

Astragalus membranaceus: A Review of Its Antitumor Effects on Non-Small Cell Lung Cancer

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Abstract: The rising global morbidity and mortality rates of non-small cell lung cancer (NSCLC) underscore the urgent need for more effective treatments. Current therapeutic modalities—including surgery, radiotherapy, chemotherapy, and targeted therapy—face several limitations. Recently, *Astragalus membranaceus*, a traditional Chinese medicine (TCM), has captured significant attention due to its broad pharmacological properties, such as immune regulation, anti-inflammatory effects, and the modulation of reactive oxygen species (ROS) and enzyme activities. This review delivers a comprehensive summary of the most recent advancements and ongoing applications of *Astragalus membranaceus* in NSCLC treatment, underlining its potential for integration into existing treatment protocols. It also highlights essential areas for future research, including the elucidation of its molecular mechanisms, optimization of dosage and administration, and evaluation of its efficacy and safety alongside standard therapies, all of which could potentially improve therapeutic outcomes for NSCLC patients.

Keywords: non-small cell lung cancer, *Astragalus membranaceus*, antitumor activity, immunoregulation, cisplatin

Introduction

At present, lung cancer is the leading cause of cancer death globally. The 5-year survival rate for patients with lung cancer is only 10%–20% in most countries.¹ Histologically, non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer, and its current 5-year survival rate remains below 20%.² The traditional therapies for NSCLC include surgical resection, radiation therapy, and chemotherapy.³ For NSCLC patients, chemotherapy drugs are cytotoxic drugs based on cisplatin (DDP), such as paclitaxel (PTX) and docetaxel (DTX). However, chemotherapy often accompanies serious adverse reactions, and these treatment options often have limited efficacy.⁴ Therefore, the search for new antitumor drugs with low toxicity and side effects has become a focus of research. Traditional Chinese medicine (TCM) has been used for cancer treatment in China and other Asian countries for over 1000 years. Numerous evidence has demonstrated that TCM, as an adjunctive therapy, can improve the efficacy of chemotherapy and radiation therapy and reduce side effects.⁵

Astragalus membranaceus is the dry root of *Astragalus membranaceus* (Fisch.) Bge.var. Mongolicus (Bge.) Hsiao or (*Astragalus membranaceus* (Fisch.) Bge.).^{6,7} Modern pharmacological studies have found that *Astragalus membranaceus* mainly exerts effects on anti-inflammation, antitumor, antioxidant, anti-allergy, anti-diabetes and treatment of various diseases.^{8–10} According to previous studies, *Astragalus membranaceus* can treat NSCLC through different molecular pathways, and its antitumor mechanisms include inhibiting cell proliferation, affecting cell cycle, and inducing apoptosis.⁸ Based on existing literatures, this review summarizes the existing research results, introduces the active ingredients, pharmacological effects, and clinical applications of *Astragalus membranaceus* in the treatment of NSCLC.

The Active Ingredients and Pharmacological Effects of *Astragalus membranaceus*

The effective pharmacological components of *Astragalus membranaceus* include Astragalus polysaccharides (APS), saponins, flavonoids, as well as other components such as vanillic acid, riboflavin, chlorogenic acid, folate, and

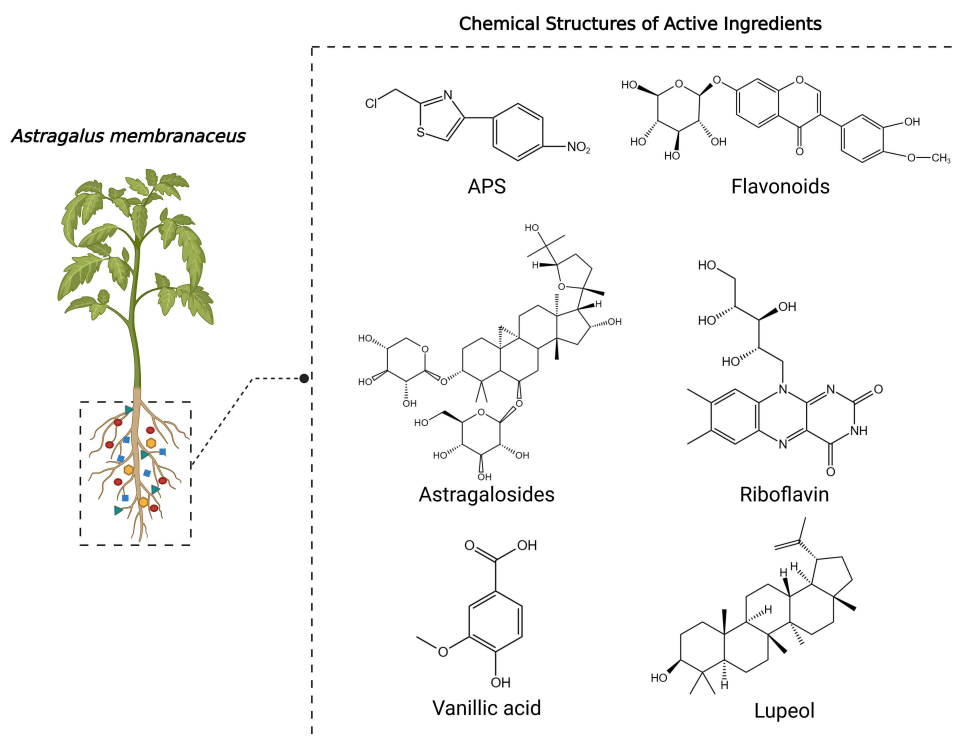


Figure 1 Chemical structures of key active ingredients in *Astragalus membranaceus*. Depicted above are the chemical structures of various active ingredients extracted from *Astragalus membranaceus*, including Astragalus polysaccharides (APS), flavonoids, astragalosides, riboflavin, vanillic acid, and lupeol. These compounds are highlighted for their significant roles in pharmacological applications, contributing to the plant's efficacy in traditional and modern medicine practices.

sterols.^{7,11} Among them, APS has been extensively studied, and it has multiple biological functions, including immune regulation, antioxidant stress, and anti-apoptosis.¹² Experimental results have confirmed the immunomodulatory and anti-inflammatory activities of APS¹³ and its antitumor effects.^{14,15} To better understand the molecular basis of these effects, Figure 1 presents the chemical structures of these key active ingredients, elucidating their potential roles in the pharmacological activities of *Astragalus membranaceus*.

APS

APS is one of the most important macromolecular active substances in *Astragalus membranaceus*, mainly divided into heteropolysaccharides and glucans.¹⁶ Numerous studies have explored that APS has multiple biological functions, such as antioxidant, anti-inflammatory, and immunomodulatory activities,¹⁷ and has the potential to treat nervous system disease,¹⁸ cardiovascular disease,¹⁹ diabetes²⁰ and cancers.^{21,22}

APS can promote the proliferation of bone marrow-derived dendritic cells (DCs), enhance T cell proliferation and antigen presentation ability, and induce the production of Interferon gamma (IFN- γ) and IL-2 and upregulation of CD80 and CD86 expression.²³ APS can also promote the phagocytic function of macrophages, promoting the secretion of nitric oxide (NO) and inducible nitric oxide synthase (iNOS) by macrophages.²⁴ Meanwhile, APS can stimulate macrophages to produce IL-6 and IL-1 β , tumor necrosis factor- α (TNF- α) and NO, stimulating macrophage activation.²⁵ A recent study has proved that APS can attenuate Ochratoxin A (OTA)-induced immune stress in vitro and in vivo by activating the AMPK/SIRT-1 signaling pathway, significantly alleviating OTA-induced splenic injury in mice.²⁶

The antitumor effects of APS can be summarized as APS directly inhibiting tumor cell proliferation and promoting cell apoptosis, APS combining with chemotherapy drugs to improve the efficacy of chemotherapy drugs, and APS exerting antitumor effects by regulating immune function. Chemotherapy is one of the effective treatments for highly invasive and metastatic cancers, while the long-term clinical application is limited by its dose-related toxicity. APS has been proven to promote chemosensitization on tumors, which can improve the efficacy of chemotherapy drugs.²⁷ The

combination of APS and 10-hydroxycamptothecin can elevate the expression of apoptosis-related genes and cysteinyl aspartate-specific proteinase (caspase-9/-3) that contain cysteine, in NSCLC cells. Moreover, they facilitate cell autophagy by inhibiting mitogen activated protein kinase-3 (MAP4K3) and downregulating the signal transduction of mechanical target of rapamycin (mTOR), thereby achieving antitumor effects.²⁸ Compared with treatment with cisplatin alone, the combination of APS and cisplatin can significantly increase the ratio of Bax/Bcl2 to suppress tumor cell proliferation and enhance apoptosis.²⁹ Gefitinib is an epidermal growth factor receptor tyrosine kinase inhibitor that can be used to treat NSCLC. However, patients may develop resistance to gefitinib chemotherapy after 9–13 months of treatment. APS can reverse acquired chemoresistance in lung cancer cells by inhibiting the PD-L1/sterol regulatory element-binding protein-1/epithelial mesenchymal transition (EMT) signaling pathway.³⁰ In vitro experiments have exhibited that APS had no direct cytotoxicity to mouse breast cancer cells (4T1), but APS could act on macrophages, further inducing cell cycle arrest (G2 phase) and apoptosis to significantly inhibit the growth of 4T1 cells.³¹ In addition, the benefits of APS in alleviating cancer-related fatigue and improving the quality of life of patients with advanced cancer have also been confirmed in clinical studies.³²

Astragaloside (AS)

AS, a saponin compound extracted from *Astragalus membranaceus*, can be divided into AS-I, AS-II, and AS-IV.³³ Among them, AS-IV, as a tetracyclic triterpenoid saponin in the form of lanolin ester alcohol, possesses the strongest biological activity and has multiple biological functions such as antitumor, antioxidant, anti-inflammatory, and immune regulation.³⁴ It has been reported that AS-IV can reduce various types of inflammatory damage, such as organ damage induced by lipopolysaccharide (LPS), ischemia-reperfusion injury, allergic disease, diabetes and its complications, myocardial injury and hypertension.³⁵ Another study has also implied that AS-IV can regulate inflammatory factors (IL-1 β , TNF- α , intercellular adhesion molecules, and chemokines), inflammatory mediators (NO), and nuclear factor- κ B (NF- κ B) signal pathways and apoptosis-related genes to alleviate inflammatory injury.³⁶ AS-IV can also inhibit the expression of Toll-like receptor-4 (TLR4) and its downstream signaling molecules NF- κ B, iNOS and COX-2 proteins to clear reactive oxygen species (ROS), thereby delaying or inhibiting cell oxidation, or serves as an exogenous antioxidant to maintain or rebuild redox balance.³⁷

Many researchers have evaluated the antitumor effect of AS-IV in different cancer types (including lung cancer, colon cancer, liver cancer, stomach cancer and breast cancer) by cultivating cancer cell lines in vitro and xenotransplantation tumor animal models in vivo.³⁴ Accumulating evidence has proved that the antitumor effect of AS-IV is mainly achieved by promoting cell apoptosis and autophagy, inhibiting cell proliferation, invasion, migration, and metastasis, as well as regulating the tumor microenvironment (TME) (including angiogenesis and innate and acquired immunity).³⁸ EMT is a mechanism by which normal epithelial cells are transformed into mesenchymal cells, which in turn transform into malignant tumor cells. During the development of tumor, transforming growth factors (TGF)- β -1 or epidermal growth factor receptor (EGFR) can initiate endodermal transfer. Therefore, drugs that suppress EMT have therapeutic potential in cancer treatment. AS-IV regulates several signaling pathways related to endometrial transformation and autophagy, such as phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT), mitogen activated protein kinase (MAPK)/ERK, Wnt/ β Connexin and Transforming Growth Factor- β /SmadD signaling pathways, which are closely correlated with multiple tumors.³⁹ Bax induces cell apoptosis, while Bcl2 inhibits cell apoptosis. The relative ratio of these two proteins (Bax/Bcl2) is essential for stimulating cell apoptosis. AS-IV induces Bax expression and decreases Bcl2 expression by inhibiting the activation of Akt/GSK-3 β /b-catenin axis. In addition, as the concentration of AS-IV increases, AS-IV exerts obvious inhibitory effects on tumor cell metastasis.⁴⁰ A previous study has also suggested that AS-IV could affect EMT to repress the invasion and metastasis of cervical cancer by inhibiting the phosphorylation of P38, MAPK, PI3K, AKT, and mTOR in cultured SiHA cervical cancer cells.⁴¹

Astragalus Flavone

Astragalus flavone, as one of the active substances extracted from *Astragalus membranaceus*, also has diverse biological activities, including antioxidant, anti-aging, anti-inflammatory, myocardial protection, antitumor, and immune enhancement effects.⁴² It has been found that total flavone of *Astragalus membranaceus* (TFA) can alleviate atherosclerosis and enhance plaque stability in apolipoprotein E deficient mice, which may be related to improving lipid metabolism and inhibiting

inflammation of liver and macrophages. In addition, TFA can also inhibit the adhesion between monocytes and inflammatory endothelial cells, which are associated with miR-33 expression and the inactivation of NF- κ B activity and the arrangement of genes related to lipid metabolism.⁴³

Vanillic Acid and Lupeol

Vanillic acid (VA, 4-Hydroxy-3-methoxybenzoic acid), a nutritional phenolic compound found in *Astragalus membranaceus*, has antioxidant, antimicrobial, genotoxic, and antitumor activities.⁴⁴ A recent study has exhibited that a lung cancer model was established. Swiss albino mice were treated with benzo(a)pyrene (B(A)P) to establish a lung cancer model. The mice with B(A)P group elevated levels of carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE), resulting in terminal weight loss and reduced activity of tissue enzymes and non-enzymatic antioxidants. However, these trends were evidently reversed by the combination of VA (200 mg/kg/b. wt) and B(A)P, indicating its antitumor effects on B(A)P-induced lung cancer.⁴⁴ Moreover, extracellular regulated protein kinase (ERK) signaling pathway is one of the key pathways for lung cancer metastasis. Bhatt et al have found that Lupeol represses A549 cell metastasis in lung cancer in vitro by downregulating pErk1/2 protein, N-cadherin, and vimentin through the ERK signaling pathway.⁴⁵ Another study has also displayed that Lupeol can inhibit the nuclear translocation and transcriptional activity of downstream molecule STAT3 of EGFR to suppress the phosphorylation of EGFR and downregulate the target genes of STAT3, thereby enhancing tumor cell apoptosis.⁴⁶

Pharmacological Activity of *Astragalus membranaceus* in NSCLC

The multifaceted pharmacological actions of *Astragalus membranaceus* against NSCLC are pivotal in its therapeutic potential. These actions include inhibiting cell proliferation and promoting apoptosis, reducing cell invasion and metastasis, inhibiting angiogenesis, regulating cell autophagy, enhancing immune function, and improving the efficacy and safety of chemotherapy agents like cisplatin. Figure 2 summarizes these mechanisms, illustrating the comprehensive role of *Astragalus membranaceus* in modulating various molecular pathways in NSCLC.

Astragalus membranaceus Inhibits NSCLC Cell Proliferation and Promotes Apoptosis

NF- κ B is a protein complex that is an important nuclear transcription factor within cells.⁴⁷ They control the expression of many genes that play critical roles in growth, apoptosis, tumorigenesis, differentiation, embryonic development, tumor metastasis, as well as immune and inflammatory responses.⁴⁸ Wu et al⁴⁹ explored the antitumor activity of APS in human lung cancer cell lines A549 and NCI-H358. They found that APS significantly inhibited the proliferation of these cell lines. The NF- κ B activator PMA weakened APS's antitumor activity, while the NF- κ B inhibitor Bay 11-7082 enhanced it. In vivo, APS delayed the growth of A549 cell xenografts in BALB/C nude mice. Mechanistically, APS inhibited the transcriptional activity of NF- κ B subunit p65, reducing the expression of p50, cyclin D1, and Bcl-xL proteins, thereby inhibiting tumor cell proliferation.⁴⁹ In addition, Wang et al⁵⁰ studied the antitumor effects of the Qilian Formula (AAF) in a bone metastasis model using NCI-H460-luc2 lung cancer cells in mice tibiae. AAF, which includes *Astragalus membranaceus*, significantly inhibited tumor growth, suppressed osteoclast formation, and induced apoptosis through increased expression of Bcl2, Bax, and caspase 3 genes, highlighting the therapeutic potential of *Astragalus membranaceus* in cancer treatment. Moreover, AS-IV can enhance paclitaxel-induced cell apoptosis and cell cycle arrest at G2/M phase and inhibit tumor cell proliferation to facilitate the chemotherapy sensitivity of cancer cells to paclitaxel.⁵¹

Astragalus membranaceus Inhibits NSCLC Cell Invasion and Metastasis

Early metastasis is the leading cause of death in patients with NSCLC.^{52,53} Metastasis involves a series of complex processes, including the shedding of tumor cells, degradation of extracellular matrix (ECM), invasion, migration, and adhesion of endothelial cells, as well as the reconstruction and growth at a distance, which require the interaction of different signaling pathways.⁵⁴ *Astragalus membranaceus* has attracted widespread attention in TCM treating NSCLC due to its synergistic effect and minimal side effects. Early studies have shown that *Astragalus membranaceus* can inhibit the invasion and metastasis of tumor cells.^{55,56} EMT endows cancer cells with invasive and metastatic characteristics by promoting their mobility and invasiveness.⁵⁷

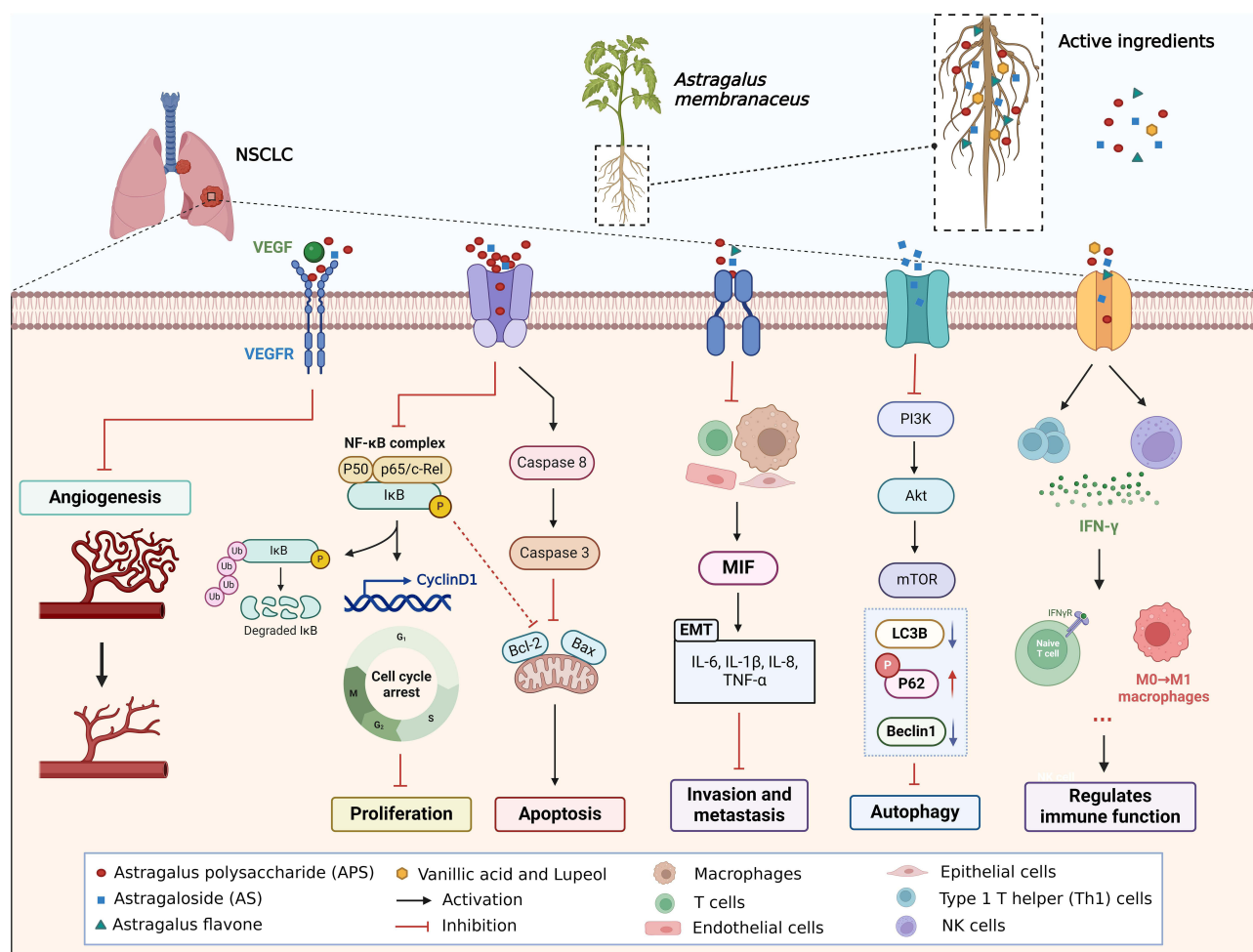


Figure 2 Pharmacological activity of *Astragalus membranaceus* in NSCLC. The diagram presents a comprehensive view of the antitumor effects exerted by *Astragalus membranaceus* against Non-Small Cell Lung Cancer (NSCLC). It highlights the plant's active compounds - including Astragalus polysaccharide (APS), Astragaloside (AS), and Astragalus flavone - and their interactions with key cellular pathways. These compounds target and modulate multiple processes: they inhibit angiogenesis via VEGF and VEGFR signaling; they suppress tumor proliferation by downregulating the NF-κB pathway and CyclinD1 expression; they promote apoptosis through caspase activation and balancing Bcl-2/Bax proteins. Additionally, the diagram indicates the role of *Astragalus membranaceus* in immune regulation, enhancing the activity of Th1 cells and M1 macrophages, while reducing T cell suppression. It also illustrates the inhibition of autophagy, a process that may enhance the apoptosis of tumor cells, thus potentially serving as a beneficial therapeutic agent in the treatment of NSCLC.

It has been reported that macrophage migration inhibitory factor (MIF) significantly affects anchoring independence, mobility, and invasiveness of lung adenocarcinoma cells.⁵⁸ MIF can directly or indirectly elevate the levels of IL-6, IL-1β, IL-8, and TNF-α to enhance the occurrence of EMT.⁵⁹ In vitro models and severe combined immunodeficiency disease (SCID) mouse models were established to investigate the roles of APS in lung adenocarcinoma A549 and CL1-2 cells. The findings have revealed that APS exerts no effects on the growth of these tumor cells, while it inhibits the secretion of MIF, thereby repressing tumor cell migration and invasion.⁶⁰ MicroRNA (miRNA) is a type of non-coding RNA with tumor suppressive or carcinogenic functions that is considered to play an indispensable role in the occurrence, progression, and metastasis of various cancers, including NSCLC.⁶¹ Tao et al⁶² have suggested that the upregulation of miR-195-5p is positively correlated with the survival rate of lung cancer patients through bioinformatics analysis. It has also been proved that APS can inhibit the invasion and metastasis of NSCLC cells, specifically A549 and NCI-H1299 cells, by upregulating miR-195-5p.

Astragalus membranaceus Inhibits Angiogenesis in NSCLC

The development of tumors mainly relies on vascular supply, which is promoted by the angiogenic activity within malignant tissues.⁶³ Inhibition of angiogenesis is regarded as a promising method for treating NSCLC.⁶⁴ As

a downstream effector of EGFR, transcription activating factor 3 (STAT3) activates through EGFR-induced signaling cascade, leading to transcriptional regulation of cell proliferation, angiogenesis, and metastasis. Obtained data have indicated that *Astragalus membranaceus*, Angelica sinensis, Trichosanthin, and Docetaxel (DTX) induce apoptosis in NSCLC H460 cells by inhibiting the EGFR and STAT3 signaling pathways.⁶⁵ DTX-mediated NSCLC H460 cell apoptosis is alleviated by increasing apoptosis of apoptotic marker proteins including cleaved caspase-7 and cleaved PARP. In addition, the combination of *Astragalus membranaceus*, Angelica sinensis, and Trichosanthin suppresses angiogenesis by downregulating the angiogenic marker CD31. DTX also has an inhibitory effect on the expression of vascular endothelial growth factor.⁶⁵ Previous studies have shown that a combination of *Astragalus membranaceus*, Angelica sinensis, and Trichosanthin can suppress tumor angiogenesis by inhibiting VEGF-induced VEGFR2 activation. Although this combination did not affect the viability of H460 NSCLC cells in vitro, it significantly reduced tumor growth in vivo. This reduction was associated with decreased levels of VEGF-related markers, such as p-VEGFR2, and an increase in apoptosis markers in the tumor tissues.⁶⁶

Astragalus membranaceus Regulates Cell Autophagy

Autophagy is the autophagy of cytoplasmic organelles to degrade misfolded proteins, damaged organelles, or cancer cells.⁶⁷ Autophagy and cell apoptosis are important mechanisms contributing to cancer progression.⁶⁸ Cisplatin resistant NSCLC A549 and H1299 cell lines (A549Cis, H1299Cis) were treated with different concentrations of cisplatin (0, 20, and 60 μ M) for 24 h, the expression of GRP78 and PERK (two endoplasmic reticulum stress-related proteins) and autophagy-related proteins (Beclin1, Lc3 II/I) in A549Cis and H1299Cis are significantly increased in a dose-dependent manner. Compared with cells treated with cisplatin (20 μ M), the expression of GRP78 and Beclin1 in A549Cis and H1299Cis is significantly downregulated after combination of AS-IV and cisplatin, indicating that AS-IV may enhance the antitumor effect of cisplatin by inhibiting endoplasmic reticulum stress and autophagy. Moreover, A549Cis and H1299Cis cells are treated with autophagy activator rapamycin (100 nM) and endoplasmic reticulum stress inducer tuniarnycin (5 μ g/mL) and the results have revealed that both rapamycin and tranexamycin can increase the survival rate of A549Cis and H1299Cis cells and reduce cell apoptosis rate, which further proves that AS-IV facilitates sensitivity of NSCLC cells to cisplatin by inhibiting endoplasmic reticulum stress and autophagy.⁶⁹ P62 is responsible for identifying ubiquitin labeled substrates as autophagy targets, while LC3 is the main effector factor of autophagy, and its conversion from LC3-I to LC3-II may activate autophagy.⁷⁰ Bevacizumab (BV) can inhibit tumor growth in various cancers, including lung adenocarcinoma, but its therapeutic effect is significantly weakened due to drug resistance. A recent study utilizing the A549 lung adenocarcinoma cell line has demonstrated that AS-IV significantly enhances BV's inhibitory effects on cell proliferation and promotes apoptosis by inhibiting autophagy, thereby improving BV's overall efficacy against lung adenocarcinoma. In experiments involving the A549 cell line, treatment with AS-IV and BV resulted in significantly higher levels of autophagy-related proteins P62, LC-3I, and LC-3II compared to treatment with BV alone. These findings indicate that AS-IV can mitigate BV resistance and enhance its antitumor effects by modifying autophagic activity.⁷⁰

Astragalus membranaceus Regulates Immune Function

There are various immune cells in the tumor microenvironment, among which Th1, Tc, DC, and NK cells, as well as M1 type tumor associated macrophages (TAMs), are closely related to antitumor immunity and tumor suppression. Th2 and M2 cells can affect immune suppression and induce tumor development.⁷¹ Th1 type cytokines such as IFN- γ stimulate the differentiation of M1 macrophages, while Th2 cytokines such as IL-4 trigger the expression of M2 macrophages.⁷² A clinical study has revealed that the decrease in ratio of Th1/Th2 cytokines and M1/M2 TAMs is closely related to cancer progression and poor patient prognosis.⁷³ *Astragalus membranaceus* has the ability to enhance macrophage phagocytic function and cytotoxic activity of NK cells and CD8⁺T cells, while inhibiting the function of regulatory T cells.^{74,75} Another study has also found that the combination of *Astragalus membranaceus* and Angelica sinensis can significantly elevate the IFN- γ level in the serum of tumor-bearing mice to promote the differentiation of tumor cells Tc, NK cells, and M1 TAMs. Meanwhile, it can also rebalance the Th/Tc cell ratio and suppress the expression of IL-2 and M2 TAM.⁷⁶ These findings have demonstrated that *Astragalus membranaceus* possesses immune regulatory function by

stimulating the activation of Th1 and NK cells, the secretion of IFN- α , and differentiation of Tc cells and M1 TAM, ultimately inhibiting tumor growth.

Bamodu et al¹⁵ have displayed that APS significantly elevates the polarization ratio of M1/M2 macrophages in NSCLC H441 and H1299 cells, and APS induces the increase of tumor M1 cells in vitro, which is positively correlated with downregulation of tumor promoting factors IL-6 and IL-10 in NSCLC cell conditioned medium, while inhibiting cell proliferation, clone formation, and tumor sphere formation. APS can also promote the functional maturation of DCs, thereby enhancing T cell-mediated antitumor immune responses.

Astragalus membranaceus Enhances Sensitivity to Cisplatin and Prevents Cisplatin-Induced Acute Renal Injury

In cancer chemotherapy, most antitumor drugs exhibit resistance to cancer cells, leading to chemotherapy failure and tumor recurrence. Cisplatin is one of the first-line antitumor drugs for treating solid tumors, but its resistance remains the main obstacle to chemotherapy efficacy in NSCLC patients.⁷⁷ Acute renal injury caused by cisplatin is a common complication of chemotherapy, but there is still a lack of effective preventive measures in clinical practice.⁷⁸ The transformation of tumor drug resistance can be mediated by various parameters, such as regulating drug efflux/inflow, altering drug detoxification systems, expressing apoptosis, and genes/proteins in drug distribution.⁷⁹ Yu Ping Feng San (YPFS) is a famous ancient Chinese medicine combination formula consisting of *Astragalus membranaceus*, *Atractylodes macrocephala*, and Fangfengcao, which is commonly used in clinical practice to treat immune diseases. Du et al⁸⁰ have demonstrated that YPFS stimulates the accumulation of cisplatin in cultured A549 cells or its cisplatin-resistant A549/DDP cells, leading to a reduction in tumor cell viability. Moreover, YPFS results in reduced expression of NF- κ B p65 subunit, leading to an increase in the ratio of Bax/Bcl-2, which enhances apoptosis in tumor cells. It can be speculated that YPFS reduces the activity and expression of ATP binding cassette transporters and glutathione S-transfers (GST), thereby increasing cisplatin content in A549/A549-DDP cells. Meanwhile, YPFS downregulates the NF- κ B p65 subunit to increase proportion of Bax/Bcl-2. Finally, YPFS triggers cell death with cisplatin synergistically.

APS inhibits cisplatin induced mitochondrial and intracellular ROS production in human renal tubular epithelial cells (HK-2). APS can block the opening of mitochondrial permeability transition pores induced by cisplatin to maintain the normal morphology of mitochondria and reduce the overflow of cytochrome c. And then APS represses cisplatin-induced apoptosis in mouse kidney cells and HK-2 cells.⁸¹ In summary, this study proves that APS pretreatment may prevent cisplatin-induced renal injury by relieving oxidative damage, protecting mitochondria, and improving mitochondrial-mediated cell apoptosis.⁸¹

Discussion

Existing evidences have indicated that *Astragalus membranaceus* has significant effects on NSCLC, and its mechanism is complex and diverse. The antitumor effect of *Astragalus membranaceus* has been confirmed in NSCLC cells in vitro and NSCLC animal models. *Astragalus membranaceus* can promote apoptosis and autophagy of NSCLC cells, inhibit the proliferation, invasion, metastasis, and EMT of tumor cells, enhance the activity of immune cells, and facilitate the transformation of M2 macrophages into M1 macrophages. In addition, *Astragalus membranaceus* also increases the sensitivity of NSCLC cells to cisplatin and other chemotherapy drugs, improving the efficacy of chemotherapy and immunotherapy. In conclusion, the antitumor effect of *Astragalus membranaceus* is mainly achieved by upregulating or downregulating different signaling pathways or other mechanisms. These findings highlight the antitumor effects of *Astragalus membranaceus* and its potential as an anti-NSCLC drug or adjuvant for NSCLC treatment.

At present, complete resection surgery is the most effective method for treating NSCLC. However, most patients diagnosed with NSCLC have missed the opportunity for surgery at the time of diagnosis.⁸² Chemotherapy is the main method for treating advanced NSCLC, and cisplatin is the first-line chemotherapy drug.⁸³ Cisplatin directly kills cancer cells by inducing apoptosis, while long-term use of cisplatin often leads to drug resistance, leading to treatment failure.⁸⁴ Cisplatin induces apoptosis in NSCLC cells through upregulation of glucose regulatory protein 78 (GRP78)-mediated endoplasmic reticulum stress.⁸⁵ Accumulating evidence has found that P21 activated kinase 4 (PAK4) is highly expressed

in cisplatin-resistant NSCLC cells and is associated with increased intracellular calcium concentration and endoplasmic reticulum stress, revealing the important role of PAK4 in regulating cell resistance and endoplasmic reticulum stress. PAK4 inhibitors suppress the resistance of NSCLC cells to cisplatin, demonstrating that targeting PAK4 can reverse the resistance of NSCLC to cisplatin.⁸⁶ PAK4 knockout can reduce the expression of GRP78 in A549-res and NCI-H520-res cells. A previous study has also revealed that endoplasmic reticulum stress is regulated by GRP78. AS-IV can inhibit endoplasmic reticulum stress and autophagy by downregulating GRP78, thereby increasing the sensitivity of NSCLC cells to cisplatin.⁶⁹ Therefore, we propose a hypothesis that AS-IV can act on the PAK4 target to reduce the expression of GRP78, thereby stimulating the sensitivity of NSCLC to cisplatin. These findings provide new targets and strategies for the treatment of NSCLC.

Conclusion and Future Perspectives

This review has comprehensively explored the promising antitumor properties of *Astragalus membranaceus* in the context of NSCLC. With its diverse pharmacological effects, including the modulation of immune responses, induction of apoptosis, inhibition of cell proliferation, and enhancement of chemotherapy sensitivity, *Astragalus membranaceus* presents a valuable adjunct to conventional cancer therapies. However, despite these encouraging findings, several gaps remain in the translation of preclinical results into clinical practice.

To better integrate *Astragalus membranaceus* into clinical settings for the treatment of NSCLC, future research should prioritize several key areas. First, robust, large-scale clinical trials are crucial to validate its efficacy and safety, focusing on determining optimal dosing regimens and identifying potential interactions with standard chemotherapy agents. Additionally, although significant progress has been made in understanding the biological activities of *Astragalus membranaceus*, the detailed molecular mechanisms behind its antitumor effects still need further elucidation, which could reveal new therapeutic targets. Another critical area of research is investigating how *Astragalus membranaceus* can overcome or prevent resistance to existing therapies, a major hurdle in NSCLC treatment. Finally, considering its benefits on patient well-being and side effect management, further studies should also explore its impact on the quality of life, particularly in palliative care settings, to fully assess its potential as a supportive treatment option.

By addressing these research gaps, *Astragalus membranaceus* could be better positioned as a clinically viable option for NSCLC treatment, potentially improving patient outcomes and expanding the arsenal against this challenging disease.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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