

Exosome-Based Delivery and Functional Regulation of Bioactive Components from Traditional Chinese Medicine for Lung Cancer Treatment

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Abstract: Lung cancer remains one of the leading causes of cancer-related mortality worldwide. Despite continuous advances in antitumor therapy, challenges such as drug resistance, toxic side effects, and insufficient tumor-targeted accumulation of drugs still persist. Exosomes (EXOs), as natural nanovesicles with a diameter of 30–150 nm, serve not only as key mediators of intercellular communication but also as ideal drug delivery vehicles, playing critical roles in tumor proliferation, epithelial–mesenchymal transition (EMT), drug resistance, and remodeling of the immune microenvironment. In recent years, nanotechnology engineering strategies—including surface modification of exosomes, construction of hybrid exosomes, and engineering modifications—have significantly enhanced the utilization of bioactive components from traditional Chinese medicine (TCM). This article systematically reviews two core pathways through which TCM intervenes in lung cancer via exosomes: functional regulation and nano-delivery. It also incorporates the direct antitumor effects of plant-derived exosome-like vesicles (PELVs), thereby establishing a bidirectional interaction framework between exosomes and TCM. This framework provides new directions for the development of TCM-based nanomedicines for lung cancer and their clinical translation.

Keywords: Lung cancer, Exosomes, Bioactive components of traditional Chinese medicine, Nano-delivery, Tumor microenvironment.

1. Introduction

Lung cancer ranks first among all malignant tumors worldwide in both incidence and mortality. According to statistics from the International Agency for Research on Cancer (IARC) of the World Health Organization, in 2022 there were approximately 2.48 million new cases globally (accounting for 12.4%) and approximately 1.81 million deaths (accounting for 18.7%), with East Asia being a high-incidence region, accounting for 55% of new cases worldwide [1]. In 2022, China reported over 1.06 million new cases and over 733,000 deaths [2], accounting for 22.0% and 28.5% of global incidence and mortality, respectively, both ranking first and showing an upward trend [3]. Among these, non-small cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases.

Traditional Chinese medicine (TCM) approaches the prevention and treatment of lung cancer with the general principle of “strengthening the body’s resistance and eliminating pathogenic factors” (Fuzheng Quxie), emphasizing holistic treatment based on syndrome differentiation. Although ancient literature does not record a specific disease name for “lung cancer,” based on its clinical manifestations of cough, sputum production, hemoptysis, chest pain, and weight loss, it can be classified under categories such as “cough” (Kesou), “hemoptysis” (Kexue), “chest pain” (Xiongtong), “Xiben” (dyspnea with a mass), and “Feiji” (lung accumulation). The symptoms described in the Nanjing (Classic of Difficult Issues), Chapter 56 — “The accumulation of the lung is called Xiben, located below the right hypochondrium, covering an area as large as a cup; if it persists for a long time, it causes alternating chills and fever,

wheezing and coughing, and lung congestion” — are highly consistent with those of lung cancer. The Suwen (Basic Questions), Chapter on Extraordinary Diseases, states: “The disease presents with fullness below the hypochondrium and reversed flow of qi, persisting for two to three years without resolution... the disease is named Xiji (breath accumulation),” which describes its protracted and refractory nature. The Jisheng Fang (Prescriptions for Saving Lives) also describes Xiben: “The appearance of Xiben is located below the right hypochondrium, covering an area as large as a cup, with rapid and rushing breathing.” The Waike Zhengzong (Orthodox Manual of External Medicine) further elaborates on “Feiyan” (lung rock) and “Tanhe” (phlegm node), and subsequent physicians have continuously enriched and refined the TCM theoretical system of syndrome differentiation and treatment for lung cancer.

Active ingredients of traditional Chinese medicine (TCM) possess advantages such as multi-target anti-tumor effects [4–5], and regulation of the tumor microenvironment [6]. However, limitations including poor water solubility, low bioavailability, short half-life, and lack of tumor targeting restrict their in vivo efficacy [7]. On the one hand, active ingredients of TCM can directly intervene in the secretion, release, and cargo loading of exosomes (EXOs) from lung cancer cells, and downregulate the expression of pro-tumor miRNAs and immune checkpoint molecules (such as PD-L1) in exosomes. On the other hand, they can serve as natural nanocarriers to load active ingredients of TCM, encapsulating active molecules such as quercetin and triptolide inside EXOs, thereby overcoming shortcomings including poor water solubility, rapid in vivo metabolism, and insufficient targeting of monomeric compounds. This ultimately inhibits tumor proliferation and metastasis, reverses targeted therapy and

chemotherapy resistance, and reprograms tumor-associated macrophage polarization, achieving an intervention effect on lung cancer.

2. Concept of EXOs

EXOs are a class of nanoscale small extracellular vesicles actively secreted by biological cells, and are therefore also known as small extracellular vesicles (sEVs) [8-9]. They possess an intact phospholipid bilayer membrane structure, are mostly spherical or approximately spherical in morphology, and are structurally stable and uniform in texture [10]. They contain bioactive molecules such as DNA, RNA, and proteins [11]. The secretion of EXOs is ubiquitous; the vast majority of living cells in the human body (such as stem cells, immune cells, epithelial cells, endothelial cells, tumor cells, fibroblasts, etc.) are capable of secreting them [12]. They are distributed throughout almost all body fluids and tissue microenvironments, including blood, cerebrospinal fluid, urine, milk, and interstitial fluid, serving as a core mediator of intercellular information exchange and molecular transport [13]. EXOs possess good biocompatibility, low immunogenicity, and the ability to cross biological barriers [14-15]. They can effectively load TCM monomers and TCM compound formulas (such as Huoluo Xiaoling Dan [16], Shugan Yishen Fang [17], Zuojin Wan, etc. [18]), and achieve enrichment through homologous targeting (i.e., homing) [19]. They demonstrate multiple synergistic therapeutic potentials in reversing tumor drug resistance and regulating the tumor microenvironment, making them ideal natural nanodelivery carriers.

3. EXOs Delivery of Active Ingredients of Traditional Chinese Medicine for the Treatment of Lung Cancer

3.1 Sources of EXOs for Traditional Chinese Medicine Delivery

3.1.1 PELVs

PELVs are rich in maternal plant-derived miRNAs, metabolites, and other active components, and possess natural targeting ability and low immunogenicity, enabling the synergistic delivery of multiple active ingredients [20-21], PELVs related to lung cancer treatment are summarized in Table 1.

3.1.2 Animal-Derived Sources

Animal-derived exosomes have a wide range of sources, and different cells can be selected as carriers according to different requirements. Tumor-derived exosomes (TEX) possess natural homologous targeting ability and can specifically home to primary tumor tissues [22]. Mesenchymal stem cell (MSC)-derived exosomes are abundant in yield and inherently possess tumor tropism, but their targeting ability depends on induction under specific conditions. For example, paclitaxel intervention can upregulate SDF-1 expression by 2.2–5.4 fold, significantly enhancing tumor-directed enrichment efficiency and achieving higher yield [23]. Macrophage-derived EXOs can also serve as carriers for loading TCM monomers such as osthole [24].

3.1.3 Milk-Derived Sources

Milk-derived EXOs are natural nanocarriers with high yield (over 10^{14} nanovesicles can be extracted per liter of milk [25].) and inherently carry various bioactive molecules such as miRNAs (e. g., miR-181a, miR-30a-5p), proteins (e. g., lactoferrin), and lipids [26 -28]. By regulating pathways including NF- κ B, MAPK, STAT3, and PI3K/AKT, they exert anti-inflammatory, anti-tumor, and immunomodulatory functions [29]. They can not only improve chemotherapeutic drug delivery but also achieve targeted sensitization.

Table 1: Studies on PELVs related to lung cancer therapy

PELVs Source	Research Model/Type	Mechanism	Reference
Houttuynia cordata	A549, H1975, H520 cells; tumor-bearing mice	Houttuynia cordata-derived EXOs (aHELNs) carry miRNAs and metabolites that directly induce lung cancer cell apoptosis, regulate gut microbiota via the gut-tumor axis, reprogram tumor-associated macrophages, mediate anti-tumor immune remodeling, and inhibit tumors.	[30]
Curcuma	A549 cells; tumor-bearing mice	Curcuma-derived EXOs (TEVs) integrated with the metal-organic framework ZIF-8 to construct the ZeiT nanoformulation, which induces ICD, blocks the Wnt/ β -catenin pathway, and inhibits PD-L1, synergistically remodeling the lung cancer immune microenvironment and inhibiting lung metastasis through a triple mechanism.	[31]
Catharanthus roseus	RAW 264.7 macrophages and primary splenic lymphocytes; cyclophosphamide-induced immunosuppressed mouse model	Catharanthus roseus leaf-derived EXOs (CLDENs) stimulate TNF- α secretion, activate the NF- κ B signaling pathway, and upregulate the transcription factor PU.1, exerting immune effects. Although not yet validated in lung cancer, their post-chemotherapy immune adjuvant function and ability to alleviate myelosuppression suggest potential as an adjuvant therapeutic strategy after lung cancer chemotherapy.	[32]
Ginger	A549, PC-9 cells	Ginger-derived EXO nanoparticles (GELNs), through components such as 10-gingerol, regulate GSK3B/PGR/SRC targets and inhibit the proliferation of A549 and PC-9 cells.	[33]
Ginseng	A549, H1299 cells; LLC tumor-bearing mice	Ginseng-derived EXOs (G-Exos) downregulate PD-L1 expression in cancer cells, thereby restoring T cell activity and alleviating immune evasion.	[34]
Celery	LLC tumor-bearing mice	Celery-derived EXOs (CDEVs) downregulate the p-STAT3/PD-L1 axis, inhibit lung cancer cells, and restore T cell killing function, while also serving as targeted transporters for chemotherapeutic drugs, achieving synergistic immuno-chemotherapy.	[35]
Dandelion	LLC tumor-bearing mice	Dandelion-derived EXOs (TM-EVLPs) inhibit NSCLC by inducing mitochondrial dysfunction (decreased membrane potential, increased ROS, reduced ATP).	[36]
Pinellia ternata	Lung adenocarcinoma model	Pinellia ternata-derived EXOs (PEVs) inhibit key serine synthesis enzymes (PHGDH/PSAT1/PSPH), activate the JAK-STAT pathway, induce M1-type anti-tumor polarization of tumor-associated macrophages (TAMs), and directly induce S-phase arrest in lung cancer cells.	[37]
Bamboo shoot	A549 cells	Bamboo shoot-derived EXOs (BSNs) are selectively taken up by A549 cells and	[38]

Garlic	A549, HDF, A498 cells	regulate the Akt/p53 pathway to induce apoptosis, with minimal effects on normal cells. Garlic-derived EXOs (SEVs) inhibit A549 cell proliferation and activate the caspase pathway to induce apoptosis, with minimal effects on normal cells.	[39-40]
Artemisia annua	RAW264.7 macrophages; LLC, C57BL/6 tumor-bearing mice	Artemisia annua-derived EXOs (ADNVs), through their carried plant mitochondrial DNA (mtDNA), activate the cGAS-STING pathway in TAMs, induce M1-type anti-tumor polarization of TAMs, reprogram the immune microenvironment, and inhibit lung cancer progression.	[41]
Ganoderma lucidum	A549 cells	Ganoderma lucidum-derived EXOs (GLEVs) are taken up by A549 cells and inhibit lung cancer proliferation, invasion, and migration.	[42]
Lemon	A549 cells; chronic myeloid leukemia (CML) xenograft tumor model	Lemon-derived EXOs activate the TRAIL apoptosis signaling pathway, inhibit A549 cell proliferation, and suppress the growth of CML xenograft tumors.	[43-44]
Astragalus-Curcuma	A549, C57BL/6, LLC tumor-bearing mice	Astragalus-Curcuma co-decoction-derived EXOs (AC-NPs) combined with 5-fluorouracil (5-FU) improve oral bioavailability, enhance synergistic therapeutic efficacy against lung cancer, and reduce toxicity.	[45]
Selaginella moellendorffii	Lung cancer	Self-derived PELVs upregulate FABP4/PPARG, inhibit the GPX4/xCT axis to induce ferroptosis, and suppress lung cancer growth and metastasis.	[46]

Notes:

1. LLC: Lewis lung carcinoma, a lung tumor cell line derived from C57BL/6 mice.
2. A549, PC-9, H1299, C57BL/6: human non-small cell lung cancer cell lines.
2. HDF: human dermal fibroblasts.
3. A498 cells: derived from human renal clear cell carcinoma cells.

Table 2: Half-life of curcumin

Experimental Subject	Formulation	Elimination Half-life (t _{1/2})	Reference
Rat	Free curcumin / Curcumin solid lipid nanoparticles	4.71 ± 1.18 h / 17.16 ± 1.61 h	[61]
Rat	Curcumin raw material / Curcumin PVP-EPO solid dispersion	11.6 ± 0.9 h / 9.5 ± 2.7 h	[62]
Human	Free curcumin (400 mg dose) / Free curcumin (2,000 mg dose) / Curcumin formulation (BNT-C060)	6.74 h / 21.70 h / 22.28–24.92 h	[63]

3.2 EXOs**3.2.1 Flavonoids****1) Curcumin (Cur)**

Cur is a diketone polyphenolic compound extracted from the rhizome of turmeric, with well-established anti-inflammatory, antioxidant, and anti-tumor activities. It induces tumor cell apoptosis by inhibiting pathways such as NF-κB, STAT3, and Wnt/β-catenin, and suppresses lung cancer metastasis and chemotherapy resistance [47-49]. However, its poor water solubility [50-51], short in vivo half-life, significant first-pass metabolism (see Table 2), and low bioavailability [52-53] restrict its application. The lipid bilayer of EXOs can effectively encapsulate and solubilize Cur, reduce drug degradation in vivo, and extend in vivo circulation through passive targeting and surface modification-mediated active targeting, thereby increasing tumor accumulation [54-57]. Camel milk-derived EXOs loaded with Cur (ExoCUR) show significantly enhanced efficacy against both sensitive and drug-resistant lung cancer cells, mechanistically associated with inhibition of EGFR/STAT3 [58]. Turmeric-derived EXOs (TELNs) exert anti-NSCLC effects by activating the hMOF-H4K16ac pathway [59]. Milk-derived EXOs loaded with Cur have also been confirmed to possess anti-proliferative capacity against various cancer cell lines including lung cancer [60]. In addition, PELVs themselves are rich in active components such as Cur, possessing dual functions as both carrier and drug.

2) Quercetin (Que)

Que is an active substance found in medicinal materials such as Sophora japonica flowers and Ginkgo biloba leaves, possessing functions including antioxidant [64], anti-inflammatory [65-66], induction of tumor cell apoptosis [67-72], and inhibition of tumor cell EMT [73-74]. Que inhibits lung cancer proliferation and metastasis by regulating

pathways such as Ras/ERBB/MAPK and PI3K/AKT [75-77]. Similarly, the poor water solubility of Que (approximately 7 μg/mL) [78] and its low oral absorption limit its in vivo efficacy [79]. Nanoengineering approaches such as microalgae-derived EXOs and Que-loaded liposomal nanocarriers have been demonstrated to effectively inhibit EMT, cell migration, and TGF-β1 release, and reduce reactive oxygen species levels in a bleomycin-induced A549 model [80], providing a feasible strategy for enhancing the bioavailability and anti-tumor effects of Que.

3.2.2 Terpenoids

Terpenoids are hydrocarbons and their oxygen-containing derivatives derived from the mevalonic acid (MVA) pathway [81], with molecular formulas that are multiples of isoprene units. According to the number of isoprene units, they can be classified into monoterpenes, sesquiterpenes, diterpenes, triterpenes, etc [82]. And can exert pharmacological activities such as anti-tumor, antibacterial, and anti-inflammatory effects [83].

1) Paclitaxel (PTX)

PTX is a diterpenoid compound extracted from the bark of Taxus plants [84] and is a first-line drug for NSCLC with confirmed efficacy. However, its water solubility is extremely poor, and the clinically used Cremophor EL-solubilized formulation can easily cause severe allergic reactions and peripheral neurotoxicity [85]. To improve these limitations, EXO engineering modification strategies hold high research value. At the drug delivery level, EXOs from different cell sources each have their own advantages: folate-modified bovine colostrum EXOs loaded with PTX achieve a high tumor inhibition rate (55%) in lung cancer while avoiding Cremophor EL-related toxicity [86]; EGFR-targeting peptide-modified EXOs and PEG-AA-modified EXOs loaded with PTX achieve targeted sensitization of EGFR-positive lung cancer and enhanced pulmonary accumulation,

respectively [87-88]; CAR-T cell-derived EXOs delivered by nebulized inhalation for PTX delivery demonstrate high efficacy and low toxicity [89]; after MSC treatment with PTX, the homing factor SDF-1 expression is upregulated and synergizes with 11 anti-tumor miRNAs to strengthen the cell-killing effect in a one-step manner [23]; A549 cell-derived EXOs loaded with PTX show superior tumor inhibition compared to commercial formulations [90]. In addition, TCM monomers such as α -hederin can reprogram miRNA loading in tumor cell sEVs, blocking the transmission of drug resistance and thereby restoring NSCLC sensitivity to PTX [91]; however, tumor cells can also transmit TPX2 via EXOs and activate the Wnt/ β -catenin pathway, inducing the dual risk of metastasis and drug resistance [92]. Therefore, the risk of EXO-mediated drug resistance transmission must be taken into account in EXO engineering modification.

2) Triptolide (TL)

TL is an epoxy diterpenoid lactone active ingredient extracted from the Celastraceae plant *Tripterygium wilfordii*, with well-established anti-tumor [93], apoptosis-inducing, heat shock response-regulating [94], and tumor angiogenesis-modulating [95]. However, its narrow therapeutic window and significant hepatorenal toxicity make widespread clinical application difficult [96]. In EXO delivery research, studies have confirmed [97] that hybrid EXOs co-loaded with TL and CYP3A4-siRNA exhibit significant anti-tumor effects in lung metastatic melanoma, although the model is not lung cancer. In ovarian cancer, SKOV3 cell-derived EXOs loaded with TL show superior anti-proliferative effects compared to free drug, indirectly suggesting anti-lung cancer potential [98]. Currently, research on EXO-mediated TL delivery mostly focuses on ovarian cancer and melanoma, while in lung cancer, liposomal delivery remains predominant. Therefore, EXO-mediated TL delivery for lung cancer still requires further exploration.

3) Artemisinin (ART) and Its Derivatives

ART is a sesquiterpene lactone ($C_{15}H_{22}O_5$) compound containing a peroxide group, extracted from *Artemisia annua* [99]. Structural derivatives such as dihydroartemisinin (DHA) and artesunate not only improve the deficiencies in solubility and bioavailability but also retain anti-tumor activity [100-101]. Studies have shown [102], that the combination of DHA and cisplatin can regulate iron homeostasis and enhance ferroptosis sensitivity in lung cancer, with superior effects in squamous cell carcinoma compared to adenocarcinoma, suggesting differences in ferroptosis sensitivity among different lung cancer subtypes. At the drug delivery level, bovine milk-derived EXOs loaded with DHA (Exo-DHA) inhibit the proliferation and migration of melanoma and triple-negative breast cancer cells, but direct evidence in lung cancer is insufficient [103-104]. In summary, ART and its derivatives possess direct killing effects in lung cancer treatment, but EXOs/PELVs represent a feasible strategy for achieving reduced toxicity and enhanced efficacy.

3.2.3 Alkaloids

Alkaloids, as important active anti-tumor ingredients of traditional Chinese medicine, are a class of nitrogen-containing basic organic compounds that can achieve targeted sensitization and synergistic therapy through EXO delivery. Camptothecin delivered by TEX targeting sensitizes radiotherapy by regulating the cell cycle [105]; engineered TEX co-loaded with perfluorocarbon, photosensitizer ICG, and camptothecin achieves efficient targeted therapy of melanoma through alleviating tumor hypoxia and synergizing phototherapy with chemotherapy [106].

3.2.4 Polysaccharides

Astragalus polysaccharides (APS) are the core component of *Astragalus membranaceus*, characterized by multi-target and multi-pathway anti-tumor effects. In immune regulation, APS can promote T cell proliferation and, through mitochondrial metabolic regulation, reduce the proportion of exhausted PD-1hiCD8⁺ T cells within tumors and enhance their IFN- γ secretion capacity, thereby strengthening anti-tumor immunity [107]. Meanwhile, by regulating the TLR4/NF- κ B/STAT3 pathway, APS reverses TAMs from the M2 phenotype to the anti-tumor M1 phenotype, thereby enhancing the chemotherapeutic effect of gemcitabine and overcoming its resistance [108]. In terms of anti-tumor activity, APS can inhibit tumor angiogenesis [109], regulate CEACAM7, and mediate the EMT pathway to inhibit lung cancer proliferation, invasion, and migration [110]. In addition, APS induces apoptosis in multiple lung cancer cell lines by promoting the expression of apoptotic proteins Bax/Caspase-3 and reducing the level of the anti-apoptotic protein Bcl-2, with more significant effects when combined with chemotherapeutic drugs such as cisplatin [111-114]. APS can also regulate the TLR4/NF- κ B pathway, altering the protein composition of lung cancer cell-derived EXOs to modulate the tumor immune microenvironment, suggesting a close interaction between APS and EXOs. Therefore, encapsulating APS in EXOs is expected to synergistically exert dual effects of immune activation and targeted anti-tumor activity.

3.2.5 Saponins

Saponins are glycoside compounds with complex structures, composed of a sapogenin (aglycone) combined with a sugar chain. According to the structure of the sapogenin, they can be classified into two major categories: triterpenoid saponins and steroidal saponins, and possess functions such as hemolysis, anti-inflammation, immune regulation, and anti-tumor activity [115]. EXO delivery strategies significantly enhance their efficacy: TMTP1 peptide-modified TEX delivering ginsenoside Rb1 (Rb1@T-exo) effectively overcomes immune resistance in PI3K-mutant NSCLC by inhibiting the PI3K/AKT/mTOR pathway and remodeling the immune microenvironment [116]. In addition, ginseng-derived EXOs (Gn-Exo) are rich in ginsenoside Rh2 (Gn-Rh2), which promotes ubiquitination and degradation of RRM2 by competitively binding to the deubiquitinase USP22 and blocking its interaction with the RRM2 protein, thereby inhibiting NSCLC proliferation, migration, and lung metastasis, and sensitizing cisplatin [117].

Table 3: Exosome-mediated delivery of other active monomers from traditional Chinese medicine

Natural Product	Classification	Source	EXOs Delivery System	Mechanism	Reference
Sipeimine	Alkaloids	Fritillaria cirrhosa	ELVs nanoplatform targeting integrin $\alpha 3 \beta 1$	Enhances anti-tumor activity and reduces toxicity	[118]
Hydroxycitric acid tripotassium	Organic acids	Garcinia genus plants	Folate-modified milk EXOs	Inhibits ACLY and downstream fatty acid synthesis	[119]
Cannabidiol (CBD)	Phenolics (cannabinoids)	Cannabis genus plants	Folate-modified colostrum EXOs (FA-ExoCBD)	Anti-proliferative, anti-inflammatory	[120]
Pterostilbene	Stilbenes	Blueberry, grape, Pterocarpus santalinus, etc.	Lactoferrin-functionalized grapefruit EVs (LF/PS-GEV)	Downregulates VEGF/cyclin D1, upregulates BAX/caspase-3, inhibits p53	[121]
Grifola frondosa extract	Polysaccharides	Grifola frondosa (edible-medicinal fungus)	MSC-derived exosomes	Modulates NF- κ B and MAPK pathways	[122]
Resveratrol	Stilbenes	Polygonum cuspidatum, grape, etc.	Res-pretreated human umbilical cord MSC exosomes	Delivers reduced Wnt5a, antagonizes Wnt/ β -catenin, upregulates E-cadherin	[123]
Withaferin A	Terpenoids (steroidal lactones)	Withania somnifera (Solanaceae plants)	Milk EXOs (ExoWFA)	Lung cancer xenograft, tumor inhibition rate 74% vs 50% (free drug)	[124]
β -Elemene	Terpenoids (sesquiterpenes)	Curcuma wenyujin (Zingiberaceae, Curcuma genus)	Self-induced EXOs	SYNCRIP mediates miR-127-3p loading into EXOs $\rightarrow$ targets MAPK4 inactivation, Akt/mTOR-induced autophagy; inhibits ZC3H4 to promote macrophage M1 polarization	[125]

3.3 EXOs Delivery of Traditional Chinese Medicine Compound Formulas

Compared with studies on the EXO-mediated delivery of TCM monomers, research on EXO-mediated delivery of TCM compound formulas for NSCLC is relatively limited. The delivery modes are mainly divided into two categories: first, functional regulation-type EXOs induced by compound formula pretreatment, i.e., EXOs with altered secretion function from tumor cells after stimulation by compound formulas, which do not themselves contain active ingredients of the compound formula; second, artificial drug-loaded EXOs, i.e., EXOs artificially loaded with compound formula extracts to achieve targeted delivery and enhanced efficacy with reduced toxicity. For example: EXOs extracted from the co-decoction of the Astragalus-Curcuma drug pair (ACELNs) are rich in active ingredients such as astragaloside IV, calycosin, and curcuminol, which not only significantly improve oral bioavailability but also achieve synergistic efficacy enhancement and toxicity reduction when combined with 5-fluorouracil in lung cancer models [45]. In addition, Curcuma-derived EXOs loaded with Astragalus components (AC-CELNs) can promote the uptake and transport of Astragalus active ingredients by tumor cells and enhance anti-tumor activity [126], preliminarily validating the application potential of EXOs loaded with compound formulas.

4. Traditional Chinese Medicine Active Ingredients Regulating TEX for the Treatment of Lung Cancer

TEX are EXOs secreted by tumor cells, carrying various bioactive cargoes such as miRNAs, proteins, lipids, and immune checkpoint molecules. They are extensively involved in pathological processes including tumor cell proliferation, EMT, invasion and metastasis, chemotherapy and targeted therapy resistance, TAM M2 polarization, and immune evasion, continuously driving malignant progression by mediating tumor-stroma and tumor-immune cell signal transmission. TCM monomers can act on tumor cells to intervene at the source in the generation, release, and cargo

loading of TEX, downregulate pro-tumor miRNAs, glycolytic proteins, and immunosuppressive molecules within them, and block TEX-mediated pro-tumor signaling networks. For example, natural products such as alkaloids can regulate the expression of non-coding RNAs (ncRNAs) in TEX, thereby inhibiting tumor progression, metastasis, and drug resistance [127]. This provides a modern biological micro-level interpretation for lung cancer.

Table 4: TCM active components regulating tumor-derived exosomes (TEX) for lung cancer therapy

TCM Active Ingredient/Compound Formula	Mechanism	Reference
Feiyanning Formula (FYN)	Inhibits the JAK2/STAT3/c-Fos/NFATc1 pathway and exosomal miR-328-mediated pro-metastatic signaling	[128]
α -Hederin	Inhibits the TGF β /SMAD2 pathway and reduces unsaturated fatty acid synthesis; reprograms exosomal miRNA loading (promotes miR-21-5p, miR-23a-3p, and miR-125b-5p entry into sEVs targeting TGF β /SMADs), blocks drug resistance transmission via sEVs, and reverses paclitaxel resistance in NSCLC	[91]
Hedyotis diffusa-Scutellaria barbata	Regulates the TGF- β /Smad pathway, inhibits the NLRP3/NF- κ B/MAPK pathway, downregulates exosomal PD-L1, and synergistically inhibits proliferation, induces apoptosis, and blocks immune evasion	[129-130]
Solanum lyratum steroidal alkaloids	Regulates TEX, inhibits the JAK2/STAT3 pathway, suppresses EMT, and inhibits NSCLC metastasis	[131-132]
Shikonin	Targets exosomal PKM2, inhibits glycolysis, reduces exosomal PKM2-mediated cisplatin resistance signaling, and sensitizes cisplatin	[133]
Tanshinone IIA	Alters the exosomal miRNA expression profile of A549 cells and inhibits HUVEC angiogenesis ("activating blood circulation and removing blood stasis" inhibits tumor neovascularization)	[134]

5. Conclusion

The pathogenesis of lung cancer is complex, with healthy qi

deficiency as the root and cancer toxins, phlegm, and blood stasis as the branch manifestations. Clinically, there remain practical challenges such as high incidence of drug resistance, metastasis and recurrence, and limited therapeutic benefit. EXO nanodelivery provides an important tool for overcoming the shortcomings in druggability of TCM active ingredients and demonstrates tremendous potential in the field of NSCLC treatment. TCM active ingredients can intervene through two dimensions: functional regulation and nanodelivery. Exosome-mediated delivery of single TCM ingredients has accumulated substantial basic data, while research on exosomes loaded with TCM compound formulas, though still in its infancy, best reflects the characteristics of TCM. At present, this field still faces many challenges, including preparation technology, quality control standardization, multi-component co-loading of compound formulas, and in vivo translation. In the future, it is necessary to base efforts on TCM compatibility theory, combine them with the biological characteristics of exosomes, and promote the advancement of TCM-exosome nanoformulations from single ingredients to compound formulas, from basic research to clinical application, and from experience-based to standardization. Their excellent application potential provides novel ideas and technological directions for the research and development of innovative TCM anti-lung cancer drugs.

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