

Functional Mechanisms and Clinical Translation of Resveratrol for Lung Cancer Intervention

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Abstract. Lung cancer patients commonly suffer from tumor immune escape and acquired chemotherapy resistance, and conventional comprehensive treatment schemes still have prominent clinical limitations. Resveratrol, a low-toxicity natural polyphenol, has become a key research focus for adjuvant lung cancer therapy. This paper systematically reviews the anti-lung-cancer mechanisms of resveratrol, relevant epidemiological evidence, and bottlenecks hindering its clinical translation. Resveratrol remodels macrophages to secrete interleukin-18 (IL-18) and subsequently activate CD8⁺T cells; it blocks the STAT3/HIF-1 α /VEGF signalling cascade to suppress tumour angiogenesis and hinders the TLR4/NLRP3 inflammatory axis to mitigate immunosuppressive tumour microenvironments. Moreover, resveratrol upregulates microRNA-506 to repress sphingosine kinase 1 (SPHK1), arresting tumour cell cycle progression and triggering apoptosis, and it reverses chemotherapy resistance in lung cancer through multiple synergistic pathways. Population-based studies have confirmed that dietary resveratrol intake correlates with a reduced risk of lung cancer onset. Nevertheless, several obstacles remain, including low bioavailability of resveratrol, a scarcity of lung cancer-specific clinical trials, and ongoing debates over standardized dosing regimens. This paper integrates current research findings to provide theoretical support for the development of optimized nanoformulations and combinatorial adjuvant therapeutic strategies for lung cancer.

Keywords: Resveratrol, lung cancer, immunity, anti-inflammation, cell apoptosis

1. Introduction

Lung cancer ranks first in global morbidity and mortality among all malignant tumors, and it is clinically divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Most patients are diagnosed at intermediate or advanced disease stages, and conventional radiotherapy, chemotherapy, and immunotherapy are plagued by emerging drug resistance, severe toxic side effects, and high long-term recurrence rates. This creates an urgent demand for low-toxicity natural bioactive compounds that can serve as synergistic adjuvants for lung cancer treatment [1].

Resveratrol, a polyphenolic compound widely distributed in fruits, vegetables and medicinal herbs, exhibits broad-spectrum anti-tumour activities including anti-inflammatory effects, immunomodulation, inhibition of tumour cell proliferation, and suppression of angiogenesis,

coupled with favourable in vivo safety profiles. It has therefore garnered extensive research interest in the field of lung cancer prevention and intervention [2].

Existing mechanistic studies have validated that resveratrol directly induces lung cancer cell senescence, modulates sphingolipid metabolism, and triggers tumour cell apoptosis to restrain malignant proliferation. A growing body of evidence further indicates that resveratrol indirectly exerts stable anti-tumour effects in vitro and in vivo by targeting immune cells, stromal cells and cancer stem-like cells within the tumour microenvironment, regulating core inflammatory signalling pathways, remodelling the tumour microenvironment and alleviating chronic inflammation, while concurrently counteracting therapeutic resistance.

However, its clinical application is restricted by poor bioavailability and insufficient large-scale clinical trials. Optimized delivery formulations and combinatorial medication regimens are required to advance resveratrol as a chemotherapy-sensitizing adjuvant into routine clinical practice. Prior publications predominantly report isolated single signalling pathways, and comprehensive, coherent reviews systematically summarizing resveratrol's anti-lung-cancer effects remain scarce [3].

Against this backdrop, this paper systematically consolidates preclinical and population research data published in recent years. It elaborates on three core therapeutic effects of resveratrol—immunomodulation, anti-inflammation, and suppression of tumour proliferation—as well as its capacity to reverse chemotherapy resistance. We further summarize epidemiological data and clinical trial status, dissect translational barriers and academic controversies within the field, integrate its multi-target anti-tumour signalling networks, and identify future research directions covering nanoformulation optimization and clinical trial design [4]. This paper provides a holistic overview of existing research on resveratrol against lung cancer, offering theoretical foundations for developing novel nanocarrier delivery systems and combinatorial adjuvant therapeutic regimens for lung cancer.

2. Multi-target anti-lung cancer molecular mechanisms of resveratrol

2.1. Immune regulatory functions of resveratrol

2.1.1. Macrophage reprogramming to activate CD8⁺ T cell-mediated anti-tumor immunity

Tumor immune escape is a complex pathological process that leads to immunotherapy failure. CD8⁺ cytotoxic T lymphocytes act as core effector cells of anti-tumor immunity, whose quantity and functional activity directly determine the clinical response of immune treatment [5].

Existing experimental data prove that resveratrol's immune regulatory capacity serves as its primary anti-tumor effect, while direct cytotoxicity against tumor cells remains weak. To solve the defects of poor water solubility and low bioavailability of free resveratrol, researchers prepared a resveratrol- β -cyclodextrin inclusion complex (Rsv- β CD) for in vivo functional verification with subcutaneous lung adenocarcinoma xenograft mouse models. The core regulatory pathway is confirmed as Rsv- β CD reprogramming tumor-associated macrophages (TAMs) to secrete interleukin-18 and further activate intratumoral CD8⁺ T cells to suppress tumor growth [6].

Tumour-associated macrophages predominantly polarize into immunosuppressive M2 phenotypes, which act as key mediators of immune evasion in lung adenocarcinoma. Rsv- β CD significantly reverses TAM polarization: in vivo assays revealed a marked reduction in total intratumoral TAMs, alongside depleted M2-type TAMs and suppressed transcription of the M2 biomarker CD206 (MRC1), while the population of anti-tumour M1-type TAMs remained largely unchanged. In vitro experiments confirmed dose-dependent activation of M1 macrophages

following Rsv- β CD treatment, accompanied by upregulated gene expression and protein secretion of pro-inflammatory factors TNF- α and IL-6. Though supernatant IL-10 protein levels slightly increased, its transcriptional expression showed no significant alteration, which attenuates the immunosuppressive capacity of M2 macrophages and prevents sustained tumour immune suppression.

Macrophages remodelled toward the M1 phenotype secrete abundant IL-18—the central mediator linking macrophage activity to CD8⁺ T cell anti-tumour function—whereas secretion of other canonical immune-activating cytokines did not rise significantly. Peritumoral injection of Rsv- β CD *in vivo* resulted in markedly reduced tumour volume and weight, elevated tumour cell apoptosis, and prolonged overall survival in model mice. Flow cytometric immune profiling detected drastically enhanced activation of intratumoral IFN- γ ⁺ CD8⁺ T cells, despite an overall reduction in total CD8⁺ T cell proportion, confirming an antigen-independent bystander activation pathway.

Co-cultivation of macrophages and tumour-infiltrating CD8⁺ T cells demonstrated that M1 macrophages treated with Rsv- β CD possess far stronger capacity to activate CD8⁺ T cells than M2 macrophages. Neutralization assays using IL-18 blocking antibodies abrogated CD8⁺ T cell activation, definitively verifying that macrophage-derived IL-18 is an indispensable cytokine required for resveratrol-mediated CD8⁺ T cell stimulation. In summary, Rsv- β CD reprograms TAMs to boost IL-18 secretion, which triggers antigen-independent bystander activation of CD8⁺ T cells to eliminate tumour cells.

2.1.2. Inhibition of hypoxia-driven pathological angiogenesis

Continuous neovascularization supplies nutrients and metabolic substrates to sustain solid tumour proliferation. Rapid expansion of solid tumours generates a hypoxic tumour microenvironment, which aberrantly activates the STAT3/HIF-1 α /VEGF (vascular endothelial growth factor) signalling cascade. STAT3 functions as a core oncogenic transcription factor driving NSCLC progression; upon activation, it upregulates downstream hypoxia-inducible factor 1 α (HIF-1 α). Within hypoxic tumour tissue, HIF-1 α initiates transcription of VEGF, triggering abnormal endothelial proliferation, increased vascular permeability, and *de novo* angiogenesis. Blocking vascular formation substantially restrains proliferation of both primary and metastatic tumour lesions.

Researchers constructed orthotopic NSCLC rat models via A549 cell implantation, and set a blank control group, untreated model group and resveratrol intervention group. The intervention group exhibited significantly lowered lung weight index and tumour burden, alleviated pathological lung injury detected via haematoxylin-eosin (HE) staining, and elevated tumour cell apoptosis measured by TUNEL assays. Molecular analysis showed markedly elevated mRNA and protein expression of STAT3, HIF-1 α and VEGF in lung tissue from the untreated NSCLC model relative to blank controls; resveratrol treatment concurrently downregulated all three molecules ($P < 0.05$). This study was the first to validate this regulatory pathway in an orthotopic rat NSCLC model, identifying the STAT3/HIF-1 α /VEGF axis as a potential therapeutic target for resveratrol against non-small cell lung cancer [7].

Collectively, resveratrol suppresses NSCLC through the following molecular cascade: it inhibits upstream STAT3 expression, which sequentially represses downstream HIF-1 α and VEGF, hindering tumour angiogenesis, arresting lesion progression, remodelling the hypoxic tumour microenvironment, and ultimately eliciting anti-tumour effects.

2.2. Anti-inflammatory effects mediated by TLR4/NLRP3 inflammasome axis

Chronic inflammation is recognized as the seventh hallmark of cancer and a primary driver of lung cancer initiation and progression. Inflammatory signalling facilitates tumour cell proliferation and differentiation, activates oncogenic pathways, induces oxidative stress, and establishes an immunosuppressive microenvironment that promotes tumour survival.

As a natural anti-inflammatory agent, resveratrol exerts anti-tumour effects and enhances anti-cancer therapeutic efficacy. Free resveratrol suffers from poor water solubility, weak chemical stability, rapid *in vivo* metabolism, and minimal tumour accumulation, limiting its anti-proliferative potency. In this research, resveratrol liposomes (Rsv-Lip) were fabricated via thin-film hydration as a nano-delivery platform. Leveraging the enhanced permeability and retention (EPR) effect unique to solid tumours, these liposomes selectively accumulate in lung neoplasms and improve intracellular drug uptake by tumour cells. They exert anti-lung-cancer activity *in vivo* through three synergistic mechanisms: inflammatory pathway blockade, tumour immune microenvironment remodelling, and induction of tumour cell apoptosis.

Rsv-Lip dual-blocks upstream TLR4/MyD88 inflammatory signal transduction. TLR4 ligands enriched within the lung tumour microenvironment continuously activate TLR4 receptors to initiate downstream inflammatory cascades. Rsv-Lip suppresses TLR4 and MyD88 expression at both mRNA transcriptional and protein translational levels, impedes signal transmission through intermediate mediators including IRAK4, TRAF6 and TAB1/2, and inhibits TAK1 phosphorylation, terminating inflammatory signalling at its source. Disruption of upstream signalling prevents NLRP3 inflammasome assembly and activation, reducing transcription and protein expression of NLRP3, ASC, Caspase-1 and the pyroptosis effector GSDMD. This inhibits maturation of functional inflammasome complexes and cellular pyroptosis, limiting release of mature pro-inflammatory cytokines IL-1 β and IL-18 in both local tumour tissue and peripheral circulation, breaking the vicious cycle whereby chronic inflammation fuels malignant tumour advancement.

The release of mature IL-1 β and IL-18 recruits massive myeloid-derived suppressor cells (MDSCs) into tumor tissue to form immune suppressive barriers. By inhibiting core inflammatory factors, Rsv-Lip reduces intratumoral MDSC infiltration, relieves immune tolerance and elevates the infiltration quantity of CD4⁺ and CD8⁺ T cells. It upregulates the expression of T cell effector molecules IFN- γ , granzyme A and granzyme B to recover specific anti-tumor adaptive immunity.

In vivo validation using an orthotopic LLC lung cancer mouse model confirmed that Rsv-Lip inhibits tumour growth, extends median survival of tumour-bearing mice, and displays no overt systemic toxicity. In conclusion, resveratrol liposomes target and block the TLR4/NLRP3 inflammasome pathway to slow lung cancer progression and potentiate anti-tumour immune responses, representing a promising novel therapeutic strategy for lung cancer [8].

2.3. Suppressive effect on lung cancer cell proliferation via miR-506/SPHK1 axis

As a low-toxicity natural polyphenol, resveratrol demonstrates unambiguous anti-proliferative activity in *in vitro* NSCLC models. Modulation of microRNA-associated molecular pathways constitutes a key research frontier in this field. *In vitro* experiments were performed using human lung adenocarcinoma A549 cells to fully characterize the molecular regulatory mechanisms of resveratrol against lung cancer cells.

Experimental results revealed that resveratrol suppresses A549 cell proliferation in a dose- and time-dependent manner, arresting the majority of cells at the G0-G1 resting phase while reducing the proportion of cells undergoing DNA replication in the S phase. It also robustly induces tumour cell

apoptosis, with maximal anti-proliferative and pro-apoptotic effects observed following 48-hour incubation with 100 $\mu\text{mol/L}$ resveratrol.

MicroRNA-506 (miR-506) acts as a tumour-suppressive microRNA markedly downregulated in lung cancer cells. Sphingosine kinase 1 (SPHK1), a lipid kinase with oncogenic properties, accelerates tumour cell proliferation and inhibits apoptosis; prior research has confirmed that SPHK1 is a direct target of miR-506. Quantitative real-time PCR analysis demonstrated that resveratrol treatment upregulates intracellular miR-506 expression. Transfection of miR-506 inhibitor fragments to deplete endogenous miR-506 simultaneously elevated SPHK1 transcription and protein synthesis, exacerbating malignant proliferative phenotypes. Co-administration of resveratrol alongside miR-506 inhibitor transfection restored miR-506 levels and downregulated SPHK1 mRNA and protein, fully validating the upstream-downstream regulatory relationship between the two molecules.

Resveratrol functions as an upstream regulator to upregulate cellular miR-506 and directly repress SPHK1 transcription and translation. This abrogates SPHK1-mediated pro-proliferative and anti-apoptotic signalling: on one hand, it halts tumour cell DNA replication, arresting cell cycle progression at G0-G1 to restrain continuous proliferation; on the other hand, it removes SPHK1-mediated blockade of apoptotic signalling to trigger lung cancer cell death [9]. Previous studies have established that SPHK1 drives lung cancer progression and chemotherapy resistance via lipid second messengers and the Akt/NF- κB axis. This research identifies a novel molecular pathway through which natural resveratrol targets lung cancer cells, providing in vitro experimental evidence for low-toxicity adjuvant NSCLC therapy and microRNA-targeted drug development.

2.4. Multi-path mechanisms of resveratrol reversing lung cancer chemotherapy resistance

Acquired chemotherapy resistance is the primary cause of treatment failure for intermediate and advanced lung cancer patients. Chronic inflammation, hypoxic angiogenesis and abnormal activation of oncogenic signals jointly mediate the formation of drug insensitivity. Resveratrol can reverse chemotherapy resistance through multiple synergistic signal pathways.

A chronic inflammatory microenvironment is a key inducement of drug tolerance: resveratrol blocks the TLR4/NLRP3 inflammasome cascade to recover CD4⁺ and CD8⁺ T cell functions and eliminate inflammation-mediated drug insensitivity. In doxorubicin-resistant small cell lung cancer H69AR cells, sustained activation of the STAT3/VEGF axis within inflammatory microenvironments promotes drug efflux and suppresses apoptosis. Resveratrol downregulates this signalling pathway, reduces chemotherapeutic efflux, and restores doxorubicin sensitivity in tumour cells. Hypoxic conditions within solid tumours activate the STAT3/HIF-1 α /VEGF cascade to drive aberrant angiogenesis and induce NSCLC drug resistance; resveratrol inhibits angiogenesis and promotes apoptosis of resistant tumour cells [10]. Additionally, the miR-506/SPHK1 axis participates in resistance regulation: resveratrol upregulates miR-506 and represses SPHK1 transcription and translation to arrest cell cycling, induce apoptosis, and mitigate chemotherapy refractoriness.

3. Epidemiological evidence and clinical research progress

3.1. Population-based prospective cohort epidemiological evidence

Two large-scale 13-year follow-up prospective cohort studies recruited participants from the United Kingdom and Japan, recording confirmed lung cancer cases throughout the observation period [11].

After adjusting for confounding variables including age, smoking history, underlying pulmonary disease, and dietary habits, statistical analysis indicated that individuals with sustained high dietary resveratrol intake exhibited a reduced risk of developing lung cancer, validating the preventive potential of natural dietary resveratrol against lung cancer.

Nevertheless, cohort studies possess notable limitations: dietary questionnaires alone were used to estimate resveratrol intake without direct measurement of *in vivo* blood concentrations; cohorts including red wine consumers were confounded by alcohol exposure, making it difficult to isolate the independent protective effects of resveratrol; stratified subgroup analysis targeting high-risk lung cancer populations remains insufficient.

3.2. Clinical trial research status

Literature retrieval results display that most existing resveratrol clinical trials belong to Phase I pharmacokinetic and oral tolerance research, while large-sample multi-center Phase II and III efficacy verification trials are scarce. Completed trials mainly enroll patients with colorectal cancer, liver cancer and multiple myeloma; intervention trials specially targeting NSCLC and SCLC are extremely limited.

Current clinical research has multiple defects: most trials adopt free resveratrol without solubility-improved nano preparations; patient grouping lacks stratification based on gene mutation status and treatment history; most research takes inflammatory cytokines as surrogate endpoints without hard indexes such as overall survival; long-term safety follow-up data are insufficient to support routine clinical application of resveratrol monotherapy [12].

3.3. In vivo safety and risks of combined medication

The safe therapeutic window of resveratrol varies greatly depending on its dosage. When taken at physiological levels via regular food intake, this compound shows good tolerance in human bodies and does not bring notable toxic damage to internal organs. If people keep taking doses close to the maximum tolerable threshold over a sustained period, the gastrointestinal lining will become irritated, which further leads to stomach and bowel upset alongside slight rises in transaminase levels. Extremely high oral dosages place heavy metabolic stress on both the liver and kidneys. Such intake suppresses the activity of liver CYP450 enzymes, turns on the NLRP3 inflammatory signalling cascade to spark oxidative damage in hepatic and renal tissues, and breaks down the protective barrier of the stomach lining, ultimately bringing on symptoms like nausea and diarrhoea.

Resveratrol can slow platelet clumping to a mild degree. When used together with anticoagulant drugs including warfarin, it will compete with these medicines for liver metabolic routes, lengthen blood clotting time and sharply raise the chance of bleeding events. Extra care should also be taken for patients suffering from hormone-sensitive tumours. Before formulating combined clinical treatment plans, clinicians need to fully assess each patient's liver and kidney performance as well as all other medicines they are taking at the same time. Individuals undergoing concurrent anticoagulant therapy need routine blood coagulation checks, while tight upper limits on resveratrol dosage should always be maintained to prevent safety risks stemming from long-term high-dose supplementation.

4. Existing research limitations and academic controversies

4.1. Core clinical transformation barriers

First, resveratrol has inherent physical and chemical defects including extremely low water solubility and obvious gastrointestinal first-pass effect after oral administration. Conventional oral preparations cannot reach effective therapeutic concentration inside pulmonary tumor lesions. Second, clinical trial construction is imperfect. Most existing research only stays at Phase I pharmacokinetic detection; large-sample efficacy trials specific to lung cancer are absent, and a unified effective human dosage cannot be defined. Third, the therapeutic safety window is narrow. Ultra-high dosage causes liver and kidney toxicity; combined use with anticoagulants raises bleeding risks, while unified clinical dosage and combined medication guidelines have not been established.

4.2. Prevailing academic disputes in the field

Three core controversial viewpoints exist within current academic research. The first viewpoint concerns dose-dependent dual biological properties of resveratrol. Low-concentration resveratrol delivers antioxidant and tumor inhibitory protective effects, while excessive drug concentration applied in cell experiments may trigger oxidative injury to normal epithelial tissues. Academic circles have not formed unified standards for safe and effective clinical administration dosages suitable for human bodies. The second debate focuses on inconsistent efficacy performance under *in vitro* and *in vivo* experimental conditions. Resveratrol shows prominent proliferation-inhibiting capacity in single-cell culture systems, yet oral administration cannot generate enough effective drug concentration inside human circulation, which makes scholars hold different opinions about the clinical application potential of resveratrol used alone. The third disputed issue covers matching schemes of combined treatment. Relevant research has not reached consistent conclusions about suitable matching drugs, administration dosage ratios and medication sequences when resveratrol is combined with chemotherapy, targeted treatment and immune intervention approaches.

5. Conclusion

Resveratrol delivers prominent anti-tumour effects against lung cancer through multiple distinct biological routes: tuning host anti-tumour immunity, dampening pro-inflammatory signalling cascades, restraining the excessive reproduction of malignant cells, and overcoming the drug-resistant traits frequently observed during lung cancer chemotherapy. When formulated together with β -cyclodextrin, resveratrol can remodel tumour-associated macrophages and prompt these cells to release IL-18; this cytokine further triggers indirect activation of CD8⁺ cytotoxic T lymphocytes inside lung adenocarcinoma lesions. The compound can also disrupt the STAT3/HIF-1 α /VEGF signalling axis, which curbs aberrant angiogenesis induced by hypoxic tumour microenvironments and slows the advancement of cancerous lesions.

When encapsulated into liposomal carriers, resveratrol can specifically act on the TLR4/NLRP3 inflammasome complex. This intervention lowers the recruitment of myeloid-derived suppressor cells (MDSCs) and relieves the immune-suppressive state inside tumour tissue. Aside from the above signalling axes, resveratrol elevates the expression level of miR-506 to repress SPHK1 activity. This molecular shift locks lung cancer cells in the G0-G1 cell cycle stage and eventually triggers tumour cell apoptosis. The combined functions of anti-inflammation, hypoxia inhibition and

microRNA regulation enable resveratrol to counteract broad-spectrum chemoresistance in lung cancer patients. Existing population cohort investigations indicate that regular dietary uptake of resveratrol correlates with a lower probability of developing lung cancer, but solid clinical proof to endorse its routine use as a therapeutic agent is still insufficient at present.

Current research on resveratrol's anti-lung cancer capacity mostly focuses on isolated signalling pathways with scattered findings. This review assembles these scattered results to build a complete theoretical system that systematically explains how resveratrol fights lung cancer, which offers solid theoretical foundations for developing better nanoscale delivery carriers and designing combined auxiliary treatment schemes for lung cancer. Even so, several critical obstacles restrict its clinical transformation. First, unfavourable natural physical and chemical properties severely cut down resveratrol's bioavailability after entering living organisms. Second, there are no large-scale, multi-centre clinical trials specially carried out for lung cancer treatment, and unified medication dosage standards have not been formed. Third, researchers still hold conflicting views on its dual concentration-dependent effects, as well as the inconsistent therapeutic outcomes between cell culture experiments and animal in vivo tests. Fourth, co-administration of resveratrol and anticoagulants may bring potential safety hazards, which demands strict monitoring throughout clinical treatment.

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