

Salviae miltiorrhiza against human lung cancer: A review of its mechanism (Review)

QINGWEN AN^{1,2*}, MENGTING WU^{1,2*}, CHUQI YANG^{1,2}, YEWEN FENG^{1,2},
XUEFEI XU^{1,2}, HANG SU^{1,2} and GUANGJI ZHANG¹⁻³

¹School of Basic Medical Sciences, Zhejiang Chinese Medical University;

²Key Laboratory of Blood-Stasis-Toxin Syndrome of Zhejiang Province; ³Traditional Chinese Medicine

'Preventing Disease' Wisdom Health Project Research Center of Zhejiang, Hangzhou, Zhejiang 310053, P.R. China

Received August 23, 2022; Accepted January 10, 2023

DOI: 10.3892/etm.2023.11838

Abstract. Lung cancer is one of the commonest malignant tumors in the world today, causing millions of mortalities every year. New methods to treat lung cancer are urgently needed. *Salviae miltiorrhiza* Bunge is a common Chinese medicine, often used for promoting blood circulation. In the past 20 years, *Salviae miltiorrhiza* has made significant progress in the treatment of lung cancer and is considered to be one of the most promising methods to fight against the disease. A great amount of research has shown that the mechanism of *Salviae miltiorrhiza* against human lung cancer mainly includes inhibiting the proliferation of lung cancer cells, promoting lung cancer cell apoptosis, inducing cell autophagy,

regulating immunity and resisting angiogenesis. Research has shown that *Salviae miltiorrhiza* has certain effects on the resistance to chemotherapy drugs. The present review discussed the status and prospects of *Salviae miltiorrhiza* against human lung cancer.

Contents

1. Introduction
2. Active ingredients of *Salvia miltiorrhiza*
3. Mechanisms of active ingredients of *Salvia miltiorrhiza* against lung cancer
4. *Salvia miltiorrhiza* combined against lung cancer
5. Conclusions

Correspondence to: Professor Guangji Zhang, School of Basic Medical Sciences, Zhejiang Chinese Medical University, 526 Binwen Road, Hangzhou, Zhejiang 310053, P.R. China
E-mail: zgjtem@zcmu.edu.cn

*Contributed equally

Abbreviations: 3-MA, 3-methyladenine; CCL2, C-C motif chemokine ligand 2; CDK1, cyclin-dependent kinase; CHOP, CCAAT/enhancer binding protein homologous protein; CT, cryptotanshinone; CTN, methanol extract of *Salviae miltiorrhiza*; DDP, cisplatin; DR5, TRAIL receptor 2; DT, diterpene tanshinone; EMT, epithelial-mesenchymal transition; FHIT, fragile histidine triad; FMG, compatibility of *Salviae miltiorrhiza* and ginseng; ICTS, dihydrotanshinone; LLC, Lewis lung cancer; MDC, monosaccharide-based cardavelin; MDR1, multidrug resistance-associated protein 1; miR, microRNA; MMP, mitochondrial membrane potential; NAMPT, nicotinamide phosphoribosyl transfer Enzyme; NSCLC, non-small cell lung cancer; ROS, reactive oxygen species; S-3-1, a 2-allyl-3,4-dihydroxybenzaldehyde; Sal A, salvianolic acid A; Sal B, salvianolic acid B; STS, sodium tanshinone IIA sulfonate; T I, tanshinone I; T IIA, tanshinone IIA; TAM, Tumor-associated macrophages; TDT, tanshinones

Key words: *Salviae miltiorrhiza*, lung cancer, molecular mechanisms, review, traditional Chinese medicine

1. Introduction

Lung cancer is one of the commonest malignancies with the fastest growth in morbidity and mortality, and a great threat to human health and life (1). According to the GLOBOCAN 2020 global cancer morbidity and mortality statistical analysis compiled by the International Agency for Research on Cancer, lung cancer is still the main cause of cancer mortalities (18% of the total cancer mortalities) (2). Nearly half of newly diagnosed lung cancer cases are at an advanced stage at which the therapeutic effect is limited and the treatment process is painful (1). Although great progress has been made in the molecular mechanism of lung cancer, therapeutic interventions for lung cancer have only achieved modest benefits (3). Conventional chemotherapy also has the disadvantage of cytotoxicity to normal tissues (4). Therefore, finding more effective and safe drugs to prevent, inhibit or reverse the occurrence of lung cancer is still the focus of research.

The root of *Salvia miltiorrhiza* Bunge was first recorded in the *Shennong's Herbs* (5,6). It has the functions of promoting blood circulation, removing blood stasis and calming the mind. Promoting blood circulation and removing blood stasis is one of the common therapeutic principles in traditional Chinese medicine (TCM) for malignant tumors (7-9). Studies

of the anti-tumor effects of *Salvia miltiorrhiza* date back to the 1960s (10).

Since the 1980s, a number of studies have shown that *S. miltiorrhiza* has a prominent anti-tumor effect, especially the against lung cancer (5,11-13). Therefore, a number of experiments have been conducted to explore its mechanism against lung cancer. However, research on the anti-tumor effects of *S. miltiorrhiza* (Chinese name: Danshen) can be traced back to the 1970s. At that time, it was proposed that *S. miltiorrhiza* injection could promote lung metastasis in animal transplanted tumors (14), which attracted clinical interest. Subsequently, a study suggested that Tanshinone IIA sulfonate had no effect on promoting growth and metastasis of Lewis cancer and noted that different experimental methods of previous researchers resulted in different experimental results (15). Since the beginning of the 21st century, the research on anti-tumor effects of *S. miltiorrhiza* has been continuous and the results of these studies have been fruitful (16-19). The purpose of the present review was to summarize the mechanism of the active ingredients of *S. miltiorrhiza* against lung cancer in the past 20 years or so in order to evaluate the clinical value of *S. miltiorrhiza* against lung cancer.

S. miltiorrhiza is the dry root and rhizome of *S. miltiorrhiza*. It has been used in traditional Chinese medicine to treat obstruction of qi in the chest, heartache, abdominal pain, insomnia, irregular menstruation, skin ulcers and other diseases with the functions of analgesic and eliminating carbuncles (20). In modern times, the use of *S. miltiorrhiza* has been studied in the treatment of various cardiovascular and endocrine diseases, including coronary artery disease (21,22), angina (23), hepatitis (24,25), cancer and menstrual disorders (26,27). Related experimental research has also made good progress. In the past 20 years, a number of studies have focused on the mechanism of active components of *S. miltiorrhiza* against lung cancer (19,28).

2. Active ingredients of *Salvia miltiorrhiza*

S. miltiorrhiza contains a number of chemical constituents. According to the Chinese Pharmacopoeia (2020) (29), *S. miltiorrhiza* can be divided into lipophilic terpenes and water-soluble phenolic acids, fatty acids, lactones, polysaccharides, flavonoids and other components (Table I; Fig. 1). In addition, *S. miltiorrhiza* contains nitrogen-containing compounds, lactone compounds, polysaccharides, flavonoids, steroids, triterpenes and other active ingredients. *S. miltiorrhiza* has anti-atherosclerosis, cardioprotective and neuroprotective effects (5,11). In addition, *S. miltiorrhiza* can also lower blood sugar, regulate intracellular calcium ion concentration, inhibit inflammatory response, resist oxidation and scavenge oxygen free radicals together with other pharmacological effects (30-33). Modern pharmacological studies have shown that *S. miltiorrhiza* can be used for the treatment of various diseases, including cerebrovascular disease (34,35), coronary heart disease (36,37), Parkinson's disease (38), Alzheimer's disease (39-41), peptic ulcers (42), scars (43), chronic kidney disease (44,45), liver cirrhosis (46), osteoporosis, lung cancer and other diseases (40). *S. miltiorrhiza* is one of the traditional Chinese medicines that can be used as a health food, as announced by the National Health Commission of China (47).

It is compatible with other traditional Chinese medicines for the treatment of various diseases.

Phenolic acids. The main water-soluble components of *S. miltiorrhiza* are phenolic acids; among which salvianolic acids, salvianolic acid A (Sal A) and salvianolic acid B (Sal B) are the most abundant components (47,48). Salvianolic acid in *S. miltiorrhiza* has recognized biological activity (11). Whether *in vivo* or *in vitro*, most salvianolic acids have anti-inflammatory, antioxidant and free radical scavenging activities, which can protect cells from a variety of harmful factors (40,45,46). Although salvianolic acid can directly scavenge free radicals, they may not be present in the body at a high concentration (49). The antioxidant activity of salvianolic acid may increase the expression of antioxidant enzymes by activating nuclear factor E2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway (9), thus reducing the expression of peroxidase (50).

Diterpenoids. At present, >40 diterpenoids have been found in *S. miltiorrhiza* and they can be divided into two types according to their structure, namely o-quinone-type tanshinone and p-quinone-type rolitazone (17). Tanshinones are lipophilic light unstable active ingredients in *S. miltiorrhiza* including tanshinone IIA (T IIA), cryptotanshinone (CT), dihydrotanshinone (ICTS) and tanshinone I (T I), among others. The content of T IIA in tanshinone was the highest, followed by CT (51).

3. Mechanisms of active ingredients of *Salvia miltiorrhiza* against lung cancer

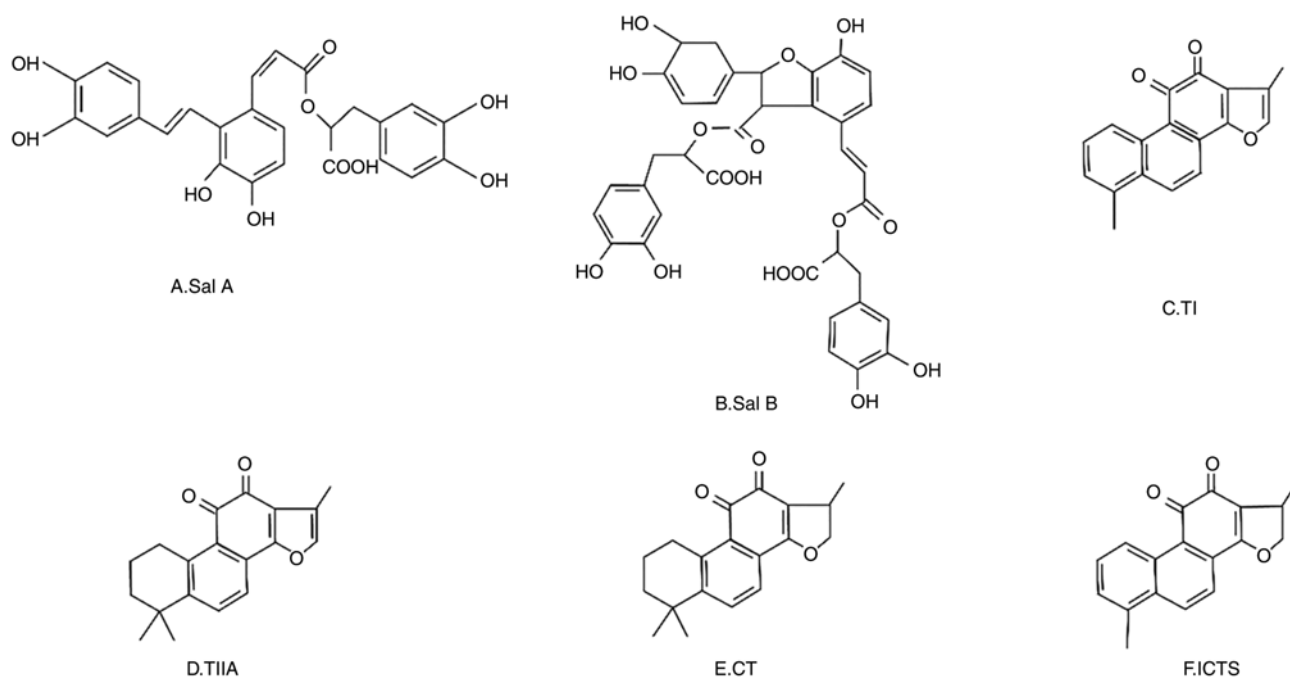
A number of studies have shown that different parts and different components of *S. miltiorrhiza* have effects against different types of non-small cell lung cancer (NSCLC) and the same component against the same type of lung cancer cells may involve multiple mechanisms of action, such as inhibiting cell proliferation, promoting cell apoptosis, inducing cell autophagy, regulating immune-related, fighting tumor angiogenesis and inhibiting cell migration and invasion (47,49,52,53) (Fig. 2).

Inhibiting lung cancer cell proliferation and growth. The continuous proliferation and growth of tumor cells is the basis of tumor invasion and malignant transformation (54). The mechanism of *S. miltiorrhiza* against the growth of lung cancer has been widely studied (47,55,56). Sal A, Sal B, CT and T IIA have been found to inhibit lung cancer A549 cells, SPC-A-1 cells, H1299 cells *in vitro* and Lewis cells *in vivo* (57,58). The main target proteins involved include p53, p21, the cyclin-dependent kinase inhibitor (CDKN) family, cyclin family, c-myc and Aurora-a (59). Target genes include c-myc, AURKA, EGFR, and microRNA (miR)-34a (60,61). Signal pathways include P46 [JNK/stress-activated protein kinases (SAPK)], phosphatase and tensed homolog (PTEN)/Akt, miR-146a-5p/EGFR axis and phosphoinositide 3-kinase/Akt (62).

Sal A, one of the active components from *S. miltiorrhiza*, suppresses the growth of mouse tumors (63). S-3-1 (a 2-allyl-3,4-dihydroxybenzaldehyde) is a synthetic intermediate of a Sal A derivative with strong inhibitory effects on the growth of cancer cells *in vitro* (64,65). In 2002, Li *et al* (64) found that S-3-1 at 20 mg/ml could significantly enhance gap junction-to-cell communication, reverse the transformed phenotype and inhibit tumors in human lung epithelial cancer

Table I. Classification of *Salvia miltiorrhiza*.

Classification of components of <i>Salvia miltiorrhiza</i>	Specific ingredients
Diterpenoids	Tanshinone IIA, Tanshinone IIB, Cryptotanshinone, Tanshinone I and dihydrotanshinone
Phenolic acids	Rosmarinic acid, salvianolic acid A, salvianolic acid B, danshensu and protocatechualdehyde
Other	Linoleic acid, linolenic acid, salvia lactone, neosalvianen, Baicalin β -Sitosterol, ursolic acid and carotene

Figure 1. The chemical structure of six *Salviae miltiorrhiza* monomers, which are widely considered by researchers to be effective anti-cancer compounds.

W1-38 cells and human lung adenocarcinoma A549 cells. S-3-1 inhibits the expression of c-myc gene in A549 cells (49). S-3-1 also inhibits the expression of P46 (JNK/SAPK) in A549 cells (66). Bi *et al* (67) noted that Sal A negatively mediates A549 lung cancer cell line growth or apoptosis, probably by positively regulating PTEN protein level. Sal A treatment significantly decreases A549 cell growth, promoting partial apoptosis and increasing mitochondrial membrane permeability. Western blot analysis showed that Sal A upregulates the PTEN protein level, while consistently downregulating Akt phosphorylation.

Shi *et al* (68) found that the growth rate and colony formation rate of SPC-A-1 cells are significantly reduced following T IIA treatment. T IIA can inhibit the growth and clonal formation of SPC-A-1 cells and may inhibit DNA synthesis by significantly upregulating the expression of p53 and P21 and downregulating the expression of CDKN2 (68). Chen *et al* (55) observed that following treatment of A549 cells with CT, the expression of cyclin B1, CDK1 and Cdc25C is downregulated at the gene and protein levels, while p21 is upregulated. The Cdc25 phosphatase family regulates the dephosphorylation of

cyclin B/cyclin-dependent kinase (CDK1) and triggers entry into mitosis and inhibits p53-induced growth inhibition (69). P21 (CIP1/WAF1) acts as a regulator of cell cycle progression and is controlled by the tumor suppressor protein p53. Growth inhibition of p21 can promote cell differentiation and death, prevent cell proliferation (59). Qi *et al* (66) showed that CT can inhibit the expression of EGFR in NSCLC cells and downregulation of EGFR can inhibit cell proliferation and cell cycle. EGFR is a direct target of mirNA-146A-5p and CT can inhibit the proliferation and growth of lung cancer by regulating miR-146A-5p/EGFR axis.

Zhang *et al* (70) showed that CT not only inhibits the basic phosphorylation levels of insulin-like growth factor 1 receptor (IGF-1R) and RAC- α serine/threonine protein kinase (Akt), but also blocks igF-1-induced igF-1R and Akt phosphorylation, thereby inhibiting the proliferation and migration of lung cancer cells. Another study demonstrated a novel mechanism of miR-34a regulation in human malignancies in which NF- κ B could regulate miR-34a expression (71). miR-34a targets TGF β R2 which inhibits the apoptosis of NSCLC cells. Studies have confirmed

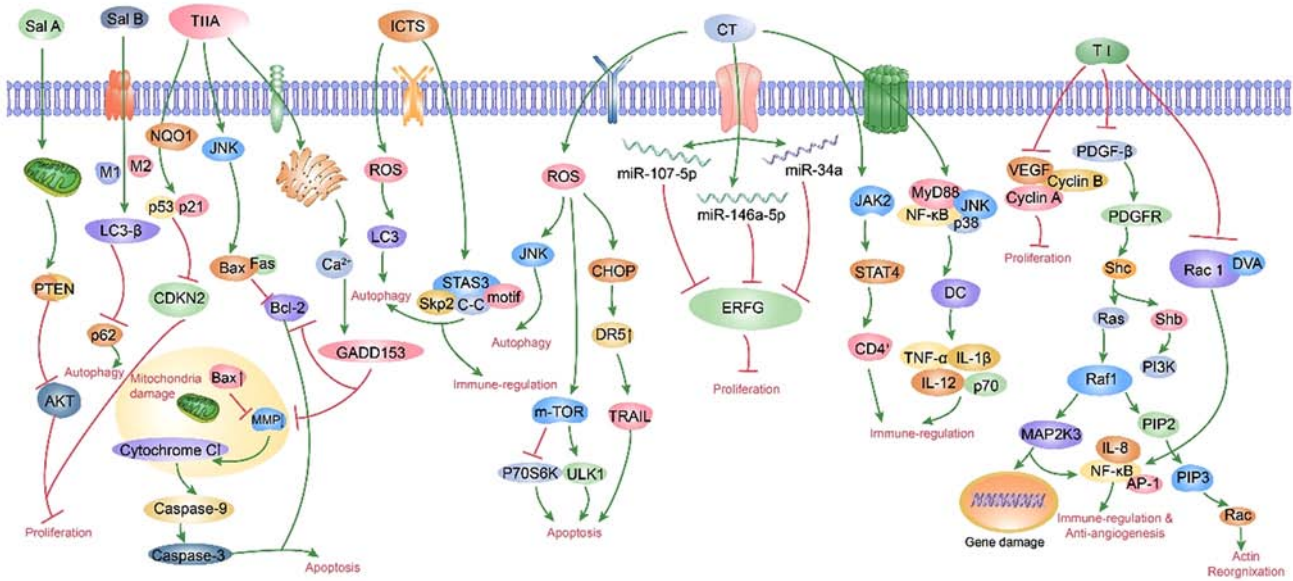


Figure 2. The active ingredients of *Salviae miltiorrhiza* signaling pathways against lung cancer include JAK/STAT, PTEN, p53, NF κB, Ras and mTOR signals and the targets include NQO1, MMP, STAT3 and CD4+. PTEN, recombinant phosphatase and tensin homolog; NQO1, NADPH quinone acceptor oxidoreductase 1; GADD153, Growth arrest and DNA damage-inducible 153.

that miR-34a can inhibit the tumor progression of lung cancer (72,73). miR-25, miR-32 and miR-92a/b are in the same miR family (74). Based on this, they may serve a role in specific cancers, mainly inhibiting cell proliferation and promoting apoptosis and preventing the cell cycle process (9,63). Shi *et al* (68) showed that ICTS I, T I, T IIA and CT all have a proliferation inhibitory effect on the SPC-A-1 cell line. The results showed that the structure of aromatic ring A can enhance cytotoxicity and the structure of Furan ring C can affect cytotoxicity. Aurora-A is recognized as an important molecular target for cancer treatment (75-77) and is a member of the carcinogenic family of novel mitotic serine/threonine kinases. A large body of evidence indicates the role of Aurora-A in centrosome maturation (78), spindle formation (79) and G₂-M transition (80). Aurora-A is frequently overexpressed in different types of cancers (81-85). The suppression of Aurora-A using short hairpin RNA inhibits tumor growth (86-89). Li *et al* (56) showed that tanshinone significantly downregulates the expression level of Aurora-A *in vitro*, whereas TI significantly downregulates the protein level of Aurora-A *in vivo*. CT and T I inhibit cell proliferation by preventing the cell cycle in the S phase, while T IIA prevents the cell cycle in the G₂-M phase. Cdc2, also known as CDK1 (cyclin-dependent kinase), serves an important role in the progression of the cell cycle and is considered an indispensable molecular target for the design of therapeutic anticancer drugs (90). Li *et al* (56) found that the expression of CDK2 is particularly inhibited by CT or T I treatment. Tung *et al* (91) compared the effects of T I and T IIA against lung cancer cells and concluded that T I inhibits the growth of lung cancer cells in a dose-dependent manner by inhibiting the expression of VEGF, Cyclin A and Cyclin B proteins and its effect is superior compared with T IIA. Their research confirmed that T I can eliminate lung function damage and the formation of lung adenocarcinoma.

Tian *et al* (92) found that T I could change lung adenocarcinoma gene expression and signal pathway. Simultaneously, hydrochloride ester can inhibit the growth of lung adenocarcinoma in nude mice and downregulate the expression levels of ATP7A and ATP7B.

Gao *et al* (93) confirmed that Tan IIA, as an EGFR signaling inhibitor, inhibits NSCLC cells by targeting egFR-Akt-mcl1 axis to inhibit EGFR signaling pathway. Tan IIA destroys the stability of McL-1, shortens the half-life and promotes the ubiquitination and degradation of McL-1. Tan IIA reduces the cell viability and colony formation of EGFR wild-type and activates mutant cell lines and inhibits tumor growth *in vivo*. Wang *et al* (94) observed that sodium *S. miltiorrhiza* inhibits the activity, migration and invasion of A549 and NCI-H1299 cells, promotes apoptosis and reduces the expression of proliferating cell nuclear antigen, MMP9 and Bcl-2, while upregulating Bax expression and inhibiting the PI3K/AKT pathway in A549 and NCI-H1299 cells. However, there was no cytotoxic effect on beAS-2B cell proliferation activity.

Promoting cell apoptosis. Inducing cell cycle arrest and apoptosis is one of the important mechanisms of anti-cancer compounds (95). CT, T IIA and methanol extract of *S. miltiorrhiza* (CTN) have been found to be effective in inhibiting NSCLC including *in vitro* tumor cells A549 cells, SPC-A-1 cells, H596-NQO1, Glc-82 cells, *in vivo* nude mouse lung tumors and nude mouse Glc-82 xenografts (19,68,96). *Salvia miltiorrhiza* promotes apoptosis of lung cancer cells, mainly through ferroptosis receptors, mitochondria and endoplasmic reticulum, stimulating p53, Bax, Fas, CCAAT/enhancer binding protein homologous protein (CHOP), caspase family, NQO1, ATF-4 and other target proteases as well as ERS-induced apoptosis pathway, such as IRE1α, Caspase 12 and PI3K/Akt (97,98).

Zinnah and Park (99) noted that CT can transform drug-resistant lung A549 cancer cells into tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-sensitive

cells. Mechanistically, CT-induced TRAIL receptor2 (DR5) does not depend on p53, but depends on the induction of CCAAT/CHOP. The cancellation of CHOP abolishes CT-induced DR5 expression and TRAIL-mediated cell death-related enhancement. The *in vitro* and *in vivo* experiments of Chen *et al* (55) showed that CT enhances the expression of p53 and Bax and downregulates the expression of Bcl-2. This apoptosis may be mediated by caspases. CT can cause growth inhibition of human lung cancer, cell cycle arrest, apoptosis and tumor formation *in vitro* and *in vivo*.

He *et al* (100) treated SPC-A-1 cells with T IIA and observed a large number of apoptotic cells using electron microscopy. Flow cytometry showed that the apoptosis index of tanshinone group was significantly higher than that of cisplatin (DDP) group and control group. They hypothesized that T IIA can induce the apoptosis of lung cancer SPC-A-1 cells via upregulating p53, Bax, Fas and downregulating the expression of Bcl-2.

Results of *in vivo* experiments showed that anticancer ketones have an antitumor effect on Lewis lung cancer in mice and its mechanism may be related to the induction of tumor cell apoptosis (101). Chiu and Su (57) noted that T IIA significantly inhibits the proliferation of A549 cells in a dose- and time-dependent manner. FACS results showed that when A549 cells were incubated with different concentrations of T IIA (control, 2.5, 5 and 10 mg/ml) for 48 h, the sub-G₁ phase increases. T IIA induces the production of ROS, Ca²⁺ and reduces mitochondrial membrane potential (MMP). Western blotting results showed that after 6, 12 and 24 h of culture with T IIA (5 mg/ml), p53 and Bax protein expression increased, but the proto-oncogene Bcl-2 significantly decreased. T IIA may induce apoptosis by reducing MMP and inducing a higher Bax/Bcl-2 ratio, thereby inhibiting the proliferation of NSCLC A549 cells (97). Liu *et al* (102) observed through *in vivo* experiments that T IIA induced NQO1 (+) A549 cells and H596-NQO1 cells to produce excessive ROS, DNA damage and apoptosis, but NQO1 (-) H596 cells without T IIA did not produce excessive ROS, DNA damage and apoptosis. T IIA treatment significantly delayed the growth of A549 tumor xenotransplantation, activated ROS triggered p53 independent and caspase-dependent mitochondrial apoptosis cell death pathway, cytochrome c release, and subsequent caspase activation and PARP-1 cleavage. Zhang *et al* (103) noted out that T IIA inhibits the growth of A549 cells, induces JNK signal activation and triggers caspase cascade apoptosis mediated by cytochrome c release. During the induction process, changes in mitochondrial morphology and loss of MMP are observed. In addition, T IIA induces apoptosis in A549 cells and this has been confirmed by typical morphological changes, in which cytochrome c is released from mitochondria and Bax is translocated into mitochondria. Caspase activity data shows that T IIA activates mitochondrial-mediated apoptosis of caspase-9 and caspase-3, but does not activate receptor-mediated apoptosis of caspase-8, which can be largely rescued by SP600125 (a JNK inhibitor). Kim *et al* (104) showed that T IIA increases TRAIL-induced cell death by selectively activating PERK/ATF4 and inhibiting STAT3-mediated DR5 upregulation and Survivin downregulation, indicating that the combined intervention of T IIA and TRAIL is a new treatment strategy for human NSCLC. NSCLC cells shows resistance to

TRAIL-mediated cell death, but the combined treatment of T IIA and TRAIL synergistically reduces cell viability and increases the apoptosis of TRAIL-resistant NSCLC cells. T IIA can greatly induce death receptor (DR) 5, but not DR4. Liu *et al* (105) found that NAMPT inhibition can synergistically induce NQO1 activation to induce apoptotic cell death. NAMPT catalyzes the first rate-limiting step in the conversion of nicotinamide to NAD(+), which is essential for a number of enzymes and regulatory proteins involved in various cellular processes, including deacetylation of the enzyme SIRT I, which can regulate a variety of tumor suppressors, including p53 and forkhead box (FOX)O. In Liu's study, NQO1 substrates T IIA and β -lapachone (β -lap) induce rapid depletion of the NAD(+) pool, but adaptively significantly upregulate NAMPT. The non-toxic inhibitory effect of FK866 on NAMPT significantly enhances the apoptosis induced by the NQO1 targeting agent. Compared with T IIA or β -lap treatment alone, co-treatment with FK866 induces more significant NAD(+) depletion and SIRT I activity inhibition, thereby increasing the accumulation of acetylated FOXO1 and activating apoptosis pathways.

Tanshinone significantly induces apoptosis of lung cancer cells *in vitro*, which is related to the downregulation of Bcl-2 and survivin gene expression and protein levels and increases the Bax/Bcl-2 ratio, which is a more reliable indicator of apoptosis (106-108). CT, T I and T IIA treatment induces dose-dependent apoptosis. Among the three tanshinones, T IIA is the most effective at inducing apoptosis. At a concentration of 2 μ M, its apoptosis increased by 5 times (from 2 to 10%) (90).

TRAIL is a promising anticancer drug. It has a unique cancer cell-specific pro-apoptotic effect, but its potential is greatly inhibited by acquired drug resistance (109). Stimulation with CT, T I or T IIA can effectively enhance the activity of TRAIL, thereby reducing the activity and inhibiting the proliferation of TRAIL-resistant TOV-21G and SKOV3. Among them, T IIA is the most effective and its IC₅₀ is 2.00 \pm 0.36 μ M (110). Zhang *et al* (103) found that tan IIA may induce cytochrome caspase cascade apoptosis through the JNK pathway. It induces apoptosis through mitochondrial release of cytochrome c and Bax migration towards mitochondria.

Shen *et al* (111) showed that diterpene tanshinone (DT) can induce apoptosis in nine human cancer cell lines with an IC₅₀ of 4.37-29 μ g/ml, of which PC9 and MCF-7 have the lowest values of IC. Fluorescence staining showed that the DT had a lethal effect on PC9 cells. Western blotting showed that caspase 3/9 and ATF-4 protein expression gradually decreased. However, the expression of PARP, cleaved caspase 3/9 and phosphorylated (p-)eIF2 α , p-JNK and caspase-12 gradually increased in a dose-dependent manner. Lou *et al* (112) noted that the endoplasmic reticulum stress-mediated apoptosis pathway is an effective way to promote tumor cell apoptosis and may be an important target for DT against lung cancer. The team used human lung adenocarcinoma PC9 cell line and nude mouse xenograft model as examples to verify the anti-lung cancer effect of DT *in vivo* and *in vitro* and clarified the IRE1 α /caspase 12 apoptosis pathway induced by ERS Its underlying mechanism. The results showed that, *in vivo*, DT can promote PC9 cell apoptosis in a concentration-dependent manner, upregulate the expression of Bip, IRE1 and TRAF2 proteins in tumor tissues and reduce tumor weight and weight

loss. *In vitro*, DT inhibits the proliferation of PC9 cell lines in a concentration-dependent manner, destroys the mitochondrial structure of PC9 cells, promotes the expression of Bax, IRE1 α , Bip, TRAF2 and caspase 12 proteins and reduces the expression of Bcl-2 protein. DT shows good anti-lung cancer effects both *in vivo* and *in vitro*. The mechanism is related to the activation of IRE1 α /caspase 12 apoptosis pathway induced by ERS and the promotion of apoptosis.

CTN is a methanol extract of *S. miltiorrhiza* and is an active compound that induces apoptosis through the mitochondrial apoptosis pathway and PTEN-mediated PI3K/Akt pathway inhibition. CTN induces significant ($P < 0.05$) and dose-dependent apoptosis in Glc-82 cells. Cell cycle analysis shows that CTN induces G₂/M phase arrest and significantly ($P < 0.05$) increases p53 and p21 levels and activates caspase-3/9 and PARP1 expression, suggesting that mitochondria are involved in apoptosis signals. In addition, CTN reduces the expression of anti-apoptotic proteins Bcl-2 and Bcl-x1 and increases the expression of pro-apoptotic protein Bax. The results also showed that CTN can increase the expression level of PTEN and reduce the phosphorylation level of Akt in Thr 308 and Ser 473 domains (19).

Xie *et al* (113) showed that tan IIA can restrain cell proliferation, induce apoptosis and arrest cell cycle at the S phase. It may block VEGF/VEGFR signal pathway, cause cell cycle arrest and indirectly inhibit downstream signal pathway and then upregulate the expression of apoptosis genes, downregulate anti-apoptosis genes and then inhibit the development, and promote the apoptosis, of tumor cells.

Kim *et al* (104) showed that tan IIA induced TRAIL sensitization of lung cancer cells by selective induction of endoplasmic reticulum stress. So, tan IIA may induce apoptosis of TRAIL via upregulating DR5 and downregulating Survivin via selective activation of PERK/ATF and inhibition of STAT3, respectively.

Chiu and Su (57) showed that tan IIA induces apoptosis by the abduction of ROS and by diminishing the mitochondrial membrane potential in A549 cells. Tan IIA might decrease the expression of Bcl-2 and increase Bax, p53 and Cyto-c and may work via the abduction of ROS and a higher scale of Bax/Bcl-2.

Liu *et al* (102) suggested that the apoptosis pathway by NQO1-activated and p53-independent mechanism determines the antitumor function of tan IIA against NSCLC. Tan IIA may activate ROS triggered, p53-independent and caspase-dependent mitochondria apoptotic mechanism by increased Bax/Bcl-xL, disruption of mitochondrial membrane potential, release of cytochrome c and caspase excitation and PARP-1 cleavage.

Some studies have also found that sodium T IIA sulfonate (STS) directly binds to fragile histidine triad diadenosine triphosphatase (FHIT) protein and inhibits the activity of FHIT AP3A hydrolase through competitive binding with the FHIT substrate binding site and induces tumor cell apoptosis (114,115).

Wu *et al* (116) found that dihydroisotanshinone I can inhibit the growth of A549 cells and H460 cells through apoptosis and ferroptosis and inhibit the transfer of A549 cells in a nude mouse model.

Inducing cell autophagy. Autophagy is essential for maintaining intracellular homeostasis and is also a mechanism of cell survival, involving the degradation and recycling of

cytoplasmic longevity proteins and organelles (117). Constitutive autophagy shows a clear pro-survival effect in cell damage and the imbalance of autophagy is considered a detrimental role in cell function and survival (118). There is convincing clinical and experimental evidence that macrophages promote cancer development and malignant progression. In response to activation signals, macrophages are 're-educated' and polarized to the M1 phenotype (pro-inflammatory) or M2 phenotype (anti-inflammatory). Tumor-associated macrophages mainly exhibit an M2-like phenotype (119) and a special subpopulation of macrophages may be an important new therapeutic target.

Li *et al* (120) proposed a new M2 macrophage tumor-promoting model, called 'autophagy angiogenesis effect'; polarized M2 macrophages induce the occurrence of abnormal autophagy, resulting in the degradation of autophagosome the level of NO and ROS in vascular endothelial cells increases, which in turn leads to abnormal vasodilation to stimulate hyperplasia and tumor progression. Consistent with this hypothesis, the study found that M2 macrophages lead to abnormal angiogenesis accompanied by abnormal autophagy, which eventually leads to tumorigenesis, while clodronate liposomes cause macrophage depletion, chloroquine-induced autophagy prevention or salvianolic acid B-induced vascular protection significantly reduced the occurrence of abnormal angiogenesis and lung cancer.

Hao *et al* (121) found that CT induces pre-death autophagy by activating JNK signaling mediated by increased intracellular ROS production. CT induces the formation of intracellular (ROS) in a concentration- and time-dependent manner, N-acetyl-L-cysteine (NAC), catalase, biphenyldiiodonium (DPI), pyrrole Alkyl dimethyl thiocarbamate (PDTC) and dichloromalo reverse this. In addition, NAC, JNK siRNA and SP600125 suppress CT-induced autophagy. NAC reverses CT-induced phosphorylation of JNK. NAC, 3-methyladenine (3-MA) and SP600125 partially reverse CT-induced cell death. CT (10 mg/kg) significantly inhibits tumor growth by 48.3% in A549 xenograft nude mice and this was completely reversed by NAC (50 mg/kg) combined therapy.

STAT3 is a potential drug target for chemotherapy. Guo *et al* (122) found that ICTS significantly inhibits STAT3 activity. ICTS inhibits the constitutive and inducible phosphorylation of STAT3 at Y705 without affecting the phosphorylation of STAT3 at S727 in A549 lung cancer cells. In addition, ICTS inhibits the nuclear translocation of STAT3. ICTS induces autophagy, as manifested by the accumulation of autophagic vesicles and increased expression of LC3 protein and autophagosomes. The autophagy inhibitor chloroquine can partially reverse ICTS-induced cell death. Docking assay predicts that both ICTS and CTS bind to the SH2 domain of STAT3. ICTS forms hydrogen bonds and pi-pi interactions with nearby amino acid residues of Lys591, Arg609 and Ser636. These findings indicate that ICTS (a natural compound) is a potent STAT3 inhibitor. ICTS induces apoptosis and promotes autophagy in A549 cells. Compared with CTS, ICTS has a stronger inhibitory effect on STAT3 phosphorylation and A549 cytotoxicity. ICTS induces autophagy, as manifested by the accumulation of autophagic vesicles and increased expression of LC3 protein and autophagosomes. The autophagy inhibitor chloroquine can partially reverse ICTS-induced cell death.

Zhang *et al* (123) found that tanshinone can upregulate the expression of miR-137 and miR-137 can significantly inhibit the proliferation of NSCLC cell lines through autophagy. The study proposes ULK2 and IBTK as potential targets for miR-137. ULK2 can act on the 3-kinase upstream of phosphatidylinositol that regulates the formation of autophagosomes and autophagosome precursors. As an inhibitor of BTK tyrosine kinase activity, IBTK plays a role in the development of B cells and interferes with BTK-mediated calcium mobilization and NF- κ B-mediated transcription.

The findings of Gao *et al* (124) indicate that total tanshinone (TDT)-induced apoptosis of 95D cells and protective autophagy are mediated by increased intracellular ROS production. TDT induces the production of ROS, while N-acetylcysteine (NAC) reverses it. NAC also reversed TDT-induced $\Delta\psi$ depolarization, monosaccharide-based cardavalin (MDC) staining, Bax upregulation, PARP lysis, Beclin-1, LC3-II and cell viability. Compared with T IIA, TDT showed more cytotoxic effects on 95D cells. Annexin V/7-AAD double staining, MMP depolarization ($\Delta\psi$), upregulation of pro-apoptotic proteins (e.g., cleaved PARP, cleaved caspase-3, Bax and Bad) and The downregulation of anti-apoptotic protein Bcl-2 is evidence of TDT-induced apoptosis. TDT-induced autophagy was demonstrated by up-regulation of MDC staining and autophagy-related proteins (such as LC3-II, Beclin-1, Atg3, Atg5, Atg7 and Atg12). Autophagy inhibitors 3-MA and bafilomycin A1 enhance TDT-induced cell death. 3-MA pretreatment enhances TDT-induced upregulation of Bax and PARP cleavage.

Wu *et al* (116) found that compared with the control group, the T IIA different concentration groups had a significant proliferation inhibitory effect on A549 cells and showed a time-dose-dependent relationship; T IIA can reduce the expression level of cyclin D1 of A549 cells and cause cell cycle arrest in G0 phase; it can also increase the ratio of LC3-II/LC3-I of A549 cells, decrease the expression of p62 and induce autophagy in cells. T IIA may induce cell cycle arrest by upregulating autophagy in human NSCLC A549 cells, thereby inhibiting cell proliferation and exerting anti-tumor effects (123).

Immune regulation. Tumor-associated macrophages (TAM) are derived from peripheral blood mononuclear cells recruited from tumors (119). The tumor promotion function of macrophages at the primary site includes supporting tumor-associated angiogenesis and promoting tumor cell invasion, migration and intravascular migration. TAMs may provide a microenvironment for the invasion and development of NSCLC (125). There is evidence that macrophages are affected by the tumor microenvironment, so they can stimulate tumor metastasis by releasing multiple compounds (including cytokines) (126). Chemokine (CC motif) ligand 2 (CCL2), previously known as monocyte chemoattractant protein-1, was first identified by its ability to attract monocytes *in vitro* (127,128). In lung cancer, the CCL2 signaling pathway is an important mechanism by which TAMs activate lung cancer cell growth and metastasis through two-way crosstalk between macrophages and lung cancer cells (129).

Man *et al* (130) noted that cryptotanshinone effectively inhibits tumor growth of H446 cells and proliferation of CD4⁺ T cells. Cryptotanshinone treatment increases the cytotoxicity

of CD4⁺ T cells, but does not affect the cytotoxicity of CD8⁺ T cells. Meanwhile, cryptotanshinone induces p-JAK2 and p-STAT4 protein expression in CD4⁺ T cells. These results suggest that cryptotanshinone inhibits lung tumor cell growth by activating the JAK2/STAT4 pathway to increase CD4⁺ T cell toxicity.

CT not only upregulates p53, downregulates cyclinB1 and Cdc2 and inhibits the proliferation of mouse Lewis lung cancer (LLC) cells, but it also induces LLC cell cycle arrest and is involved in the activation of NF- κ B, P38 and JNK. CO stimulation and MHC molecules upregulated by CT stimulates dendritic cells to produce TNF α , IL-1 β and IL-12P70. CT, when used in combination with low-dose anti-PD-L1, is effective against LLC tumors and induces subsequent long-term anti-LLC specific immunity. CT therapy promotes T cell infiltration and increases expression of genes typical for Th1 polarization in LLC tumor tissue (131). Wu *et al* (132) found that DT represses the phosphorylation of STAT3, the protein expression of S-phase kinase associated protein-2 (Skp2), including CCL2 and suppresses the macrophage recruitment ability of lung cancer cells. *S. miltiorrhiza* mediates the interruption of crosstalk between lung cancer cells and macrophages and the blocking of lung cancer cell proliferation. T I significantly inhibits the migration, invasion and gelatinase activity of CL1-5 cells stimulated by macrophage conditioned culture medium *in vitro* and reduces the tumorigenesis and metastasis of cl1-5 mice with severe combined immunodeficiency. T I decreases the transcriptional activity of interleukin-8 and stimulates DNA binding activity in CL1-5 cells by decreasing activator protein-1 and nuclear factor κ B. T I has anticancer effects *in vitro* and *in vivo* mainly mediated by interleukin-8, RAS-mitogen-activated protein kinase and Rac1 signaling pathway (133).

Inhibition of tumor angiogenesis. Angiogenesis is a key step in tumor growth. Compared to normal tissues, tumor vasculature is abnormal because of its high permeability, tortuosity and high inter-tissue pressure. The majority of patients with lung cancer who have failed treatment have distant metastases (134). Tumor cell metastasis is a complex, multi-step process involving the interaction between cancer cells and their surrounding microenvironment (135). Angiogenesis is a key step for tumor growth and metastasis (136). The expression level of VEGF-A 165 is positively correlated with the growth and spread of cancer cells (137,138). The development of drugs targeting VEGF-A 165 is an important focus of research.

Li *et al* (56) showed that T I inhibits the growth of H1299 tumors in *in vivo* and *in vitro* experiments, which is related to the inhibition of tumor angiogenesis. Jin *et al* (139) found that T I inhibits the expression of angiogenic factor IL-8 through the NF- κ B and AP-1 pathways, thereby inhibiting tumorigenesis, angiogenesis and metastasis. Chen *et al* (65) showed that T I inhibited the growth of lung cancer cells in a dose-dependent manner by inhibiting the expression of VEGF, Cyclin a and Cyclin B proteins, and its effect was better than T IIA. In addition, the transgenic mouse model of lung cancer induced by human vascular endothelial growth factor A165 (hVEGF-A165) gene was further tested for the treatment of lung cancer *in vivo*. TI significantly reduced the overexpression of hVEGF-A1-65 in transgenic mice to the normal level.

Therefore, the key mechanism of anti-tumor effect of TI treatment on angiogenesis and angiogenesis (56).

Sal A promotes the apoptosis of NSCLC cells, inhibits the migration and invasion ability of NSCLC cells and ultimately prevents the formation of vasculogenic mimicry by reducing the levels of EphA2, vascular endothelial cadherin and MMP2. Salvianolic acid A significantly blocked the expression of P-PI3K, p-Akt and p-mTOR in NSCLC cells, thereby affecting the PI3K/Akt/mTOR pathway. Therefore, Sal A can block the formation of vascular mimicry in human NSCLC through PI3K/AKT/mTOR pathway (91). Salvicine is a pharmacologically active derivative from *S. miltiorrhiza* and can effectively reduce the capillary-like tube formation of HMEC. In addition, it (30 μ M) significantly reduces the mRNA expression of bFGF in A549 cells, while the mRNA expression of VEGF remains unchanged (140).

Lung cancer cell invasion. Cell invasion is the first and most important step of metastasis. This is a complex process that involves the invasion of nearby cells by invasive cancer cells, which spread through the extracellular matrix (to the auxiliary sites) (30,32). Zhang *et al.* (141) propose that T II A can reduce the adhesion of lung cancer cells; methylpyrazine, T II A and rudulin can inhibit the invasion of PGCL3 cells in Boyden Chamber assay and conclude that blood activating drugs can inhibit or promote the invasion and metastasis of PGCL3 and PAa cells. Wang *et al.* (142) found through *in vitro* studies that in the process of inhibiting human NSCLC, STAT3 is not the only target of CT. It has been confirmed that CT upregulates the expression levels of miR-30d-5p, miR-126-3p, miR-133a, miR-338-3p and miR-451a and downregulates the expression levels of miR-21-5p and miR-96-5p, miR-182-5p and miR-205-5p. Among them, miR-133a was most significantly upregulates. miR-133a targets and downregulates the expression of MMP14; however, MMP15, MMP16 and MMP24 are unaffected. It has been determined that this process is independent of tissue inhibitors of metalloproteinase. CT can inhibit the invasion of human NSCLC, which may be due to the inhibition of MMP14 expression. T IIA can inhibit the growth of human NSCLC A549 and H1299 cells in a concentration-dependent manner and significantly reduce the number and size of cell clone clusters and inhibit the proliferation ability of A549 cells *in vitro*. Following T IIA treatment, A549 cell invasion and migration ability are reduced, the expression level of integrin α 2, integrin β 1, MMP2, MMP9, β -catenin and N-cadherin mRNA in the cells decreases and the expression level of E-cadherin mRNA increases (143).

4. *Salvia miltiorrhiza* combined against lung cancer

In recent years, researchers have turned their attention to *S. miltiorrhiza* combined with traditional anti-cancer therapy and *S. miltiorrhiza* compounds to fight lung cancer and have achieved certain results (65). *S. miltiorrhiza* can effectively reverse drug resistance (such as DDP and gefitinib) resistance, can improve the efficacy of radio-chemotherapy, effectively avoid drug resistance, enhance the body's anti-cancer sensitivity and has no toxic effect on the body (71,144). The main mechanism of action includes the reduction of the lung cancer multidrug resistance gene multidrug resistance-associated protein 1 (MDR1), inhibition of the c-met/AKT/mTOR

signaling pathway and inhibition of the Nrf2 pathway, thereby inhibiting the growth and proliferation of lung cancer cells and promoting cancer cell apoptosis (145). The mechanism of Dihydrotanshinone I against lung cancer includes inhibition of PTEN/PI3K/AKT pathway-induced apoptosis in lung cancer cells and inhibition of STAT3/VEGF/CDK2 to exert anti-angiogenesis and apoptosis effects (146).

***S. miltiorrhiza* combined with anti-cancer therapy.** Drug resistance is one of the main reasons for chemotherapy failure in the treatment of NSCLC. Chen *et al.* (147) divided human lung cancer A549 cells into normal control group and drug group and determined their MDR1 expression level by reverse transcription-quantitative PCR, which confirmed that Sal A reduced lung cancer multidrug resistance gene MDR1 may be regulated by miRNA expression and target gene. The effect of the method provides an experimental basis for further elucidating the mechanism of Chinese medicines in reversing multidrug resistance. Tang *et al.* (148) found that Sal A can improve the chemotherapeutic efficacy of DDP, indicating that Sal A and DDP have a synergistic effect, which mainly enhances the A549/DDP cells. The sensitivity of DDP effectively prevents the upregulation of multidrug resistance-associated protein 1 (MDR1) in A549/DDP cells.

Xia *et al.* (149) indicate that CT may be developed as a potential sensitizer in cooperation with anti-cancer drugs to combat chemoresistance cancer by inhibiting the Nrf2 pathway. CT can enhance the sensitivity of A549/DDP cells to DDP. In A549/DDP cells, the endogenous expression levels of Nrf2 and its target genes, including GCLC, GCLM, HO-1, NQO1 and MRP1, are much higher than that of A549 cells and CT partly restores the sensitivity of A549/DDP cells to DDP by muting Nrf2. Compared with DDP monotherapy, the combination of CT and DDP leads to cell death and apoptosis by sensitizing A549/DDP cells to DDP. Nrf2 knockout can eliminate this reversal effect. At the same time, it was also found that CT triggers other signals related to chemical resistance, such as MAPKs, Akt and STAT3 pathways.

CT can prevent radiation-induced lung injury (RILI) (150). CT can effectively maintain lung function in RILI rats, reduce early lung inflammation and infiltration and significantly reduce the levels of IL-6 and IL-10. In addition, CT is superior to prednisone in reducing collagen deposition and pulmonary fibrosis, while HYP (collagen indicator) and α -SMA (myofibroblast marker) are significantly reduced. In terms of mechanism, CT inhibits the expression of fibrosis signals TGF- β 1 and NOX-4 and at the same time increases the level of anti-fibrotic enzyme MMP-1 in lung tissue. CT treatment is superior compared with PND in enhancing MMP-1 levels. However, CT has little effect on the activation of CTGF and the inhibition of COX-2. Finally, CT treatment significantly reduces radiation-induced activation of CCL3 and its receptor CCR1.

T IIA can be developed as a new drug in postoperative adjuvant therapy together with other anti-tumor drugs and improve the sensitivity of chemotherapy drugs to NSCLC with fewer side effects. T IIA combined with doxorubicin can synergistically inhibit migration, induce apoptosis and prevent the cell cycle in S and G₂ phases of A549 cells. The two groups of monotherapy and combination therapy upregulate the expression of cleaved caspase-3 and Bax and downregulate

the expression of VEGF, VEGFR2, p-PI3K, p-Akt, Bcl-2 and caspase-3 protein. The molecular docking algorithm shows that, compared with doxorubicin, T IIA can be docked to the active sites of all tested proteins through H-bond and aromatic interactions (143). The experiment of Li (96) proved the anti-tumor activity of T IIA combined with cyclophosphamide on Lewis lung cancer mice and its effect on cellular immune function and concluded that the combination of T IIA and cyclophosphamide can downregulate Bcl-2 in lung cancer tissues and upregulates the expression of Bax, inhibits neovascularization of tumor tissue, enhances immune function and has significant anti-tumor activity. The combined treatment of T IIA and DDP has been shown to synergistically disrupt cell migration and invasion, arrest the cell cycle at S phase and induce apoptosis in A549 and PC9 cells. Kyoto Encyclopedia of Genes and Genomes pathway analysis and molecular docking indicate that T IIA may mainly affect the phosphatidylinositol 3-kinase-Akt signaling pathway. In all treatment groups, the expression levels of Bax and cleaved caspase-3 were upregulated, while the expression levels of Bcl-2, caspase-3, p-Akt and p-PI3K proteins were downregulated (151).

Gefitinib resistance is a major obstacle to the treatment of NSCLC. T IIA combined with gefitinib enhances the cytotoxic effect in gefitinib-resistant NSCLC cells and enhances the inhibitory effect on the proliferation, migration and invasion of gefitinib-resistant NSCLC cells. In addition, T IIA enhances the pro-apoptotic effect of gefitinib in gefitinib-resistant NSCLC cells by increasing the level of cleaved caspase 3. Simultaneously, T IIA increases the sensitivity of HCC827/ gefitinib cells to gefitinib by downregulating the VEGFR2/Akt pathway. *In vivo* experiments further confirmed that the combination of gefitinib and T IIA inhibits tumor growth in the mouse xenograft model of HCC827/ gefitinib (152).

S. miltiorrhiza can also be used with radiotherapy to enhance the effect of radiotherapy. Cao *et al* (153) noted that *S. miltiorrhiza* plus radiotherapy significantly prolonged tumor growth delay and inhibited tumor growth. The study proposes that *S. miltiorrhiza* is expected to become a sensitizer for chemotherapy and radiotherapy to enhance anticancer agents [such as TNF- α (154), 5-fluorouracil (155) and γ -ray cytotoxicity (156)]. *S. miltiorrhiza* enhances the radiation response of LLC in a mouse model and its mechanism may be related to the relief of tumor cell hypoxia after *S. miltiorrhiza* plus radiotherapy treatment, which is due to the improvement of tumor microcirculation and the remodeling of tumor vasculature.

S. miltiorrhiza injection and DDP chest injection combined to treat lung cancer malignant pleural effusion has special advantages; a definite curative effect and few side effects (157). The clinical observations of Wang *et al* (158) suggest that *S. miltiorrhiza* can effectively relieve venous thrombosis and can improve the completion rate of chemotherapy in lung cancer patients. T IIA can promote the anti-cancer effect of DDP, reduce the nephrotoxicity and bone marrow suppression caused by DDP and increase the levels of CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺ and NK cytokines in nude mice with lung cancer. The mechanism is related to downregulating the expression of IL-2 and IL-10 and regulating the Toll-like receptor 4 signaling pathway.

Bi *et al* (97) research on the compatibility of *S. miltiorrhiza* and *Panax ginseng* (FMG) shows that on the one hand, FMG may induce the apoptosis of lung cancer A549 cells, thereby affecting the proliferation of lung cancer, by reducing the formation of microfilaments, which can ultimately inhibit the proliferation, adhesion and metastasis of lung cancer. They found that FMG selectively inhibits lung cancer cell proliferation and induces apoptosis, but it does not have any cytotoxic effect on normal lung epithelial BEAS-2B cells. Moreover, FMG inhibits the migration and invasion of lung cancer cells. FMG significantly promotes p-PTEN expression and subsequently inhibits the PI3K/AKT signaling pathway. After FMG binds to PTEN protein, the phosphatase activity of PTEN protein increases, indicating that PTEN is one of FMG-targeting proteins. In addition, FMG regulates the expression of some marker proteins related to apoptosis, migration and invasion. The same team later discovered that the *S. miltiorrhiza*-FMG formula can inhibit tumor metastasis and growth by inhibiting epithelial-mesenchymal transition (EMT) involved in the PTEN/PI3K/AKT pathway in lung cancer cells (19,159) and can inhibit the invasion and migration of lung cancer cells by targeting PTEN. *In vivo*, the anti-tumor and anti-metastatic effects of *S. miltiorrhiza* formula treatment are related to the inhibition of EMT (97).

Geng *et al* (160) used compounded *S. miltiorrhiza* injection combined with Shenmai regimen to treat patients. Later, patients with advanced NSCLC were treated with compounded *S. miltiorrhiza* injection and Shenmai injection intravenously in combination with chemotherapy (pulmonary squamous cell carcinoma using CAP treatment plan, lung adenocarcinoma using a MAF plan) to treat NSCLC patients. The total improvement rate of intravenous injection of compound *Salvia miltiorrhiza* injection and Shenmai injection combined with chemotherapy was 69.7%, the total improvement rate of quality of life was 66.7%, and the median survival time was 10.7 months [5.6 months in the control group (P<0.01)]. The treatment group significantly reduced the toxic and side effects of chemotherapy and completed the chemotherapy course as scheduled. Zhang *et al* (6) used compound salvia miltiorrhiza and 654-2 injection combined with chemotherapy to treat 27 cases of NSCLC. The effective rate of the combined treatment was 37%, while the effective rate of the non-combined group was only 19.7%. It is hypothesized that the combination of compounded *S. miltiorrhiza* and 654-2 injection combined with chemotherapy can improve the efficacy of NSCLC.

Liang *et al* (11) used compounded *S. miltiorrhiza* dripping pills plus a gefitinib + DDP regimen to treat advanced NSCLC. The survival time of patients with advanced NSCLC is prolonged is significantly improved. One study investigated the role of c-met in DDP-resistant human lung cancer cell line A549/DDP and the reversal mechanism of salvianolic acid A, the active component of salvianolic acid. It found that salvianolic acid A can improve the chemotherapy effect of cisplatin, indicating that salvianolic acid A and cisplatin have synergistic effect. In addition, the present study found that salvianolic acid A enhanced the sensitivity of A549/DDP cells to cisplatin mainly by inhibiting the c-met/AKT/mTOR signal pathway. In conclusion, salvianolic acid A inhibits the expression of c-met and enhanced the

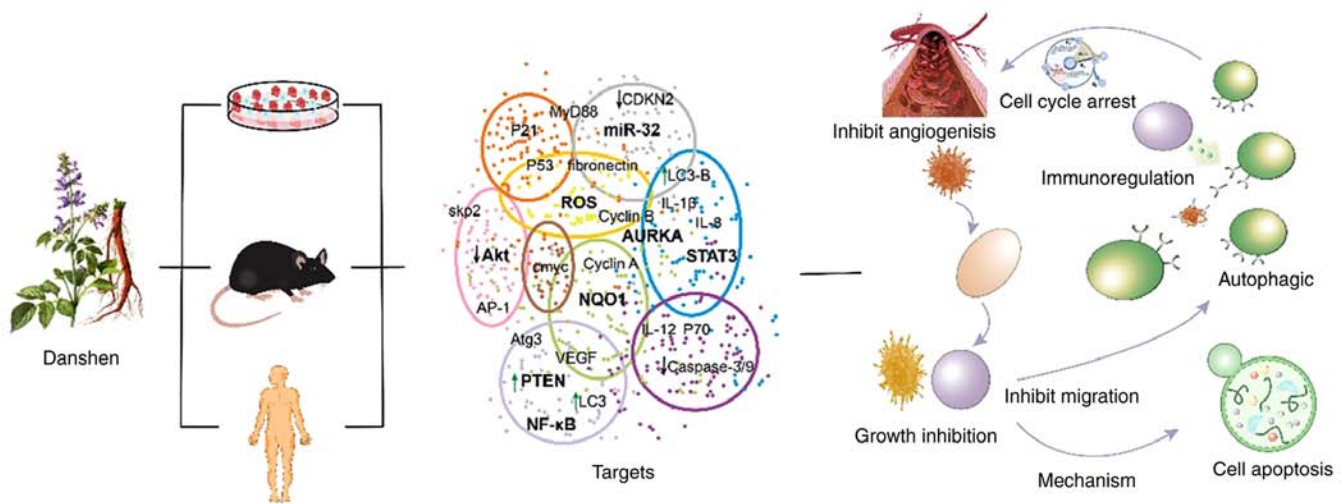


Figure 3. *Salviae miltiorrhiza* has anti-cancer effects on lung cancer cells in mice and humans with lung cancer and the mechanism of action mainly includes inhibiting cell proliferation promoting cell apoptosis, inducing cell autophagy, regulating immune-related macrophages, fighting tumor angiogenesis and preventing tumor cell invasion and metastasis.

sensitivity of lung adenocarcinoma A549 cells to cisplatin through AKT/mTOR signal pathway (148).

5. Conclusions

Research over the past 20 years has shown that *S. miltiorrhiza* has reached the status of 'single drug, multiple targets and multiple diseases'. *S. miltiorrhiza* and its compounds have achieved certain results in cell experiments, animal experiments and clinical studies. These results showed that *S. miltiorrhiza* can inhibit the proliferation and growth of lung cancer cells, induce cancer cell apoptosis, promote cancer cell autophagy and regulate immunity, fight tumor angiogenesis and inhibit cancer cell invasion. In addition, *S. miltiorrhiza* can effectively reverse the multi-drug resistance caused by traditional radiotherapy and chemotherapy, reduce its side effects, improve the efficacy of radiotherapy and chemotherapy and improve the quality of life of patients (Fig. 3). These studies provide a good proof for the anti-tumor effect of *S. miltiorrhiza*. However, there are still a number of imperfections in the anti-tumor research into *S. miltiorrhiza*: *S. miltiorrhiza* and its compounds had few studies on small cell lung cancer and more data is required; it is not known whether the clinical treatment results of *S. miltiorrhiza* for different types of lung cancer are different and the limitations and side effects of *S. miltiorrhiza* in the treatment of lung cancer are rarely reported. Generally, *S. miltiorrhiza* contains a variety of active ingredients with the potential to treat lung cancer and other tumors (19,136,161) and is expected to become a sensitizer for anti-cancer drugs and therapies; *S. miltiorrhiza* in combination with other Chinese medicines or chemotherapy drugs or radiation therapy can also treat lung cancer and other tumors in a number of ways. For example, Dan's participation in combination with oxaliplatin can reduce the neuropathic pain caused by chemotherapy and reduce the malignant tumor of glioblastoma cells (162). *S. miltiorrhiza* has a large research scope in the treatment of tumors and research into *S. miltiorrhiza* in the treatment of lung cancer has broad prospects.

A previous study evaluated the water extracts of 12 kinds of Chinese herbal medicines (Anemarrhena, Ginkgo, Myrrh, Pinellia, Rhododendron, Acacia, Ligustrum, Rhubarb, Rubia, Salvia, Yellow S and Uncaria) and found that all crude water extracts showed growth-inhibiting active cell lines for some or all kinds of cancers, indicating the potential use of traditional Chinese medicine as anti-tumor drugs and suggesting further separation of their mechanism of action and active anti-tumor compounds (163). The advantage of traditional Chinese medicine in anti-tumor is that it changes the biological behavior of tumor cells so as to inhibit their growth and development and to protect the normal function of the body, so that patients can survive with tumor, enjoy an extended life, a reduction in pain and a good quality of life. The main theoretical principle of traditional Chinese medicine treatment of cancer is 'Fu Zheng Qu Xie', which here means 'enhance the body's protective anti-cancer immune response and at the same time eliminate cancer cells or induce cancer cells to become normal cells. Chinese medicine or prescriptions have this dual ability to treat cancer and *S. miltiorrhiza* is the representative Chinese medicine with this dual ability. In recent years, the combination of prescriptions and anti-tumor research has provided new opportunities for the treatment of malignant tumors. The treatment of tumors with traditional Chinese medicine may become a breakthrough for humans to fight tumors. The study of traditional Chinese medicine prevention and treatment of cancer is of great significance to the health of all mankind.

Acknowledgements

The authors would like to thank Professor Guangji Zhang (School of Basic Medical Sciences, Zhejiang Chinese Medical University) for providing financial support for the publication of the present study. In addition the authors would like to thank the Zhejiang Chinese Medical University Library for its assistance in providing document access and account numbers.

Funding

The present study was supported by the research and development plan of Zhejiang Province-research on innovative drugs of traditional Chinese medicine (grant no. 2019C03072) and Key research project of Zhejiang Provincial Science and Technology Plan of Traditional Chinese Medicine Study (grant no. 2019ZZ006).

Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

QA and MW reviewed relevant literature and wrote the manuscript. YF and CY conceived the present study. GZ suggested revisions to the manuscript. HS and XX revised the manuscript. All authors read and approved the final manuscript. Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

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.

References

- Bade BC and Dela Cruz CS: Lung cancer 2020: Epidemiology, etiology, and prevention. *Clin Chest Med* 41: 1-24, 2020.
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
- Spiro SG and Silvestri GA: One hundred years of lung cancer. *Am J Respir Crit Care Med* 172: 523-529, 2005.
- Rébé C and Ghiringhelli F: Cytotoxic effects of chemotherapy on cancer and immune cells: How can it be modulated to generate novel therapeutic strategies? *Future Oncol* 11: 2645-2654, 2015.
- Su CY, Ming QL, Rahman K, Han T and Qin LP: *Salvia miltiorrhiza*: Traditional medicinal uses, chemistry, and pharmacology. *Chin J Nat Med* 13: 163-182, 2015.
- Zhang JP, Zhang YY, Zhang Y, Gao YG, Ma JJ, Wang N, Wang JY, Xie Y, Zhang FH and Chu L: *Salvia miltiorrhiza* (Danshen) injection ameliorates iron overload-induced cardiac damage in mice. *Planta Med* 79: 744-752, 2013.
- Xiong XJ, Wang Z and Wang J: Innovative strategy in treating angina pectoris with Chinese patent medicines by promoting blood circulation and removing blood stasis: Experience from combination therapy in Chinese medicine. *Curr Vasc Pharmacol* 13: 540-553, 2015.
- Tawil N and Rak J: Blood coagulation and cancer genes. *Best Pract Res Clin Haematol* 35: 101349, 2022.
- Qi Y: Progress of modern research on tumor blood stasis syndrome and its treatment with the method of promoting blood circulation by removing blood stasis. *J Tradit Chin Med* 15: 68-76, 1995.
- Li ZM, Xu SW and Liu PQ: *Salvia miltiorrhiza* Burge (Danshen): A golden herbal medicine in cardiovascular therapeutics. *Acta Pharmacol Sin* 39: 802-824, 2018.
- Liang WY, Chen WJ, Yang GH, Zhu D, Mao X, Shao YY, Wu LF, Zhang XX and Zhang LZ: Research progress on salvianolic acids of *Salvia miltiorrhiza*. *Zhongguo Zhong Yao Za Zhi* 41: 806-812, 2016 (In Chinese).
- Wang J, Xu J, Gong X, Yang M, Zhang C and Li M: Biosynthesis, chemistry, and pharmacology of polyphenols from Chinese *Salvia* species: A review. *Molecules* 24: 155, 2019.
- Pang H, Wu L, Tang Y, Zhou G, Qu C and Duan JA: Chemical analysis of the herbal medicine *Salviae miltiorrhizae* Radix et Rhizoma (Danshen). *Molecules* 21: 51, 2016.
- Guo R, Li L, Su J, Li S, Duncan SE, Liu Z and Fan G: Pharmacological activity and mechanism of tanshinone IIA in related diseases. *Drug Des Devel Ther* 14: 4735-4748, 2020.
- Liu MZ, Huang YS and Xiao WQ: No promoting effects of sodium tanshinone II-A sulfonate on growth and metastasis of Lewis carcinoma. *Zhongguo Yao Li Xue Bao* 12: 534-537, 1991 (In Chinese).
- Zhou J, Jiang YY, Chen H, Wu YC and Zhang L: Tanshinone I attenuates the malignant biological properties of ovarian cancer by inducing apoptosis and autophagy via the inactivation of PI3K/AKT/mTOR pathway. *Cell Prolif* 53: e12739, 2020.
- Yin ZK, Liu ZZ, Yuan X, Feng ZM, Jiang JS, Zhang X, Zhang PC and Yang YN: Thirteen undescribed diterpenoid quinones derived from the rhizomes of *Salvia miltiorrhiza* and their anti-tumor activities. *Phytochemistry* 191: 112902, 2021.
- Wang Y and Zhang D: Tanshinol inhibits growth of malignant melanoma cells via regulating miR-1207-5p/CHPF pathway. *Arch Dermatol Res* 312: 373-383, 2020.
- Ye YT, Zhong W, Sun P, Wang D, Wang C, Hu LM and Qian JQ: Apoptosis induced by the methanol extract of *Salvia miltiorrhiza* Bunge in non-small cell lung cancer through PTEN-mediated inhibition of PI3K/Akt pathway. *J Ethnopharmacol* 200: 107-116, 2017.
- Chen X, Guo J, Bao J, Lu J and Wang Y: The anticancer properties of *Salvia miltiorrhiza* Bunge (Danshen): A systematic review. *Med Res Rev* 34: 768-794, 2014.
- Qian W, Wang Z, Xu T and Li D: Anti-apoptotic effects and mechanisms of salvianolic acid A on cardiomyocytes in ischemia-reperfusion injury. *Histol Histopathol* 34: 223-231, 2019.
- Tang SM, Xing XY, Deng XH, Zhao NN, Li G, Yang RC, Sun GB and Sun XB: Research progress of Guanxin Danshen formula and its effective components in treating coronary artery heart disease. *Zhongguo Zhong Yao Za Zhi* 41: 3721-3726, 2016 (In Chinese).
- Ren J, Fu L, Nile SH, Zhang J and Kai G: *Salvia miltiorrhiza* in treating cardiovascular diseases: A review on its pharmacological and clinical applications. *Front Pharmacol* 10: 753, 2019.
- Shi MJ, Yan XL, Dong BS, Yang WN, Su SB and Zhang H: A network pharmacology approach to investigating the mechanism of Tanshinone IIA for the treatment of liver fibrosis. *J Ethnopharmacol* 253: 112689, 2020.
- Tang YX, Liu M, Liu L, Zhen BR, Wang TT, Li N, Lv N, Zhu Z, Sun G, Wang X and Chen S: Lipophilic constituents in *Salvia miltiorrhiza* Inhibit activation of the hepatic stellate cells by suppressing the JAK1/STAT3 signaling pathway: A network pharmacology study and experimental validation. *Front Pharmacol* 13: 770344, 2022.
- Tseng YJ, Hung YC, Kuo CE, Chung CJ, Hsu CY, Muo CH, Hsu SF and Hu WL: Prescription of #adix *Salvia miltiorrhiza* in Taiwan: A population-based study using the national health insurance research database. *Front Pharmacol* 12: 719519, 2021.
- Lee SR, Jeon H, Kwon JE, Suh H, Kim BH, Yun MK, Lim YJ and Kang SC: Anti-osteoporotic effects of *Salvia miltiorrhiza* Bunge EtOH extract both in ovariectomized and naturally menopausal mouse models. *J Ethnopharmacol* 258: 112874, 2020.
- Chen J, Wang Y, Wang S, Zhao X, Zhao L and Wang Y: Salvianolic acid B and ferulic acid synergistically promote angiogenesis in HUVECs and zebrafish via regulating VEGF signaling. *J Ethnopharmacol* 283: 114667, 2022.
- Xu X, Xu H, Shang Y, Zhu R, Hong X, Song Z and Wang Z: Development of the general chapters of the Chinese Pharmacopoeia 2020 edition: A review. *J Pharm Anal* 11: 398-404, 2021.
- Nie JM and Li HF: Therapeutic effects of *Salvia miltiorrhiza* injection combined with telmisartan in patients with diabetic nephropathy by influencing collagen IV and fibronectin: A case-control study. *Exp Ther Med* 16: 3405-3412, 2018.

31. Wang H, Kang Y, Li H, Huang S, Li W, Zheng M, Huang R, Lei B and Yang X: *Salvia miltiorrhiza* Derived carbon dots and their heat stress tolerance of Italian lettuce by promoting growth and enhancing antioxidant enzyme activity. *ACS Omega* 6: 32262-32269, 2021.
32. Duan ZZ, Li YH, Li YY, Fan GW, Chang YX, Yu B and Gao XM: Danhong injection protects cardiomyocytes against hypoxia/reoxygenation- and H₂O₂-induced injury by inhibiting mitochondrial permeability transition pore opening. *J Ethnopharmacol* 175: 617-625, 2015.
33. Li L, Sha Z, Wang Y, Yang D, Li J, Duan Z, Wang H and Li Y: Pre-treatment with a combination of Shenmai and Danshen injection protects cardiomyocytes against hypoxia/reoxygenation- and H₂O₂-induced injury by inhibiting mitochondrial permeability transition pore opening. *Exp Ther Med* 17: 4643-4652, 2019.
34. Wang Y, Shi Y, Zou J, Zhang X, Liang Y, Tai J, Cui C, Wang M and Guo D: Network pharmacology exploration reveals a common mechanism in the treatment of cardio-cerebrovascular disease with *Salvia miltiorrhiza* Burge. and *Carthamus tinctorius* L. *BMC Complement Med Ther* 20: 351, 2020.
35. Jin Y, Yu L, Xu F, Zhou J, Xiong B, Tang Y, Li X, Liu L and Jin W: Pharmacokinetics of active ingredients of *Salvia miltiorrhiza* and *Carthamus tinctorius* in compatibility in normal and cerebral ischemia rats: A comparative study. *Eur J Drug Metab Pharmacokinet* 45: 273-284, 2020.
36. Sun G, Li X, Wei J, Zhang T, Li B, Chen M, Wang Y, Chen K and Li Y: Pharmacodynamic substances in *Salvia miltiorrhiza* for prevention and treatment of hyperlipidemia and coronary heart disease based on lipidomics technology and network pharmacology analysis. *Biomed Pharmacother* 141: 111846, 2021.
37. Zhang Y, Wang J, Liu YM, Chen YY, Yang XC and Duan L: The synergistic effects of astragalus mongholicus and *Salvia miltiorrhiza* on coronary heart disease identified by network pharmacology and experiment. *Drug Des Devel Ther* 15: 4053-4069, 2021.
38. Subedi L and Gaire BP: Tanshinone IIA: A phytochemical as a promising drug candidate for neurodegenerative diseases. *Pharmacol Res* 169: 105661, 2021.
39. Chong CM, Su H, Lu JJ and Wang Y: The effects of bioactive components from the rhizome of *Salvia miltiorrhiza* (Danshen) on the characteristics of Alzheimer's disease. *Chin Med* 14: 19, 2019.
40. Guo Y, Li Y, Xue L, Severino RP, Gao S, Niu J, Qin LP, Zhang D and Brömme D: *Salvia miltiorrhiza*: An ancient Chinese herbal medicine as a source for anti-osteoporotic drugs. *J Ethnopharmacol* 155: 1401-1416, 2014.
41. Guo Y, Dong X, Zhang R, Zhong Y, Yang P and Zhang SY: *Salvia miltiorrhiza* improves Alzheimer's disease: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 99: e21924, 2020.
42. Liu L and Zhang HQ: Effects of Danshen Decoction on experimental gastric ulcer in rats and mice. *Zhong Xi Yi Jie He Xue Bao* 3: 35-38, 2005 (In Chinese).
43. He S, Yang Y, Liu X, Huang W, Zhang X, Yang S and Zhang X: Compound astragalus and *Salvia miltiorrhiza* extract inhibits cell proliferation, invasion and collagen synthesis in keloid fibroblasts by mediating transforming growth factor- β /Smad pathway. *Br J Dermatol* 166: 564-574, 2012.
44. Zhang W, Li J, Yang P, Wang G, Yue Y, Zhong Y, Liu H, Gui D, Xu Y and Wang N: Efficacy and safety of *Salvia miltiorrhiza* for treating chronic kidney diseases: A systematic review and meta-analysis. *Evid Based Complement Alternat Med* 2022: 2117433, 2022.
45. Ahn YM, Kim SK, Lee SH, Ahn SY, Kang SW, Chung JH, Kim SD and Lee BC: Renoprotective effect of tanshinone IIA, an active component of *Salvia miltiorrhiza*, on rats with chronic kidney disease. *Phytother Res* 24: 1886-1892, 2010.
46. Cao T, Lu Y, Zhu M, Cheng J, Ye B, Fang N, Cui Y, Xue B, Lari Najafi M and Kazemi E: Effects of *Salvia miltiorrhiza* and *Radix astragali* on the TGF- β /Smad/Wnt pathway and the pathological process of liver fibrosis in rats. *Cell Mol Biol (Noisy-le-grand)* 66: 46-51, 2020.
47. Shi M, Huang F, Deng C, Wang Y and Kai G: Bioactivities, biosynthesis and biotechnological production of phenolic acids in *Salvia miltiorrhiza*. *Crit Rev Food Sci Nutr* 59: 953-964, 2019.
48. Du G, Song J, Du L, Zhang L, Qiang G, Wang S, Yang X and Fang L: Chemical and pharmacological research on the polyphenolic acids isolated from Danshen: A review of salvianolic acids. *Adv Pharmacol* 87: 1-41, 2020.
49. Xu H, Li Y, Che X, Tian H, Fan H and Liu K: Metabolism of salvianolic acid A and antioxidant activities of its methylated metabolites. *Drug Metab Dispos* 42: 274-281, 2014.
50. Jin YM, Tao XM, Shi YN, Lu Y and Mei JY: Salvianolic acid B exerts a protective effect in acute liver injury by regulating the Nrf2/HO-1 signaling pathway. *Can J Physiol Pharmacol* 98: 162-168, 2020.
51. Jiang Z, Gao W and Huang L: Tanshinones, critical pharmacological components in *Salvia miltiorrhiza*. *Front Pharmacol* 10: 202, 2019.
52. Shahzadi I, Ali Z, Bukhari S, Narula AS, Mirza B and Mohammadinejad R: Possible applications of salvianolic acid B against different cancers. *Explor Target Antitumor Ther* 1: 218-238, 2020.
53. Zeng W, Shan W, Gao L, Gao D, Hu Y, Wang G, Zhang N, Li Z, Tian X, Xu W, *et al*: Inhibition of HMGB1 release via salvianolic acid B-mediated SIRT1 up-regulation protects rats against non-alcoholic fatty liver disease. *Sci Rep* 5: 16013, 2015.
54. Raudenská M, Navrátil J, Gumulec J and Masařík M: Mechanobiology of cancerogenesis. *Klin Onkol* 34: 202-210, 2021.
55. Chen L, Wang HJ, Xie W, Yao Y, Zhang YS and Wang H: Cryptotanshinone inhibits lung tumorigenesis and induces apoptosis in cancer cells *in vitro* and *in vivo*. *Mol Med Rep* 9: 2447-2452, 2014.
56. Li Y, Gong Y, Li L, Abdolmaleky HM and Zhou JR: Bioactive tanshinone I inhibits the growth of lung cancer in part via down-regulation of Aurora A function. *Mol Carcinog* 52: 535-543, 2013.
57. Chiu TL and Su CC: Tanshinone IIA induces apoptosis in human lung cancer A549 cells through the induction of reactive oxygen species and decreasing the mitochondrial membrane potential. *Int J Mol Med* 25: 231-236, 2010.
58. Han G, Wang Y, Liu T, Gao J, Duan F, Chen M, Yang Y and Wu C: Salvianolic acid B acts against non-small cell lung cancer A549 cells via inactivation of the MAPK and Smad2/3 signaling pathways. *Mol Med Rep* 25: 184, 2022.
59. Warfel NA and El-Deiry WS: p21WAF1 and tumourigenesis: 20 Years after. *Curr Opin Oncol* 25: 52-58, 2013.
60. Guan Z, Chen J, Li X and Dong N: Tanshinone IIA induces ferroptosis in gastric cancer cells through p53-mediated SLC7A11 down-regulation. *Biosci Rep* 40: BSR20201807, 2020.
61. Li Z, Zhang Y, Zhou Y, Wang F, Yin C, Ding L and Zhang S: Tanshinone IIA suppresses the progression of lung adenocarcinoma through regulating CCNA2-CDK2 complex and AURKA/PLK1 pathway. *Sci Rep* 11: 23681, 2021.
62. Li J, Wang K, Chen X, Meng H, Song M, Wang Y, Xu X and Bai Y: Transcriptional activation of microRNA-34a by NF- κ B in human esophageal cancer cells. *BMC Mol Biol* 13: 4, 2012.
63. Sun C, Su S, Zhu Y, Guo J, Guo S, Qian D, Yu L, Gu W and Duan JA: *Salvia miltiorrhiza* stem-leaf active components of salvianolic acids and flavonoids improved the hemorheological disorder and vascular endothelial function on microcirculation dysfunction rats. *Phytother Res* 34: 1704-1720, 2020.
64. Li HY, Li Y, Yan CH, Li LN and Chen XG: Inhibition of tumor growth by S-3-1, a synthetic intermediate of salvianolic acid A. *J Asian Nat Prod Res* 4: 271-280, 2002.
65. Chen XG, Li Y, Yan CH, Li LN and Han R: Cancer chemopreventive activities of S-3-1, a synthetic derivative of danshinone. *J Asian Nat Prod Res* 3: 63-75, 2001.
66. Qi P, Li Y, Liu X, Jafari FA, Zhang X, Sun Q and Ma Z: Cryptotanshinone suppresses non-small cell lung cancer via microRNA-146a-5p/EGFR axis. *Int J Biol Sci* 15: 1072-1079, 2019.
67. Bi L, Chen J, Yuan X, Jiang Z and Chen W: Salvianolic acid A positively regulates PTEN protein level and inhibits growth of A549 lung cancer cells. *Biomed Rep* 1: 213-217, 2013.
68. Shi H, Zhang Q, Li H, Chu T, Jin H and Mao S: Growth inhibition of tanshinones on SPC-A-1 cell line and their structure-activity relationship. *Zhongguo Fei Ai Za Zhi* 14: 7-12, 2011 (In Chinese).
69. Miyazaki T and Arai S: Two distinct controls of mitotic cdk1/cyclin B1 activity requisite for cell growth prior to cell division. *Cell Cycle* 6: 1419-1425, 2007.
70. Zhang J, Wen G, Sun L, Yuan W, Wang R, Zeng Q, Zhang G and Yu B: Cryptotanshinone inhibits cellular proliferation of human lung cancer cells through downregulation of IGF-1R/PI3K/Akt signaling pathway. *Oncol Rep* 40: 2926-2934, 2018.
71. Chen Y, Li H, Li M, Niu S, Wang J, Shao H, Li T and Wang H: *Salvia miltiorrhiza* polysaccharide activates T Lymphocytes of cancer patients through activation of TLRs mediated-MAPK and-NF- κ B signaling pathways. *J Ethnopharmacol* 200: 165-173, 2017.

72. Bandi N and Vassella E: miR-34a and miR-15a/16 are co-regulated in non-small cell lung cancer and control cell cycle progression in a synergistic and Rb-dependent manner. *Mol Cancer* 10: 55, 2011.
73. Shi Y, Liu C, Liu X, Tang DG and Wang J: The microRNA miR-34a inhibits non-small cell lung cancer (NSCLC) growth and the CD44hi stem-like NSCLC cells. *PLoS One* 9: e90022, 2014.
74. Wahlquist C, Jeong D, Rojas-Muñoz A, Kho C, Lee A, Mitsuyama S, van Mil A, Park WJ, Sluijter JP, Doevendans PA, *et al*: Inhibition of miR-25 improves cardiac contractility in the failing heart. *Nature* 508: 531-535, 2014.
75. Harrington EA, Bebbington D, Moore J, Rasmussen RK, Ajose-Adeogun AO, Nakayama T, Graham JA, Demur C, Hercend T, Diu-Hercend A, *et al*: VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. *Nat Med* 10: 262-267, 2004.
76. Dar AA, Goff LW, Majid S, Berlin J and El-Rifai W: Aurora kinase inhibitors-rising stars in cancer therapeutics? *Mol Cancer Ther* 9: 268-278, 2010.
77. Görgün G, Calabrese E, Hideshima T, Ecsedy J, Perrone G, Mani M, Ikeda H, Bianchi G, Hu Y, Cirstea D, *et al*: A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma. *Blood* 115: 5202-5213, 2010.
78. Hannak E, Kirkham M, Hyman AA and Oegema K: Aurora-A kinase is required for centrosome maturation in *Caenorhabditis elegans*. *J Cell Biol* 155: 1109-1116, 2001.
79. Marumoto T, Zhang D and Saya H: Aurora-A-a guardian of poles. *Nat Rev Cancer* 5: 42-50, 2005.
80. Hirota T, Kunitoku N, Sasayama T, Marumoto T, Zhang D, Nitta M, Hatakeyama K and Saya H: Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. *Cell* 114: 585-598, 2003.
81. Lentini L, Amato A, Schillaci T, Insalaco L and Di Leonardo A: Aurora-A transcriptional silencing and vincristine treatment show a synergistic effect in human tumor cells. *Oncol Res* 17: 115-125, 2008.
82. Kaestner P, Stolz A and Bastians H: Determinants for the efficiency of anticancer drugs targeting either Aurora-A or Aurora-B kinases in human colon carcinoma cells. *Mol Cancer Ther* 8: 2046-2056, 2009.
83. Compérat E, Bièche I, Dargère D, Laurendeau I, Vieillefond A, Benoit G, Vidaud M, Camparo P, Capron F, Verret C, *et al*: Gene expression study of Aurora-A reveals implication during bladder carcinogenesis and increasing values in invasive urothelial cancer. *Urology* 72: 873-877, 2008.
84. Lee ECY, Frolov A, Li R, Ayala G and Greenberg NM: Targeting Aurora kinases for the treatment of prostate cancer. *Cancer Res* 66: 4996-5002, 2006.
85. Matarasso N, Bar-Shira A, Rozovski U, Rosner S and Orr-Urtreger A: Functional analysis of the Aurora kinase A Ile31 allelic variant in human prostate. *Neoplasia* 9: 707-715, 2007.
86. Kumano M, Miyake H, Terakawa T, Furukawa J and Fujisawa M: Suppressed tumour growth and enhanced chemosensitivity by RNA interference targeting Aurora-A in the PC3 human prostate cancer model. *BJU Int* 106: 121-127, 2010.
87. Addepalli MK, Ray KB, Kumar B, Ramnath RL, Chile S and Rao H: RNAi-mediated knockdown of AURKB and EGFR shows enhanced therapeutic efficacy in prostate tumor regression. *Gene Ther* 17: 352-359, 2010.
88. Li Y, Zhang ZF, Chen J, Huang D, Ding Y, Tan MH, Qian CN, Resau JH, Kim H and The BT: VX680/MK-0457, a potent and selective Aurora kinase inhibitor, targets both tumor and endothelial cells in clear cell renal cell carcinoma. *Am J Transl Res* 2: 296-308, 2010.
89. Wang X, Dong L, Xie J, Tong T and Zhan Q: Stable knockdown of Aurora-A by vector-based RNA interference in human esophageal squamous cell carcinoma cell line inhibits tumor cell proliferation, invasion and enhances apoptosis. *Cancer Biol Ther* 8: 1852-1859, 2009.
90. Pérez de Castro I, de Cárcer G, Montoya G and Malumbres M: Emerging cancer therapeutic opportunities by inhibiting mitotic kinases. *Curr Opin Pharmacol* 8: 375-383, 2008.
91. Tung YT, Chen HL, Lee CY, Chou YC, Lee PY, Tsai HC, Lin YL and Chen CM: Active component of Danshen (*Salvia miltiorrhiza* Bunge), tanshinone I, attenuates lung tumorigenesis via inhibitions of VEGF, cyclin A, and cyclin B expressions. *Evid Based Complement Alternat Med* 2013: 319247, 2013.
92. Tian H, Li Y, Mei J, Cao L, Yin J, Liu Z, Chen J and Li X: Effects of *Salvia miltiorrhiza* extract on lung adenocarcinoma. *Exp Ther Med* 22: 794, 2021.
93. Gao F, Li M, Liu W and Li W: Inhibition of EGFR signaling and activation of mitochondrial apoptosis contribute to tanshinone IIA-mediated tumor suppression in non-small cell lung cancer cells. *OncoTargets Ther* 13: 2757-2769, 2020.
94. Wang M, Tang W, Gong N and Liu P: Sodium Danshensu inhibits the progression of lung cancer by regulating PI3K/Akt signaling pathway. *Drug Dev Res* 83: 88-96, 2022.
95. Lu Z, Zhou R, Kong Y, Wang J, Xia W, Guo J, Liu J, Sun H, Liu K, Yang J, *et al*: S-equol, a secondary metabolite of natural anticancer isoflavone daidzein, inhibits prostate cancer growth in vitro and in vivo, though activating the Akt/FOXO3a pathway. *Curr Cancer Drug Targets* 16: 455-465, 2016.
96. Li Q, Hu K, Tang S, Xu LF and Luo YC: Anti-tumor activity of tanshinone IIA in combined with cyclophosphamide against Lewis mice with lung cancer. *Asian Pac J Trop Med* 9: 1084-1088, 2016.
97. Bi L, Yan X, Yang Y, Qian L, Tian Y, Mao JH and Chen W: The component formula of *Salvia miltiorrhiza* and *Panax ginseng* induces apoptosis and inhibits cell invasion and migration through targeting PTEN in lung cancer cells. *Oncotarget* 8: 101599-101613, 2017.
98. Yan XJ, Yang Y, Bi L, Chen SS, Zhu JJ and Chen WP: Effects of component formula of *Salviae miltiorrhizae* Radix et Rhizoma and *Ginseng Radix et Rhizoma* on cell proliferation, apoptosis and skeleton in lung cancer A549 cells. *Zhongguo Zhong Yao Za Zhi* 39: 4436-4441, 2014 (In Chinese).
99. Zinnah KMA and Park SY: Sensitizing TRAIL-resistant A549 lung cancer cells and enhancing TRAIL-induced apoptosis with the antidepressant amitriptyline. *Oncol Rep* 46: 144, 2021.
100. He J, Zhou Q, Yuan S, Wang Y, Chen X and Qin J: The growth-inhibiting effect and its molecular mechanism of Tanshinone on human lung cancer cell line in vitro. *Zhongguo Fei Ai Za Zhi* 5: 123-125, 2002 (In Chinese).
101. Hu H, Zhang Y, Huang F and Deng H: Inhibition of proliferation and induction of apoptosis by tanshinone II A in NCI-H460 cell. *Zhong Yao Cai* 28: 301-304, 2005 (In Chinese).
102. Liu F, Yu G, Wang G, Liu H, Wu X, Wang Q, Liu M, Liao K, Wu M, Cheng X and Hao H: An NQO1-initiated and p53-independent apoptotic pathway determines the anti-tumor effect of tanshinone IIA against non-small cell lung cancer. *PLoS One* 7: e42138, 2012.
103. Zhang J, Wang J, Jiang JY, Liu SD, Fu K and Liu HY: Tanshinone IIA induces cytochrome c-mediated caspase cascade apoptosis in A549 human lung cancer cells via the JNK pathway. *Int J Oncol* 45: 683-690, 2014.
104. Kim EO, Kang SE, Im CR, Lee JH, Ahn KS, Yang WM, Um JY, Lee SG and Yun M: Tanshinone IIA induces TRAIL sensitization of human lung cancer cells through selective ER stress induction. *Int J Oncol* 48: 2205-2212, 2016.
105. Liu HY, Li QR, Cheng XF, Wang GJ and Hao HP: NAMPT inhibition synergizes with NQO1-targeting agents in inducing apoptotic cell death in non-small cell lung cancer cells. *Chin J Nat Med* 14: 582-589, 2016.
106. Israels LG and Israels ED: Apoptosis. *Oncologist* 4: 332-339, 1999.
107. Xu X, Lai Y and Hua ZC: Apoptosis and apoptotic body: Disease message and therapeutic target potentials. *Biosci Rep* 39: BSR20180992, 2019.
108. Pistritto G, Trisciuglio D, Ceci C, Garufi A and D'Orazi G: Apoptosis as anticancer mechanism: Function and dysfunction of its modulators and targeted therapeutic strategies. *Aging (Albany NY)* 8: 603-619, 2016.
109. Wu GS: TRAIL as a target in anti-cancer therapy. *Cancer Lett* 285: 1-5, 2009.
110. Chang CC, Lai JS, Tsai CS, Ma SW, Lin JY, Huang LR, Lu CH, Liao EC and Ho TF: Proapoptotic and TRAIL-sensitizing constituents isolated from *Salvia miltiorrhiza* (Danshen). *J Biosci Bioeng* 116: 516-523, 2013.
111. Shen L, Lou Z, Zhang G, Xu G and Zhang G: Diterpenoid tanshinones, the extract from Danshen (*Radix Salviae miltiorrhizae*) induced apoptosis in nine human cancer cell lines. *J Tradit Chin Med* 36: 514-521, 2016.
112. Lou ZH, Xia RM, Li XJ, Cheng RB, Shao KD and Zhang GJ: Anti-lung cancer mechanisms of diterpenoid tanshinone via endoplasmic reticulum stress-mediated apoptosis signal pathway. *Zhongguo Zhong Yao Za Zhi* 43: 4900-4907, 2018 (In Chinese).

113. Xie J, Liu J, Liu H, Liang S, Lin M, Gu Y, Liu T, Wang D, Ge H and Mo SL: The antitumor effect of tanshinone IIA on anti-proliferation and decreasing VEGF/VEGFR2 expression on the human non-small cell lung cancer A549 cell line. *Acta Pharm Sin B* 5: 554-563, 2015.
114. Chen D, Lin XX, Huang WH, Zhang W, Tan ZR, Peng JB, Wang YC, Guo Y, Hu DL and Chen Y: Sodium tanshinone IIA sulfonate and its interactions with human CYP450s. *Xenobiotica* 46: 1085-1092, 2016.
115. Zhou X, Pan Y, Wang Y, Wang B, Yan Y, Qu Y and Ke X: Tanshinones induce tumor cell apoptosis via directly targeting FHIT. *Sci Rep* 11: 12217, 2021.
116. Wu CY, Yang YH, Lin YS, Chang GH, Tsai MS, Hsu CM, Yeh RA, Shu LH, Cheng YC and Liu HT: Dihydroisotanshinone I induced ferroptosis and apoptosis of lung cancer cells. *Biomed Pharmacother* 139: 111585, 2021.
117. Singh R and Cuervo AM: Autophagy in the cellular energetic balance. *Cell Metab* 13: 495-504, 2011.
118. Sridhar S, Botbol Y, Macian F and Cuervo AM: Autophagy and disease: Always two sides to a problem. *J Pathol* 226: 255-273, 2012.
119. Fukuda K, Kobayashi A and Watabe K: The role of tumor-associated macrophage in tumor progression. *Front Biosci (Schol Ed)* 4: 787-798, 2012.
120. Li GG, Guo ZZ, Ma XF, Cao N, Geng SN, Zheng YQ, Meng MJ, Lin HH, Han G and Du GJ: The M2 macrophages induce autophagic vascular disorder and promote mouse sensitivity to urethane-related lung carcinogenesis. *Dev Comp Immunol* 59: 89-98, 2016.
121. Hao W, Zhang X, Zhao W, Zhu H, Liu ZY, Lu J and Chen X: Cryptotanshinone induces pro-death autophagy through JNK signaling mediated by reactive oxygen species generation in lung cancer cells. *Anticancer Agents Med Chem* 16: 593-600, 2016.
122. Guo S, Luo W, Liu L, Pang X, Zhu H, Liu A, Lu J, Ma DL, Leung CH, Wang Y and Chen X: Isocryptotanshinone, a STAT3 inhibitor, induces apoptosis and pro-death autophagy in A549 lung cancer cells. *J Drug Target* 24: 934-942, 2016.
123. Zhang B, Ma Z, Li X, Zhang C, Shao Y, Liu Z, Li Y and Jin Y: Tanshinones suppress non-small cell lung cancer through up-regulating miR-137. *Acta Biochim Biophys Sin (Shanghai)* 48: 768-770, 2016.
124. Gao H, Sun W, Zhao W, Hao W, Leung CH, Lu J and Chen X: Total tanshinones-induced apoptosis and autophagy via reactive oxygen species in lung cancer 95D cells. *Am J Chin Med* 43: 1265-1279, 2015.
125. Yuan A, Hsiao YJ, Chen HY, Chen HW, Ho CC, Chen YY, Liu YC, Hong TH, Yu SL, Chen JJ and Yang PC: Opposite effects of M1 and M2 macrophage subtypes on lung cancer progression. *Sci Rep* 5: 14273, 2015.
126. Pollard JW: Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer* 4: 71-78, 2004.
127. Valente AJ, Graves DT, Vialle-Valentin CE, Delgado R and Schwartz CJ: Purification of a monocyte chemotactic factor secreted by nonhuman primate vascular cells in culture. *Biochemistry* 27: 4162-4168, 1988.
128. Yoshimura T, Robinson EA, Tanaka S, Appella E, Kuratsu J and Leonard EJ: Purification and amino acid analysis of two human glioma-derived monocyte chemoattractants. *J Exp Med* 169: 1449-1459, 1989.
129. Schmall A, Al-Tamari HM, Herold S, Kampschulte M, Weigert A, Wietelmann A, Vipotnik N, Grimminger F, Seeger W, Pullamsetti SS and Savai R: Macrophage and cancer cell cross-talk via CCR2 and CX3CR1 is a fundamental mechanism driving lung cancer. *Am J Respir Crit Care Med* 191: 437-447, 2015.
130. Man Y, Yang L, Zhang D and Bi Y: Cryptotanshinone inhibits lung tumor growth by increasing CD4⁺ T cell cytotoxicity through activation of the JAK2/STAT4 pathway. *Oncol Lett* 12: 4094-4098, 2016.
131. Liu S, Han Z, Trivett AL, Lin H, Hannifin S, Yang D and Oppenheim JJ: Cryptotanshinone has curative dual anti-proliferative and immunotherapeutic effects on mouse Lewis lung carcinoma. *Cancer Immunol Immunother* 68: 1059-1071, 2019.
132. Wu CY, Cherng JY, Yang YH, Lin CL, Kuan FC, Lin YY, Lin YS, Shu LH, Cheng YC, Liu HT, *et al*: Danshen improves survival of patients with advanced lung cancer and targeting the relationship between macrophages and lung cancer cells. *Oncotarget* 8: 90925-90947, 2017.
133. Lee CY, Sher HF, Chen HW, Liu CC, Chen CH, Lin CS, Yang PC, Tsay HS and Chen JJ: Anticancer effects of tanshinone I in human non-small cell lung cancer. *Mol Cancer Ther* 7: 3527-3538, 2008.
134. Chu YW, Yang PC, Yang SC, Shyu YC, Hendrix MJ, Wu R and Wu CW: Selection of invasive and metastatic subpopulations from a human lung adenocarcinoma cell line. *Am J Respir Cell Mol Biol* 17: 353-360, 1997.
135. Chen JJ, Peck K, Hong TM, Yang SC, Sher YP, Shih JY, Wu R, Cheng JL, Roffler SR, Wu CW and Yang PC: Global analysis of gene expression in invasion by a lung cancer model. *Cancer Res* 61: 5223-5230, 2001.
136. Carmeliet P and Jain RK: Molecular mechanisms and clinical applications of angiogenesis. *Nature* 473: 298-307, 2011.
137. Tammela T, Enholm B, Alitalo K and Paavonen K: The biology of vascular endothelial growth factors. *Cardiovasc Res* 65: 550-563, 2005.
138. Ferrara N, Gerber HP and LeCouter J: The biology of VEGF and its receptors. *Nat Med* 9: 669-676, 2003.
139. Jin L, Chen C, Huang L, Bu L, Zhang L and Yang Q: Salvianolic acid A blocks vasculogenic mimicry formation in human non-small cell lung cancer via PI3K/Akt/mTOR signalling. *Clin Exp Pharmacol Physiol* 48: 508-514, 2021.
140. Zhang Y, Wang L, Chen Y and Qiang C: Anti-angiogenic activity of salvicine. *Pharm Biol* 51: 1061-1065, 2013.
141. Zhang P, Pei Y and Qi Y: Influence of blood-activating drugs on adhesion and invasion of cells in lung cancer patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 19: 103-105, 1999 (In Chinese).
142. Wang H, Zhang Y, Zhang Y, Liu W and Wang J: Cryptotanshinone inhibits lung cancer invasion via microRNA-133a/matrix metalloproteinase 14 regulation. *Oncol Lett* 18: 2554-2559, 2019.
143. Xie J, Liu JH, Liu H, Liao XZ, Chen Y, Lin MG, Gu YY, Liu TL, Wang DM, Ge H and Mo SL: Tanshinone IIA combined with adriamycin inhibited malignant biological behaviors of NSCLC A549 cell line in a synergistic way. *BMC Cancer* 16: 899, 2016.
144. Zhang XZ, Qian SS, Zhang YJ and Wang RQ: *Salvia miltiorrhiza*: A source for anti-Alzheimer's disease drugs. *Pharm Biol* 54: 18-24, 2016.
145. He SB, Zhang BX, Wang HH, Wang Y and Qiao YJ: Study on mechanism of *Salvia miltiorrhiza* treating cardiovascular disease through auxiliary mechanism elucidation system for Chinese medicine. *Zhongguo Zhong Yao Za Zhi* 40: 3713-3717, 2015 (In Chinese).
146. Chuang MT, Ho FM, Wu CC, Zhuang SY, Lin SY, Suk FM and Liang YC: 15,16-Dihydrotanshinone I, a compound of *Salvia miltiorrhiza* bunge, induces apoptosis through inducing endoplasmic reticular stress in human prostate carcinoma cells. *Evid Based Complement Alternat Med* 2011: 865435, 2011.
147. Chen FY, Bi L, Qian L, Gao J, Jiang YC and Chen WP: Identification of multidrug resistance gene MDR1 associated microRNA of salvianolic acid A reversal in lung cancer. *Zhongguo Zhong Yao Za Zhi* 41: 3279-3284, 2016 (In Chinese).
148. Tang XL, Yan L, Zhu L, Jiao DM, Chen J and Chen QY: Salvianolic acid A reverses cisplatin resistance in lung cancer A549 cells by targeting c-met and attenuating Akt/mTOR pathway. *J Pharmacol Sci* 135: 1-7, 2017.
149. Xia C, Bai X, Hou X, Gou X, Wang Y, Zeng H, Huang M and Jin J: Cryptotanshinone reverses cisplatin resistance of human lung carcinoma A549 cells through down-regulating Nrf2 pathway. *Cell Physiol Biochem* 37: 816-824, 2015.
150. Jiang Y, You F, Zhu J, Zheng C, Yan R and Zeng J: Cryptotanshinone ameliorates radiation-induced lung injury in rats. *Evid Based Complement Alternat Med* 2019: 1908416, 2019.
151. Liao XZ, Gao Y, Huang S, Chen ZZ, Sun LL, Liu JH, Chen HR, Yu L, Zhang JX and Lin LZ: Tanshinone IIA combined with cisplatin synergistically inhibits non-small-cell lung cancer in vitro and in vivo via down-regulating the phosphatidylinositol 3-kinase/Akt signalling pathway. *Phytother Res* 33: 2298-2309, 2019.
152. Wang R, Luo Z, Zhang H and Wang T: Tanshinone IIA reverses gefitinib-resistance in human non-small-cell lung cancer via regulation of VEGFR/Akt pathway. *Oncotargets Ther* 12: 9355-9365, 2019.

153. Cao HY, Ding RL, Li M, Yang MN, Yang LL, Wu JB, Yang B, Wang J, Luo CL and Wen QL: Danshensu, a major water-soluble component of *Salvia miltiorrhiza*, enhances the radioresponse for Lewis lung carcinoma xenografts in mice. *Oncol Lett* 13: 605-612, 2017.
154. Kim JH, Jeong SJ, Kwon TR, Yun SM, Jung JH, Kim M, Lee HJ, Lee MH, Ko SG, Chen CY and Kim SH: Cryptotanshinone enhances TNF- α -induced apoptosis in chronic myeloid leukemia KBM-5 cells. *Apoptosis* 16: 696-707, 2011.
155. Su CC: Tanshinone IIA potentiates the efficacy of 5-FU in Colo205 colon cancer cells *in vivo* through downregulation of P-gp and LC3-II. *Exp Ther Med* 3: 555-559, 2012.
156. Ye Y, Xu W, Zhong W, Li Y and Wang C: Combination treatment with dihydrotanshinone I and irradiation enhances apoptotic effects in human cervical cancer by HPV E6 down-regulation and caspases activation. *Mol Cell Biochem* 363: 191-202, 2012.
157. Xia R and Chen X: Effects of Danshen injection on the malignant obstructive jaundice in the SD rat model. *J Huazhong Univ Sci Technolog Med Sci* 26: 686-689, 2006.
158. Wang T, Fu X and Wang Z: Danshen Formulae for Cancer: A Systematic Review and Meta-Analysis of High-Quality Randomized Controlled Trials. *Evid Based Complement Altern Med* 2019: 2310639, 2019.
159. Yang Y, Qiu S, Qian L, Tian Y, Chen Y, Bi L and Chen W: OCF can repress tumor metastasis by inhibiting epithelial-mesenchymal transition involved in PTEN/PI3K/AKT pathway in lung cancer cells. *PLoS One* 12: e0174021, 2017.
160. Geng QX, Zhu XL and Zhang XH: Effect of combined therapy of shenmai and compound danshen injection on myocardial reperfusion injury after percutaneous coronary intervention in patients with acute myocardial infarction. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 24: 496-499, 2004 (In Chinese).
161. Zhang X, Luo W, Zhao W, Lu J and Chen X: Isocryptotanshinone induced apoptosis and activated MAPK signaling in human breast cancer MCF-7 cells. *J Breast Cancer* 18: 112-118, 2015.
162. Di Cesare Mannelli L, Piccolo M, Maione F, Ferraro MG, Irace C, De Feo V, Ghelardini C and Mascolo N: Tanshinones from *Salvia miltiorrhiza* Bunge revert chemotherapy-induced neuropathic pain and reduce glioblastoma cells malignancy. *Biomed Pharmacother* 105: 1042-1049, 2018.
163. Shen YD, Tian YX, Bu XZ and Gu LQ: Natural tanshinone-like heterocyclic-fused ortho-quinones from regioselective Diels-Alder reaction: Synthesis and cytotoxicity evaluation. *Eur J Med Chem* 44: 3915-3921, 2009.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.