Targeting lung cancer with tanshinones: Current mechanistic evidence and emerging opportunities (Review)

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Received January 20, 2026; Accepted April 23, 2026

DOI: 10.3892/or.2026.9141

Abstract. Lung cancer (LC) remains a leading cause of cancer-related morbidity and mortality worldwide, with non-small cell lung cancer (NSCLC) comprising ~85% of cases. Although therapeutic options have expanded in recent years, drug resistance and tumor relapse continue to limit durable responses, highlighting the need for novel treatment strategies and effective adjuvant agents. Tanshinones are major bioactive diterpenoid quinones derived from *Salvia miltiorrhiza* (Danshen) and exhibit diverse pharmacological activities, including anti-inflammatory, anti-angiogenic, and antitumor effects. Growing evidence indicates that tanshinones suppress LC progression through multi-level regulation of cancer hallmarks, including inhibition of proliferation, induction of apoptosis, attenuation of invasion and metastasis, and modulation of antitumor immunity. Notably, tanshinones have also shown promise as sensitizers in combination regimens, where they enhance the efficacy of standard anticancer agents and may help overcome acquired resistance in LC models. In the present review, current mechanistic evidence on tanshinone-mediated anticancer actions in LC was synthesized and opportunities and challenges for clinical translation are examined, with the aim of informing the development of tanshinone-based therapeutic strategies and next-generation derivatives.

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Abbreviations: ATA, acetyltanshinone IIA; AR, androgen receptor; ATF4, activating transcription factor 4; CHOP, CCAAT/enhancer-binding protein homologous protein; circRNAs, circular RNAs; CPT, cryptotanshinone; Cyt c, cytochrome *c*; DR5, death receptor 5; DT, dihydrotanshinone; eEF-2K, eukaryotic elongation factor-2 kinase; EMT, epithelial-mesenchymal transition; FOXO3, Forkhead box O3; JNK, c-Jun N-terminal kinase; LC, lung cancer; LPS, lipopolysaccharide; LUAD, lung adenocarcinoma; MAE, microwave-assisted extraction; miRNAs, microRNAs; NK, natural killer; NSCLC, non-small cell lung cancer; ROS, reactive oxygen species; SCLC, small-cell lung cancer; SFE, supercritical CO_2 fluid extraction; STS, sodium tanshinone IIA sulfonate; Tan I, tanshinone I; Tan IIA, tanshinone IIA; TG2, transglutaminase 2; UPR, unfolded protein response; VEGF, vascular endothelial growth factor; 3'-UTR, 3'-untranslated region

Key words: lung cancer, non-small cell lung cancer, tanshinones, molecular mechanisms, immune modulation

Contents

1. Introduction

LC is the most common malignancy and the leading cause of cancer-related mortality worldwide, ranking among the cancers with the lowest survival rates (1). In recent years, both the incidence and mortality of LC have continued to rise globally (2). In 2022, ~2.5 million new LC cases and over 1.8 million deaths were reported worldwide. Epidemiological data indicate that LC has the highest incidence and mortality rates among men, and ranks second only to breast cancer among women (3). Histopathologically, LC is classified into two major types: Small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter accounting for approximately 80-85% of all LC cases (4). The development of LC is closely associated with environmental factors and genetic alterations, among which cigarette smoking remains the most recognized risk factor (5). Current therapeutic strategies for LC include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. However, the toxic side effects of chemotherapeutic agents and the emergence of resistance to targeted

therapies and immunotherapies continue to contribute to poor prognosis and low long-term survival rates among patients with LC (6,7). Therefore, exploring novel therapeutic agents and strategies is of great clinical significance to improve the prognosis of patients with LC (8-11).

Natural compounds derived from plants possess extensive pharmacological potential and have traditionally been used to treat various diseases, including cancer. Tanshinones are natural terpenoid compounds and the major bioactive constituents isolated from *Salvia miltiorrhiza*, a traditional Chinese medicine widely applied in the treatment of cardiovascular and cerebrovascular diseases (12,13). Based on their structural differences, tanshinones can be classified into several types, among which tanshinone IIA (Tan IIA), dihydrotanshinone (DT), tanshinone I (Tan I), and cryptotanshinone (CPT) are considered the most representative and biologically significant (14,15). Modern pharmacological studies have demonstrated that tanshinones exhibit antiangiogenic (16), antioxidant (17), antibacterial (18), and anti-inflammatory (19) activities. Moreover, tanshinones have shown notable antitumor potential in a variety of malignancies, including gastric (20), hepatic (21), breast (22), and colorectal cancers (23), by modulating diverse cellular processes such as proliferation, invasion, metastasis, and angiogenesis. In the context of LC, tanshinones also exert significant therapeutic effects. However, the underlying molecular mechanisms remain insufficiently elucidated, and challenges such as potential drug resistance and recurrence in clinical applications need to be further addressed.

Therefore, the present review provides a systematic overview of the pharmacological mechanisms of tanshinones in LC treatment, aiming to offer a comprehensive theoretical basis and novel perspectives for optimizing tanshinone-based therapeutic strategies and promoting their translational potential in LC management (Fig. 1).

2. Structure, sources, extraction and pharmaceutical properties of tanshinones

Miltiorrhizae Radix et Rhizoma (commonly known as Danshen) is derived from the dried roots of *Salvia miltiorrhiza*. To date, >100 chemical constituents have been isolated and structurally identified from *Salvia miltiorrhiza* (24). The major active components of Danshen are generally categorized into two groups: Water-soluble salvianolic acids and lipid-soluble tanshinones.

The lipid-soluble constituents mainly include Tan I ($C_{18}H_{12}O_3$), Tan IIA, ($C_{19}H_{18}O_3$), DT, CPT, isotan I, isotan IIA, and isocryptotanshinone. The water-soluble constituents comprise salvianolic acid A, salvianolic acid B, salvianolic acid C, rosmarinic acid, protocatechuic acid, and danshensu, among others (14) (Fig. 2).

Among these, the lipid-soluble tanshinones have attracted particular attention due to their high efficacy (25), low toxicity (26), favorable safety profile (27), and diverse pharmacological properties, including anticancer (28), antibacterial (29), antioxidant (30), anti-inflammatory (31), vasodilatory (32), antithrombotic (33), anti-atherosclerotic (34), neuroprotective (35), microcirculation-improving (36), anti-pulmonary fibrosis (37), and immunomodulatory effects (38). In recent years, the lipophilic components of tanshinones have been demonstrated to exhibit potent anticancer activities in LC cells.

With the increasing clinical application of tanshinones, extraction and isolation technologies have evolved considerably. These processes primarily focus on the separation of lipid-soluble diterpene quinones and water-soluble polyphenolic acids. Extraction of the lipophilic diterpene quinones mainly employs methods such as ethanol extraction, ultrasonic extraction, supercritical CO_2 fluid extraction (SFE), microwave-assisted extraction (MAE), pressurized liquid extraction, and high-speed counter-current chromatography (39). Because terpenoid compounds typically possess low polarity, chloroform, ethyl acetate, or petroleum ether are commonly used as initial extraction solvents. For compounds with slightly higher polarity, the roots are often defatted before extraction with polar solvents or mixed chloroform-methanol solutions in various ratios (14).

Modern extraction technologies optimize efficiency through physical enhancement techniques, effectively overcoming the limitations of traditional methods such as time consumption, excessive solvent use, and degradation of active components. Compared with conventional methanol extraction, SFE provides higher yield and recovery, making it particularly suitable for isolating lipophilic tanshinones (40). Both ultrasonic-assisted extraction and MAE can be performed at room temperature, avoiding the degradation of thermolabile compounds. These techniques offer several advantages, including minimal sample requirement, short extraction time, high efficiency, and reduced thermal loss (41,42).

Pharmaceutical properties of tanshinones, including their stability, toxicological safety, and metabolic behavior, have also attracted considerable attention. In general, tanshinones exhibit limited stability in aqueous solutions, a property closely associated with their chemical structure. Specifically, the quinone moiety in tanshinones confers redox-cycling activity, making them prone to structural transformation and reactions with other substances (43). As a representative diterpene phenanthrenequinone compound, Tan IIA is particularly sensitive to temperature, light, and pH conditions, and readily undergoes degradation under harsh environments such as high temperature, strong light, and extreme pH; notably, its stability can be markedly improved after encapsulation in nanocarriers (44). Toxicological research has shown that tanshinones carry a markedly low overall safety risk, with no evident acute toxicity, cytotoxicity, or genotoxicity, as demonstrated by methyl thiazolyl tetrazolium cytotoxicity assays and hypoxanthine-guanine phosphoribosyltransferase genotoxicity tests (43). Regarding *in vivo* metabolism, Tan IIA is preferentially distributed to the reticuloendothelial system following either intravenous or oral administration, particularly to the liver and lungs (45). Existing studies indicate that tanshinones are mainly metabolized in the liver through phase I reactions, such as hydroxylation and dehydrogenation mediated by enzymes including cytochrome P450 3A4, as well as phase II pathways such as glucuronidation; notably, phase I metabolism depends on the saturation of the core scaffold and the nature of substituent groups (46,47). Owing to their poor water solubility, low membrane permeability, and susceptibility to first-pass metabolism, several delivery strategies,

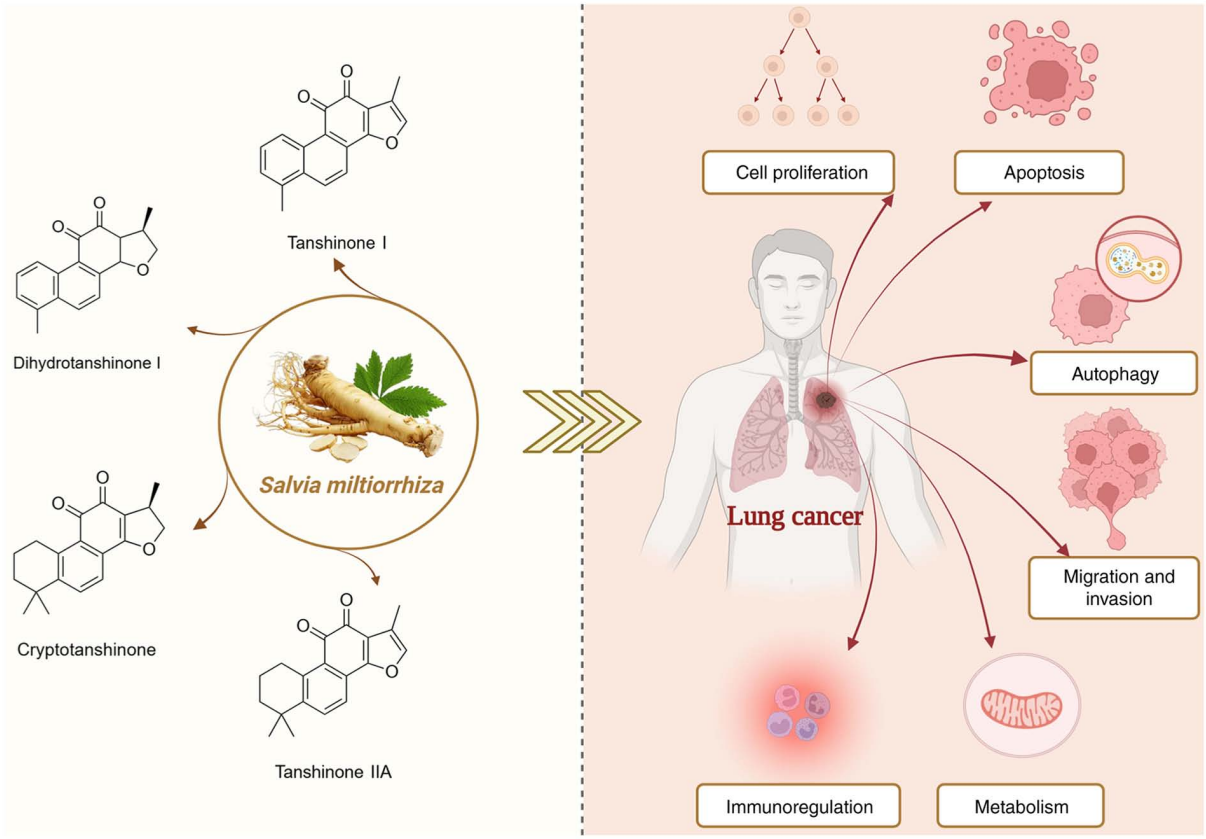

Figure 1. Anti-lung cancer effects and mechanisms of tanshinone bioactive compounds.

such as injectable emulsions, micelles, and solid lipid nanoparticles, have been developed to effectively improve their bioavailability and plasma concentration (48,49).

3. Antitumor mechanisms of bioactive tanshinones in LC

Inhibition of LC cell proliferation. Cell proliferation refers to the increase in cell number and is a hallmark of tumor growth, which requires dysregulated proliferative signaling. Alterations in the expression or activity of cell cycle-related proteins are principal indicators of proliferative status (50,51). Numerous studies have demonstrated that tanshinones can suppress the cell cycle and thereby inhibit tumor cell proliferation (9,52,53).

Cell cycle regulation exerts a major influence on tumor cell proliferation by controlling the expression of relevant genes and the activity of intracellular enzymes, proteins, and signaling factors (54,55). Existing research has shown that the Tan IIA derivative TA25 dose-dependently promotes the generation of reactive oxygen species (ROS) in A549 LC cells, thereby inducing S-phase arrest. In addition, TA25 was demonstrated to suppresses the PI3K/Akt/mTOR proliferative signaling pathway and to activate the tumor suppressor p53 in a ROS-dependent manner, ultimately inhibiting cell proliferation through cell-cycle regulation (56). Huang *et al* (57) showed that acetyltanshinone IIA (ATA) decreased synthesis of cell cycle proteins such as cyclin D3 in NSCLC cells via degradation of p70S6K, while concurrently increasing p53 and p21 levels; these effects together block G_1/S progression and inhibit proliferation, suggesting a promising strategy for targeted therapy in LC.

MicroRNAs (miRNAs or miRs) are a class of endogenous small non-coding regulatory RNAs that modulate protein expression by binding to the 3'-untranslated region (3'-UTR) of target messenger RNAs, thereby repressing translation or promoting mRNA degradation. They play essential roles in normal development and in maintaining homeostatic balance (58). In pathological conditions such as cancer, miRNAs that are underexpressed often function as tumor suppressors, inhibiting tumor progression by regulating oncogenes and/or genes involved in cell differentiation and apoptosis (59). Previous studies have shown that the androgen receptor (AR) can regulate miR-32 expression by binding to AR-binding sites located near the miR-32 genomic locus (60). Based on this regulatory mechanism, Ma *et al* (61) further demonstrated that Tan I downregulates AR expression, thereby relieving its transcriptional activation of miR-32 and leading to increased miR-32 expression in NSCLC cells. The upregulated miR-32 was shown to directly target and suppress the mRNA and protein expression of the oncogenic factor Aurora kinase A (AURKA), disrupt cell-cycle progression, and ultimately inhibit NSCLC cell proliferation. Similarly, tanshinones can also upregulate let-7a-5p expression, enabling it to bind to the 3'-UTR of AURKA and repress its translation, thereby directly downregulating AURKA; notably, clinical NSCLC specimens exhibit a negative correlation between let-7a-5p and AURKA, further supporting the specificity of this pathway (62). Zhang *et al* (63) demonstrated that Tan I, Tan IIA, and CPT markedly upregulate miR-137 in NSCLC

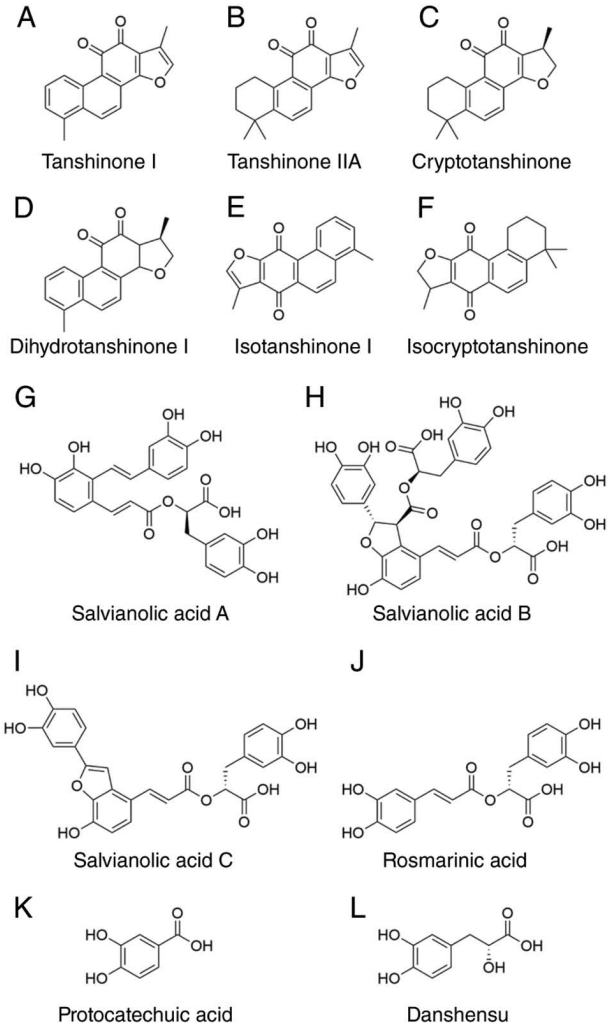

Figure 2. Schematic diagram of chemical structure classification of tanshinone bioactive compounds. (A-F) Lipid-soluble tanshinones. (G-L) Water-soluble salvianolic acids.

cells, thereby reducing the expression of its oncogenic targets, Unc-51-like kinase 2 (ULK2) and inhibitor of Bruton tyrosine kinase (IBTK), suppressing cell proliferation, and inhibiting cell-cycle progression (Fig. 3).

Induction of apoptosis and autophagy in LC cells. Apoptosis is a programmed cell-death process that removes damaged cells in an ordered manner; dysregulation of apoptosis is a hallmark of cancer and contributes to tumorigenesis and therapeutic resistance (64,65). Tanshinones induce apoptosis in LC cells primarily via mitochondria-dependent (intrinsic) and endoplasmic reticulum (ER) stress-related pathways and through modulation of associated signaling cascades (66).

Mitochondria are central organelles that influence cancer initiation, growth, survival, and metastasis (67). ROS generated by mitochondria participate in stress signaling in normal cells, whereas excessive mitochondrial oxidative stress can trigger apoptosis in tumor cells (68). Research has shown that Tan IIA induces ROS generation in human NSCLC A549 cells, reduces mitochondrial membrane potential, and thereby activates the mitochondria-dependent apoptotic pathway. Concurrently, Tan IIA was demonstrated to downregulate the anti-apoptotic protein Bcl-2 while upregulating Bax, p53, and cytochrome *c* (Cyt c), thereby further amplifying apoptosis through an increased Bax/Bcl-2 ratio (69). Similarly, Ye *et al* (70) demonstrated in NSCLC cells that Tan IIA and CPT induce G_2/M-phase arrest, markedly upregulate p53 expression, activate caspase-3/9 and poly(ADP-ribose) polymerase 1 (PARP1), and simultaneously downregulate the anti-apoptotic proteins Bcl-2 and Bcl-xL while upregulating the pro-apoptotic protein Bax. These findings further support the central role of mitochondria in tanshinone-induced apoptosis in LC cells. In addition to these mechanisms, an NAD(P)H quinone dehydrogenase 1 (NQO1)-initiated, p53-independent mitochondrial apoptotic pathway was also shown to be involved in the effects of Tan IIA on LC cells. Liu *et al* (71) found that Tan IIA increases the Bax/Bcl-xL ratio, disrupts mitochondrial membrane potential, promotes Cyt c release, activates caspases, and induces PARP1 cleavage, thereby triggering a ROS-mediated, p53-independent but caspase-dependent mitochondrial apoptotic pathway. Moreover, myeloid cell leukemia 1 (Mcl-1), another key anti-apoptotic member of the Bcl-2 family, was demonstrated to stabilize the outer mitochondrial membrane and thereby block intrinsic apoptosis (72). Gao *et al* (73) further confirmed that Tan IIA binds to and inhibits epidermal growth factor receptor (EGFR) phosphorylation in a dose-dependent manner, blocks downstream Akt activation, and promotes ubiquitin-mediated degradation of Mcl-1, leading to Cyt c release from mitochondria and activation of the caspase cascade, ultimately inducing LC cell apoptosis through the mitochondria-dependent intrinsic apoptotic pathway.

Proper control of protein folding is a fundamental function of the ER in maintaining cellular homeostasis, and disruption of protein processing in the secretory pathway elicits the unfolded protein response (UPR). When the UPR fails to restore ER homeostasis, pro-apoptotic signaling is activated (74,75). A previous study demonstrated that Tan IIA markedly induces the expression of GRP78, an ER stress sensor protein, selectively activates the protein kinase R (PKR)-like ER kinase (PERK)-activating transcription factor 4 (ATF4) arm of ER stress in NSCLC cells, upregulates CCAAT/enhancer-binding protein homologous protein (CHOP), and subsequently induces death receptor 5 (DR5) expression, thereby promoting apoptosis (76). Zhang *et al* (77) reported that Tan IIA dose-dependently increases cytosolic Ca^{2+} levels in LC cells, thereby triggering ER stress; it was also shown to upregulate phosphorylated eukaryotic initiation factor-2α (eIF2A), CHOP, and ATF4, promote phosphorylation and activation of c-Jun N-terminal kinase (JNK), and suppress the nuclear factor of activated T cells 1 (NFAT2)/c-Myc signaling pathway, ultimately leading to apoptosis.

Forkhead box O3 (FOXO3) is a key regulator of apoptosis (78). Experimental research has shown that tanshinones can activate FOXO3a expression and subsequently stimulate its downstream effector caspase-3, thereby triggering the apoptotic cascade through the FOXO3a/caspase-3 signaling pathway and effectively inducing apoptosis (79) (Fig. 4).

Inhibition of LC cell invasion and migration. Tumor metastasis, the process by which tumor cells detach from the primary site and gradually proliferate in distant organs, is the leading

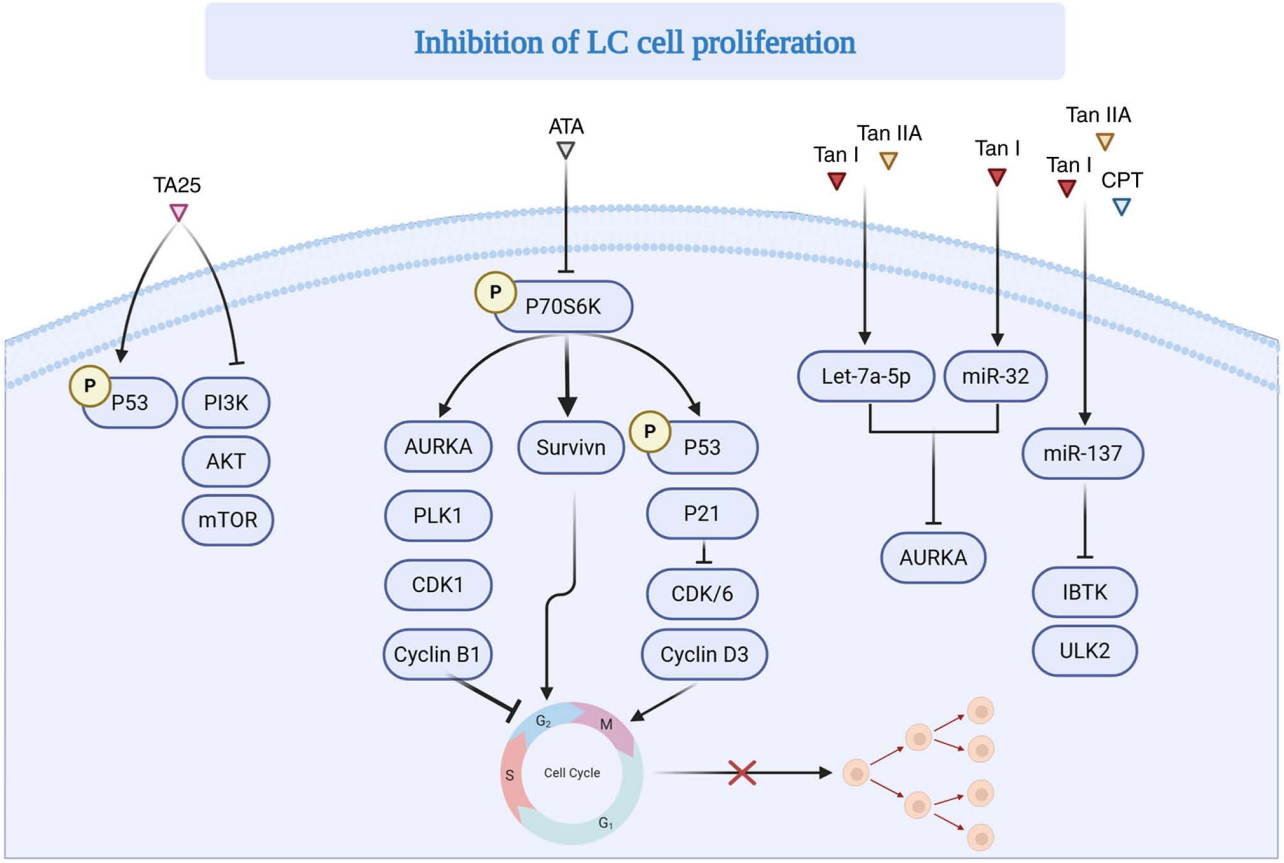

Figure 3. Schematic diagram of signaling pathways related to inhibition of LC cell proliferation by tanshinone bioactive compounds. LC, lung cancer; ATA, acetyltanshinone IIA; Tan, tanshinone; miR, microRNA; CPT, cryptotanshinone; AURKA, Aurora kinase A; ULK2, Unc-51-like kinase 2; PLK1, polo-like kinase 1; IBTK, inhibitor of Bruton tyrosine kinase.

cause of cancer-related mortality (80). The fundamental steps of invasion and metastasis include detachment of tumor cells from the extracellular matrix, invasion into surrounding tissues and basement membranes, intravasation into the bloodstream, survival and transport in circulation, extravasation, and colonization to form metastatic lesions (81). Genes regulating miRNA networks, angiogenesis, and epithelial-mesenchymal transition (EMT) are all involved in the metastatic potential of LC cells.

Extensive research has revealed that miRNAs can interfere with tumor cell migration and invasion by directly repressing or activating target mRNAs or by regulating the expression of downstream effector molecules (82). A study in human LC A549 cells showed that CPT and Tan IIA can selectively suppress miR-21-5p expression while upregulating the tight junction-associated proteins occludin and zonula occludens-1 (ZO-1), particularly at the transcriptional and protein expression levels of occludin. This effect improved the tight junction integrity of tumor vascular endothelial cells and consequently reduced the migratory capacity of A549 cells (83).

Circular RNAs (circRNAs) are a novel class of non-coding RNAs that can act as molecular sponges for miRNAs, thereby blocking miRNA-mediated suppression of downstream target genes and exerting oncogenic effects in tumors (84,85). Tanshinones can downregulate abnormally overexpressed circRNAs in tumors, restore the silencing effect of miRNAs on downstream oncogenic genes, and thereby inhibit tumor cell migration and invasion (86). Sun *et al* (87) demonstrated that Tan IIA suppresses the expression of circ_0020123 in A549 and H292 cells, thereby relieving its sponge effect on miR-1299 and restoring the expression and function of miR-1299. This, in turn, enabled miR-1299 to effectively target and inhibit the downstream oncogene high mobility group box 3 (HMGB3), ultimately suppressing the migration and invasion of NSCLC cells.

EMT is a biological process in which epithelial cells lose their epithelial characteristics and acquire mesenchymal traits, thereby promoting invasive and metastatic phenotypes (88). Experimental research has shown that Tan IIA inhibits the migration of SCLC cells by reducing PI3K and phosphorylated Akt expression, thereby blocking the PI3K/Akt signaling pathway, while simultaneously suppressing EMT through upregulation of E-cadherin and downregulation of vimentin (8). A previous study also showed that Cavin-1 is closely associated with tumor cell migration, invasion, EMT, and extracellular matrix degradation (89). Wang *et al* (90) reported that treatment of NCI-H1299 cells with DT for 24 h significantly downregulated the expression of Snail and Slug by inhibiting Cavin-1 expression, while also reducing the levels of MMP2, MMP7, and MMP9. These changes alleviated EMT, basement membrane damage, and extracellular matrix deposition. In addition, DT inhibited the activation of the ERK and mothers against decapentaplegic homolog 2 (Smad2) signaling pathways

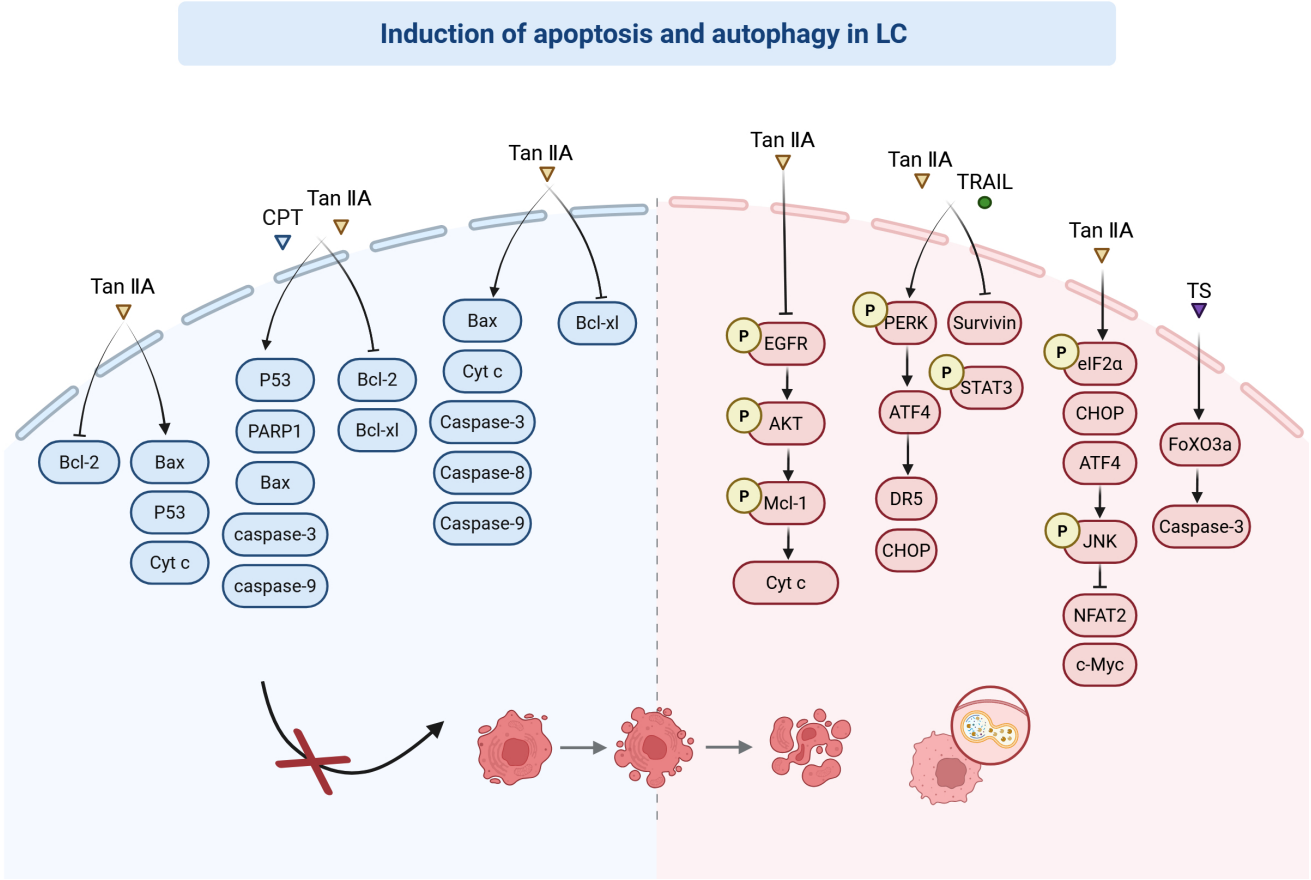

Figure 4. Schematic diagram of signaling pathways related to induction of apoptosis and autophagy in LC cells by tanshinone bioactive compounds. LC, lung cancer; Tan, tanshinone; TS, tanshinones; Cyt c, cytochrome *c*; Mcl-1, myeloid cell leukemia 1; PERK, protein kinase R (PKR)-like ER kinase; ATF4, activating transcription factor 4; DR5, death receptor 5; CHOP, CCAAT/enhancer-binding protein homologous protein; eIF2α, eukaryotic initiation factor-2α; NFAT2, nuclear factor of activated T cells 1; FOXO3, Forkhead box O3.

in vitro, thereby effectively attenuating Cavin-1-mediated metastasis of NSCLC cells.

Transglutaminase 2 (TG2) is a widely distributed multifunctional protein with both enzymatic and non-enzymatic activities, and accumulating evidence has confirmed its role in promoting the migration and invasion of LC cells (91). Wang *et al* (92) found that eukaryotic elongation factor-2 kinase (eEF-2K) knockdown combined with sodium Tan IIA sulfonate (STS) inhibited TG2 expression in A549 cells, reduced phoshorylated (p)-ERK1/2 levels, and weakened TG2/ERK signaling, thereby synergistically suppressing the migration and invasion of A549 cells and providing a potential therapeutic target for lung adenocarcinoma (LUAD).

Angiogenesis plays a crucial role in tumor growth and metastasis (93), and inhibition of angiogenesis represents an important antitumor strategy. Vascular endothelial growth factor (VEGF) is central to tumor angiogenesis; blockade of VEGF signaling can cause vascular regression and inhibit tumor growth (94). Tung *et al* (95) reported that Tan I effectively suppressed tumor growth, invasion, and metastasis by blocking VEGF overexpression in Clara cells and preventing neovascularization. Similarly, Xie *et al* (96) confirmed by western blot analysis that Tan IIA downregulates the protein expression of VEGF and VEGF receptor 2 (VEGFR2) in A549 cells and blocks the VEGF/VEGFR signaling pathway to inhibit tumor angiogenesis. Molecular docking experiments further revealed the structural basis of its action, verifying that this compound can stably bind to the kinase domain of the VEGFR2 protein. Its distinctive binding mode enables the formation of a hydrogen bond with cysteine 917 and π-π stacking with valine 848, thereby blocking the downstream signaling pathway of VEGF/VEGFR and exerting an anti-angiogenic effect in tumors. Dysregulation of miRNAs has been shown to be associated with tumor angiogenesis (97). Wang *et al* (98) found that STS upregulates the expression of miR-874 to target and inhibit eEF-2K, which in turn downregulates the expression of TG2, thus suppressing angiogenesis in LUAD and inhibiting LUAD progression (Fig. 5).

Regulation of anti-inflammation and immune balance. Inflammatory dysregulation and immune imbalance are key drivers of cancer initiation, progression, invasion, and metastasis (99). Remodeling the tumor microenvironment toward an anti-inflammatory state and restoring antitumor immune homeostasis are therefore considered core mechanisms for effective cancer intervention.

Tumor-associated macrophages are important innate immune cells in the body. Among them, M1-polarized macrophage-mediated inflammatory responses can promote tumor invasion and metastasis, thereby creating a vicious 'inflammation-cancer' cycle, while lipopolysaccharide (LPS) is a major stimulus that induces macrophage polarization toward

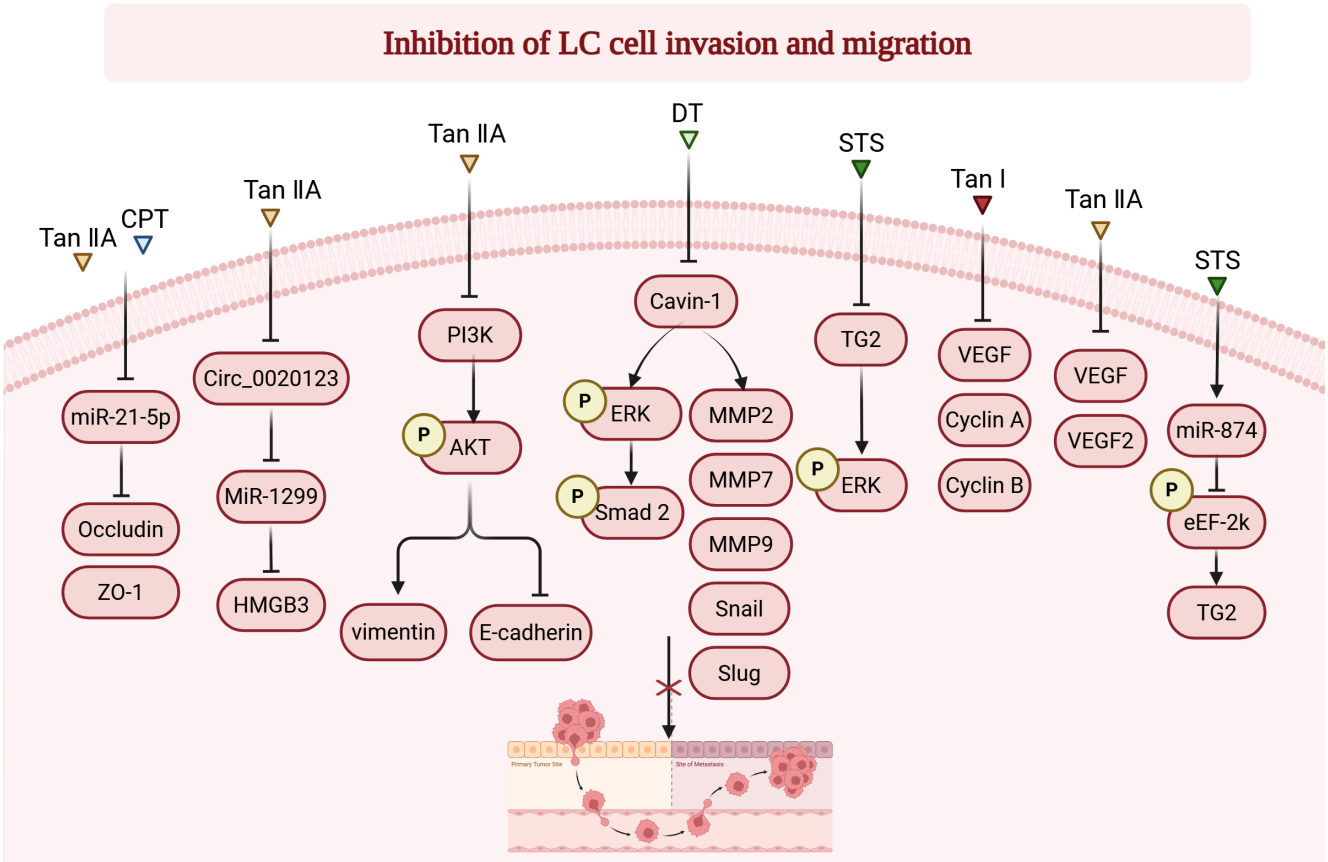

Figure 5. Schematic diagram of signaling pathways inhibiting invasion and migration of LC cells by tanshinone bioactive compounds. LC, lung cancer; Tan, tanshinone; CPT, cryptotanshinone; DT, dihydrotanshinone; ZO-1, zonula occludens-1; HMGB3, high mobility group box 3; Smad2, mothers against decapentaplegic homolog 2; TG2, transglutaminase 2; eEF-2K, eukaryotic elongation factor-2 kinase; STS, sodium tanshinone IIA sulfonate.

the M1 phenotype (100,101). Research has shown that DT can upregulate the endothelial barrier tight junction proteins ZO-1 and occludin, thereby maintaining intestinal mucosal integrity and reducing LPS levels in the tumor microenvironment. This, in turn, was shown to suppress activation of the Toll-like receptor 4 (TLR4)-mediated NF-κB inflammatory pathway and ultimately inhibit LC progression through modulation of the gut-lung inflammatory axis (102).

Programmed death-ligand 1 (PD-L1), a ligand of the classical immune co-inhibitory system, plays a decisive role in determining the antitumor efficacy of immunotherapy through its expression in tumor cells (103). A previous study revealed that Tan IIA induces ER stress and promotes phosphorylation of c-Jun-S73, a downstream target of JNK, thereby upregulating PD-L1 expression in tumor cells through the JNK/c-Jun axis. Moreover, when combined with anti-PD-1 inhibitors, Tan IIA was shown to activate antitumor immunity dominated by $CD8^+$ T cells within the tumor microenvironment and promote the secretion of IFN-γ, TNF-α, and granzyme B (GzmB), thereby enhancing the efficacy of anti-PD-1 immunotherapy (77). Natural killer (NK) cells are a specialized type of immune effector cell that play a crucial role in immune responses against abnormal cells (104). Sun *et al* (105) found that Tan IIA upregulates the protein expression of p-PERK, ATF4, and CHOP in NSCLC cells, thereby activating the PERK-ATF4-CHOP ER stress signaling pathway. Through ATF4 and CHOP, Tan IIA was further shown to increase the expression of UL16-binding protein-1 (ULBP1) and DR5, enhance NK cell recognition of and degranulation against tumor cells, and ultimately markedly strengthen NK cell-mediated cytotoxicity against NSCLC cells (Fig. 6).

Modulation of metabolism. Metabolic reprogramming is one of the hallmarks of cancer, and enhanced aerobic glycolysis together with aberrantly activated anabolic metabolism are major contributors to tumor initiation, invasion, metastasis, and drug resistance (106). Therefore, targeting dysregulated tumor metabolism is of great significance for improving cancer therapy.

Glycolysis is a central pathway in cellular energy metabolism and is essential for maintaining the malignant biological behavior of tumor cells (107). Increasing evidence suggests that tanshinones exert antitumor effects by regulating key glycolytic molecules and signaling pathways in cancer cells (108). Qi *et al* (109) demonstrated that Tan IIA downregulates the mRNA and protein expression of sine oculis homeobox homolog 1 (SIX1) *in vitro*, which in turn reduces the expression of pyruvate kinase M2 (PKM2), hexokinase 2 (HK2), and lactate dehydrogenase A (LDHA) in A549 cells, thereby significantly suppressing glycolysis in NSCLC cells and exerting anti-LC effects. Wang *et al* (56) further found that the Tan IIA derivative TA25 induces S-phase arrest by modulating the ROS-mediated PI3K/Akt/mTOR pathway, a

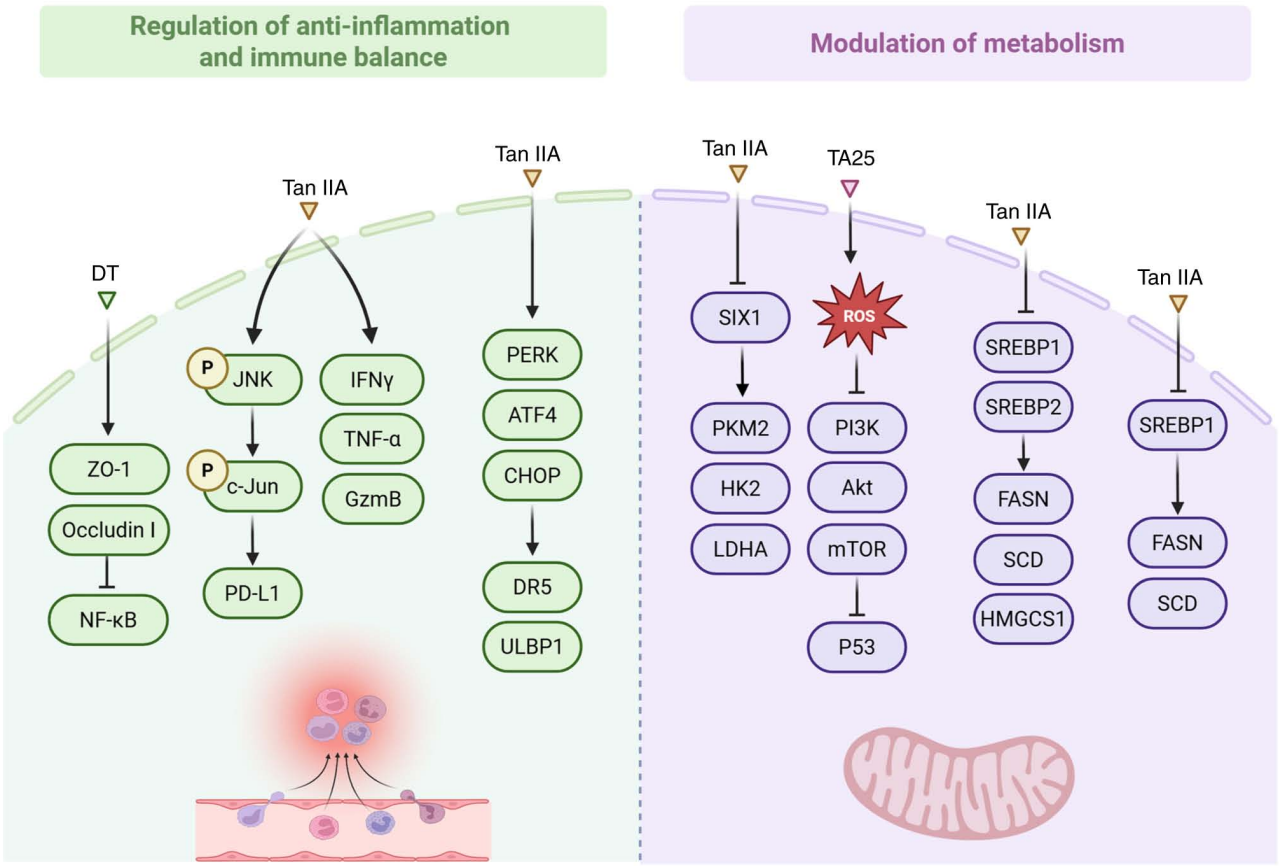

Figure 6. Schematic diagram of signaling pathways regulating anti-inflammation, immune balance and metabolism by tanshinone bioactive compounds. DT, dihydrotanshinone; Tan, tanshinone; ZO-1, zonula occludens-1; PD-L1, programmed death-ligand 1; GzmB, granzyme B; PERK, protein kinase R (PKR)-like ER kinase; ATF4, activating transcription factor 4; CHOP, CCAAT/enhancer-binding protein homologous protein; DR5, death receptor 5; ULBP1, UL16-binding protein-1; SIX1, sine oculis homeobox homolog 1; PKM2, pyruvate kinase M2; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; ROS, reacive oxygen species; SREBP1, sterol regulatory element-binding protein 1; SREBP2, sterol regulatory element-binding protein 2; FASN, fatty acid synthase; SCD, stearoyl-CoA desaturase; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1.

key pathway involved in glycolytic regulation, thereby inhibiting LC cell migration.

Cancer cells require substantial amounts of lipids to meet the energy demands of rapid division and unrestricted expansion, and their lipid metabolism is highly dependent on *de novo* lipogenesis. Sterol regulatory element-binding protein 1 (SREBP1) is a key transcription factor that has been shown to regulate this process (110,111). Cao *et al* (112) demonstrated that Tan IIA combined with osimertinib suppresses *de novo* lipogenesis and reduces lipid accumulation in LC cells by downregulating SREBP1 and its downstream targets, including fatty acid synthase (FASN), stearoyl-CoA desaturase (SCD), and 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1). Concurrently, this combination was demonstrated to increase the proportion of polyunsaturated fatty acids in the membranes of resistant cells, enhance lipid peroxidation and oxidative stress-induced damage, and thereby overcome acquired resistance of NSCLC to osimertinib. Similarly, Zhang *et al* (113) found that Tan IIA markedly suppresses the expression and transcriptional activity of SREBP1 in NSCLC cells and downregulates its downstream lipogenesis-related protein mSREBP1, thereby altering the cellular lipid profile. In addition, Tan IIA was shown to induce lipid peroxidation by suppressing SCD expression and increasing ROS and malondialdehyde levels, ultimately reversing gefitinib resistance in EGFR-mutant NSCLC both *in vitro* and *in vivo* and enhancing the therapeutic sensitivity of resistant cells to gefitinib (Fig. 6).

4. Combination therapy and reversal of drug resistance

Drug resistance is a key cause of chemotherapy failure in LC (114). Combining traditional Chinese medicine with chemotherapeutic agents has been shown to reverse tumor resistance and enhance drug efficacy (115).

Platinum-based chemotherapy remains the mainstay of LC treatment, but its side effects and resistance limit clinical outcomes (116). Research has shown that DT enhances the antitumor activity of cisplatin (DDP) by targeting heat shock protein family D (Hsp60) member 1 (HSPD1) and inducing ROS-mediated ER stress in LC cells, upregulating the expression of p-JNK and activating the JNK pathway (11). Moreover, Liao *et al* (117) found that co-administration of Tan IIA with DDP enhanced chemosensitivity by downregulating the protein expression of p-PI3K and p-Akt to inhibit the PI3K/Akt signaling pathway, allowing for reduced DDP dosage while improving efficacy and reducing toxicity.

Gefitinib (Iressa), a selective EGFR inhibitor, plays a vital role in controlling cell growth, apoptosis, and angiogenesis (118). It is clinically used to treat patients with NSCLC with chemotherapy resistance, but acquired resistance remains

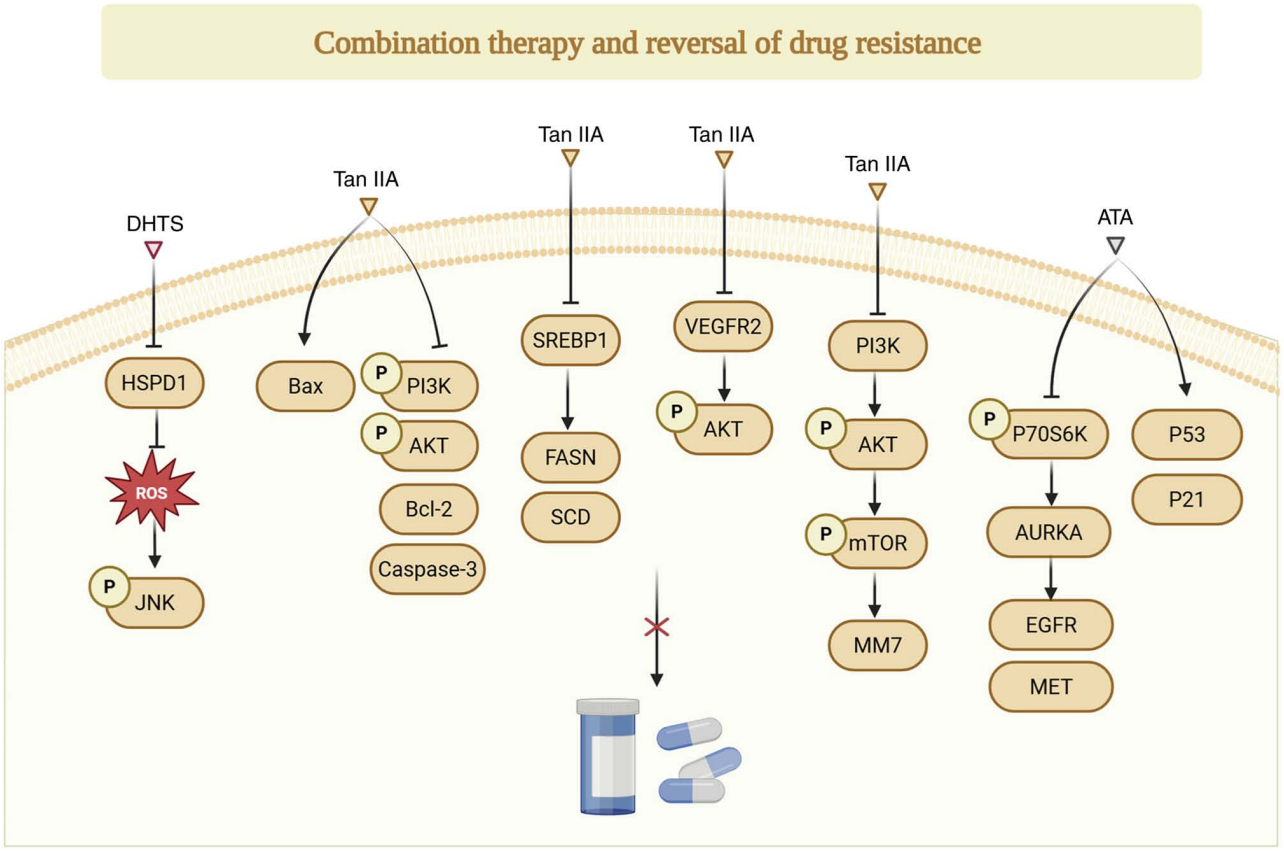

Figure 7. Schematic diagram of signaling pathways for combined therapy and reversal of drug resistance using tanshinone bioactive compounds. DHTS, dihydrotanshinone I; HSPD1, heat shock protein family D (Hsp60) member 1; ROS, reacive oxygen species; Tan, tanshinone; SREBP1, sterol regulatory element-binding protein 1; FASN, fatty acid synthase; SCD, stearoyl-CoA desaturase; ATA, acetyltanshinone IIA; AURKA, Aurora kinase A.

a major challenge (119). Tan IIA was found to downregulate SREBP1 and its downstream targets, alter lipid metabolism, and reverse gefitinib resistance in EGFR-mutant NSCLC cells both *in vitro* and *in vivo* (113). Wang *et al* (120) further confirmed that Tan IIA enhanced gefitinib cytotoxicity in gefitinib-resistant NSCLC cells. Moreover, the combination of Tan IIA and gefitinib enhanced the sensitivity of gefitinib-resistant HCC827 cells to gefitinib by reducing the phosphorylation level of VEGFR2 and thereby inhibiting activation of the VEGFR2/Akt signaling pathway, ultimately improving the therapeutic efficacy of the combination treatment. In addition, combined molecular docking and *in vitro* experiments showed that Tan IIA exhibits strong binding affinity toward PIK3R1, AKT1, mammalian target of rapamycin (mTOR), and MMP7, with binding free energies of -8.1, -12.3, -9.3, and -8.8 kcal/mol, respectively. Tan IIA was shown to form stable hydrogen bonds with key amino acid residues in these proteins, thereby inhibiting PI3K-AKT-mTOR signaling, downregulating downstream MMP7 expression, and directly suppressing MMP7 activity, ultimately inhibiting the proliferation of paclitaxel-resistant NSCLC A549/Tax cells (121). Huang *et al* (57) further reported that ATA binds to the ATP-binding pocket of p70S6K, thereby preventing its phosphorylation while simultaneously promoting its ubiquitin-mediated degradation. This was shown to lead to reduced synthesis of p70S6K-dependent cell cycle-related proteins, such as AURKA, downregulation of EGFR and MET expression, and concomitant upregulation of p53 and p21, ultimately inducing G_1/S cell-cycle arrest. Consequently, tanshinones have been demonstrated to effectively block protein synthesis and proliferative signaling pathways, thereby reversing drug resistance (Fig. 7).

5. Discussion

The therapeutic potential of tanshinones in oncology has attracted considerable attention and remains a major focus of current research. A growing body of preclinical studies and experimental models has demonstrated that tanshinones can effectively inhibit tumor growth, induce cancer cell apoptosis, and modulate multiple signaling pathways involved in cancer progression. Among these, the PI3K/Akt/mTOR signaling pathway, mitochondria-dependent apoptotic pathway, VEGF/VEGFR-mediated angiogenic pathway, and key molecular regulators such as AURKA and p53 represent shared core targets through which tanshinones and their derivatives exert broad-spectrum antitumor effects in LC as well as in other malignancies, including liver, breast, and colorectal cancers. Pan-cancer mechanistic studies have shown that tanshinones can block cell-cycle progression and induce apoptosis by downregulating the PI3K/Akt/mTOR pathway (56,122,123); activate mitochondria-dependent apoptosis by modulating the Bcl-2/Bax ratio (124-126); inhibit tumor angiogenesis by suppressing VEGF/VEGFR2 signaling (16,96); and simultaneously target AURKA (61,127,128) and activate the p53

Table I. Antitumor mechanisms of tanshinone bioactive compounds in lung cancer.

Bioactive tanshinones	Real modules (*In vitro*/*In vivo*)	Doses	Possible mechanisms	Targets	(Refs.)
Tanshinone IIA derivatives TA25	*In vitro*	20 μM	Inhibit the proliferation, migration and invasion of lung cancer cells	PI3K↓, Akt↓, mTOR↓, p53↑	(56)
Acetyltanshinone IIA	*In vitro* and *in vivo*	2 μM, 25 mg/kg	Reduce cyclin synthesis, inhibit cell proliferation, and suppress the growth of drug-resistant lung cancer cells	p70S6K↓, AURKA↓, PLK1↓, CDK1↓, cyclin D3↓, Survivin↓, p53↑, p21↑	(57)
Tanshinone I	*In vitro*	4 μM	Inhibit cell proliferation, promote cell death, and hinder the progression of the cell cycle	miR-32↑, AURKA↓	(61)
Tanshinone I and Tanshinone IIA	*In vitro*	10 μM; 10 μM	Inhibit cell proliferation, block the cell cycle, and promote cell apoptosis	let-7a- 5p↑, AURKA↓	(62)
Tanshinone I, Tanshinone IIA and Cryptotanshinone	*In vitro*	4 μM; 4 μM; 5 μM	Induce cell apoptosis, hinder cell cycle progression, and inhibit cell proliferation	miR-137↑, IBTK↓, ULK2↓	(63)
Tanshinone IIA	*In vitro*	2 μg/ml	Inhibit cell proliferation and induce cell apoptosis	Bax↑, Bcl-2↓, p53↑, Cyt c↑	(69)
Tanshinone IIA and Cryptotanshinone	*In vitro* and *in vivo*	40 μM; 40 mg/kg	Activate the mitochondrial apoptotic pathway and induce cell apoptosis	p53↑, caspase-3↑, caspase-9↑, PARP1↑, Bax↑, Bcl-2↓, Bcl-xl↓	(70)
Tanshinone IIA	*In vitro* and *in vivo*	40 μM; 20 mg/kg	Activate the mitochondrial apoptosis pathway and induce cell apoptosis	NQO1↑, Bax↑, Bcl-xl↓, Cyt c↑, Caspase3↑, Caspase8↑, Caspase9↑	(71)
Tanshinone IIA	*In vitro* and *in vivo*	5 μM; 10 mg/kg	Activate the mitochondrial apoptosis pathway and induce cell apoptosis	EGFR↓, Akt↓, Mcl-1↓, Cyt c↓	(73)
Tanshinone IIA	*In vitro*	20 μM	Induce endoplasmic reticulum stress response, induce cell apoptosis, and reduce the activity of drug-resistant cells	PERK↑, ATF4↑, DR5↑, CHOP↑, STAT3↓, Survivin↓	(76)
Tanshinone IIA	*In vitro* and *in vivo*	8 μM; 40 mg/kg	Induce endoplasmic reticulum stress response, inhibit cell growth, and promote immune regulation	p-eIF2α↑, CHOP↑, ATF4↑, JNK↑, NFAT2↓, c-Myc↓	(77)
Tanshinones	*In vitro*	20 μM	Inhibit cell proliferation and induce cell apoptosis	FOXO3a↑, Caspase-3↑	(79)
Cryptotanshinone and Tanshinone IIA	*In vitro* and *in vivo*	CPT: 6 μg/ml; 10 mg/kg; Tan IIA: 4 μg/ml; 10 mg/kg	Inhibit cell proliferation and tumor growth, inhibit cell migration and invasion, promote cell apoptosis	miR-21-5p↓, Occludin ↑, ZO-1↑	(83)
Tanshinone IIA	*In vitro* and *in vivo*	40 μM; 30 mg/kg	Inhibit cell proliferation, migration and invasion, and promote cell apoptosis	circ_0020123↓, miR-1299↑, HMGB3↓	(87)
Tanshinone IIA	*In vitro* and *in vivo*	2 μM; 10 mg/kg	Inhibit cell proliferation and metastasis	E-cadherin↑, vimentin↓, PI3K↓, Akt↓	(8)

Table I. Continued.

Bioactive tanshinones	Real modules (*In vitro*/*In vivo*)	Doses	Possible mechanisms	Targets	(Refs.)
Diterpenoid tanshinone	*In vitro*	5 μg/ml	Inhibit cell migration and invasion	Cavin-1↓, MMP2↓, MMP7↓, MMP9↓, ERK↓, Snail↓, Slug↓	(90)
Tanshinone IIA sulfonate	*In vitro*	20 μM	Inhibit cell proliferation, migration and invasion	TG2↓, p-ERK1↓, p-ERK2↓	(92)
Tanshinone I	*In vitro* and *in vivo*	10 μM; 1 mg/kg	Block the cell cycle and inhibit angiogenesis	VEGF↓, cyclin A↓, cyclin B↓	(95)
Tanshinone IIA	*In vitro*	31 μM	Inhibit cell proliferation, induce cell apoptosis, and inhibit angiogenesis	VEGF↓, VEGFR2↓	(96)
Sodium tanshinone IIA sulphate	*In vitro*	100 μM	Inhibit cell proliferation, migration, invasion and angiogenesis	miR-874↑, eEF-2K↓, TG2↓	(98)
Diterpenoid Tanshinones	*In vitro* and *in vivo*	5 μg/ml; 60 mg/kg	Inhibit cell growth, proliferation and migration, and improve the tumor immune microenvironment	ZO-1↑, Occludin I↑, NF-κB↓	(102)
Tanshinone IIA	*In vitro* and *in vivo*	8 μM; 40 mg/kg	Induce endoplasmic reticulum stress response, inhibit tumor growth, and promote immune regulation	JNK↑, c-Jun↑, PD-L1↑, IFN-γ↑, TNF-α↑, GzmB↑	(77)
Tanshinone IIA	*In vitro* and *in vivo*	10 μM; 0.5 mg/kg	Enhance cell lysis sensitivity and regulate cellular immunity	p-PERK↑, ATF4↑, CHOP↑, ULBP1↑, DR5↑	(105)
Tanshinone IIA	*In vitro* and *in vivo*	5 μM, 20 mg/kg	Inhibit aerobic glycolysis and block the energy metabolism of tumor cells	SIX1↓, PKM2↓, HK2↓, LDHA↓	(109)
Tanshinone IIA derivative TA25	*In vivo*	20 μM	Promote excessive generation of ROS and inhibit the proliferation, migration and invasion of cells	PI3K↓, Akt↓, mTOR↓, p53↑	(56)
Tanshinone IIA	*In vitro* and *in vivo*	2.5 μM; 20 mg/kg	Regulating lipid reprogramming to reverse acquired resistance to osimertinib	SREBP1↓, SREBP2↓, FASN↓, SCD↓, HMGCS1↓	(112)
Tanshinone IIA	*In vitro* and *in vivo*	2.5 μM; 20 mg/kg	Alter the lipid profile of cells and affect lipid metabolism in mutant lung cancer	SREBP1↓, FASN↓, SCD↓,	(113)
Dihydrotanshinone I	*In vitro* and *in vivo*	H520: 4.0 μM, H520: 3.5 μM; 10 mg/kg	Induce endoplasmic reticulum stress response and synergize with cisplatin to enhance the antitumor effect	HSPD1↓, JNK↑	(11)
Tanshinone IIA	*In vitro and in vivo*	4 μM Tan IIA + 0.2 μM Cisplatin; 15 mg/kg Tan IIA + 3 mg/kg Cisplatin	The combination of cisplatin exhibits a synergistic antitumor effect, inhibiting cell migration and invasion, blocking the cell cycle, and inducing cell apoptosis	Bax↑, Bcl-2↓, Caspase-3↓, p-Akt↓, p-PI3K↓	(117)
Tanshinone IIA	*In vitro and in vivo*	2.5 μM Tan IIA + 1 μM Gefitinib; 20 mg/kg Tan IIA + 25 mg/kg Gefitinib	Overcoming gefitinib resistance	SREBP1↓, FASN↓, SCD↓	(113)

Table I. Continued.

Bioactive tanshinones	Real modules (*In vitro*/*In vivo*)	Doses	Possible mechanisms	Targets	(Refs.)
Tanshinone IIA	*In vitro and in vivo*	2 μM Tan IIA + 40 nM Gefitinib; 20 mg/kg Tan IIA + 150 mg/kg Gefitinib	Reverse gefitinib resistance, promote cell apoptosis, inhibit cell growth, and suppress cell migration and invasion	VEGFR2↓, Akt↓	(120)
Tanshinone IIA	*In vitro*	60 μM, 12 μM	Inhibit cell proliferation and reverse paclitaxel resistance	PI3K↓, AKT↓, mTOR↓, MMP7↓	(121)
Acetyltanshinone IIA	*In vitro* and *in vivo*	2 μM; 25 mg/kg	Reduce the synthesis of cyclins, inhibit cell proliferation, and reverse the resistance to tyrosine kinase inhibitors	p70S6K↓, AURKA↓, EGFR↓, MET↓, p51↑, p21↑	(57)

TA25, tanshinone IIA derivative 25; ATA, acetyltanshinone IIA; CPT, cryptotanshinone; ROS, reactive oxygen species; miR, microRNA; circ, circular RNA; AURKA, Aurora kinase A; PLK1, polo-like kinase 1; CDK1, cyclin-dependent kinase 1; IBTK, inhibitor of Bruton tyrosine kinase; ULK2, Unc-51-like kinase 2; PARP1, poly(ADP-ribose) polymerase 1; NQO1, NAD(P)H quinone dehydrogenase 1; Cyt c, cytochrome c; PERK, protein kinase R (PKR)-like ER kinase; ATF4, activating transcription factor 4; CHOP, CCAAT/enhancer-binding protein homologous protein; DR5, death receptor 5; STAT3, signal transducer and activator of transcription 3; NFAT2, nuclear factor of activated T cells 2; FOXO3a, forkhead box O3a; ZO-1, zonula occludens-1; HMGB3, high mobility group box 3; TG2, transglutaminase 2; ERK, extracellular signal-regulated kinase; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; eEF-2K, eukaryotic elongation factor-2 kinase; NF-κB, nuclear factor-κB; PD-L1, programmed death-ligand 1; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor alpha; GzmB, granzyme B; ULBP1, UL16-binding protein-1; SIX1, sine oculis homeobox homolog 1; PKM2, pyruvate kinase M2; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; SREBP1, sterol regulatory element-binding protein 1; SREBP2, sterol regulatory element-binding protein 2; FASN, fatty acid synthase; SCD, stearoyl-CoA desaturase; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; HSPD1, heat shock protein family D (Hsp60) member 1; MET, mesenchymal-epithelial transition factor.

pathway (71,128,129), thereby coordinately promoting tumor cell apoptosis and reversing chemoresistance. These common molecular mechanisms provide a strong mechanistic basis for the cross-cancer antitumor application of tanshinones.

LC remains one of the most lethal malignancies worldwide. Owing to its high invasiveness, marked drug resistance, and highly complex tumor microenvironment, its clinical management is considerably more challenging than that of other solid tumors such as gastric, breast, and colorectal cancers, and its prognosis is similarly poor to that of liver cancer. In view of these pathological characteristics, the regulatory effects of tanshinones in LC appear to place greater emphasis on improving the tumor microenvironment. In terms of inflammatory regulation, tanshinones can maintain intestinal mucosal integrity, reduce LPS levels in the lung tumor microenvironment, suppress activation of the TLR4/NF-κB inflammatory signaling pathway, and thereby modulate the gut-lung inflammatory axis; to date, clear evidence for this specific mechanism has not been reported in other cancers such as gastric or liver cancer (102). At the immune level, Tan IIA can upregulate key ligands such as ULBP1 and DR5, directly acting on core signaling axes involved in NK cell recognition and killing of tumor cells, thereby enhancing the susceptibility of NSCLC cells to NK cell-mediated lysis and establishing a LC-specific mode of immune microenvironment intervention (105). By contrast, the anticancer effects of tanshinones in other malignancies may differ substantially according to the distinct pathological features of each cancer type. Taken together, tanshinones possess broad-spectrum antitumor potential. Their shared pan-cancer mechanisms provide the basis for cross-cancer application, whereas their LC-specific regulatory effects on inflammation and immunity differ markedly from the more common pathway-dependent modes of action observed in other malignancies. These distinctive features may offer novel directions and a stronger rationale for the targeted treatment of LC.

LC remains a major global health challenge accompanied by a heavy disease burden and severe clinical therapeutic dilemmas (130,131). Tanshinones exert significant antitumor effects against LC through multiple mechanisms, playing an important role in its treatment (Table I). They can block the cell cycle and regulate miRNA expression to suppress LC cell proliferation and viability, primarily by modulating diverse molecular pathways such as inhibition of the PI3K/Akt/mTOR signaling cascade and upregulation of miR-137. Moreover, tanshinones attenuate LC cell invasion and migration by regulating EMT, VEGF, and related signaling pathways, including ERK/Smad2 and EGF/VEGFR.

In addition, tanshinones have been shown to overcome immune escape, the major bottleneck in cancer immunotherapy, by modulating PD-L1 expression, activating NK cells, and remodeling the tumor immune microenvironment. Suppression of apoptosis and downregulation of tumor suppressors are major contributors to LC chemoresistance. As natural bioactive compounds, tanshinones can effectively reverse chemotherapy resistance when used in combination with conventional agents. Collectively, these findings highlight

the notable potential of tanshinones as promising therapeutic candidates for LC.

However, the clinical application of tanshinones remains limited due to their poor water solubility, low bioavailability, and potential drug resistance. The development and application of nanodrug delivery systems offer a promising strategy to overcome these challenges by improving the pharmacokinetic profiles of tanshinones, enabling targeted delivery, reducing resistance, and significantly enhancing therapeutic efficacy. Common nanoparticle formulations include liposomes, polymeric nanoparticles, dendrimers, nanoemulsions, micelles, and solid lipid nanoparticles (132). For instance, Lee *et al* (133) developed a tanshinone nanoemulsion that exhibited superior stability, enhanced permeability, and efficient tumor-site accumulation, thereby markedly improving its inhibitory effect on LC cell proliferation and growth. The multifunctionality and high efficiency of such delivery systems provide novel opportunities for LC treatment.

Despite these advances, several challenges remain to be addressed before tanshinones can be widely applied in clinical settings. Conventional extraction methods are insufficient to meet the demand for large-scale, high-purity production, while modern directional extraction and heterologous biosynthesis technologies are still at an early stage of development. Moreover, the extremely low aqueous solubility of tanshinones results in poor bioavailability and a short half-life, severely restricting their therapeutic potential. Clinical validation also lags behind preclinical progress, as most available studies are limited in quantity and quality, making it difficult to fully assess safety and efficacy. In addition, research on tanshinone-loaded nanoparticles and other nanocarriers remains limited, and large-scale industrial production continues to face technical challenges. Finally, although short-term combination therapies have shown no major adverse effects, the long-term safety profiles, optimal dosage ratios, and potential risks of such regimens require further investigation.

In summary, current evidence indicates that tanshinones hold great promise for the treatment of LC, although several challenges must be addressed before clinical translation. Future research should focus on elucidating the core regulatory networks underlying the multi-target actions of tanshinones, optimizing their pharmacokinetic properties through advanced delivery technologies, and integrating these insights into rational clinical trial design. Such efforts will provide novel perspectives for the development of tanshinone-based targeted formulations and their clinical applications in LC therapy.

Acknowledgements

Not applicable.

Funding

No funding was received

Availability of data and materials

Not applicable.

Authors' contributions

ZG wrote the manuscript and generated the figures. XL and PS collected and organized the literature. ZL and RL critically synthesized and interpreted findings. CC designed the scope and structure of the review. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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