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Advances in the Role of Active Ingredients of Astragalus in Lung Cancer-Related Signaling Pathways

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Abstract: *Modern clinical studies have shown that the Chinese herbal medicine Astragalus plays an important role in reducing the toxic side effects of radiotherapy and chemotherapy for lung cancer, improving the quality of survival, stabilizing the tumor, and preventing tumor recurrence and metastasis after surgery. Due to the complex pathogenesis of lung cancer, the wide range of effective components of Astragalus and the complex action pathways, this paper reviews the pharmacological mechanisms of Astragalus in lung cancer treatment and the related signaling pathways by integrating the literature on the anti-lung cancer of Astragalus at home and abroad and combining the main components of Astragalus, methyloside, polysaccharides and flavonoids, in order to provide an effective pharmacological basis for the treatment of lung cancer by Astragalus and to facilitate the further development and utilization of Astragalus resources.*

Keywords: *astragalus active ingredients; lung cancer; signaling pathway*

1. Introduction

Lung cancer is the leading cause of death for both men and women in China [1], with a younger age of onset and an aging population structure, making the incidence and mortality rate of lung cancer the highest among middle-aged and elderly patients (see Table 1), and although Western medical treatments have made some progress, the overall treatment effect is poor (see Figure 1), and the treatment of lung cancer is imminent. China has incorporated the characteristic advantages of Chinese medicine into lung cancer treatment, promoting the strengths of Chinese medicine and complementing the weaknesses of Western medicine. Real-world clinical studies and many high-level evidence-based medical studies have confirmed that the clinical efficacy of combining Chinese and Western medicine in the whole course of lung cancer treatment is better than that of Western medicine alone [2,3]. In ancient Chinese medical texts, lung cancer-related diseases are named as "lung accumulation, Xiben", etc., and the evidence belongs to the deficiency of the root and the symptoms of the disease, and the specific pathogenesis is shown in Figure 2. In terms of medication, the efficacy of Astragalus fits the pathogenesis of lung cancer "positive deficiency" and has been widely used in clinical practice since ancient times.As early as in the Shen Nong Ben Cao Jing [4], it is recorded that Astragalus treats the accumulation of obstruction in the masses. In modern medical treatment, Astragalus is involved in the comprehensive treatment of lung cancer to help improve the quality of survival, assist in radiotherapy to reduce toxicity and increase effectiveness, and enhance the effect of immunotherapy.

Table 1: Lung cancer incidence and death among Chinese residents in different age groups, male and female, 2019 (/100,000)

Age	Morbidity		Mortality	
	Male	Female	Male	Female
0-19	0.53	0.38	0.31	0.22
20-39	14.06	8.75	10.55	6.24
40-59	227.94	103.62	185.68	80.58
60-79	1491.07	582.05	1377.71	536.05
80-	685.63	256.49	751.13	291.11

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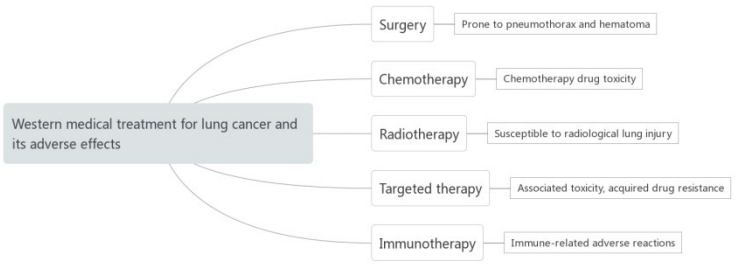

Figure 1: Western medical treatments for lung cancer and related adverse effects

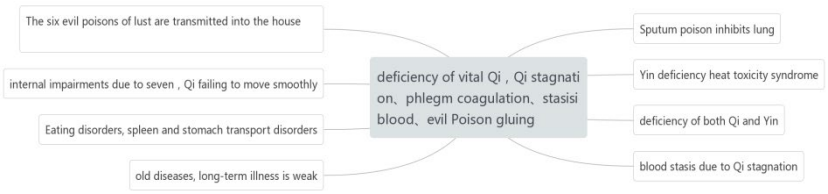

Figure 2: Etiology and pathogenesis of lung cancer

Astragalus is the root of Astragalus membranaceus, family Leguminosae, sweet in taste, slightly warm in nature, enters the spleen and lung meridians, tonifies the middle and benefits the qi, consolidates the surface and induces diuresis, and restores pus and toxicity and generates muscle. Modern pharmacological studies have found that the main chemical components of Astragalus include polysaccharides, saponins and flavonoids, which have various pharmacological effects such as immune modulation, antitumor, anti-inflammatory, antioxidant and cardiovascular protection [5], as shown in Figure 3. With the utilization of Chinese medicine resources, the advantages of Astragalus alone or in combination with other drugs in the treatment of lung cancer are gradually emerging. In this paper, we systematically describe the research progress of Astragalus membranaceus methylglucoside, polysaccharide and flavonoids in the treatment of lung cancer related signal transduction pathways, and provide an effective basis for the prevention and treatment of lung cancer as well as the development of Astragalus membranaceus resources.

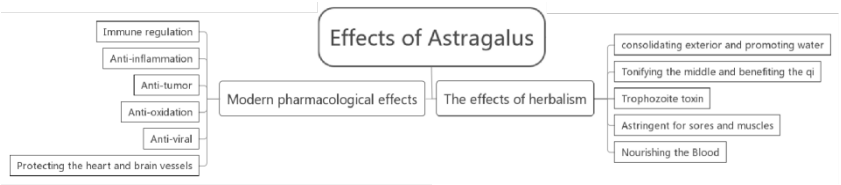

Figure 3: Efficacy and modern pharmacological effects of Astragalus membranaceus

2. Clinical study of Astragalus membranaceus against lung cancer

Astragalus is clinically effective in the treatment of lung cancer alone, in pairs with other herbs, in herbal combinations, and in combination with Western therapies. Studies have shown that herbal prescriptions containing Astragalus can enhance the effect of chemotherapy against lung cancer with radiotherapy, platinum and paclitaxel drugs, and also act as a radioprotective agent to reduce the toxicity of radiotherapy [6,7]. Astragalus polysaccharides help normalize neutrophils and lymphocytes (NLR), enhance sensitivity to immune drugs, regulate cancer-related fatigue, and prolong overall survival in lung cancer patients receiving immunotherapy [8]. Zomei He [9] et al. retrospectively analyzed 7435 NSCLC cases and found that astragalus was used second only to licorice, and that astragalus-wolfberry and astragalus-ginseng pairs were used more frequently. Zhao Linlin [10] et al. found that the abluminal soup with Huangqi as the monarch medicine significantly prolonged the survival of patients with advanced lung cancer and improved the cachexia status of advanced lung cancer. Wang Su-Fen [11] et al. clinical study found that Astragalus polysaccharide combined with AP (pemetrexed disodium + cisplatin) regimen for advanced non-small cell lung cancer, the level of lung cancer markers, lung cancer therapeutic function score, and immune index levels in the combined group were better than those in the AP group, effectively improving patients' survival quality with satisfactory recent efficacy. In conclusion, the tumor-suppressive and antitumor effects of Astragalus

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are widely used in the treatment of lung cancer and better improve the clinical outcomes of lung cancer patients.

3. Specific mechanism of action of Astragalus membranaceus against lung cancer

3.1. Effect of Astragalus on interleukin-6 (IL-6), Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway in lung cancer

The JAK/STAT3 signaling pathway plays various biological roles in human tumor development, and the activation of this pathway is closely related to the proliferation, inflammation, survival and prognosis of lung cancer [12,13]. JAK is a heterotransformer of IL-6 present in the tumor microenvironment that activates the STAT3 signaling pathway, leading to tumorigenesis, progression and inhibition of antitumor immune effects. In addition, IL-6 can also target and induce STAT3 gene expression, which drives the proliferation and migration of tumor cells by the cyclin D1 and MMP2 proteins [14]. Therefore, blocking any link in the IL-6/JAK/STAT3 signaling axis can significantly improve the anti-cancer effect, so a large number of novel IL-6, JAK and STAT3 inhibitory drugs such as cetuximab and tolimumab are available in the clinic. Zhang Shiwen [15] et al. found that astragalus polysaccharide inhibited lung cancer cell migration by reducing the transcriptional activation effect of JAK/STAT3 signaling pathway through decreasing IL-6, a signaling factor emitted by proto-oncancer cells. Zhang Zhihong [16] et al. found that astragaloside was effective in inhibiting STAT3 gene transcription, P-JAK1 and P-STAT3 protein expression and thus the proliferation and metastasis of A549 lung cancer cells in a dose-dependent manner at low toxic doses of 5, 10 and 20 μmol/L. Qi Yanshang [17] et al. showed that the combination of Astragalus membranaceus total flavonoids with cisplatin downregulated STAT3 protein levels, and the change in tumor volume and immune system response was better than that of cisplatin alone, which had an attenuating and potentiating effect, probably through the IL-6/STAT3 pathway to inhibit tumor growth. In conclusion, Astragalus alone or in combination with chemotherapeutic agents can block IL-6/JAK/STAT3 signaling pathway or one of its links, inhibit lung cancer cell proliferation and migration, regulate the body's immunity, enhance the efficacy of chemotherapeutic agents, and improve the long-term benefit of patients.

3.2. Effect of Astragalus on phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway in lung cancer

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway is a fundamental mechanism of mammalian enzyme-related receptors in transducing signals or biological processes that regulate cell growth, proliferation, motility, metabolism, and many other physiological functions [18]. Studies have shown that the PI3K/Akt/mTOR pathway is over-activated in 50%-70% of non-small cell lung cancers [19], and is centrally involved in the development and progression of lung cancer. Inhibition of this pathway can effectively regress tumors and is a noteworthy therapeutic target in the treatment of lung cancer [20]. The specific mechanism of action is shown in Figure 4, PI3K is activated by extracellular growth factors, hormones, cytokines and other stimuli with surface receptors and converted to phosphatidylinositol 3,4,5-trisphosphate (PIP3), PIP3 induces the activation of phosphatidylinositol-dependent kinase-1 (PDK1) and AKT downstream targets, which in turn activates downstream pathway effectors mTOR (mTORC1 and mTORC2), mTOR can also reverse AKT hyperphosphorylation to overactivate PI3K/Akt/mTOR, so blocking a link molecule of this pathway is a potentially effective way to treat lung cancer.

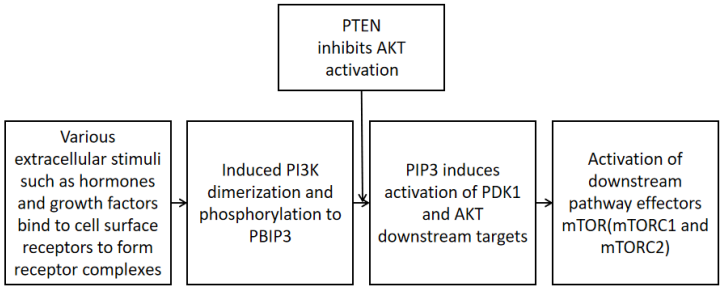

Figure 4: Astragalus acts on PI3K/Akt/mTOR-related pathway

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The active ingredients of Astragalus affect the PI3K/Akt/mTOR pathway in a direct or indirect manner to achieve cancer inhibition and anti-cancer purposes. Akt is a direct downstream effector of PI3K and mTOR is a downstream effector of PI3K and Akt signaling involved in autophagy, cell growth, proliferation and survival. Related studies have shown that high expression of autophagy-related protein P62 inhibits the mTORC1 signaling pathway [21], and Yang Qi [22] et al. found that Astragalus polysaccharide can upregulate the expression of autophagy-related protein P62, downregulate the expression of LC3B and Beclin1, and negatively regulate the PI3K/Akt/mTOR signaling pathway to inhibit the autophagic effect of tumor cells. Phosphatase and tensin homolog (PTEN) is an important nodal gene for PI3K/Akt/mTOR, and studies have shown that PTEN overexpression inhibits lung cancer cell proliferation, chemoresistance, and promotes tumor cell apoptosis [23]. Jia Liwei [24] et al. found that astragaloside could counteract PTEN deletion or reduced expression and affect the activation of PI3K/Akt/mTOR pathway, which subsequently inhibited proliferation, migration and induced apoptosis in lung cancer A549 cells.

Astragalus can also act on a link in the PI3K/Akt/mTOR signaling pathway to exert anti-tumor effects. The relevant literature reports that nearly 90% of patients with non-small cell lung cancer have PI3K/Akt signaling pathway [25]. Liu Ye [26] et al. showed that Astragalus polysaccharide down-regulated the expression level of glycoprotein P-gp on the membrane of drug-resistant cells and reversed cellular drug resistance, and the mechanism may be related to blocking PI3K/AKT signaling pathway. Liu Yuxia [27] et al. suggested that astragaloside significantly reduced the expression of immunoglobulin-like transcription factor 4 (ILT4) in A549 cells, inhibited the activation of PI3K/Akt pathway, and affected the expression of immunomodulatory molecule B7 family members (B7-H3) to impede the immune escape of lung cancer cells and affect the subsequent progression of lung cancer. Annie Wu [28] et al. found that Astragalus A inhibited the proliferation and promoted the apoptosis of A549 and SPC-A1 cells by decreasing the phosphorylated Akt in the activated state, and the Akt signaling pathway was one of the mechanisms involved in this process. In addition, it was shown that hypoxia-inducible factor-1α (HIF-1α) is regulated by PI3K/AKT/mTOR signaling pathway to exert anti-tumor angiogenic effects [20]. In conclusion, Astragalus polysaccharide and methyloside inhibit proliferation, migration and immune escape of lung cancer cells through regulating PI3K/Akt/mTOR signaling pathway or counter-signaling pathway, anti-tumor angiogenesis, induce autophagy and apoptosis of tumor cells and reverse drug resistance.

3.3. Effect of Astragalus on anti-angiogenic factors hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF-β1) in lung cancer

Lung cancer is a highly vascularized tumor, and real-world data suggest that anti-angiogenic therapy in the treatment of lung cancer significantly improves median survival and is an indispensable option for the treatment of progressive lung cancer [29]. Hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF-β1) are highly expressed in non-small cell lung cancer and are positively correlated with the development and evolution of lung cancer [30]. Tumor vascular growth is triggered by hypoxia-mediated upregulation of hypoxia-inducible factor-1α (HIF-1α) mRNA and protein. Therefore, the active ingredients of Astragalus play an inhibitory role in lung angiogenesis based on HIF-1α molecule. High expression of HIF-1α can upregulate the expression of downstream target gene VEGF gene, and HIF-1α/VEGF signaling pathway plays a key role in lung cancer angiogenesis [31]. Li Yang [32] et al. found that Astragalus polysaccharide could correct the decrease in immune downregulation due to cisplatin drugs and inhibit tumor growth, progression, and migration by downregulating the expression of HIF-1α, VEGF, and MMP-2 to suppress tumor angiogenesis. Xu Chengyong [33] et al. showed that Astragalus-Curculigo reduced tumor tissue microvessel density and restrained tumor growth and metastasis by downregulating TGF-β1, p38MAPK, HIF-1α, and VEGF expression in the TGF-β1/MAPKs/HIF-1α pathway.

3.4. Effect of Astragalus on signaling pathways such as Wnt/β-catenin, Toll-like receptor (TLR4)/myeloid differentiation protein (MyD88)/nuclear factor-κB (NF-κB) in lung cancer

Astragalus also exerts anti-lung cancer effects through various signaling pathways, such as Wnt/β-catenin, TLR4/MyD88/NF-κB signaling pathway. Aberrant Wnt/β-catenin signaling is closely linked to cancer onset, progression, prognosis, and death [34]. Activation of this pathway initiates C-myc and Cyclin D1, the main target genes of the downstream signaling pathway, so inhibition of Wnt/β-catenin signaling pathway is a potential way to treat tumors. The results of Wei Zhou [35] showed

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that astragaloside inhibited the activation of Wnt/β-catenin signaling pathway by down-regulating Wnt-1, β-catenin, C-myc, and Cyclin D1 expression, which led to the clarification of lung histopathological structure, reduced the level of lung cancer markers, and improved the survival quality of mice. A study by Teng Gang [36] et al. also demonstrated that the addition of Huangqi Glycyrrhiza glabra soup with Huangqi as the ruling herb inhibited lung cancer cell proliferation, metastasis, and tumor stem cell activity, and induced apoptosis associated with Wnt/β-catenin signaling pathway activation. Hu Kandei [37] et al. found that Astragalus polysaccharide could alter the inflammatory microenvironment suitable for tumor growth through TLR4/MyD88/NF-κB signaling pathway or regulate the extracellular matrix, affecting inflammatory factor signaling, inhibiting the immune escape process and thus controlling tumor growth, proliferation and migration. In addition, Astragalus polysaccharide [38] can also inhibit tumor cell proliferation and metastasis by blocking the activation of NF-κB/ and mitogen-activated protein kinase (MAPK) signaling pathways, mediating apoptosis in the mitochondrial pathway, and acting as a mitogenic and potent agent when combined with cisplatin. Astragalus flavonoids [39] down-regulates ERs response factor (XBP1) mediated expression of endoplasmic reticulum stress (ERs) signaling pathway and promotes endoplasmic reticulum apoptosis pathway. There are various other signaling pathways of Astragalus anti-lung cancer, which will not be discussed here.

4. Discussions

In summary, the three active ingredients of Astragalus are involved in lung cancer development, progression, and prognosis through various signaling pathways such as IL-6/JAK/STAT3, PI3K/Akt/mTOR, and HIF-1α/VEGF. These signaling pathways are not unrelated but interact with each other, for example, EGFR is an upstream regulator of PI3K signaling pathway, and EGFR/PI3K/Akt signaling pathway can affect downstream HIF-1α/VEGF/related protein expression involved in angiogenesis of lung cancer tissue [31]. Astragalus flavonoids, polysaccharides and methyloside exert anti-angiogenic, inhibit tumor cell growth, invasion and induce apoptosis effects through different signaling pathways. Astragalus polysaccharides and Astragalus methyloside can affect the activation of PI3K/Akt/mTOR pathway to exert anti-tumor effects. Single active ingredients exert different effects through different signaling pathways. Astragalus polysaccharide inhibits lung cancer cell migration by reducing the transcriptional activation effect of JAK/STAT3 signaling pathway, and also blocks PI3K/AKT signaling pathway to reverse cisplatin resistance. It was also demonstrated that the active ingredients of Astragalus affect lung cancer survival, growth, proliferation, apoptosis, and drug resistance through multi-level, multi-target, and multi-factor effects.

5. Conclusions

With the in-depth research on lung cancer, the aim of clinical treatment of lung cancer has changed from eliminating tumors to how to precisely change the potential of tumor invasion and metastasis. Astragalus is involved in clinical lung cancer treatment or adjuvant therapy with various advantages such as high efficiency, high safety and low price. In this paper, we review the signaling pathways involved in the anti-lung cancer of Astragalus methyloside, polysaccharides and flavonoids, and the specific mechanism of action involves various signaling pathways such as IL-6/JAK/STAT3, PI3K/Akt/mTOR, TGF-β1/MAPKs/HIF-1α, TLR4/MyD88/NF-κB, etc. These signal pathways and effector molecules involved in them are superimposed on each other, which play a synergistic role in inhibiting the survival, growth, proliferation, migration and immune escape of lung cancer tissues, mediating the apoptosis of lung cancer cells and reversing drug resistance. It has guiding significance for the clinical treatment of lung cancer with astragalus. However, Astragalus also contains amino acids, trace elements, sterols and other components. The study of the signaling pathway of Astragalus active ingredients against lung cancer is still at the basic stage, and the study of the specific signaling mechanism and the targets and upstream and downstream effectors involved in the signaling pathway still needs to continue to be improved, which has constructive significance for further research on Astragalus in the treatment of lung cancer.

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