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Research Progress on the Mechanism of Action of Huangqin (*Scutellaria baicalensis*) in the Treatment of Lung Cancer

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Abstract: This article summarizes recent domestic literature on the use of Huangqin (*Scutellaria baicalensis*) in the treatment of lung cancer. It reviews the mechanism of action of Huangqin in treating lung cancer from six aspects: inhibiting the growth of lung cancer cells, inducing apoptosis of lung cancer cells, inducing autophagy of lung cancer cells, inhibiting the migration of lung cancer cells, promoting the differentiation of lung cancer cells, and improving immune function. The aim is to provide a reference for the material basis and further research on the anti-inflammatory and anti-tumor efficacy of Huangqin.

Keywords: Huangqin; Lung Cancer; Mechanism of Action; Inhibiting the Growth of Lung Cancer Cells

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1. Introduction

Lung cancer is one of the most common malignancies worldwide and has the highest incidence and mortality rates in China. Currently, there are many drugs available for the clinical treatment of lung cancer, but their efficacy is not ideal. Therefore, it is particularly important to study new treatment methods. Traditional Chinese medicine has unique advantages in tumor treatment, which can exert anti-tumor effects through mechanisms such as inhibiting tumor cell proliferation, inducing apoptosis, or promoting tumor cell differentiation. Huangqin is a commonly used Chinese herbal medicine [1,2]. In recent years, with the deepening of people‘s understanding of traditional Chinese medicine theory and related modern scientific knowledge, the use of Huangqin in the treatment of lung cancer has received increasing attention. Its mechanism of action involves immune regulation, induction of cell apoptosis, enhancement of body immunity, and other aspects, which have become new research hotspots [3,4].

2. Inhibiting the growth of lung cancer cells

Research has shown that Huangqin extract can reduce the expression levels of proliferation-related genes (such as P16, CCND2, c-Myc) and regulate the expression of protein kinase A (PKA) in lung cancer cell lines, thereby inhibiting the growth of lung cancer cells [5]. Studies have found that the ethanol extract of Huangqin can induce G2 phase arrest and inhibit proliferation in A549 and H460 cell lines [6]. Another study showed that the main component of Huangqin, flavonoids, inhibited the proliferation of human lung adenocarcinoma NCI-H89 cells by down-regulating the expression of Akt and Bim genes in the PI3K/AKT pathway [7]. Additionally, it has been found that Huangqin and its effective components can increase SOD activity in the blood of lung cancer patients, increase superoxide dismutase (SOD) activity, decrease malondialdehyde (MDA) content, and increase glutathione peroxidase (GSH-Px) activity. This protective effect is related to improving the immune function in lung cancer patients [8]. The above results indicate that Huangqin has a certain inhibitory effect on lung cancer cells, possibly through the regulation of oxidative stress and inflammatory responses.

3. Inducing apoptosis in lung cancer cells

Oxidative stress and inflammatory responses in lung cancer tissues can cause mitochondrial dysfunction, leading to cell apoptosis. Research has shown that *Scutellaria baicalensis* can significantly increase the apoptosis rate of various tumor-associated macrophage lines and human lung cancer cell lines [9].

Sun Guanghui treated H295R and A549 cells with different concentrations of baicalein and detected changes in intracellular reactive oxygen species (ROS), calcium ion concentration, and mitochondrial apoptosis marker gene expression using flow cytometry. The results showed that low concentrations of baicalein could induce mitochondrial apoptosis in both lung cancer cell lines, while high concentrations of baicalein showed the opposite effect. It is speculated that this may be related to the role of the extracellular matrix protein VHL in regulating mitochondrial membrane potential [10].

In addition, studies have found that *Scutellaria baicalensis* extract (80% ethanol solution) can promote apoptosis in the human non-small cell lung cancer primary cell line A549. In this experiment, Annexin V-FITC/PI double staining was used to determine cell apoptosis [11]. The results showed that after baicalein intervention, the expression levels of p62 and caspase-3 in A549 cells increased, while Bax expression decreased, suggesting that *Scutellaria baicalensis* can induce cell apoptosis.

Furthermore, a novel antioxidant, quercetin-3 (QQ3), has been isolated from *Scutellaria baicalensis* using chemical methods, and it has been confirmed to effectively inhibit the growth of human lung cancer cell lines H1299, H460, NCI-N87, MCF-7, PC-9, HeLa, and HL-60 in a dose-dependent manner, accompanied by an increase in the rate of cell apoptosis [12]. QQ3 can induce activation of the p53 and caspase pathways in H1299 and H460 cells in vitro, leading to increased intracellular ROS and Ca2+ content, mitochondrial damage, and ultimately tumor cell apoptosis [13]. In vivo, QQ3 can upregulate the activity of the Nrf2 pathway, enhance the activity of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), reduce the production of reactive oxygen species, enhance the synthesis of glutathione in cells, reduce damage caused by oxygen free radicals, and finally achieve anti-tumor effects [14].

It can be seen that *Scutellaria baicalensis* and its active ingredients can cause intracellular ROS generation, activate the PI3K/AKT signaling pathway, upregulate Nrf2 transcription, induce target gene expression, and finally lead to cell apoptosis.

4. Inducing autophagy in lung cancer cells

Mammalian target of rapamycin (mTOR), as a key signaling hub regulating autophagy, plays a dual role in lung cancer cell proliferation: promoting growth under normal physiological conditions, while inducing excessive autophagy leading to cell death under drug intervention [15]. Studies have shown that baicalin can induce autophagy in lung cancer cells by regulating the AMPK/mTOR signaling pathway, thereby inhibiting lung cancer cell proliferation and promoting apoptosis [16]. Furthermore, research has indicated that baicalin can also inhibit the Nrf2/GPX4 signaling axis in lung cancer cells, inducing ferroptosis and autophagy synergistically, demonstrating potential in reversing lung cancer drug resistance [17].

5. Inhibition of lung cancer cell migration

Inflammatory factors in the lung cancer microenvironment are key factors inducing malignant progression and metastasis of the tumor. In an inflammatory microenvironment, the extracellular matrix (ECM) undergoes remodeling, which may alter the ECM structure and lead to its degradation or reorganization. This makes the ECM loose, weakens its adhesion function, and reduces its barrier effect on tumor cell migration.

Research has found that *Scutellaria* can inhibit the migration of alveolar epithelial cell line A549 and reduce the expression of extracellular matrix metalloproteinase 9 (MMP-9) and matrix metalloproteinase 13 (MMP-13) [18]. Additionally, the ethanol extract of *Scutellaria* can significantly reduce the expression of migration-related proteins α-SMA, FN, Vimentin, and N-cadherin in lung cancer A549 cells, suggesting that *Scutellaria* can effectively inhibit the migration of lung cancer cells [19]. This may be related to the ability of *Scutellaria* extracts to up-regulate the expression of fibroblast growth factor 21 (FGF-21). FGF21 is a proinflammatory cytokine secreted by hepatocytes that mediates the activation of immune cells and promotes the differentiation of macrophages into M2 type, which has anti-inflammatory, cell migration inhibitory, and angiogenesis inhibitory effects [20]. Therefore, *Scutellaria* reduces lung inflammatory responses in NSCLC patients by up-regulating FGF-21 expression, enhances the anti-inflammatory activity of NSCLC cells, and thereby inhibits NSCLC cell migration.

It has also been reported that the water extract of *Scutellaria* can inhibit the migration of NSCLC cells by regulating the balance of MMP-2/9 and TIMP-2/8 [20]. Additionally, some scholars believe that *Scutellaria* can also reduce the expression levels of COX-2 and ICAM-1, and inhibit the expression of basement membrane-like protein (BAP) derived from human lung cancer tissue. These results suggest that *Scutellaria* can inhibit the migration of NSCLC cells while inhibiting ERK phosphorylation [21].

Currently, the mechanism of action of *Scutellaria* in inhibiting NSCLC cell migration is still not fully understood. However, the above studies have demonstrated that *Scutellaria*, as an anti-inflammatory drug, can prevent NSCLC cell migration by inhibiting the expression of MMP-9 and TIMP-2/8. Thus, the inhibition of lung cancer cell migration by *Scutellaria* may be the result of multiple mechanisms working together, and the specific mechanism of action needs further investigation.

6. Promoting differentiation of lung cancer cells

Cancer stem cells are the main cause of drug resistance in lung cancer, and inducing their differentiation can increase their sensitivity to chemotherapy drugs. Studies have shown that *Scutellaria baicalensis* has the effect of promoting the transformation of normal cells into tumor cells [22]. For example, in vitro experiments have found

that the water extract of *Scutellaria baicalensis* promotes the invasion and metastasis of lung cancer cells by down-regulating the expression of CXCR4 on the surface of cancer stem cells, up-regulating the expression of matrix metalloproteinase 2 (MMP-2) and vascular endothelial growth factor (VEGF), and enhancing their migration ability [23]. Further research has found that *Scutellaria baicalensis* can regulate the secretion levels of various inflammatory factors such as IL-6, IL-23, TNF-α, IL-12, IL-17, IFN-γ, GM-CSF, and MIP-2 in the supernatant of human lung adenocarcinoma A549 cells by activating the TGF-β1/Smad3 signaling pathway. This may be one of the important mechanisms by which it promotes tumor cell differentiation [24].

At the same time, some scholars believe that *Scutellaria baicalensis* can induce apoptosis of lung cancer stem cells. By constructing a nude mouse xenograft model, it was observed that flavonoids can inhibit the colony formation of human non-small cell lung cancer A549 cells. Through immunofluorescence detection, it was found that *Scutellaria baicalensis* can reduce the phosphorylation of p-ERK protein, which in turn causes the accumulation of p53 in the nucleus, ultimately leading to cell apoptosis [25]. In addition, researchers have also found that flavonoids not only increase the apoptosis rate of lung cancer cells, but also reduce the expression levels of TGF-β1, CCND1, cyclinD, cyclinE, P53, and pRb proteins, effectively inducing the differentiation of lung cancer cells into normal lung tissue [26]. Therefore, *Scutellaria baicalensis* achieves cancer-promoting differentiation by regulating the expression of inflammation-related molecules.

In summary, *Scutellaria baicalensis*, as a common Chinese herbal medicine, has received widespread attention for its anti-tumor mechanism, but the specific mechanism of action has not been fully elucidated, especially in terms of molecular biology research, which requires further in-depth study. Currently, research on the anti-inflammatory effects of *Scutellaria baicalensis* is mostly focused on different types of inflammation, and its exact pharmacological mechanism remains unclear. Although the direct therapeutic effect of *Scutellaria baicalensis* on lung cancer is very limited, its regulatory effect on the human immune system deserves further exploration.

7. Enhancing immune function

*Scutellaria*e Radix can also play an immune-enhancing role in the treatment of lung cancer by regulating various immune pathways. Baicalin can promote the differentiation and activation of T cells in the body, thereby increasing the CD4+/CD8+ ratio and enhancing the immune status of patients with non-small cell lung cancer [27]. Studies have also found that baicalein can upregulate the activity of NK cells and the phagocytic function of macrophages, participate in the regulation of cytokine expression such as IFN-γ and IL-2, and improve the immunosuppressive state in the lung cancer microenvironment [28]. At the same time, research has pointed out that components of *Scutellaria*e Radix can inhibit the expression of immunosuppressive factors such as PD-L1 through the PI3K/Akt/NF-κB pathway, thereby enhancing the ability to control tumor immune escape [29]. From cells to animal models, from in vitro to clinical settings, *Scutellaria*e Radix and its derivatives are building a complex mechanism network of “immune activation - immune regulation - anti-tumor“, becoming a useful complement to immunotherapy for lung cancer.

8. Summary

Lung cancer, as the most common cancer in China, remains a challenging area of medical research in terms of

treatment and prognosis. Clinical trials have shown that *Scutellaria baicalensis* (Huang Qin in Chinese) has a good therapeutic effect on various tumors, especially lung cancer. It has been used in clinical lung cancer treatment and is characterized by its safety and few side effects. Currently, the mechanism of action of *Scutellaria baicalensis* in the treatment of lung cancer mainly focuses on inhibiting the growth of lung cancer cells, inducing apoptosis and autophagy of lung cancer cells, inhibiting migration of lung cancer cells, promoting the differentiation of lung cancer cells, and improving the body‘s immune function. However, these mechanisms are not yet fully understood and require further exploration.

The above literature shows that *Scutellaria baicalensis* compounds and their components exert anticancer effects by inducing tumor cell apoptosis or inhibiting cell migration. However, it is difficult to achieve complete inhibition of cancer cell growth with a single component or ingredient, and combination therapy is needed. This is also one of the development directions of traditional Chinese medicine antitumor drugs. In addition, *Scutellaria baicalensis* can also exert antitumor effects by regulating the body‘s immune function, possibly due to the activation of specific signaling pathways. Therefore, using gene knockout animal models combined with gene microarray technology to analyze the anti-inflammatory basis of *Scutellaria baicalensis* and its impact on the expression of related proteins during the development of lung cancer is expected to elucidate its antitumor mechanism. Meanwhile, modern pharmacological studies have confirmed that *Scutellaria baicalensis* and its effective fractions can reduce inflammatory reactions, resolve lung tissue edema, reduce fibrosis, promote lymphocyte homing to the lungs, increase the level of T cell subsets in peripheral blood and bronchoalveolar lavage fluid, and enhance the immune response in mice with acute lung injury. Therefore, combining traditional Chinese and Western medical theories to comprehensively elaborate on the mechanism of action of *Scutellaria baicalensis* in the treatment of lung cancer is important for establishing new tumor diagnosis and treatment methods and achieving precision medicine for lung cancer.

Disclosure statement

The authors declare no conflict of interest.

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