explores the advantages of Shengxian Decoction in the treatment of NSCLC from several aspects, including theoretical basis, material foundation, mechanism of action, and clinical research. From the perspective of traditional Chinese medicine, Qi deficiency is the fundamental pathogenesis underlying the occurrence and progression of tumors, and the development of NSCLC is often related to the sinking of Qi in the chest. Shengxian Decoction serves as a foundational formula to benefit and uplift the Qi in the chest. It can replenish Qi and uplift the sinking Qi back to the chest, thereby exerting therapeutic effects on NSCLC. Numerous clinical and laboratory studies have confirmed the efficacy of Shengxian Decoction in treating NSCLC. Whether used in conjunction with chemotherapy or as a standalone treatment, it can improve patients' quality of life and alleviate symptoms. When combined with chemotherapy, it can also help reduce the toxic side effects of chemotherapy. Therefore, Shengxian Decoction has a clear therapeutic effect in treating NSCLC and provides a reference for clinical treatment.

However, due to the complexity of the mechanisms involved in the occurrence and progression of NSCLC and the diversity of the components in traditional Chinese herbal formulas, there are still many shortcomings in the existing clinical and experimental research. For example, there is a lack of foundational experimental studies on the combination treatment of NSCLC with Shengxian Decoction, and further investigation into its mechanisms of action is needed. Additionally, clinical research on the use of Shengxian Decoction as a standalone treatment for NSCLC is limited, and the robustness of clinical evidence is insufficient. Therefore, extensive clinical and animal studies are still required to confirm its efficacy, elucidate the mechanisms involved, and provide scientific support for the use of traditional Chinese medicine in treating NSCLC.

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