Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ31368

The Anti-cancer and Auxiliary Effects of Astragalus Membranaceus in the Treatment of Lung Cancer

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Abstract. Lung cancer ranks among the most prevalent malignant tumors, with an extremely high mortality rate. However, current treatments still face challenges. Radiotherapy and chemotherapy can easily cause side effects such as bone marrow suppression, while targeted therapy is limited by its target dependence and acquired drug resistance. The treatment of lung cancer still requires safe and effective supportive treatments. Astragalus, often called a key herb for replenishing qi in traditional Chinese medicine, has attracted widespread attention for its potential value. The core active ingredients are astragaloside IV, Astragalus polysaccharides and flavonoids, which are the key basis for exerting pharmacological effects. The active ingredients of astragalus, such as astragaloside IV and astragalus polysaccharides, can exert anti-lung cancer effects by regulating the cell cycle and activating apoptotic pathways. In clinical applications, astragalus membranaceus and its active components can enhance the efficacy of chemotherapy and radiotherapy, improve outcomes in immunotherapy, and help reduce side effects such as bone marrow suppression and gastrointestinal reactions. In the future, it is necessary to deepen the research on the mechanism and carry out well-designed clinical trials to provide stronger evidence for its use as a supportive treatment in lung cancer.

Keywords: astragalus, lung cancer, astragaloside A, astragalus polysaccharide

1. Introduction

Lung cancer is the most common primary malignancy that begins in the lungs. Most cases start in the lining of the bronchial tubes, and thus are also called bronchogenic carcinoma. The data comes from the International Agency for Research on Cancer, a division of the World Health Organization, and lung cancer leads the world in morbidity and mortality among all cancers. In 2022, about 2.5 million new cases of lung cancer were seen globally.

These cases represent 12.4% of the total number of new cases of all cancers [1]. Lung cancer also has the highest morbidity and mortality rate among all malignant tumors in China. 2022 There were more than 1.06 million new cancer cases, and these cases accounted for 42.8% of all new lung cancer cases worldwide [2].

Currently, the core treatment options for lung cancer include five main types. These types include surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy [3]. These approaches still have significant limitations. Surgery is only suitable for early-stage patients. The risk of

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recurrence after surgery is relatively high. Chemotherapy and radiation can slow the growth of tumors. They usually produce severe side effects. These side effects include nausea, vomiting, bone marrow suppression, and lung damage. Targeted therapy works well. It requires specific genetic markers. Therefore, it is not suitable for all patients. In addition, long-term use can lead to drug resistance, and the high cost of some drugs can place a considerable financial burden on patients and their families. While immunotherapy may lead to longer-lasting efficacy, its overall response rate is relatively low, with more than half of patients initially failing to respond. With the continuous development of Chinese medicine technology. It has gained valuable experience in cancer treatment. This approach mitigates treatment-related adverse effects, including nausea, vomiting and bone marrow suppression. And it helps patients complete the treatment process successfully.

Astragalus was first found in the Shennong's Classic of the Materia Medica. It has a sweet flavor and is slightly warm in nature. It has multiple effects. These include tonifying the qi and yang, consolidating the exterior and reducing sweating. These properties make it particularly suitable for treating Qi deficiency syndrome. This syndrome is commonly seen in lung cancer patients. They provide targeted supportive effects to patients. Modern pharmacology has further confirmed a key fact. Astragalus contains many active ingredients. These include Astragaloside IV and Astragalus polysaccharide. The immune function of the body can be enhanced by these ingredients. They enhance the activity of immune cells. They also have antioxidant and anti-inflammatory effects. This provides a scientific basis for their application in adjuvant tumor therapy. Based on these findings, this study is designed to provide a comprehensive review of the evidence using Astragalus as the subject of the study. The evidence relates to Astragalus and its main active components. This paper systematically elucidates the pharmacological mechanisms of action of these core components. It systematically elucidates the clinical applications of these core components. It analyzes the existing limitations in their use. And it looks forward to the future research direction. This study furnishes a scientific foundation for the proper use of Astragalus during the combined regimens targeting lung cancer.

2. The core active ingredient of astragalus membranaceus

Astragalus exerts its anti-tumor activity through its complex bioactive components. Astragaloside and astragalus polysaccharide constitute its core material basis. Flavonoid amino acids and other substances act synergistically to enhance the overall therapeutic effect. These components together lay the material foundation for its application. It is applied to the adjuvant treatment of lung cancer.

2.1. Astragaloside IV

Astragaloside IV is an important subclass of astragalosides, is the main bioactive compound in Astragalus. It is the signature tetraterpene saponin component of Astragalus. The chemical formula is $C_{41}H_{68}O_{14}$. It is insoluble in water. Soluble in organic solvents. These solvents include methanol and ethanol. It inhibits abnormal cell proliferation by regulating key molecules in the cell cycle. Such as cell cycle protein D1. It blocks the cell during the pre-synthesis phase of DNA replication. This phase is the G1 phase. Astragaloside IV is extensively participated in the regulation of programmed cell death. It boosts the expression level of pro-apoptotic protein Bax while reducing the expression of anti-apoptotic protein Bcl-2. And it disrupts the mitochondrial membrane potential and induces the release of cytochrome c. The release of cytochrome c activates the caspase cascade reaction. It ultimately triggers apoptosis of abnormal cells. Astragaloside IV also affects the

DOI: 10.54254/2753-8818/2026.PJ31368

secretion of cell adhesion molecules, which reduces the ability of cells to migrate and weakens their ability to invade surrounding tissues.

2.2. Astragalus polysaccharide

Astragalus polysaccharides are one of the most abundant active components in Astragalus. They represent one of the most widely studied bioactive components in Astragalus. These water-soluble heteropolysaccharides are composed of monosaccharides. These monosaccharides include glucose and galactose and have molecular weight values spanning from 10 to 2000 kDa. Their biological activity is closely related to molecular weight, monosaccharide composition, type of glycosidic bond and degree of branching. Its main action is on immune cells. It promotes the proliferation and activation of immune effector cells and boosts their ability to remove abnormal cells. And it inhibits the activity of immunosuppressive cells and reduces inhibitory substances it release. Furthermore, it helps regulate the functional phenotype of macrophages, promoting their shift toward anti-inflammatory and anti-tumor states. This contributes to maintaining a stable and balanced immune microenvironment.

2.3. Other active ingredients

Flavonoids, amino acids and trace elements in Astragalus have a synergistic effect with astragaloside IV and astragalus polysaccharides. Flavonoids such as formononetin and calycosin remove harmful active substances from cells. They reduce inflammatory damage. They also help regulate cell proliferation and apoptosis. Essential amino acids such as leucine and isoleucine provide basic nutritional support for cellular metabolism. They ensure normal physiological functions. Among the micronutrients, selenium enhances antioxidant capacity. It reduces oxidative stress. Zinc is involved in the differentiation and maturation of immune cells. It further supports immune regulation

3. The anti-tumor pharmacological mechanism of astragalus membranaceus

3.1. Direct anti-tumor effect

The active components in astragalus can directly inhibit lung cancer cells through multiple pathways. Caspases act as the initiators and executors of apoptosis and are key enzymes that trigger cell death [4]. Once activated, Caspase can degrade intracellular proteins, leading cells to undergo irreversible death. Astragaloside IV primarily works by inhibiting key cell survival pathways, effectively inducing apoptosis. Its core mechanism lies in regulating the PI3K/Akt signaling pathway. This pathway is a central regulator of cell growth, proliferation, and survival. Its aberrant and sustained activation is a key mechanism that enables cells to resist apoptosis and acquire abnormal survival capabilities. Studies have shown that Astragaloside IV inhibits proliferation and induces apoptosis in non-small cell lung cancer (NSCLC) cells A549 and SPC-A1 [5]. It works by suppressing the expression of p-Akt in the Akt signaling pathway and increasing the expression of Caspase-3 and Caspase-9. Altering cell cycle distribution and inducing cell cycle arrest are considered effective approaches in cancer therapy. In in vitro studies of NSCLC, the H1299 cell line is used for research on lung squamous cell carcinoma and for analyzing drug resistance in p53-deficient lung cancer. Astragalus polysaccharide can combine with 10-hydroxycamptothecin to increase the proportion of S-phase and G2/M-phase H1299 lung cancer cells. This causes the cell cycle of H1299 lung cancer cells to stay in the S and G2/M phases [6], thereby inhibiting their normal proliferation. miR-195-5p can inhibit the proliferation and invasion of NSCLC cells. This

DOI: 10.54254/2753-8818/2026.PJ31368

miRNA can be upregulated by astragalus polysaccharides in lung cancer cells, thereby suppressing their proliferation and invasion [7]. Astragalus polysaccharide can inhibit the migration and invasion of tumor cells by suppressing the IL-6 and JAK/STAT3 pathways in A549 cells, altering the transcription levels of E-cadherin and MMP-2/9, and thereby blocking the process of epithelial-mesenchymal transition (EMT) [8].

3.2. Immunomodulatory effect

The immune system can suppress the growth of tumor cells through multiple pathways and mechanisms. Natural killer cells (NK cells) are the body's primary defense barrier, and the inhibition of their function is closely related to the reduction of NKG2D receptor expression.CD4+ T cells act as "coordinators" to orchestrate the immune response, while CD8+ T cells act as "executors" to eliminate abnormal cells. Together, these two key types form the core of the t-lymphocyte subset. Imbalance of t-lymphocyte subsets is the central problem of immunosuppression in lung cancer. This condition is mainly caused by immunosuppressive factors. These factors include TGF-β and IL-10 secreted by the tumor microenvironment. they impede CD4 + T cell activation. They induce CD8 + T cell exhaustion. As a result, The proportion of $CD4^+$ to $CD8^+$ T cells decreases. This process inhibits the activity of NK cell. It weakens the ability of the immune system to destroy cancer cells. It helps lung cancer cells to achieve immune escape. Astragalus polysaccharide combined with polysaccharide peptides significantly increased CD4 + /CD8 + T cell ratio. Enhanced NK cell activity [9]. Functional impairment of NK cells is closely related to decreased expression of NKG2D receptors. Flavonoids in Astragalus activate the NK cell pathway. They do this by enhancing the binding ability of NKG2D receptors to ligands on lung cancer cells. They further regulate molecules associated with NK cell killing function. They enhance secretion of granzyme A and IFN - γ. They enhance the transmission of killing signals [10]. Astragalus improves the tumor immune microenvironment. Astragalus polysaccharides enhance antitumor immunity by regulating macrophage polarization and promoting dendritic cell maturation, thereby boosting T-cell function [11].

3.3. Detoxification and protective effect

Chemotherapy and radiotherapy are common treatments for lung cancer, but they often cause toxic and side effects such as nausea, vomiting, liver or kidney impairment, and bone marrow suppression. Bone marrow suppression is a major reason for discontinuing chemotherapy. It is characterized by a decrease in white blood cell and platelet counts, which relates to the restraint of bone marrow stem cell proliferation and disruption of the hematopoietic microenvironment. Astragalus polysaccharides can enhance the proliferation of hematopoietic stem cells, expedite the generation of white blood cells and blood platelets, and thus alleviate chemotherapy-induced bone marrow suppression. While radiotherapy helps reduce the recurrence rate of lung cancer, it can also trigger radiation-induced bystander effects. In in vitro studies of NSCLC, the A549 cell line serves as a common model. It is used for research into the mechanisms of lung adenocarcinoma and for the screening of drugs such as KRAS inhibitors and platinum-based chemotherapies. In a study using A549 lung cancer cells and human bone marrow mesenchymal stem cells (BMSCs) exposed to 2 Gy of X-ray radiation, it was found that reactive oxygen species released from the irradiated A549 cells activated the MAPK/NF-κB signaling pathway in the BMSCs. This activation then promoted the release of inflammation-related factors and increased oxidative stress inside the cells. The normal metabolism and function of BMSCs is disrupted. This disruption leads to reduced cell viability,

DOI: 10.54254/2753-8818/2026.PJ31368

genomic instability and DNA damage. Astragalus polysaccharide regulates the MAPK/NF-κB pathway. It decreased the expression of cyclooxygenase-2 and lowered the level of reactive oxygen species. This effect significantly increased the viability of bone marrow MSCs. Enhances the colony forming ability of BMSCs. It reduces DNA damage in bone marrow MSCs. It inhibits radiation-induced bystander effect in bone marrow MSCs, which has a positive effect on reducing radiation damage [12]. Astragalus prevents chemotherapy drugs from damaging the liver and kidneys. Cisplatin works by disrupting the antioxidant system of liver cells and catalyzing the deadly lipid peroxidation chain reaction, a process that leads directly to a specific form of cell death. This cell death is called ferroptosis and can lead to liver damage. This cell death is called Ferroptosis. It can lead to liver damage. Studies have shown that Astragaloside IV reduce liver damage caused by cisplatin [13]. This is achieved by inhibiting the PPARα/FSP1 signaling pathway. It attenuates ferroptosis in this way. Astragaloside IV attenuates cisplatin-induced kidney damage. I It does so by regulating the metabolic disturbances produced by cisplatin in the body. The mechanism is to restore balance to key metabolic pathways. Examples include inhibition of pro-inflammatory arachidonic acid metabolism and enhancement of antioxidant tryptophan metabolism. This synergizes the anti-inflammatory and antioxidant effects and ultimately improves renal function indicators such as serum creatinine [14].

4. The role and clinical application of astragalus membranaceus and its bioactive components in lung cancer therapy

4.1. Improves the efficacy of both radiotherapy and chemotherapy

In clinical practice, astragalus is often used as a supportive treatment alongside chemotherapy and radiotherapy. Currently, chemotherapy is commonly employed to treat tumors, and regimens combining platinum-based drugs with other chemotherapeutic agents have become one of the first-line options for advanced lung cancer. Cisplatin is a first-line medication in lung cancer treatment, but its long-term clinical use can lead to drug resistance in tumor cells, making the chemotherapy outcomes far from ideal. Current studies confirm that combining astragalus with chemotherapy has a synergistic effect. Astragaloside IV combination therapy significantly reduces both the mRNA and protein expression levels of B7-H3 [15]. However, when B7-H3 is ectopically expressed, it weakens the ability of astragaloside IV to enhance the sensitivity of NSCLC cells to cisplatin. In reversing drug resistance, astragaloside IV can block the PI3K/AKT signaling pathway and induce the mitochondrial apoptosis pathway. It also inhibits the expression of P-glycoprotein, increases the accumulation of chemotherapy drugs inside tumor cells, and helps restore treatment sensitivity in patients with drug resistance. A clinical observation showed that [16], in NSCLC patients receiving platinum-based chemotherapy, the combined use of astragalus polysaccharide injection increased the objective response rate and disease control rate. The use of injectable astragalus polysaccharide can effectively enhance the immune status of patients with advanced-stage NSCLC after chemotherapy and strengthen their anti-cancer capacity. This improvement may be related to astragalus reversing tumor multi-drug resistance, increasing tumor cell sensitivity to chemotherapy drugs, and improving local blood perfusion in the tumor area.

4.2. Improve the effect of immunotherapy

Tumor immunotherapy, especially the application of immune checkpoint inhibitors, has revolutionized the therapeutic paradigm for advanced lung cancer. However, response rates remain

DOI: 10.54254/2753-8818/2026.PJ31368

limited (only 20-30% of patients benefit), and immune-related adverse reactions pose major clinical challenges. Astragalus and its active components show unique potential in improving immunotherapy outcomes. Astragalus can improve the immune function of lung cancer patients, which helps enhance the efficacy of immunotherapy. Clinical observations have found that astragalus paste can significantly enhance immune function of postoperative radiotherapy patients with lung qi deficiency type of lung cancer [17]. It increases the CD3 + and CD4 + ratio in T cells and enhanced NK cell activity. A well-functioning immune system is the foundation for effective immunotherapy. Astragalus also exhibits a synergistic effect in immunotherapy for mid-to-late stage NSCLC. A high neutrophil-to-lymphocyte ratio (NLR) is strongly linked to inferior outcomes in cancer immunotherapy, serving as a predictive marker for both diminished treatment response and reduced survival. A clinical study found that astragalus polysaccharide injection can reduce the NLR to normal levels in lung cancer patients receiving immune checkpoint inhibitor therapy, thereby enhancing their treatment outcomes [18].

4.3. Reduce the side effects of treatment

Astragalus has shown significant benefits in reducing the side effects of chemotherapy. Gastrointestinal reactions include nausea, vomiting and diarrhea. These reactions are common during chemotherapy. Astragalus helps harmonize the stomach and spleen. It reduces these digestive side effects. Lung cancer patients often feel fatigue, loss of appetite and weight loss. These symptoms seriously affect their quality of life. Astragalus can improve these symptoms. It helps to improve the patient's physical condition and overall health. A controlled trial showed that 100 elderly lung cancer patients were divided into two groups [19]. The two groups were the treatment group and the control group. Both groups received chemotherapy. The treatment group was given Astragaloside IV on top of the control group treatment. After two weeks, the incidence of myelosuppression was markedly reduced in the treatment group relative to the control group. Other studies have also shown relevant results. Injections of astragalus preparations may reduce the incidence of myelosuppression after chemotherapy. They may also reduce the severity of myelosuppression after chemotherapy

5. Conclusion

Astragalus, a treasure of traditional Chinese medicine, exerts a variety of effects in modern lung cancer therapy. Its active ingredients produce synergistic effects. These effects are realized through multiple pathways. The pathways include suppressing tumor cell proliferation and migration, inducing apoptosis, regulating immune function and reducing treatment-related side effects. This reflects the holistic and multi-target regulation of Chinese medicine treatment. Astragalus shows unique advantages in clinical applications. These applications include chemotherapy, radiotherapy, targeted therapy and immunotherapy. It can be used in combination with these treatments. It improves the effectiveness of these treatments and reduces the toxicity of these treatments. It significantly improves the quality of life of patients. Most of the current research is based on cell and animal experiments. Clinical evidence in this area remains relatively limited. The use of astragalus in the treatment of lung cancer reflects the combination of traditional medical wisdom and modern scientific research. Its concept of “Fuzheng Quxie” is highly compatible with the direction of tumor immunotherapy and comprehensive supportive therapy. Through standardized clinical trial design. Clarify the value of astragalus in reducing side effects associated with chemotherapy, radiotherapy and immunotherapy. And establish appropriate clinical practice guidelines. It is also

DOI: 10.54254/2753-8818/2026.PJ31368

important to explore the co-administration modalities and emerging therapeutic approaches of Astragalus. Its role in precision medicine and personalized treatment can be promoted. Multidisciplinary collaboration will help to further utilize the unique advantages of Astragalus and apply it to the comprehensive treatment of lung cancer.

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