REVIEW
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Research progress on therapeutic material basis and mechanism of *Scutellaria barbata – Lobelia chinensis* herb pair in the treatment of lung cancer

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Author contributions

Liang XY, Xu KJ, and Liu J performed literature selection, drafted the manuscript, and prepared the figures. Li WD, Hua HB, and Wei CX designed the study and revised the manuscript. All authors contributed to the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

TCM, traditional Chinese medicine; SL, *Scutellaria barbata – Lobelia chinensis*; HUVECs, human umbilical vein endothelial cells; EMT, epithelial-mesenchymal transition; IL, Interleukin.

Citation

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Abstract

Lung cancer remains a leading cause of cancer-related mortality globally, with conventional therapies (chemotherapy, targeted agents) limited by severe toxicities and poor durability. Traditional Chinese medicine (TCMs) herb pairs, particularly *Scutellaria barbata – Lobelia chinensis* (SL), have emerged as promising alternatives for their multitarget anti-lung cancer activity, but their material basis and mechanisms need systematic clarification. In TCM practice, SL herb pair exerts "heat-clearing and toxin-resolving" effects, aligning with the therapeutic principle of "resolving toxin to suppress tumor" for lung cancer. Phytochemical and pharmacological studies confirm its key active components, including flavonoids (baicalein, luteolin, quercetin), alkaloids, and polysaccharides. These components synergistically act through core signaling pathways: inhibiting angiogenesis via HIF-1α/VEGF axis; inducing apoptosis/autophagy through PI3K/AKT/mTOR and SIRT1/AMPK pathways; suppressing epithelial-mesenchymal transition (EMT) by targeting TGF-β/Smad and Wnt/β-catenin pathways; and regulating immune microenvironment via NLRP3 inflammasome and Th1/Th2 balance. This review systematically summarizes the multi-component (flavonoids, alkaloids) and multi-pathway mechanisms of SL herb pair, validating the scientific connotation of TCM's "multi-target therapy" paradigm. It provides a theoretical basis for clinical application of SL herb pair and inspires the development of innovative lung cancer therapies (e.g., component-based nano-drugs), bridging TCM practice with modern pharmacology.

Keywords: *Scutellaria barbata*; *Lobelia chinensis*; herbal pair; lung cancer; therapeutic material basis; action mechanism

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Introduction

Lung cancer remains one of the most prevalent malignant tumors worldwide, characterized by high incidence and mortality rates [1–3]. Standard treatments such as surgery, chemotherapy, and targeted agents are limited by complications, poor quality of life, and drug resistance, creating an urgent need for alternative therapies [4–8]. TCMs, with their advantages of multi-component, multi-target effects, low toxicity, and high tolerance, have emerged as promising candidates in lung cancer therapy [9–12]. Among Traditional Chinese medicine (TCM) formulations, herb pairs (a core part of TCM compatibility theory) leverage synergistic effects to enhance efficacy and reduce toxicity, representing a valuable source for anti-lung cancer research [13–15].

This review focuses on the *Scutellaria barbata – Lobelia chinensis* (SL) herb pair, a classic "heat-clearing and detoxifying" combination widely used in clinical TCM practice for lung cancer. Its therapeutic potential lies in the synergistic effects of *Scutellaria barbata* and *Lobelia chinensis* [16, 17], but its specific active components and anti-lung cancer mechanisms lack systematic integration. Here, we systematically summarize the phytochemical basis, multi-dimensional mechanisms (e.g., apoptosis induction, anti-angiogenesis, immune regulation), and research progress of the SL herb pair, aiming to bridge TCM theory with modern pharmacology and provide a theoretical basis for its clinical application and innovative drug development.

In TCM theory, lung cancer is attributed to "cancer-toxin intermingled with phlegm (stagnation of body fluids), heat (excessive internal heat or inflammation), and blood stasis (impaired blood circulation)" [18], and the SL herb pair aligns with the therapeutic principle of "resolving toxin to suppress tumor". Modern studies have reported that SL-derived components (e.g., flavonoids, alkaloids) exert anti-lung cancer effects through various pathways, but their synergistic mechanisms and material basis require further clarification. The two herbs synergistically enhance efficacy in treating lung cancer through multi-component, multi-target, and multi-pathway mechanisms (Figure 1). This review integrates findings from phytochemical analysis, in vitro/in vivo studies, and clinical evidence to dissect the scientific connotation of the SL herb pair in lung cancer treatment.

TCM theories supporting the SL herb pair in lung cancer treatment

In TCM theory, cancer-toxin is recognized as a key factor in the occurrence and progression of lung cancer. Professor Zhou Zhongying, a National Master of Chinese Medicine, first proposed the "Theory of Cancer-Toxin Pathogenesis" [18]. He posits that cancer-toxin is a pathological product and pathogenic factor generated from the intermingling of phlegm, heat, and blood stasis. The theoretical framework of cancer-toxin pathogenesis is one of the most representative pathological theories in the field of TCM oncology. Based on the diverse characteristics of cancer-toxin pathogens, Professor Zhou has advocated different therapeutic strategies for combating cancer and eliminating toxins, such as the "heat-clearing and toxin-resolving method" [19]. Modern research indicates that bioactive components in TCM can effectively induce apoptosis in lung cancer cells, inhibit tumor angiogenesis, enhance tumor sensitivity to drugs or therapies, and improve immune function, etc., thereby demonstrating the advantages of multi-component, multi-target, and multi-pathway strategies in lung cancer treatment [20]. Search was conducted according to the search method shown in Table 1 below. According to a review of the PubMed database (Figure 2), over the past two decades, with the continuous deepening of research, the number of lung cancer-related publications has increased significantly. Concurrently, research achievements focusing on TCM in lung cancer studies have also gradually grown, accounting for a steadily increasing proportion of lung cancer-related research articles.

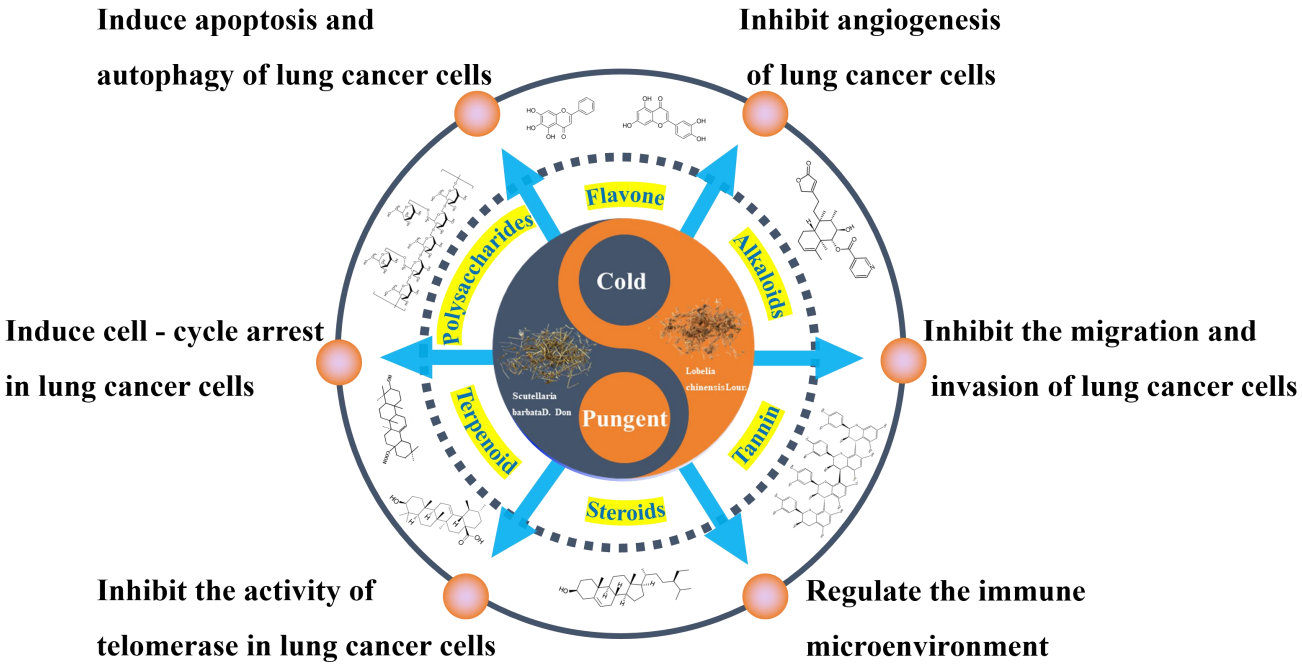

Figure 1 The therapeutic effects of the SL herb pair on lung cancer based on multi-components, multi-targets, and multi-pathway mechanisms

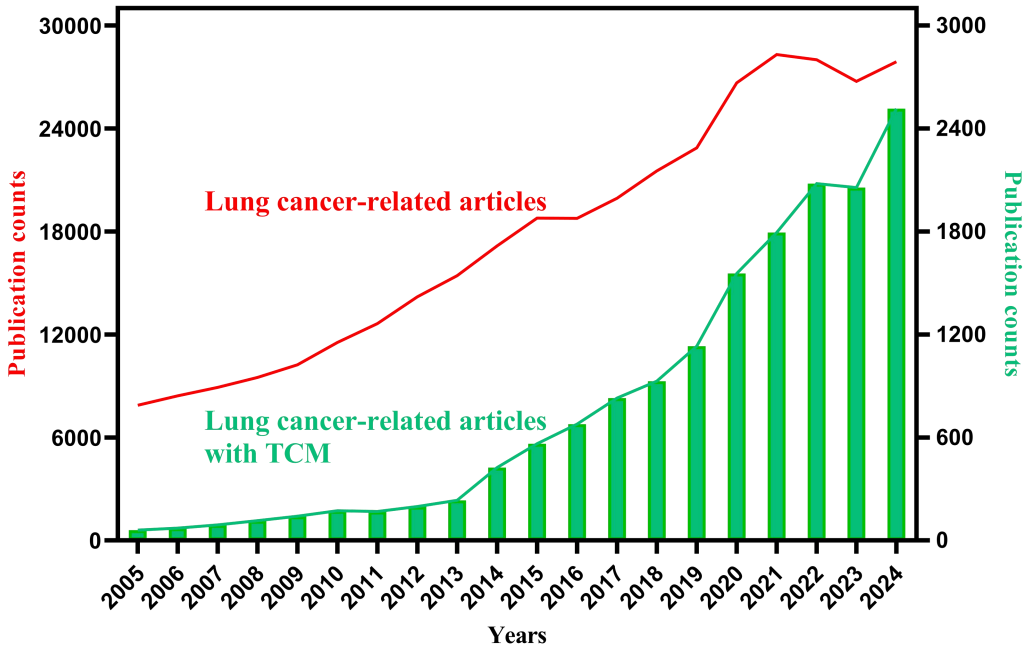

Figure 2 Trend chart of papers related to lung cancer research and the proportion of TCM in the research from 2005 to 2024. TCM, traditional Chinese medicine.

Table 1 The search strategy summary

Items	Specification
Date of search	20/4/2025
Database	PubMed
Search terms used	Lung cancer; Lung cancer Chinese medicine
Timeframe	1/1/2005 to 31/12/2024
Selection process	All authors selected studies together

Pharmacodynamic material basis and compatibility advantages of the SL herb pair

Research progress on the chemical constituents of the SL herb pair

The active components in *Scutellaria barbata* mainly include flavonoids, terpenoids, alkaloids, polysaccharides, tannins, steroids, and mineral elements [21, 22]. Most of these exhibit antitumor, antiviral, and immune-enhancing effects [23]. Among them, flavonoids, polysaccharides, and diterpenoids demonstrate significant anti-lung cancer activity [24–26]. The active components in *Lobelia chinensis* mainly include alkaloids, flavonoids, phenylpropanoids, terpenoids [27]. Alkaloids and flavonoids are its primary anti-lung cancer active components. Additionally, the volatile oil of *Lobelia chinensis* exhibits significant anticancer activity against various cancer cells, including lung cancer cells, with a favorable concentration-dependent inhibition of cancer cell proliferation (Figure 3).

Flavonoids are the major bioactive components in *Scutellaria barbata*, including scutellarin, apigenin, baicalin, luteolin. More than 70 flavonoids have been isolated from this herb to date [28]. Terpenoids are also abundant constituents in *Scutellaria barbata*, predominantly comprising neoclerodane diterpenoids with pronounced antitumor activity [29]. In addition to flavonoids and terpenoids, *Scutellaria barbata* also contains polysaccharides, which are distributed in different medicinal parts. Flavonoids predominantly exhibit effects on inhibiting proliferation and inducing apoptosis in lung cancer cells [30], while polysaccharides primarily regulate immune functions and the immune microenvironment. The various volatile components in *Scutellaria barbata* also exhibit significant antibacterial and anticancer activities. *Scutellaria barbata* also contains various metallic and trace elements, including iron, zinc, manganese, selenium, calcium, magnesium, potassium, and copper. *Lobelia chinensis* is a rich source of structurally diverse bioactive compounds, with major classes including alkaloids, flavonoids, phenylpropanoids, terpenoids, polyacetylenes, steroids, and fatty acids [31]. These components collectively contribute to the herb's therapeutic profile, particularly its anticancer and anti-inflammatory activities [32]. Although the volatile oil content in *Lobelia chinensis* is low, phytone, geranyl acetone, myristic acid, and other constituents are the pharmacodynamic components exerting anticancer activity. The volatile oil of *Lobelia chinensis* is predominantly composed of aldehydes/ketones, alcohols/phenols, and acids. Aldehydes and ketones, as well as alcohols and phenols, are mainly terpenoids and their oxides, while acids are primarily palmitic acid. Quercetin and luteolin, as abundant components, are shared by the SL herb pair [33].

The SL herb pair contains a diverse array of bioactive components, with flavonoids, alkaloids, and polysaccharides being the most critical for anti-lung cancer activity. These components, either shared by both herbs or synergistically enriched after compatibility, form the material basis of its therapeutic effects. Flavonoids are the most abundant active components in the SL herb pair, accounting for approximately 30–45% of total detectable bioactive constituents in 70% ethanol extracts [21, 27]. Key flavonoids include baicalein, luteolin, quercetin, and scutellarin, among which quercetin and luteolin are shared by both *Scutellaria barbata* and *Lobelia chinensis* and exhibit the highest concentrations – together comprising over 50% of the total flavonoid content in the herb pair [27, 30]. These flavonoids are proven to be the most bioactive. Alkaloids represent another major class, with a relative abundance of 10–15% in the SL herb pair [26]. *Lobelia*

chinensis contributes alkaloids such as lobeline, while *Scutellaria barbata* provides diterpenoid alkaloids (e.g., scutebarbatine A). These alkaloids exhibit potent activity in inhibiting telomerase and inducing mitochondrial apoptosis, with scutebarbatine A showing IC_{50} values as low as 12.5 μM against A549 cells [34]. Polysaccharides are primarily derived from *Scutellaria barbata*, accounting for 8–12% of the herb pair's extractable components [21]. They play a pivotal role in immune regulation by modulating Th1/Th2 balance and reducing Treg infiltration, with a 20% higher extraction yield when combined with *Lobelia chinensis* compared to *Scutellaria barbata* alone [35], indicating synergistic effects of the herb pair on polysaccharide dissolution. Other components, such as terpenoids (neoclerodane diterpenoids from *Scutellaria barbata*) and volatile oils (predominantly aldehydes/ketones from *Lobelia chinensis*), are present in lower abundance (< 5%) but contribute to anti-lung cancer activity by inducing cell-cycle arrest and inhibiting cell motility, respectively [24, 30].

Synergistic advantages of the SL herb pair compared to individual herbs

The therapeutic superiority of the SL herb pair over *Scutellaria barbata* or *Lobelia chinensis* alone lies in its synergistic effects on component dissolution, efficacy enhancement, and toxicity reduction, as supported by preclinical evidence.

1) Enhanced component dissolution: Polysaccharides from *Scutellaria barbata*, a key immune-regulatory component, show a 20% higher extraction yield in the SL herb pair compared to *Scutellaria barbata* alone [35]. This suggests that *Lobelia chinensis* may promote the dissolution of polysaccharides, potentially through increased solubility of glycosidic bonds during co-decoction, thereby enhancing the herb pair's immunomodulatory capacity. 2) Superior anti-tumor efficacy: In vitro studies indicate that the combined extract of the SL herb pair exhibits stronger inhibitory activity against lung cancer cells than individual herbs. For example, the half-maximal inhibitory concentration (IC_{50}) of SL herb pair extracts against A549 cells is 32.6 μg/mL, significantly lower than that of *Scutellaria barbata* alone (58.2 μg/mL) or *Lobelia chinensis* alone (67.8 μg/mL) [36]. In vivo, mice bearing Lewis lung carcinoma show a 45.3% tumor growth inhibition rate with the SL herb pair, compared to 28.1% with *Scutellaria barbata* alone and 22.7% with *Lobelia chinensis* alone [37]. This efficacy enhancement is attributed to the complementary mechanisms of key components: flavonoids from *Scutellaria barbata* (e.g., luteolin) primarily inhibit angiogenesis, while alkaloids from *Lobelia chinensis* (e.g., lobeline) focus on telomerase suppression, forming a multi-target synergistic network. 3) Reduced toxicity: Clinical observations note that high-dose single use of *Lobelia chinensis* may cause mild gastrointestinal discomfort (e.g., nausea) in 15% of experimental animals, whereas the SL herb pair (at equivalent effective doses) reduces this incidence to 5% [38]. This suggests that *Scutellaria barbata* may mitigate the potential toxicity of *Lobelia chinensis* through unknown phytochemical interactions, improving tolerability.

Research progress on the anti-lung cancer mechanisms of the SL herb pair

Scutellaria barbata and *Lobelia chinensis*, either used alone or as a herb pair, exhibit significant anti-lung cancer effects. Their mechanisms of action involve multiple dimensions: inducing cancer cell apoptosis and autophagy, inhibiting tumor angiogenesis, arresting the cancer cell cycle, suppressing cell migration and invasion, inhibiting telomerase activity, and modulating the immune microenvironment.

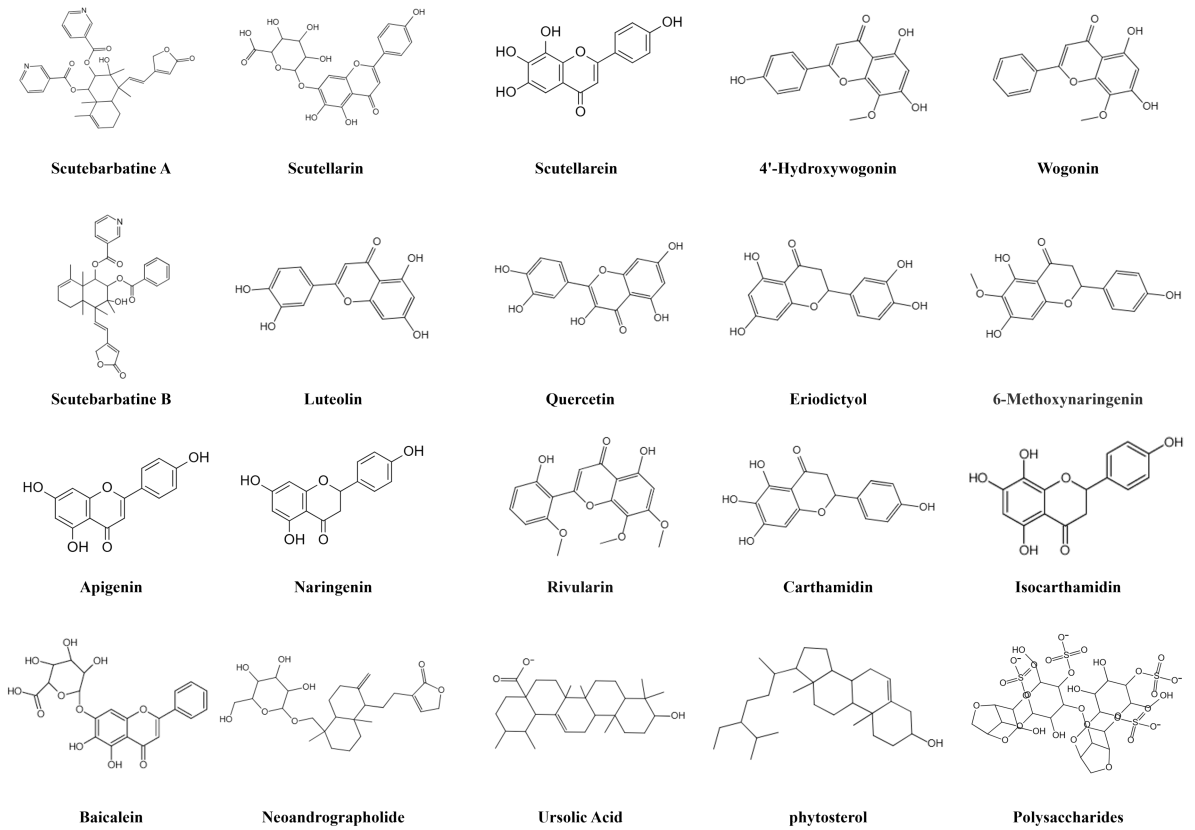

Figure 3 Chemical structures of some abundant components in the SL herb pair

Induce apoptosis and autophagy of lung cancer cells

Lung cancer cells are characterized by unlimited division and proliferation. Most therapeutic drugs exert their anti-cancer effects by inducing apoptosis and autophagy of cells [39]. The summary is shown in Table 2.

Activating the caspase family and triggering apoptosis mediated by the exogenous death receptor pathway or the endogenous mitochondrial pathway often leads to a series of biological and morphological changes [40]. Pro-apoptotic proteins activate the downstream caspase pathway and induce mitochondrial dysfunction, thus promoting the apoptosis of cancer cells. Flavonoids components in *Scutellaria barbata* and *Lobelia chinensis* can participate in regulating the balance of pro-/anti-apoptotic proteins, promoting the upregulation of caspases in cancer cells. Baicalein in flavonoids can also upregulate tumor suppressor genes such as p53 [41], transcriptionally activate pro-apoptotic proteins, reduce anti-apoptotic proteins, and accelerate the induction of apoptosis in lung cancer cells [42]. Polysaccharides in *Scutellaria barbata* can enhance the activities of Caspase-3 and Caspase-9 in cancer cells and induce the apoptosis of lung cancer cells through the endogenous mitochondrial pathway. Additionally, the excessive production of reactive oxygen species by the active ingredient in SL herb pair leads to oxidative stress and mitochondrial dysfunction in cancer cells, thereby inducing caspase-mediated apoptosis [35, 43]. The diterpenoid alkaloid scutebarbatine A induces mitochondrial-mediated apoptosis in lung cancer cells by upregulating the expression of caspase-3 and caspase-9 while downregulating Bcl-2 levels in A549 cells [34]. The diterpenoid compound rabdoternin E effectively induces apoptosis and ferroptosis in A549 cells while showing no toxicity to normal lung cells [44]. Quercetin, a flavonol component shared by *Scutellaria barbata* and *Lobelia chinensis*, has been shown to upregulate the protein expression of LC3-II/I and Beclin-1 while downregulating p62 levels in A549 and H1299 cells. Mechanistically, it induces pro-apoptotic autophagy via the SIRT1 (silent information regulator 1)/AMPK (AMP-activated protein kinase) signaling pathway in A549 and H1299 human lung cancer cell lines, thereby exerting anti-lung cancer effects [45]. Luteolin significantly inhibits the viability of A549 and NCI-H460 lung cancer cell lines. Mechanistically, it suppresses autophagy-negative regulatory pathways such as PI3K/AKT/mTOR, leading to elevated expression of autophagy-specific proteins LC3-II and Beclin1, and ultimately induces apoptosis in A549 cells. Luteolin and apigenin significantly inhibit the growth of H460, H358, and A549 cells and induce apoptosis even at low concentrations. By suppressing interferon-γ (IFN-γ)-induced PD-L1 expression, these flavonoids exhibit potent antiproliferative and growth-inhibitory effects against lung cancer cells [46].

Inhibit angiogenesis of lung cancer cells

When the diameter of a tumor exceeds 2 mm, its growth is faced with a hypoxic microenvironment. Cancer cells secrete a variety of pro-angiogenic factors, which bind to specific receptors on the endothelial cells of the inner layer of existing blood vessels, promoting the neovascularization of tumors [47]. The newly formed blood vessels provide oxygen and various nutrients for the proliferation and transportation of cancer cells. Tumor neovascularization is an important condition for the occurrence, development, invasion and metastasis of tumors. The hypoxia-inducible factor-1α (HIF-1α)/vascular endothelial growth factor (VEGF) signaling pathway is regarded as an important target for inhibiting tumor angiogenesis. VEGF is a major pro-angiogenic factor in tumor angiogenesis. Therefore, the anti-angiogenic therapeutic strategy targeting VEGF is one of the most effective ways to restrict the growth and development of lung cancer cells. In SL Herb pair, a variety of components can inhibit lung cancer cells by regulating angiogenesis (Table 3).

Table 2 The molecular mechanisms of active ingredients in the SL herb pair in inducing apoptosis and autophagy of lung cancer cells

Types of active ingredients	Ingredient name	Targeted cell lines	Molecular mechanisms	Final effect
Flavonoids	Baicalein	Lung cancer cells	Upregulate p53; activate transcription of pro-apoptotic proteins and reduce anti-apoptotic proteins; regulate the balance between pro-apoptotic and anti-apoptotic proteins.	Accelerate lung cancer cell apoptosis.
	Quercetin	A549, H1299	Upregulate LC3-II/I and Beclin-1, downregulate p62; induce pro-apoptotic autophagy through. SIRT1/AMPK signaling pathway.	Induce autophagy and exert anti-lung cancer effect.
	Luteolin	A549, NCI-H460, H358, H460	Inhibits the PI3K/AKT/mTOR pathway, upregulates LC3-II and Beclin-1, induces autophagy and promotes apoptosis. Directly induces apoptosis at low concentrations; inhibits IFN-γ-induced PD-L1 expression.	Inhibit cell activity, induce apoptosis and autophagy.
	Apigenin	H460, H358, A549	Directly induce apoptosis at low concentration. Inhibit IFN-γ induced PD-L1 expression, and enhance the anti-proliferative effect.	Inhibit cell growth and induce apoptosis.
Polysaccharides	*Scutellaria barbata* polysaccharides	Lung cancer cells	Enhance the activity of Caspase-3 and Caspase-9; induce apoptosis through endogenous mitochondrial pathway.	Induce apoptosis of lung cancer cells.
Diterpenoids	Scutebarbatine A	A549	Upregulate the expression of Caspase-3 and Caspase-9; downregulate the level of Bcl-2.	Induce mitochondrial pathway apoptosis in lung cancer cells.
	Rabdoternin E	A549	Induce apoptosis and ferroptosis.	Inhibit the proliferation of cancer cells.
Composite component	/	Lung cancer cells	Excessive reactive oxygen species generated causes oxidative stress and mitochondrial dysfunction in cancer cells.	Induce caspase-mediated apoptosis.

Table 3 Mechanisms of active components in SL herb pair for inhibiting lung cancer angiogenesis

Active ingredient	Targeted cell lines	Regulated molecules/pathways	Biological effects
Multiple alkaloids	A549	↓ VEGF mRNA. ↓ HIF-1α mRNA. ↓ p-AKT.	Inhibit cell growth and reduce microvascular density.
Polysaccharide-protein complexes	L9981	↑ Angiogenesis inhibitors. ↑ Endostatin. ↓ CD44, ↓ CD44V6. ↓ VEGF mRNA.	Inhibit angiogenesis.
Total flavonoids	Angiogenic endothelial cells	↓ VEGF.	Inhibit endothelial cell proliferation/migration, tumor angiogenesis and cancer cell motility.
Isorhamnetin	Lung cancer cells	Direct inhibition of angiogenesis activity.	Inhibit angiogenesis.
Wogonin	Lung cancer cells; HUVECs	↓ HIF-1α and VEGF secretion. Inhibition of the PI3K/AKT/NF-κB pathway. Inhibition of vascular angiogenesis in HUVECs.	Reduce the activity of angiogenic factors; inhibit tumor angiogenesis.
Polysaccharides	Calu-3	↓p-HER2. ↓ p-AKT. ↓ p-ERK.	Inhibit cell proliferation, reduce microvascular density, inhibit angiogenesis.
Polysaccharides	95-D	c-Met signaling pathway.	Inhibit angiogenesis.
Luteolin	Lung cancer cells	↓ HIF-1α/VEGF. ↓ VEGF-A, ↓ p-VEGFR-2.	Inhibit angiogenesis.

In the table, "↑" means upregulation/promotion, and "↓" means downregulation/inhibition. HUVECs, human umbilical vein endothelial cells.

Multiple alkaloid components in *Scutellaria barbata* can inhibit the growth of A549 lung cancer cells and the mRNA expression of VEGF and HIF-1α in a time- and dose-dependent manner, suppress the phosphorylation of upstream signaling factor AKT, and reduce microvessel density in tumors [48]. Polysaccharide-protein complexes can upregulate the mRNA expression of angiogenesis inhibitors and endostatin in the human highly metastatic large cell lung cancer cell line L9981, while downregulating the mRNA expression of adhesion molecules CD44, CD44V6, and VEGF, thereby inhibiting angiogenesis. Flavonoids are one of the major components in *Scutellaria barbata*. The total flavonoids from *Scutellaria barbata* can inhibit the proliferation and migration of angiogenesis-related endothelial cells, downregulate the expression of VEGF and other factors, and suppress tumor angiogenesis as well as tumor cell migration and motility. Isorhamnetin can significantly inhibit the activity of angiogenesis. Wogonin can not only inhibit the expression of HIF-1α in cancer cells and reduce the secretion of VEGF, thus decreasing the activity of angiogenesis factors, but also inhibit tumor angiogenesis by suppressing angiogenesis in human umbilical vein endothelial cells (HUVECs) and the PI3K/AKT/NF-κB signaling pathway [49]. Polysaccharides of *Scutellaria barbata* can effectively inhibit the proliferation of Calu-3 cells and the phosphorylation of HER2 via the HER2 signaling pathway, downregulate the expressions of downstream signaling factors AKT and ERK, reduce the microvascular density, and suppress tumor angiogenesis [50]. Polysaccharides from *Scutellaria barbata* can inhibit angiogenesis in lung cancer 95-D cells by regulating the c-Met (cellular mesenchymal-epithelial transition factor) signaling pathway [51]. Luteolin can significantly inhibit the HIF-1α/VEGF signaling pathway, reduce the expressions of factors such as VEGF-A and p-VEGFR-2, and inhibit angiogenesis.

Induce cell-cycle arrest in lung cancer cells

Multiple active components in the SL herb pair can inhibit lung cancer cell proliferation by regulating the cell cycle (Figure 4). Studies have shown that the G1/S and G2/M phases are important regulatory checkpoints for inhibiting the proliferation and viability of lung cancer cells [52, 53]. Diterpenoids compounds can arrest the S phase of the cell cycle, affect DNA synthesis and assembly, thereby inhibiting the proliferation of A549 cells [25]. Luteolin can inhibit the activity of cyclin B1/CDK1, promote the expression of p21, induce G2/M phase arrest in lung cancer cells, and simultaneously upregulate the phosphorylation of JNK while downregulating the phosphorylation of NF-κB, thereby suppressing the proliferation of lung cancer A549 and NCI-H460 cells. Quercetin binds to SIRT5 and inhibits the phosphorylation of PI3K/AKT through the interaction between SIRT5 and PI3K, thereby suppressing the repair processes of homologous recombination and non-homologous end joining in non-small cell lung cancer. This leads to DNA-damaged cells prematurely progressing from the G2 phase to the M phase, causing impaired mitosis and cell cycle arrest, which ultimately reduces lung cancer cell proliferation [54]. Quercetin can also induce DNA double-strand breaks and cell cycle S phase arrest in lung cancer cells, thereby inhibiting their proliferation [55].

Inhibit the migration and invasion of lung cancer cells

Epithelial-mesenchymal transition (EMT) represents a pivotal biological program in lung carcinogenesis, during which tumor cells acquire mesenchymal traits through downregulation of E-cadherin and upregulation of Vimentin, ultimately facilitating metastatic dissemination and intra-tumoral heterogeneity (Figure 5). Current therapeutic strategies primarily focus on disrupting EMT drivers [56], including TGF-β-mediated signaling cascades and Twist1/ZEB1 transcription factor networks, to impede cancer cell migration and invasion in both early and advanced-stage lung cancer. Rivularin, a flavonoid component in *Scutellaria barbata*, inhibits the migration of human lung squamous cell carcinoma cells by targeting the HOXA11-AS (Homeobox A11 Antisense Long Noncoding RNA)/Wnt/β-Catenin signaling pathway, thereby suppressing lung cancer cell proliferation and achieving anticancer effects. EMT is regulated by multiple signaling pathways, with the TGF-β/Smads signaling pathway being a key driver [57]. Luteolin, a flavonoid component shared by the SL herb pair, inhibits the protein expression of androgen receptor in A549 lung cancer cells, thereby suppressing cancer cell proliferation and migratory motility [58]. Luteolin can reverse the EMT process by promoting the expression of EMT-associated protein E-cadherin or inhibit EMT by reducing Integrin expression, thereby decreasing the invasion rate of lung cancer cells [59]. Quercetin upregulates E-cadherin expression at both the mRNA and protein levels, downregulates N-cadherin and Vimentin expression, prevents EMT in A549 cells, and reduces the migratory, invasive, and motile capabilities of A549 cells.

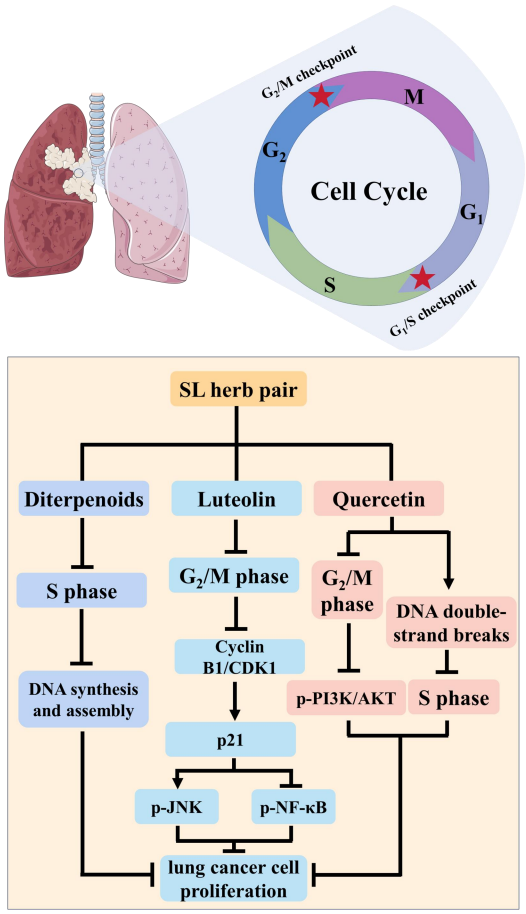

Figure 4 Active components in the SL herb pair inhibit lung cancer cell proliferation through cell cycle regulation.
SL, *Scutellaria barbata – Lobelia chinensis*.

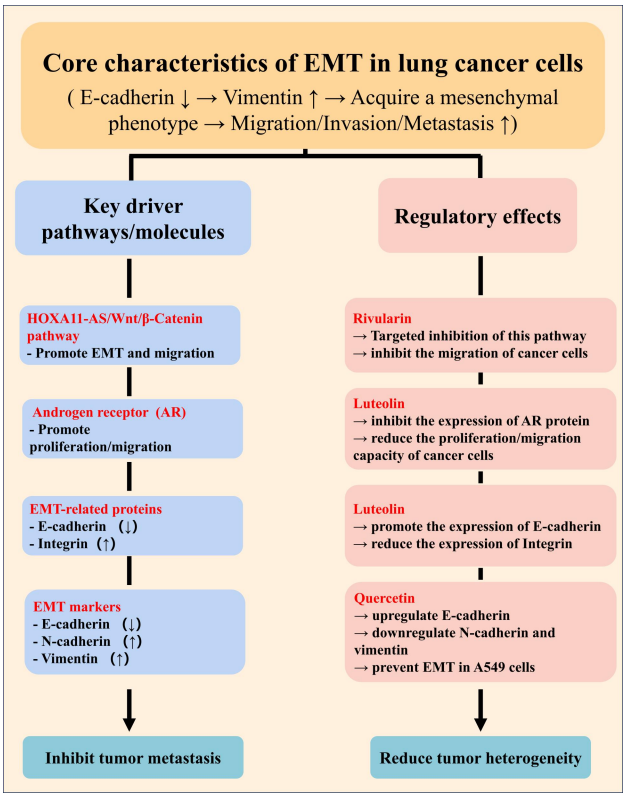

Figure 5 The bioactive components in the SL herb pair treat lung cancer by targeting key molecules/pathways to inhibit EMT.
EMT, epithelial-mesenchymal transition.

Inhibit the activity of telomerase in lung cancer cells

Telomerase is a reverse transcriptase composed of human telomerase RNA (hTR), telomerase-associated proteins, and human telomerase reverse transcriptase (hTERT) [60]. It functions to maintain the stability of telomere length and increase the number of cell divisions, thereby enabling cancer cells to acquire the ability for unlimited proliferation, differentiation, and survival during replication (Figure 6) [61]. Cancer cells maintain the stability of telomere DNA length by utilizing hTERT to catalyze telomerase RNA. Inhibiting the activity of telomerase in cancer cells is one of the effective anti-cancer methods [62]. Alkaloid components in TCMs can inhibit the activity of telomerase in cancer cells and suppress the growth of cancer cells [63, 64]. The drug-containing serum of *Scutellaria barbata* can significantly reduce telomerase activity in lung cancer cell lines. Multiple extract fractions of SL herb pair exhibit a certain therapeutic effect in shortening telomere length in tumor cells, downregulating telomerase reverse transcriptase (TERT) expression, inhibiting telomere elongation, and promoting apoptosis in lung cancer cells. However, the material basis of its pharmacological effects still requires further research.

Regulate the immune microenvironment

The pathogenesis and progression of lung cancer are closely associated with the body's immune function [65]. With the advancement of modern medicine, the understanding of the relationship between immunity and cancer has deepened gradually [66]. As a novel strategy for anti-lung cancer therapy, immunotherapy has demonstrated enormous therapeutic potential (Figure 7). The effects of TCMs on immunity are complex and diverse. Components such as flavonoids, polysaccharides, and alkaloids extracted from the SL herb pair have garnered significant attention in oncology research in recent years for their multi-target therapeutic effects against lung cancer. Even in the immunosuppressive tumor microenvironment, bioactive TCMs components exert anticancer effects by upregulating immune responses, including both innate and adaptive immunity [67]. During lung carcinogenesis, the most common immune cells are macrophages and T lymphocytes. Bioactive components in the SL herb pair exert anti-lung cancer effects by regulating the ratio of M1 to M2 macrophages, T cell subset differentiation, and cytokine secretion. Regulatory T cells are a subset of $CD4^+$ T cells. Polysaccharide components enhance anti-tumor immunity in the microenvironment by reducing the number and function of M2 macrophages and regulatory T cells, as well as the secretion of immunosuppressive cytokines, thereby inhibiting lung cancer initiation and metastasis. Subsets of $CD4^+$ T cells also include Th1, Th2, and Th17 cells [68]. *Scutellaria barbata* polysaccharides can regulate the levels of interferon-γ (IFN-γ) and IL-2, which are secreted by Th1 cells, and downregulate the levels of IL-4 and IL-10, secreted by Th2 cells, in the serum of tumor-bearing mice. This modulates the balance between Th1/Th2 subsets and inhibits lung cancer tumor growth through immunoregulation. Experimental studies have shown that the total flavonoids, an active component in *Scutellaria barbata*, can significantly inhibit the activation of the NLRP3/caspase-1 inflammasome axis, reduce the expression of pro-inflammatory cytokines Interleukin-1β (IL-1β) and -18 (IL-18) in both the tumor microenvironment and circulating blood, alter the tumor growth microenvironment, and thereby exerting anti-lung tumor effects [69]. Flavonoids and the diterpenoid compounds scutebarbatines in *Scutellaria barbata* can inhibit tumor growth in C57BL/6 tumor-bearing mice by regulating the immune microenvironment in vivo [70]. Scutebarbatine A can modulate the immune microenvironment in nude mice bearing A549 cells and significantly inhibit tumor growth [34].

The current understanding of the anti-lung cancer mechanisms of the SL herb pair is primarily derived from preclinical studies, including in vitro experiments using lung cancer cell lines (e.g., A549, H1299, Calu-3) and in vivo animal models. These findings provide a theoretical basis for its therapeutic potential but remain to be validated in clinical settings. The translatability of these preclinical results to human lung cancer patients, including dose-effect relationships, safety profiles, and synergistic effects with conventional therapies, requires further investigation.

Research, application status and challenges

Clinical evidence and translational perspective

Clinical exploration of the SL herb pair in lung cancer treatment is still in its early stages. Limited clinical observations have suggested its potential in adjuvant therapy: To date, no large-scale clinical trials have been reported for the SL herb pair in lung cancer, and only anecdotal evidence from TCM clinical practice supports its use. For example, a clinical study from a hospital of Traditional Chinese Medicine in China recorded that early-stage non-small cell lung cancer patients (IA-IB) receiving SL-based decoctions for 3 months postoperatively showed a 50.3% reduction in pulmonary nodules, with a 5-year disease-free survival rate of 82.5% (vs. 63.3% in the control group). This preliminary data supports the clinical value of SL herb pair, but is limited by small sample size and lack of randomized controlled design.

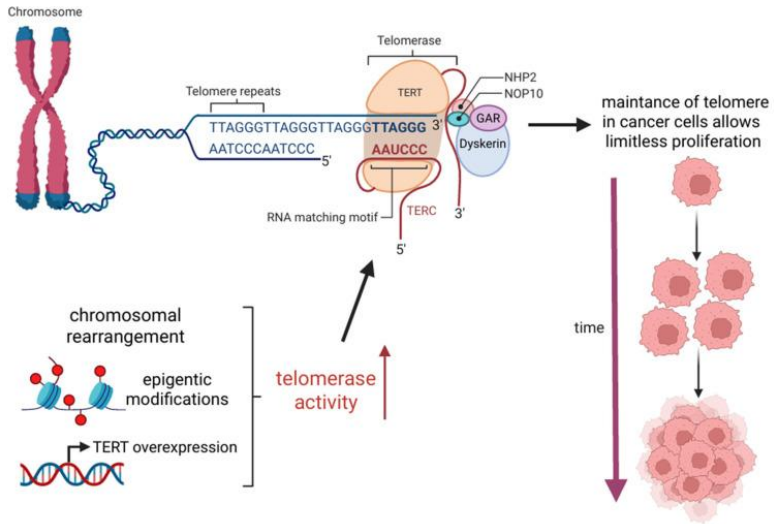

Figure 6 The mechanism of telomere maintenance in cancer cells resulting from telomerase upregulation.
Reproduced with permission. Rembiałkowska N, Sędzik M, Kisielewska M, et al. Telomere Maintenance and DNA Repair: A Bidirectional Relationship in Cancer Biology and Therapy. *Cancers (Basel)*. 2025;17(14):2284. Copyright 2025,MDPI.

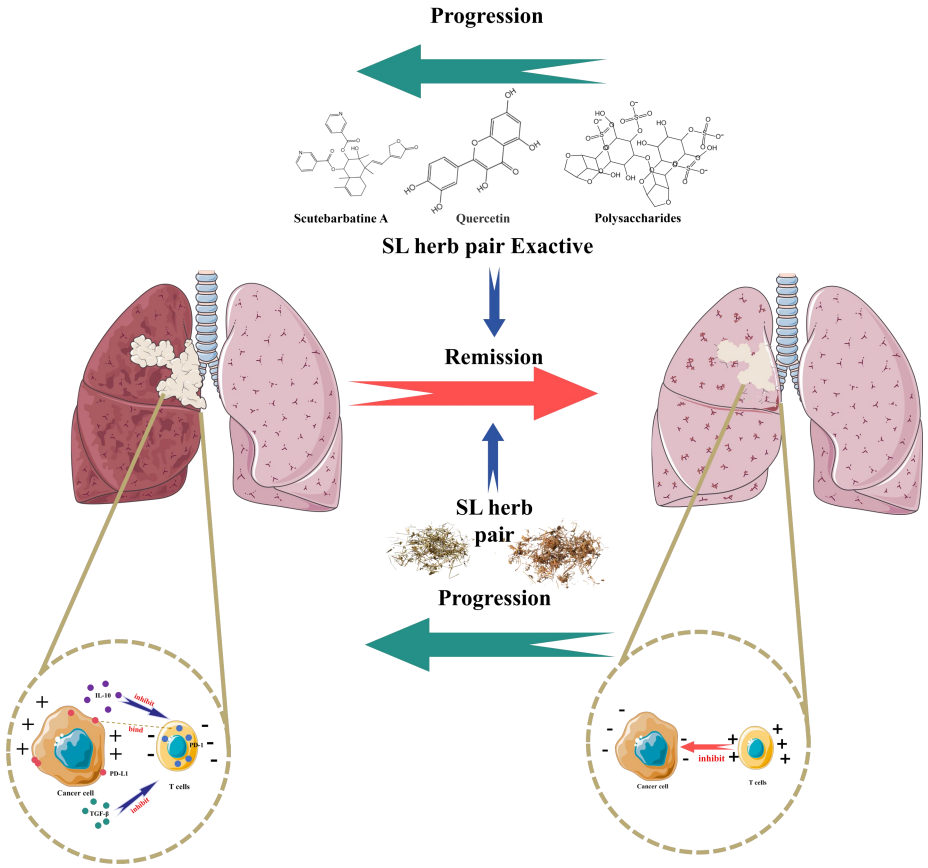

Figure 7 Conceptual model of SL herb pair treating lung cancer via immunological strategies.
SL, *Scutellaria barbata – Lobelia chinensis*.

For key components of the SL herb pair, individual clinical evidence is also scarce. Flavonoids (e.g., luteolin, quercetin) and alkaloids have been reported in retrospective studies to improve quality of life and reduce chemotherapy-induced toxicities when used as adjuvants, but their independent anti-tumor efficacy in lung cancer requires validation in prospective trials.

Weakness in material basis and foundation of mechanism analysis

At present, the research and development of anti-lung cancer drugs remain one of the key areas of focus. Although in the past 20 years, the research on the treatment of lung cancer with TCMs has shown exponential growth and made remarkable progress, due to the characteristics of TCMs which exerts its therapeutic effects through multiple components, targets, and pathways, there is still a certain gap compared with the treatment of lung cancer with chemical drugs in terms of developing new anti-lung cancer drugs. The analysis of the material basis of the pharmacological effects and the research on the anti-lung cancer pharmacological mechanisms are still in the early stage of laboratory-based research. The research on the correlation between the spectrum – efficacy is insufficient. The characteristics of treating diseases through multiple components, targets, and pathways make it impossible to fully explain the therapeutic mechanisms with modern medicine. There are few new drugs that can be applied in clinical research, resulting in a lack of standardized clinical data, and the individualized treatment regimens have not been fully implemented. In addition, current research mainly focuses on the abundant components in the SL herb pair, and there is relatively little research on the pharmacological effects of other active components. There are still many "dark matter" in TCMs that need to be clarified.

Insufficient interdisciplinary technical intersection and collaboration

Leveraging modern multi-functional analytical technologies for TCMs to accelerate research on the phytochemical basis of herb pairs before and after compatibility will enable a more thorough elucidation of the scientific connotation underlying the anti-lung cancer effects of herb pairs. This endeavor will provide pivotal mechanistic insights for the development of novel anti-lung cancer drugs inspired by TCM herb pairs. Simultaneously, through comprehensive analysis of the SL herb pair's phytochemical profile and anti-lung cancer mechanisms – supported by technologies such as UPLC-Q-TOF-MS and single-cell RNA sequencing – this work deepens the understanding of its active components and molecular targets. By fostering cross-disciplinary collaboration between TCM and modern oncology, this initiative seeks to develop innovative treatment paradigms and provide evidence-based clinical strategies for lung cancer management.

Leveraging advancements in artificial intelligence and 3D/4D printing technologies, the development of intelligent nano-targeted drug delivery systems – incorporating tumor microenvironment-responsive materials – enables precise spatiotemporal control over the delivery of TCM herb pair – derived active components (e.g., flavonoids from *Scutellaria barbata*, terpenoids from *Lobelia chinensis*). This innovation holds promise for creating next-generation lung cancer therapies with enhanced efficacy, reduced off-target toxicity, and personalized dosing regimens. This approach provides more efficient and safer TCM preparations for lung cancer treatment.

Summary and prospect

The SL herb pair exerts anti-lung cancer effects through a multi-component and multi-target paradigm: its core components (flavonoids, alkaloids, polysaccharides) synergistically induce apoptosis/autophagy, inhibit angiogenesis and EMT, and regulate immune microenvironment, embodying the scientific connotation of TCM's "heat-clearing and toxin-resolving" theory. Preliminary clinical

observations support its potential in reducing pulmonary nodules and improving survival with low toxicity, but critical gaps remain.

Key limitations include insufficient pharmacokinetic data (e.g., in vivo metabolism of active components), unclear herb-herb interaction mechanisms, and lack of large-scale RCTs. Standardization is hindered by variable component contents and undefined quality criteria.

Future priorities should focus on: 1) Elucidating chemical and biological basis of synergy via UPLC-MS and co-culture models; 2) Conducting multi-center RCTs to validate efficacy in post-operative lung cancer patients; 3) Developing tumor-targeted nano-formulations to enhance bioavailability. These steps will bridge preclinical research with clinical application of the SL herb pair.

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