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The mechanism and application of traditional Chinese medicine extracts in the treatment of lung cancer and other lung-related diseases

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Lung cancer stands as one of the most prevalent malignancies worldwide, bearing the highest morbidity and mortality rates among all malignant tumors. The treatment of lung cancer primarily encompasses surgical procedures, radiotherapy, and chemotherapy, which are fraught with significant side effects, unfavorable prognoses, and a heightened risk of metastasis and relapse. Although targeted therapy and immunotherapy have gradually gained prominence in lung cancer treatment, diversifying the array of available methods, the overall recovery and survival rates for lung cancer patients remain suboptimal. Presently, with a holistic approach and a focus on syndrome differentiation and treatment, Traditional Chinese Medicine (TCM) has emerged as a pivotal player in the prognosis of cancer patients. TCM possesses characteristics such as targeting multiple aspects, addressing a wide range of concerns, and minimizing toxic side effects. Research demonstrates that Traditional Chinese Medicine can significantly contribute to the treatment or serve as an adjunct to chemotherapy for lung cancer and other lung-related diseases. This is achieved through mechanisms like inhibiting tumor cell proliferation, inducing tumor cell apoptosis, suppressing tumor angiogenesis, influencing the cellular microenvironment, regulating immune system function, impacting signal transduction pathways, and reversing multidrug resistance in tumor cells. In this article, we offer an overview of the advancements in research concerning Traditional Chinese Medicine extracts for the treatment or adjunctive chemotherapy of lung cancer and other lung-related conditions. Furthermore, we delve into the challenges that Traditional Chinese Medicine extracts face in lung cancer treatment, laying the foundation for the development of diagnostic, prognostic, and therapeutic targets.

KEYWORDS

Chinese medicine extracts, non-small cell lung cancer, small cell lung cancer, pulmonary fibrosis, acute lung injury, treatment

1 Introduction

Primary bronchogenic lung cancer, commonly referred to as lung cancer, represents the most prevalent form of malignant tumor. It encompasses two primary subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC constituting a majority, accounting for 85%–90% of cases (Goldstraw et al., 2007). As per data from the 2020 World Cancer Report (GLOBOCAN), the global incidence of lung cancer surged to 2.2 million new cases, contributing to 11.4% of all newly reported cancer cases. Alarmingly, the number of fatalities reached 1.8 million, amounting to 18.0% of total cancer-related deaths. Both the incidence and mortality of this malignancy have consistently held the top position among malignant tumors, displaying a worrisome upward trajectory year after year (Li et al., 2023). Despite the armamentarium of Western medical interventions that encompass comprehensive approaches such as surgery, chemotherapy, radiation therapy, and molecular targeting, a staggering 80% of lung cancer patients already find themselves in the intermediate to advanced stages of the disease. Consequently, their 5-year survival rate remains dishearteningly low, at a mere 14%. Furthermore, these therapies are accompanied by significant side effects. A cascade of common toxic reactions during the chemotherapy process, including anemia, neutropenia, mucositis, or isopermeability, and special toxicity such as ototoxicity, nephrotoxicity, pulmonary toxicity, neurotoxicity, or Raynaud's syndrome (Zraik and Heß-Busch, 2021). Radiotherapy also bears noticeable side effects, such as lung injury may cause radiation pneumonia, acute respiratory distress syndrome, bronchiolitis obliterans with mechanical pneumonia, and other diseases (Latrèche et al., 2022). While targeted therapy stands out for its precision and reduced side effects compared to other modalities, it is not without its challenges, notably the potential to cause hypertension, anemia, fever, and acute phase reactions (Tímár and Uhlyarik, 2022). With the deepening exploration of traditional Chinese medicine, multiple studies have unveiled its potential to profoundly enhance the quality of life for patients and extend their survival. In clinical applications, traditional Chinese medicine has demonstrated its capacity to inhibit and eliminate tumor cells, while also alleviating the adverse reactions associated with radiotherapy and chemotherapy.

2 Treatment of lung cancer with traditional Chinese medicine extract

2.1 The mechanism of traditional Chinese medicine extract treatment for non-small cell lung cancer

2.1.1 Cell proliferation

Deregulated cell cycle progression stands as a pivotal catalyst for unbridled cell proliferation, ultimately culminating in the malignant transformation characteristic of cancer. A cornerstone in the quest to combat tumors lies in the inhibition of tumor cell proliferation. Traditional Chinese medicine extracts have emerged as a promising avenue for regulating the cell cycle by modulating the expression of genes integral to tumor proliferation, including cyclin, P53, PCNA, and reactive oxygen species, among others. For instance, a study by Zhu et al. (Zhu et al., 2021) unveiled the potential of licorice extract to curtail the growth of NSCLC. This effect was achieved by downregulating the expression of the CDK4-Cyclin complex, thus obstructing the G0/G1 phase progression in tumor cells. Furthermore, the compound resibufogenin, extracted from Venenum Bufonis, was found to activate GSK-3β in human lung cancer A549 cells, leading to the downregulation of cyclin D1 expression and instigating a G1 phase blockade (Ichikawa et al., 2015). Homoisoflavanone-1, isolated from polygonatum odoratum, exhibited notable prowess in inhibiting NSCLC growth and inducing apoptosis in a dose-dependent manner. This compound primarily arrested the cell cycle in the G2/M phase by activating the p38/p53 signaling pathway. Moreover, it spurred apoptosis in A549 cells through the regulation of mitochondrial/cysteine protease dependence and endoplasmic reticulum stress pathways (Ning et al., 2018). Salvia miltiorrhiza, specifically its methanol extract, tanshinone (CTN), demonstrated the capacity to induce cell cycle arrest in the G2/M phase. This effect was accompanied by an elevation in the expression of p53 and p21, as well as the activation of caspase-3/9 and PARP1. The net result was a pronounced inhibition of cell proliferation and the facilitation of early and late tumor cell apoptosis (Ye et al., 2017). Another extract from Salvia miltiorrhiza, tanshinone IIA, exhibited the ability to induce cell cycle arrest in the G1/S phase, impeding the progression of lung adenocarcinoma. This was achieved through the substantial downregulation of CCNA2, CDK2, AURKA, PLK1, and p-ERK expression (Li et al., 2021). Dioscin, sourced from Rhizoma Dioscoreae Nipponicae, wielded the power to significantly curtail the expression of p-AKT, MMP2, and PCNA, thereby inhibiting the *in vitro* proliferation, invasion, and migration of lung cancer cells. Additionally, it manifested the capability to reduce lung nodules, mitigate lung injury, and diminish mortality in mouse lung cancer models (Xi et al., 2022). The aqueous extract derived from Hedyotis diffusa, combined with Scutellaria barbata in an equal weight ratio (HDSB11), effectively diminished the expression of NLRP3, procapsase-1, caspase-1, PRAP, Bcl-2, and cyclin D1. This was accompanied by a reduction in the phosphorylation levels of NF-κB, ERK, JNK, and p38 MAPK, resulting in the inhibition of tumor cell proliferation (Lv et al., 2021). Hence, the multitude of traditional Chinese medicine monomers and extracts offer promise in the inhibition of tumor cell proliferation, cell cycle regulation, and the effective treatment of NSCLC.

2.1.2 Cell apoptosis

Apoptosis, known as programmed cell death (PCD), is a meticulously orchestrated process of active cell demise initiated by shifts in the body's internal and external environment or by death signals orchestrated through gene regulation. Tumors represent a complex spectrum of disorders characterized not only by abnormal cell proliferation and differentiation but also by irregular cell apoptosis. Recent research has unearthed compelling evidence regarding the impact of specific compounds on tumor cells. For instance, imperatorin derived from Angelica dahurica has been shown to modulate gene expression, upregulating p53 and Bax while simultaneously downregulating Mcl-1. This concerted action exerts a robust inhibitory effect on the autonomous growth of lung cancer cells (Choochuay et al.,

2013). Ethyl acetate extract from Selaginella doederleinii Hieron intervenes in the cell cycle, effectively blocking the S-phase. This action is achieved by upregulating Bax, downregulating Bcl-2, and activating caspase-9 and caspase-3. The resultant cascade of events leads to the loss of mitochondrial membrane potential and the induction of cell apoptosis (Sui et al., 2016). The combined effects of Ligustrum lucidum and Epimedium are marked by a decrease in α-SMA and Ki-67 protein expression, LC3-II/LC3-I ratio, and Bcl-2/Bax protein ratio. Conversely, they result in an upregulation of caspase-3, p-mTOR, and Bax, all of which inhibit lung tissue cell proliferation and autophagy while promoting apoptosis within the lung tissue and BALF (Ma et al., 2020). Research by Huang et al. (Huang et al., 2022) emphasizes the potential of Hedyotis diffusa extract to regulate VDAC2/3 activity by promoting Bax and inhibiting Bcl-2. This dynamic interaction culminates in iron-induced apoptosis within lung adenocarcinoma cells. Poria cocos extract exerts cytotoxicity on human lung adenocarcinoma cells by elevating Bax expression and Bcl-2 phosphorylation levels. Additionally, it activates caspase-3 and induces apoptosis, an effect associated with mitochondrial perturbation (Lee et al., 2018). Moreover, Tetramethylpyrazine (TMP), as demonstrated by Jiang et al. (Jiang R. et al., 2021), diminishes the expression of NLRP3, curbing the formation of inflammatory complexes, thereby reducing caspase-1 activation, cell apoptosis, and inflammatory responses. Cinnamomum cassia extracts have a dose-dependent inhibition on NSCLC cell proliferation, both *in vivo* and *in vitro*. They also induce cell apoptosis (Wu et al., 2017). Polygonatum odoratum extract modulates miR-RNA, Akt-NF-κB, and Akt-mTOR, thereby stimulating apoptosis and autophagy in lung cancer (Wu et al., 2016). Polygonatum odoratum lectin was found to inhibit the Akt-NF-κB pathway to trigger cell apoptosis, simultaneously inducing autophagy by impeding the Akt-mTOR pathway (Li et al., 2014). Acetone extract of Bupleurum scorzonerifolium (AE-BS) exhibits a dose-dependent inhibitory impact on the proliferation of A549 human lung cancer cells. This is achieved through the inhibition of telomerase activity and the activation of cell apoptosis (Cheng et al., 2003). Pure compound dihydroisotanshinone I (DT) extracted from Salvia miltiorrhiza activates caspase-3/9 and PARP1, culminating in cell arrest in the G2/M phase (Wu et al., 2021). The mechanisms underlying traditional Chinese medicine-induced apoptosis in lung cancer cells predominantly involve the regulation of apoptosis-related genes (e.g., p53, C-myc, Bax, Bcl-2), modulation of intracellular Ca^{2+} concentrations and ACMP, activation of the caspase protease family, inhibition of telomerase activity, and other facets that ultimately induce cell apoptosis and achieve the desired therapeutic effect in NSCLC.

2.1.3 Tumor angiogenesis

Tumor angiogenesis forms the cornerstone of tumor cell growth and metastasis, and the strategy for anti-tumor angiogenesis revolves around intervening in the regulatory factors of tumor vasculature and their functional connections. Among these factors, Vascular Endothelial Growth Factor (VEGF) and Cyclooxygenase-2 (COX-2) take center stage as pivotal vascular growth factors. Traditional Chinese medicine extracts have demonstrated their capability to hinder tumor growth and metastasis by effectively suppressing key vascular growth factors like VEGF and COX-2. For instance, the extract derived from Hedyotis diffusa exerts control over the Epithelial-Mesenchymal Transition (EMT) by inhibiting COX-2 protein expression. This action effectively curtails the metastatic potential of lung adenocarcinoma cells (Lin et al., 2019). In a separate study, Xie et al. (Xie et al., 2019) showcased the potential of DQA-modified paclitaxel plus ligustrazine micelles in downregulating the expression of VEGF, MMP-2, TGF-β1, and E-cadherin in lung cancer cells, thereby mitigating the metastatic tendencies of these cells. Furthermore, the extract of Ecliptae Herba has been found to significantly lower the levels of COX-2, TGF-β1, MMP-2, and α-SMA, while increasing the MMP-9/TIMP-1 ratio (You et al., 2015). This dual action serves to inhibit the formation of tumor blood vessels. Additionally, studies have revealed that the combination of Astragalus membranaceus and Angelica sinensis can reduce the expression of NF-κB, STAT3, HIF-1α, and VEGF, effectively impeding tumor growth in mice (Wu et al., 2019). Therefore, various traditional Chinese medicine monomers and extracts hold the potential to thwart tumor metastasis by intervening in tumor cell angiogenesis.

2.1.4 Tumor microenvironment

Malignant tumors encompass a complex interplay between tumor cells and non-tumor cell components, including fibroblasts, endothelial cells, lymphocytes, macrophages, and extracellular matrix. This ensemble is collectively referred to as the tumor microenvironment. The tumor microenvironment plays a pivotal role in the initiation and progression of tumors, and contemporary research endeavors are dedicated to unraveling the intricate mechanisms through which the tumor microenvironment regulates tumor development. In recent years, investigations have underscored the capacity of traditional Chinese medicine extracts to exert anti-tumor effects by influencing the tumor microenvironment.

2.1.4.1 Cell adhesion movement

Cell adhesion encompasses both homophilic adhesion between cancer cells and heterophilic adhesion between cancer cells and stromal cells. A reduction in the expression of specific adhesion molecules, such as E-cadherin, in tumor cells can lead to diminished homophilic cell adhesion. This, in turn, facilitates the detachment of tumor cells from the extracellular matrix. Epithelial-mesenchymal transition (EMT) denotes the transformation of epithelial cells into mesenchymal cells. It promotes cell metastasis and invasion, imbuing cells with stem cell characteristics, diminishing apoptosis and senescence, fostering immune evasion, and participating in physiological processes like tissue healing, organ fibrosis, and cancer initiation. Notably, during the EMT process, tumor cells develop resistance to chemotherapy and immunotherapy, allowing them to elude immune system surveillance. Metastasis stands as the primary factor contributing to the failure of lung cancer treatment, and inhibiting cell adhesion has emerged as a key focus of research within the realm of traditional Chinese medicine for curbing lung cancer metastasis. Xie et al. (Xie et al., 2019)observed that DQA-modified paclitaxel combined with ligustrazine micelles could downregulate the expression of VEGF, MMP2, TGF-β1, and E-cadherin in lung cancer cells, thus impeding lung cancer cell metastasis. Furthermore, research has revealed that the combination

of Trichosanthin (TCS) and TRAIL can regulate the expression of apoptosis-related proteins (caspase 3/8 and PARP), endogenous apoptosis-related proteins (Bcl-2 and Bax), invasion-related proteins (E-cadherin, N-cadherin, Vimentin, ICAM-1, MMP-2, MMP-9), and cell cycle-related proteins (P27, CCNE1, and CDK2) (You et al., 2018). This orchestrated modulation leads to cell apoptosis and S-phase arrest, thereby suppressing cancer cell proliferation and invasion. Cinnamomum cassia extract (CCE) inhibits TGF-β1-induced motility and invasiveness of lung cancer cells by curtailing the adhesion of damaged cells to collagen (Lin et al., 2017). In the context of TGF-β1-induced EMT, dioscin, extracted from Rhizoma Dioscoreae Nipponicae, significantly heightens the expression of epithelial markers (E-cadherin) and reduces interstitial markers (N-cadherin and Snail). This serves to inhibit EMT, effectively restraining the *in vitro* migration and invasion of lung cancer cells (Lim et al., 2017). Paeonol inhibits TGF-β1-induced EMT while concurrently upregulating the expression of miR-126-5p in lung cancer cells. This dual action results in decreased cell viability, thereby inhibiting the survival and metastasis of human lung cancer cells (Lv et al., 2022).

2.1.4.2 Extracellular matrix degradation

The successful invasion and metastasis of tumor cells within the body hinge on their ability to breach the formidable barriers presented by the basement membrane (BM) and the extracellular matrix (ECM), thereby gaining entry into the circulatory system. The pivotal steps in the invasion and metastasis process involve tumor cells initially adhering to extracellular matrix components (such as laminin, fibronectin, and collagen) through membrane surface receptors. Subsequently, they execute the degradation of the basement membrane and matrix by secreting an array of proteolytic enzymes. Finally, they undergo directed migration through the compromised basement membrane and matrix, ultimately entering the circulatory system. The expression and activity of matrix metalloproteinases (MMPs) are intricately linked with tumor invasion and metastasis, influencing various phases of tumor development. It is now established that traditional Chinese medicine can modulate the balance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) in lung cancer tissue. This modulation leads to the inhibition of urokinase-type plasminogen activator (u-PA) and cathepsin B (CB) secretion, thereby preventing the degradation of the extracellular matrix by lung cancer cells. Dioscin, extracted from Rhizoma Dioscoreae Nipponicae, serves as a potent example of this action. It significantly diminishes the expression of p-AKT, MMP-2, and PCNA, effectively restraining the proliferation, invasion, and migration of A549 and PC-9 cells. This effect extends to a reduction in lung nodules, lung injury, and mortality in mouse lung cancer models (Xi et al., 2022). By inhibiting MMP-2 and u-PA, Cinnamomum cassia extract suppresses the extracellular matrix degradation by lung cancer cells, effectively mitigating TGF-β1-induced invasion and metastasis of lung cancer cells (Lin et al., 2017). Additionally, research by Gao et al. (Gao et al., 2012) underscores the potential of Angelica sinensis extract to reduce MMP-2, MMP-9, TGF-β1, and TIMP-1 expression while elevating TIMP-2 levels. This dual action inhibits the growth and metastasis of lung cancer cells. Sinomenine, extracted from Sinomenium acutum, is another promising compound that reduces the expression of MMP-2, MMP-9, and extracellular matrix metalloproteinase inducer (EMMPRIN/CD147), while concurrently increasing the expression of RECK, TIMP-1, and TIMP-2. This effectively impedes the migration and invasion of lung adenocarcinoma cells (Shen et al., 2020). Shen et al. (Shen et al., 2017) have also identified a similar anti-metastatic mechanism within the extract of Solanum nigrum. Furthermore, solasodine exhibits an ability to reduce the expression of MMP-2, MMP-9, and extracellular matrix metalloproteinase inducer (EMMPRIN) while elevating the expression of RECK, TIMP-1, and TIMP-2, thereby thwarting cell invasion. Through the utilization of gelatin zymography, which measures the activity of matrix metalloproteinases (MMP-2/-9) in NCI-H460 cells, it has been demonstrated that cantharidin inhibits MMP-2/-9 enzyme activity in NCI-H460 cells (Hsia et al., 2016). Hence, an array of traditional Chinese medicines and their extracts wield the potential to influence the trajectory of lung cancer through their impact on the tumor microenvironment.

2.1.5 Body immunity function

Presently, research into the anti-tumor immune properties of active compounds within traditional Chinese medicine predominantly encompasses investigations into changes in immune cell activity, the expression of immune molecules, and the presentation of tumor antigens. Licorice extract, for instance, has demonstrated the ability to hinder the growth of NSCLC. It achieves this by elevating the abundance of PD-L1 protein, augmenting antigen presentation, and fostering the infiltration of $CD8^+$ T cells (Zhu et al., 2021). Jiang et al. (Jiang R. et al., 2021) discovered that Tetramethylpyrazine (TMP) can inhibit the polarization of M1-type macrophages *in vitro*, while to some extent promoting the repolarization of M2-type macrophages. This effect results in the reduction of the transcription and secretion of inflammatory factors (IL-1β, IL-18, TNF-β) induced by lipopolysaccharide (LPS). In the context of lung cancer patients, the plasma activated by phytohemagglutination (PHA) exerts an inhibitory influence on lymphocyte proliferation, CD69 expression, and the production of perforin and granzyme B. This inhibition can be partially or completely reversed by Ganoderma lucidum polysaccharides (Gl-PS) (Sun et al., 2014). Astragalus polysaccharides (PG2) play a pivotal role in significantly augmenting the M1/M2 macrophage polarization rate of NSCLC cells. This action is coupled with a substantial inhibition of cell proliferation, clone formation, and tumor sphere formation. PG2 also promotes the functional maturation of dendritic cells, thus enhancing the T cell-mediated anti-cancer immune response (Bamodu et al., 2019). In an investigation focused on the impact of Trichosanthin (TCS) on the anti-tumor immune response in a 3LL Lewis lung cancer tumor model, the results revealed that TCS elevates the percentage of effector T cells. It fosters robust proliferation of antigen-specific effector T cells and significantly augments the secretion of Th1 cytokines. Moreover, it induces the generation of more memory T cells in tumor-bearing mice. This is accomplished through TCS upregulating the expression of the lung cancer 1 tumor suppressor factor (TSLC1) in 3LL tumor cells and elevating the expression of its ligand class I restrictive T cell-related molecule (CRTAM) in effector T cells. This enhancement, in turn, intensifies the anti-tumor response and induces immune protection (Cai et al., 2011). Furthermore, in their experiment, Zhang et al.

(Zhang et al., 2015) noted that Atractylenolide I (AO-1) significantly curbed the production of TNF-α, IL-6, IL-1β, IL-13, and MIF in Bronchoalveolar Lavage Fluid (BALF), along with the production of BALF neutrophils and macrophages. Conversely, AO-1 was found to upregulate the production of IL-10 in BALF. Additionally, AO-I inhibited the expression of Toll-Like Receptor 4 (TLR4) and the activation of Nuclear Factor-Kappa B (NF-κB) induced by lipopolysaccharide (LPS).

2.1.6 Signal transduction pathways

The regulation of cellular signaling pathways has emerged as a promising frontier in the battle against lung cancer. Tanshinone IIA, for instance, induces cell cycle arrest in the G1/S phase by orchestrating the CCNA2-CDK2 complex and the AURKA/PLK1 pathway, thereby promoting apoptosis in lung adenocarcinoma cells (Li et al., 2021). In a study by Lin et al. (Lin et al., 2022), Xanthotoxol extracted from Angelica dahurica demonstrated its capacity to trigger cell cycle arrest, foster cell apoptosis, and inhibit Epithelial-Mesenchymal Transition (EMT) processes by downregulating PI3K-AKT signaling. This dual action effectively suppresses the proliferation and metastasis of NSCLC. The administration of Ligustrazine yields significant reductions in the levels of Wnt and β-catenin. Additionally, it downregulates PTEN levels and interrupts the Wnt/β-catenin signaling pathway, resulting in the inhibition of lung cancer cell invasion and proliferation (Dong et al., 2020). Cantharidin exhibits the capability to inhibit the migration and invasion of lung cancer cells, a phenomenon closely associated with the activation of the PI3K-AKT signaling pathway (Kim et al., 2013). Ophiopogon japonicus extract drives an increase in the expression of autophagy-related mediators (including the LC3-II/LC3-I ratio, Atg-3, Atg-7, and Beclin-1) in A549 cells. This activation of autophagy in lung cancer cells is rooted in the inhibition of the PI3K/Akt/mTOR signaling pathway (Chen et al., 2017). Ligustilide, extracted from Angelica sinensis, effectively regulates the proliferation, apoptosis, and aerobic glycolysis of NSCLC cells through the PTEN/AKT signaling pathway (Jiang X. et al., 2021). Astragalus polysaccharides (APS) exert their anti-tumor effects by inhibiting the protein and gene expression of S1PR1, STAT3, and p-STAT3 in the S1PR1/STAT3 signaling pathway (Shen et al., 2023). Glycyrrhizin hampers the migration and invasion of lung cancer cells, an effect intricately linked to its reduction in the activity of the JAK/STAT signaling pathway (Wu et al., 2018). A study by Wang et al. (Wang et al., 2022) unveiled that catalpol, extracted from Radix Rehmanniae, hinders the Nrf2/ARE signaling pathway, leading to a substantial decrease in the proliferation and migration abilities of lung cancer cells. The primary mechanism behind the anti-lung cancer effect of Fritillaria extract revolves around protein phosphorylation. The extract successfully inhibits tumor cell proliferation and AKT phosphorylation, with a predominant role played by the PI3K/AKT signaling pathway (Zhao et al., 2023). Salvia chinensis extract effectively inhibits the transcriptional activity of the Wnt/β-catenin pathway, eliciting significant inhibitory effects on tumor cells *in vitro* (Wang et al., 2017). Meanwhile, glycyrrhizic acid regulates autophagy related to the PI3K/AKT/mTOR pathway, thereby inhibiting the production of inflammatory factors induced by lipopolysaccharide (LPS) in Acute Lung Injury (ALI) (Qu et al., 2019). A comprehensive summary of the specific extracts and their regulatory mechanisms within traditional Chinese medicine is provided in Table 1.

2.2 Application of traditional Chinese medicine extract for non-small cell lung cancer

2.2.1 Effect on chemotherapy drugs

Cisplatin (DDP) is a widely employed chemotherapy drug for lung cancer treatment (Ju et al., 2020; Liu et al., 2022). However, the development of gefitinib resistance (GR) is an inevitable challenge in the course of NSCLC therapy. Emerging research has shown that combining various traditional Chinese medicines with cisplatin can mitigate tumor cell resistance to cisplatin and enhance their anti-tumor potency. Bamodu et al. (Bamodu et al., 2019) reported a significant time-dependent reduction in the M2-associated tumor cell population with astragalus polysaccharides (PG2) treatment. This synergistically improved the anti-cancer efficacy of cisplatin on M2 cells and suppressed the growth of xenograft tumors in a NSCLC mouse model. Furthermore, the presence of PG2 significantly alleviated the side effects linked to cisplatin treatment. Cheng et al. (Cheng Z. et al., 2022)found that the extract of Ophiopogon japonicus exhibited a more pronounced cytotoxic effect on cisplatin-resistant lung cancer cells compared to normal tumor cells. Ophiopogonin B (OP-B) was shown to reduce tumor cell resistance to cisplatin by promoting Caspase-1/GSDMD-dependent pyroptosis. Ganoderma lucidum Polysaccharide (WSG), a glucose-rich polysaccharide derived from Ganoderma lucidum, demonstrated enhanced inhibition of lung cancer both *in vitro* and *in vivo* when combined with cisplatin. This combined treatment led to a synergistic reduction in the growth of lung cancer cells, enhancing the apoptosis response mediated by cisplatin. Additionally, WSG reduced the cytotoxic effects of cisplatin on macrophages and normal lung fibroblasts (Qiu et al., 2021). Artemisia argyi extract effectively suppressed both parent and gemcitabine-resistant lung cancer cells by inducing ROS production, mitochondrial membrane depolarization, and apoptosis, while mitigating Epithelial-Mesenchymal Transition (EMT) (Su et al., 2022). The ethanol extract of Centipeda minima intensified cisplatin-induced cell apoptosis in NSCLC xenografts (Gao et al., 2023). The anti-cancer efficacy of cordycepin, both *in vitro* and *in vivo*, was found to be comparable to afatinib and even superior to gefitinib. This suggests that cordycepin, either in isolation or combined with existing targeted therapies, might provide additional treatment options for drug-resistant NSCLC (Wei et al., 2019). The combination of Cordyceps sinensis extract Cordycepin and cisplatin exhibited a synergistic effect in inhibiting proliferation and promoting apoptosis in NSCLC cells, both in the presence and absence of cisplatin resistance. This anti-tumor activity was associated with the activation of AMPK and the inhibition of the AKT pathway, thereby enhancing the inhibitory effects of cisplatin on NSCLC (Liao et al., 2021). β-elemene, extracted from Radix curcuma wenyujin, acted synergistically with cisplatin against NSCLC cells by promoting apoptosis and impairing glucose metabolism, combating multidrug resistance, and preserving stemness (Cheng G. et al., 2022). The combination of lithospermum extract shikonin with gefitinib displayed a synergistic anti-tumor effect *in vitro* and *in vivo*. The potential molecular mechanisms appeared to be linked to the inhibition of PKM2/STAT3/cyclinD1 (Tang et al., 2018). Experiments have also

TABLE 1 Mechanism of action of traditional Chinese medicine extract in the treatment of non-small cell lung cancer.

Function mechanism		Traditional Chinese medicine and its extracts	Key gene expression	References
Cell proliferation		Licorice extract	downregulating the expression of CDK4-Cyclin complex	Zhu et al. (2021)
		Venenum Bufonis (resibufogenin)	downregulating cyclin D1 expression	Ichikawa et al. (2015)
		Polygonatum odoratum (Homoisoflavanone-1)	activating the p38/p53 signaling pathway	Ning et al. (2018)
		Salvia miltiorrhiza (tanshinone)	increasing the expression of p53 and p21, activating caspase-3/9 and PARP1	Ye et al. (2017)
Cell apoptosis		Angelica dahurica (imperatorin)	upregulating the gene expression of p53 and Bax, downregulating the expression of Mcl-1	Choochuay et al. (2013)
		Ethyl acetate extract from Selaginella doederleinii Hieron	upregulating Bax, downregulating Bcl-2, activating caspase-9 and caspase-3	Sui et al. (2016)
		The extract of Ligustrum lucidum and Epimedium	downregulating Bcl-2/Bax protein ratio, Bcl-2 and Beclin-1 protein and mRNA expression, upregulating caspase-3, p-mTOR and Bax	Ma et al. (2020)
		Acetone extract of Bupleurum scorzonerifolium	inhibiting telomerase activity	Cheng et al. (2003)
Tumor angiogenesis		Hedyotis diffusa (oldenlandia polysaccharide)	inhibiting COX-2 protein expression	Lin et al. (2019)
		Ligusticum wallichii (ligustrazine)	downregulating the expression of VEGF, MMP2, TGF-β1 and E-cadherin	Xie et al. (2019)
		Ecliptae Herba extract	reducing the levels of COX-2, TGF- β1, MMP-2 and α- SMA, increasing the MMP-9/TIMP-1 ratio	You et al. (2015)
		The extract of Astragalus membranaceus and Angelica sinensis	reducing the expression of NF-κβ, STAT3, HIF-1α and VEGF	Wu et al. (2019)
Tumor microenvironment	Cell adhesion movement	Ligusticum wallichii (Ligustrazine)	downregulating the expression of VEGF, MMP-2, TGF-β1 and E-cadherin	Xie et al. (2019)
		Trichosanthes kirilowi (Trichosanthin)	regulating the expression of E-cadherin, N-cadherin, Vimentin, ICAM-1, MMP-2 and MMP-9	You et al. (2018)
		Cinnamomum cassia extract	inhibiting the adhesion of damaged cells to collagen	Lin et al. (2017)
		Rhizoma Dioscoreae Nipponicae (dioscin)	increasing the expression of epithelial marker (E-cadherin) and interstitial marker (N-cadherin and Snail)	Lim et al. (2017)
	Extracellular matrix degradation	Cinnamomum cassia extract	inhibiting the expression of MMP-2 and uPA	Lin et al. (2017)
		Angelica sinensis extract	reducing MMP-2, MMP-9, TGF-β1 and TIMP-1, increasing TIMP-2	Gao et al. (2012)
		Sinomenium acutum (Sinomenine)	reducing the expression of MMP-2, MMP-9 and EMMPRIN, increasing the expression of RECK, TIMP-1 and TIMP-2	Shen et al. (2020)
		Solanum nigrum (Solasodine)		Shen et al. (2017)
Body immunity function		Licorice extract	increasing the abundance of PD-L1 protein, antigen presentation and infiltration of CD8+T cells	Zhu et al. (2021)
		Ligusticum wallichii (ligustrazine)	reducing the transcription and secretion of inflammatory factors (IL-1β, IL-18, TNF-β)	Jiang et al. (2021a)
		Astragalus membranaceus (Astragalus polysaccharides)	increasing the M1/M2 macrophage polarization rate of NSCLC cells	Bamodu et al. (2019)
		Trichosanthes kirilowi (Trichosanthin)	upregulating the expression of TSLC1 in 3LL tumor cells and CRTAM in effector T cells	Cai et al. (2011)
Signal transduction pathways		Ligusticum wallichii (Ligustrazine)	blocking the Wnt/β-catenin signaling pathway	Dong et al. (2020)
		Ophiopogon japonicus extract	inhibiting the PI3K/Akt/mTOR signaling pathway	Chen et al. (2017)
		Licorice (Glycyrrhizin)	inhibiting the JAK/STAT signaling pathway	Wu et al. (2018)
		Radix Rehmanniae (catalpol)	inhibiting the Nrf2/ARE signaling pathway	Wang et al. (2022)

revealed that gambogenic acid, an extract from garcinia, functioned as an inhibitor of the FGFR signaling pathway, thereby enhancing the efficacy of erlotinib when used in combination (Xu et al., 2018). Aucklandia lappa DC. extract significantly enhanced the effectiveness of gefitinib, suppressing the Muv phenotype of jgIs25. Meanwhile, it also downregulated the mRNA and protein expression of EGFR in jgIs25 (Huang et al., 2017). In a study by Lee et al. (Lee et al., 2011), a low dose of gefitinib, when combined with curcumin, exhibited a significant synergistic effect on apoptosis in a lung cancer cell line. This effect was achieved by reducing the mitochondrial membrane potential and activating caspase-9/caspase-3. Pristimerin inhibited cell proliferation, induced G0/G1 arrest, and promoted cell apoptosis in A549 and NCI-H446 cells. Pristimerin effectively synergized with cisplatin, resulting in the suppression of tumor growth (Zhang et al., 2019). In conclusion, traditional Chinese medicine extracts can synergistically enhance the anti-tumor effects of chemotherapy drugs.

2.2.2 Effect on multidrug resistance

Multidrug resistance (MDR) in lung cancer cells remains a major obstacle to achieving satisfactory chemotherapy outcomes. Consequently, overcoming MDR in tumor cells to enhance chemotherapy effectiveness represents a crucial area of research. Trichosanthin (TCS), by upregulating DR4 and DR5, can trigger cell apoptosis, modulate invasion, influence cell cycle-related proteins, and heighten the sensitivity of NSCLC cells to TRAIL (You et al., 2018). Xu et al. (Xu et al., 2018) reported the successful use of gambogenic acid to overcome erlotinib resistance in NSCLC treatment through the inhibition of the FGFR signaling pathway when administered in combination. Andrographis paniculata addresses cisplatin resistance in tumor cells by acting on the miR-155-5p/SIRT1 axis (Pang et al., 2023). A synergistic inhibitory effect on lung cancer cell proliferation and invasion was observed with the combined use of Scutellaria baicalensis extract baicalin and cisplatin at specific doses and incubation times. The attenuation of cisplatin resistance was associated with the downregulation of MARK2 and p-Akt (Xu et al., 2017). Berberine, derived from Coptis chinensis extract, demonstrated its role as a naturally occurring MET inhibitor. It synergized with osimertinib in overcoming acquired resistance caused by MET amplification (Chen et al., 2022). Ming et al. (Ming et al., 2021) found that fucoxanthin, extracted from Laminaria Japonica, effectively inhibited tumor growth and heightened the sensitivity of lung cancer cells to gefitinib. This effect might be attributed to the inhibition of tumor cell proliferation and the activation of apoptosis. Artemisia annua extract dihydroartemisinin proved effective in overcoming acquired resistance to gefitinib in EGFR-mutant lung adenocarcinoma due to its STAT3 inhibitory activity and low toxicity (Xueting et al., 2017). Triptolide sensitized cancer cells to antitumor drugs both *in vitro* and in a xenograft tumor model system using lung carcinoma cells. This suggests that triptolide mitigates chemoresistance in cancer cells by targeting the Nrf2 pathway (Zhu et al., 2018). An extraction from Scutellariabarbata D. Don sensitized NSCLC cells to cisplatin treatment by downregulating the SHH signaling pathway (Chen WW. et al., 2021). Tripterygium wilfordii extract celastrol exhibited similar cytotoxic effects on both A549 parental and A549/DDP cisplatin-resistant cells. Celastrol also induced cell apoptosis in a dose- and time-dependent manner in both cell lines, accompanied by ROS accumulation, loss of mitochondrial membrane potentials, and cleavage of PARP and caspases (Shi, 2013). In summary, various traditional Chinese medicines effectively reverse the multidrug resistance observed in response to chemotherapeutic drugs. Their combined use enhances the sensitivity of these enhancers and significantly improves the effectiveness of tumor treatment. The applications of traditional Chinese medicine extracts for NSCLC are detailed in Table 2.

2.3 The application of traditional Chinese medicine extract treatment for small cell lung cancer

Small cell lung cancer (SCLC) is an aggressive and recalcitrant malady, characterized by rapid growth and early metastatic spread to regional lymph nodes and distant sites. Chemotherapy is the general treatment for SCLC, however, majority of patients who typically exhibit a sensitive response to chemotherapy will swiftly relapse with relatively drug-resistant diseases (Waqar and Morgensztern, 2017; Mi et al., 2020). Despite considerably significant progress in targeted therapy and immunotherapy has been made in treating NSCLC, the therapies have not produced similar effects in SCLC (Byers and Rudin, 2015; Parikh et al., 2016). Although Traditional Chinese Medicine (TCM) is widely applied for patients with SCLC in China, the evidence of TCM in the treatment of SCLC is limited. Compared with chemotherapy alone, those with Chinese herbal medicine and chemotherapy had better therapeutic effects, including better KPS scores, and 5-year survival rate. Moreover, the incidence of gastrointestinal reaction and bone marrow depression was lower (Chen et al., 2020). TCM combined with chemotherapy may improve therapeutic effect, quality of life, and prolong survival time (Chen et al., 2020; Chen Y. et al., 2021; Xu et al., 2021; Qi et al., 2023). Aqueous extract of Artemisia annua played a preventive role against malignancy in the lung cancer models. It also induced apoptosis and decreased intracellular reactive oxygen species (ROS) in the lung cells (Allemailem, 2022). Peng et al. (Peng et al., 2021) revealed that the combination of anlotinib and Brucea Javanica Oil (BJO) significantly inhibited the growth of SCLC liver metastases and angiogenesis more than anlotinib monotherapy. In addition, BJO alleviated some of the side effects associated with anlotinib therapy. The results of the study indicated that the combination of anlotinib with BJO is promisingly active against liver metastases of SCLC, and has clinical potential. Moreover, the combination of gemcitabine (GEM) and BJO resulted in a reduced tumor growth rate and greater apoptosis compared to the vehicle control and GEM monotherapy (Yang et al., 2020). Therefore, traditional Chinese medicine extracts have potential clinical application in SCLC.

3 Treatment of other lung-related diseases with traditional Chinese medicine extracts

3.1 Pulmonary fibrosis

In recent years, the aging trend within China's population has become increasingly prominent, and the incidence of chronic respiratory diseases has been steadily rising. Furthermore,

TABLE 2 Application of traditional Chinese medicine extract for non-small cell lung cancer.

Functional route	Traditional Chinese medicine and its extracts	Key gene expression	References
Effect on chemotherapy drugs	Ophiopogon japonicus (Ophiopogonin B)	reduces tumor cell resistance to cisplatin through the Caspase-1/GSDMD dependent pyroptosis pathway	Cheng et al. (2022a)
	Artemisia argyi extract	inducing ROS, mitochondrial membrane depolarization and apoptosis, reducing EMT	Su et al. (2022)
	Cordyceps sinensis (Cordycepin)	activating AMPK, inhibiting the AKT signaling pathway	Liao et al. (2021)
	Lithospermum (shikonin)	inhibiting PKM2/STAT3/cyclinD1	Tang et al. (2018)
	Garcinia (Gambogenic acid)	inhibiting the FGFR signaling pathway	Xu et al. (2018)
Multidrug resistance	Trichosanthes kirilowi (Trichosanthin)	upregulating DR4 and DR5	You et al. (2018)
	Scutellaria baicalensis (Baicalin)	downregulating MARK2 and p-Akt	Xu et al. (2017)
	Artemisia annua (Dihydroartemisinin)	inhibiting the STAT3 signaling pathway	Xueting et al. (2017)
	Scutellariabarbata D. Don extraction	downregulating the SHH signaling pathway	Chen et al. (2021a)
	Tripterygium wilfordii (Celastrol)	accumulating ROS, losing mitochondrial membrane potentials, slicing the dose-and-time dependence of PARP and caspases	Shi (2013)

pulmonary fibrosis, as a debilitating interstitial lung condition, presents limited treatment options. Ecliptae Herba extract has shown remarkable efficacy in ameliorating pathological lung tissue changes by reducing the levels of hydroxyproline (HYP), increasing superoxide dismutase (SOD) activity, and decreasing malondialdehyde (MDA) content. This extract, by mitigating oxidative stress, lung tissue inflammation, and epithelial-mesenchymal transition (EMT), exhibits a protective role against pulmonary fibrosis induced by bleomycin (You et al., 2015). Extracts from Radix Pseudostellariae, notably Heterophyllin B, have been found to significantly inhibit EMT and the redifferentiation of lung fibroblasts. Furthermore, it offers protection against bleomycin-induced pulmonary fibrosis by modulating the STING signaling mediated through AMPK and TGF-Smad2/3 pathways (Shi et al., 2022). Catalpol, extracted from Radix Rehmanniae, effectively inhibits NF-κB and MAPK signaling pathways mediated by TLR4, ultimately alleviating bleomycin-induced pulmonary fibrosis (Fu et al., 2014). Meanwhile, Icaritin plays a pivotal role in downregulating the expression of α-SMA and collagen I, effectively inhibiting myofibroblast differentiation, which suggests its potential in treating pulmonary fibrosis (Hua et al., 2021). Furthermore, the research by Li et al. (Li S. et al., 2022) demonstrates the inhibitory effects of pheretima protein on extracellular matrix (ECM), EMT, and anti-inflammatory markers, which contribute to the amelioration of bleomycin-induced pulmonary fibrosis. Alcohol extracts from Sceptridium ternatum (Thunb.) Lyon have exhibited anti-pulmonary fibrosis effects by targeting the SETDB1/STAT3/p-STAT3 signaling pathway (Zou et al., 2023). Qian et al. (Qian et al., 2018) have shown that Astragalus IV significantly inhibits FOXO3a hyperphosphorylation and downregulation induced by TGF-β1/PI3K/Akt, effectively reversing EMT during pulmonary fibrosis progression. Astragalus also exerts antifibrotic effects by inhibiting EMT, ROS, TGF-β1/Smads, apoptosis, and inflammatory pathways (Zhu et al., 2022). Euodia rutaecarpa (Juss.) Benth. extract evodiamine has demonstrated the ability to protect against pulmonary fibrosis-induced inflammatory damage both *in vitro* and *in vivo* by inhibiting apoptosis, inflammatory cytokine release, and activating the apelin pathway (Ye et al., 2021). Moreover, Snithin has significantly mitigated bleomycin-induced pulmonary fibrosis by downregulating the mechanism of TGF-β1/NOX4-mediated oxidative stress in lung fibroblasts (Fang et al., 2021). Salvia miltiorrhiza extract Tanshinone IIA has been instrumental in regulating the Keap1/Nrf2 signaling pathway through the activation of Sestrin2, effectively inhibiting pulmonary fibrosis (Li H. et al., 2022). Shenks exhibits its anti-fibrotic properties by blocking the TGF-β1 pathway and regulating oxidative/antioxidant balance (Chu et al., 2017). Peimine has contributed to the amelioration of pulmonary fibrosis by inhibiting M2-type macrophage polarization through the suppression of P38/Akt/STAT6 signals (Cai et al., 2022).

3.2 Acute lung injury

Acute lung injury, one of the most prevalent and severe respiratory conditions, currently lacks effective treatment options. Catalpol has proven to be effective in protecting against lipopolysaccharide-induced acute lung injury (Fu et al., 2014). Similarly, glycyrrhizic acid has shown promise in improving sepsis-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) by inhibiting HMGB1 and ameliorating inflammation in experimental sepsis rat models (Shen et al., 2022). Astragaloside IV, acting through the TLR4/NF-κB signaling pathway, has demonstrated its ability to induce cell autophagy, which, in turn, inhibits the release of inflammatory cytokines and improves the overall inflammatory response (Ying et al., 2021). Indigoin has offered relief in cases of lipopolysaccharide-induced acute lung injury by reducing malondialdehyde (MDA) levels and IL-1β and TNF-α expression in mice (Qi et al., 2017). Spatholobus stem extract has ameliorated acute lung inflammation induced by IAV

TABLE 3 Mechanism of action of traditional Chinese medicine extract in treating other lung-related diseases.

Diseases	Traditional Chinese medicine and its extracts	Key gene expression	References
Pulmonary fibrosis	Epimedium (Icaritin)	reducing the expression of α- SMA and collagen I	Hua et al. (2021)
	Earthworm (Pheretima protein)	inhibiting ECM, EMT, and anti-inflammatory markers	Li et al. (2022a)
	Astragalus membranaceus (Astragalus)	inhibiting EMT, ROS, TGF-β1/Smads	Zhu et al. (2022)
	Hedyotis diffusa (Shenks)	blocking TGF-β1 pathway and regulating oxidative/ antioxidant balance	Chu et al. (2017)
Acute lung injury	Licorice (Glycyrrhizic acid)	improving ALI/ARDS and inflammation by inhibiting HMBG1	Shen et al. (2022)
	Spatholobus stem extract	inhibiting MAPK, PI3K-AKT, and oxidative stress pathways	Cai and Zhang (2022)
	Marijuana (Euphorbia factor L2)	reducing the levels of IL-1 β, IL-6, TNF-α, IL-8 and MPO	Zhang et al. (2018)
	Astragalus membranaceus (Astragaloside IV)	inhibiting activation of RAC subunit in NADPH oxidase 2	Cheng et al. (2023)
Other lung-related diseases	The extract of Astragalus, radix paeoniae rubra, and Psoralea corylifolia	reducing KGF, sIgA, and collagen fiber deposition	Jing et al. (2017)
	Polygonum cuspidatum (Resveratrol)	activating the SIRT1 pathway	Ma and Li (2020)
	Licorice (Isoliquiritigenin)	reducing the Notch1/NF-κB and MAPK signaling pathways	Sun et al. (2022)
	Saffron crocus (Safranal)	inhibiting the MAPK and NF-κB pathways	Lertnimitphun et al. (2021)

by inhibiting the MAPK, PI3K-AKT, and oxidative stress pathways (Cai and Zhang, 2022). Furthermore, Euphorbia factor L2 (EFL2), derived from marijuana extract, has exhibited anti-inflammatory effects in a murine acute lung injury model by reducing the levels of inflammatory markers such as interleukin-1 β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and myeloperoxidase (MPO) in lung and bronchioalveolar lavage fluid (Zhang et al., 2018). Ren et al. (Ren et al., 2023) found that ergolactone, through its irreversible binding to the NACHT domain of NLRP3, effectively blocked the assembly and activation of NLRP3 inflammasomes. In a lipopolysaccharide-induced acute lung injury model, ergolactone alleviated acute lung injury in wild-type mice. Astragaloside IV targeted PRDX6 and inhibited the activation of the RAC subunit in NADPH oxidase 2, thus suppressing oxidative damage and inflammation in mice with acute lung injury (Cheng et al., 2023). Traditional Chinese medicines, along with their bioactive compounds, such as epigallocatechin-3-gallate (EGCG), kaempferol, isorhamnetin, quercetin, and β-sitosterol, predominantly regulate NF-κB, Nrf2/HO-1, NLRP3, TGF-β/Smad, MAPK, and PI3K/Akt/mTOR pathways, successfully mitigating infection and inflammation across a spectrum of lung-related diseases, including acute lung injury, chronic obstructive pulmonary disease, pulmonary fibrosis, asthma, and lung cancer (Wang et al., 2021). These findings underscore the pivotal role of traditional Chinese medicine extracts in the treatment of lung-related diseases, such as acute lung injury.

3.3 Other lung-related diseases

The incidence of various lung-related diseases, including cor pulmonale, chronic obstructive pulmonary disease, pulmonary tuberculosis, and asthma, has been steadily on the rise. It is imperative to acknowledge the clinical significance of these diseases. Traditional Chinese medicines have shown promise in addressing these conditions. Astragalus, radix paeoniae rubra, and Psoralea corylifolia have demonstrated their efficacy in reducing pulmonary keratinocytes growth factor (KGF), secretory immunoglobulin A (sIgA), and collagen fiber deposition. These effects lead to improved lung function and provide a valuable treatment approach for cor pulmonale (Jing et al., 2017). Resveratrol, extracted from Polygonum cuspidatum, acts as an activator of SIRT1 and has the potential to alleviate chronic obstructive pulmonary disease by activating the SIRT1 pathway (Ma and Li, 2020). Anemoside B4 has shown significant promise in attenuating the increased levels of inflammatory markers, including IL-1β, TGF-β, IL-8, and TNF-α, in human bronchial epithelial cells exposed to cigarette smoke extract (CSE). This is achieved by inhibiting the MAPK/AP-1/TGF-β signaling pathway, thereby preventing chronic pulmonary obstructive disease induced by cigarette smoke (Ma et al., 2022). Isoliquiritigenin effectively reduces inflammation induced by *Mycobacterium tuberculosis* (Mtb) through the Notch1/NF-κB and MAPK signaling pathways (Sun et al., 2022). Icariin, characterized by its anti-inflammatory, antioxidant, and immune-regulating properties, presents a multi-target intervention approach to asthma treatment (Yuan et al., 2022). Safranal, an extract from saffron crocus, has been shown to alleviate OVA-induced asthma by inhibiting the MAPK and NF-κB pathways, thus inhibiting mast cell activation and the production of proinflammatory factors (Lertnimitphun et al., 2021). The specific extracts and regulatory mechanisms of traditional Chinese medicine are detailed in Table 3, underscoring the potential of these remedies in addressing a variety of lung-related diseases.

4 Discussion and prospect

In conclusion, traditional Chinese medicine offers a multifaceted and layered approach to the prevention and treatment of lung cancer. Experimental research on the anti-lung cancer effects of traditional Chinese medicine has progressed from morphological observations to the microscopic levels of cells, molecules, and genes. Numerous studies have shed light on the mechanisms through which traditional Chinese medicine inhibits lung cancer growth and metastasis. These mechanisms encompass inhibiting tumor cell proliferation, inducing tumor cell apoptosis, and suppressing tumor angiogenesis. Traditional Chinese medicine also affects the cellular microenvironment, regulates immune function, modulates signal transduction pathways, and reverses multidrug resistance in tumor cells. These findings provide a robust scientific foundation for lung cancer treatment with traditional Chinese medicine and contribute to the advancement of the traditional Chinese medicine industry.

However, several challenges persist, including:

1. Overemphasis on traditional Chinese medicine compound formulas and active ingredients at the expense of single Chinese medicine and extracts in anti-lung cancer research.
2. The complex, multifaceted mechanisms of action in traditional Chinese medicine extracts, which pose challenges in pharmacokinetic research, such as determining quantitative standards, sampling times, and concentration standards in plasma or serum.
3. Interferences and uncertainties associated with single drugs and their traditional Chinese medicine extracts, raising doubts about result accuracy.
4. A predominant focus on gene regulation research in the mechanism of action, with less exploration of the interplay between various gene regulations.
5. A predominance of *in vitro* studies with limited research on *in vivo* cell apoptosis, hindering the understanding of drug metabolism and induced cell apoptosis *in vivo*.

To address these issues, we propose that future research and development of anti-lung cancer effects of traditional Chinese medicine single drugs and their extracts should involve interdisciplinary collaboration. This approach, guided by traditional Chinese medicine theory, can delve into the complex biological processes underlying tumor initiation, development, and metastasis. The goal is to develop effective formulations that target lung cancer cells through multiple avenues, including various targets, pathways, and methods. Modern pharmacology, immunology, and molecular biology are steadily unraveling the anti-lung cancer mechanisms of traditional Chinese medicine. Continuous research and exploration in this field aim to harness the full clinical therapeutic potential of traditional Chinese medicine in lung cancer treatment.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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