Traditional Herbal Medicine: A Potential Therapeutic Approach for Adjuvant Treatment of Non-small Cell Lung Cancer in the Future

Jie Huang, MM[1]*(iD), Jia-Xin Li, PhD[1]*(iD), Lin-Rui Ma, MM[1], Dong-Han Xu, PhD[1], Peng Wang, PhD[1], Li-Qi Li, MM[1], Li-Li Yu, PhD[1], Yu Li, PhD[1], Run-Ze Li, PhD[2], Hao Zhang, PhD[1], Yu-Hong Zheng, MM[1], Ling Tang, PhD[3,4,5], and Pei-Yu Yan, PhD[1]

Abstract

Lung carcinoma is the primary reason for cancer-associated mortality, and it exhibits the highest mortality and incidence in developed and developing countries. Non-small cell lung cancer (NSCLC) and SCLC are the 2 main types of lung cancer, with NSCLC contributing to 85% of all lung carcinoma cases. Conventional treatment mainly involves surgery, chemoradiotherapy, and immunotherapy, but has a dismal prognosis for many patients. Therefore, identifying an effective adjuvant therapy is urgent. Historically, traditional herbal medicine has been an essential part of complementary and alternative medicine, due to its numerous targets, few side effects and substantial therapeutic benefits. In China and other East Asian countries, traditional herbal medicine is increasingly popular, and is highly accepted by patients as a clinical adjuvant therapy. Numerous studies have reported that herbal extracts and prescription medications are effective at combating tumors. It emphasizes that, by mainly regulating the P13K/AKT signaling pathway, the Wnt signaling pathway, and the NF-κB signaling pathway, herbal medicine induces apoptosis and inhibits the proliferation and migration of tumor cells. The present review discusses the anti-NSCLC mechanisms of herbal medicines and provides options for future adjuvant therapy in patients with NSCLC.

Keywords

non-small cell lung cancer, herbal medicine, traditional Chinese medicine, adjuvant treatment

Introduction

Lung cancer is the primary cancer-associated cause of mortality and constitutes a major public health concern around the globe.[1,2] Non-small cell lung cancer (NSCLC) comprises ~85% of lung cancer cases, and the 5-year survival rate for patients with advanced NSCLC is only 15%.[3,4] In the last 20 years, conventional therapies for NSCLC have included surgical resection, radio-chemotherapy, and immunotherapy.[5] Surgical removal is the primary medical intervention for patients with early-stage NSCLC; however, >81% of clinically diagnosed patients with NSCLC are not candidates for surgery.[6] For advanced NSCLC, platinum-based chemotherapy is the first-line choice of medication, but the prognosis remains unsatisfactory.[7,8] Radio-chemotherapy often causes adverse effects in clinical

[1]Macau University of Science and Technology, Taipa, Macau, China
[2]Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China
[3]Southern Medical University, Guangzhou, Guangdong, China
[4]Guangdong Provincial Key Laboratory of Chinese Medicine Pharmaceutics, Guangzhou, Guangdong, China
[5]Guangdong Provincial Engineering Laboratory of Chinese Medicine Preparation Technology, Guangzhou, Guangdong, China

*These authors contributed equally to this work.

Corresponding Authors:
Pei-Yu Yan, Faculty of Chinese Medicine, Macau University of Science and Technology, Avenida Wai Long, Taipa, Macau 90000, China.
Email: pyyan@must.edu.mo

Ling Tang, School of Traditional Chinese Medicine, Southern Medical University, Guangzhou 510515, China.
Email: tangyuling6688@163.com

Table 1. Summary of Targeted and Immunotherapeutic Agents in Non-small Cell Lung Cancer.

Drug	Phase	Primary outcome	Adverse effects	(Refs.)
Gefitinib	III	PFS10.8 month;OS 30.5 month;	Rash/neutropenia/anemia/appetite loss/sensory neuropathy	Maemondo et al[10]
Ceritininb	II	ORR62%; PFS 9.3 months; OS 24 month	Diarrhea/Nausea/Anorexia	Lim et al[11]
Dabrafenib	II	ORR 54%;	Decreased appetite/fatigue/ asthenia/dyspnea/nausea	Planchard et al[12]
Osimertinib	III	PFS18.9 month; ORR 80%; Median overall survival 17.2 month	Rash/Acne/ Diarrhea/dry skin	Soria et al[13]
Entrectinib	II	ORR 78%	weight increase/neutropenia, nervous/cardiac system disorders	Drilon et al[14]
Pembrolizumab	I	ORR19.4%; Median overall survival 16.2 month; PFS 3.7 months; OS 12.0 month	Pneumonitis/Fatigue/colitis	Garon et al[15]
Atezolizumab	III	OS: 20.2	Asthenia/Fatigue	Spigel et al[16]
Ipilimumab + nivolumab	III	ORR 22%; SD 33%	Respiratory failure/ bronchopulmonary hemorrhage/ toxic epidermal necrolysis	Antonia et al[17]
pembrolizumab + pemetrexed carboplatin (PC)	II	ORR 56.7%; PFS 24.0 month;	Fatigue/Nausea/Anemia	Borghaei et al[18]
Pembrolizumab + stereotactic body radiotherapy	II	ORR 12 week; PFS 6.6 month; OS 15.9 months	Immune-related adverse event/ Nephritis	Theelen et al[19]

Abbreviations: PFS, progression-free survival; Bcl-2, Associated X Protein; ORR, Objective Response Rate; OS, overall survival; SD, stable disease.

practice, and drug resistance is prone to develop. These side effects may exacerbate the condition in certain patients with lung cancer and have unintended consequences. Immunotherapy is not yet commonly used in clinical practice and is expensive.[5,9] With the remarkable improvement of disease screening and diagnosis technology, targeted therapy and immunotherapy have gradually emerged in recent years. Many targeted drugs and immune checkpoint inhibitors have been approved by FDA and used in the clinic,[10-19] but with many toxic side effects including rash, diarrhea, nausea, and even nervous/cardiac system disorders (Table 1). Therefore, finding effective therapies remains a serious challenge.[8,20] Traditional Chinese herbal medicine dates back thousands of years and is a subset of traditional Chinese medicine. Recently, Chinese herbal medicine has become a widespread topic, and researchers are currently using scientific approaches to elucidate its mechanism, safety, and effectiveness. During the COVID-19 epidemic, about 90% of COVID-19 patients in China have received TCM treatment. The clinical efficiency is as high as 80% and it has nearly no toxic side effects.[21] Researchers have summarized numerous herbs or their derivatives with potential preventive and therapeutic effects on anti-COVID-19, such as Jinhua Qinggan granules, Xuebijing, Pudilan Xiaoyan Oral Liquid, and so on.[22] As an auxiliary and complementary medicine in China, traditional herbal medicine is prevalently used in clinical practice.[23,24] Traditional herbal medicine has the advantages

of alleviating clinical symptoms, enhancing autoimmunity and helping to manage the quality of life of patients.[25-27] Previous studies have reported that herbal extracts and prescriptions through multi-targeting inhibit tumor proliferation, induce tumor apoptosis, and alleviate drug resistance.[28-30] The present review focuses on recent developments in using herbal medicine to treat NSCLC and may offer a potential adjuvant treatment option.

Herbal Medicine Extracts Commonly Used in NSCLC Treatment

The identification of novel drugs against neoplasms is important for cancer treatment. Numerous observations indicate that herbal medicine may exert anticancer effects via various mechanisms, including modulating cancer-related signaling pathways, suppressing cell proliferation, and causing apoptosis and autophagy. Herbal medicine extracts help to treat various malignancies.[31,32] The following herbal extracts are examples of their effects against NSCLC (Table 2).

Thevebioside, Sesamin, and Jervine Act Against NSCLC by Inhibiting AKT Signaling

Thevebioside (THB*)*, a monomer from *Thevetia peruviana* (Pers.) K. Schum. (TPKS), may have pharmacological effects. THB has shown anti-inflammatory effects on skin

Table 2. Effects of Herbal Extracts on Non-small Cell Lung Cancer.

Herbal extract	Plant	Cell line; In vivo model	Mechanism	(Refs.)
Thevebioside	*Thevetia peruviana* (Pers) K. Schum.	A549/H460; orthotopic mice	Inactive PI3K-AKT signaling pathway	Yao et al[34]
Thymol	*Ocimum gratissimum* L. and *Satureja thymbra* L.	A549, KLN205	Arrest the cell cycle Induce apoptosis	Balan et al[53], Elbe et al[54], Koparal and Zeytinoglu[55]
Ginsenoside Rg3	*Ginseng*	A549/HCC827; A549/DDP PC9; C57BL/6 mice	Activate VRK1/P53 pathway; relieve drug resistance	Zhang et al[60], Poon et al[61], Liu et al[64], Tan et al[67], Jiang et al[68], Wang et al[69]
Cinnamaldehyde	*Cinnamomum cassia*	A549/YTMLC-90/H1299/H460; BALB/c nude mice	Suppress Wnt/β-catenin signaling Downregulate; MMP-2 and MMP-9; Arrest the cell cycle	Wu et al[73], Tian et al[74], Hong et al[75], Park and Baek[76]
Sesamin	*Sesamum indicum*	A549/H1792; BALB/nude mice	Regulate AKT/P53 signaling pathway Increase ROS	Chen et al[42], Fang et al[43], Yang et al[44]
Eupatolide	*Inula helenium*	A549/H1975; BALB/C mice	Inhibit STAT3 signaling pathway	Ma et al[80]
Piperlongumine	*Piper longum* L.	A549/NCI-H460; BALB/c nude mice	Suppress NF-κB pathway; Suppress PFN1; Inhibit STAT3	Zheng et al[85], Gagat et al[86], Lewis et al[87]
Jervine	*Veratrum rhizome*	A549/H1299; athymic nude mice	Inhibit AKT/mTOR/hedgehog signaling pathway	Lei and Huo[45]
Ophiopogon Saponin C1	*Liriope muscar*	A549; BALB/c nude mice	Block the cell cycle	Zhang et al[88]
Kaempferol	*Cruciferous vegetables*	A549/NCI-H460	Downregulate Nrf-2 signaling pathway	Fouzder et al[89]
Cordycepin	*Cordyceps sinensis*	A549/H1975/PC9; BALB/c mice	Regulate VEGF/PI3K/AKT pathway	Nakamura et al[90]

Abbreviations: PI3K, phosphatidylinositol 3-kinase; AKT, Protein Kinase B; VRK, vaccinia-related kinase; P53, tumor protein 53; MMP, matrix metalloproteinase; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor ƙB; PFN1, Profilin-1; mTOR, mammalian target of rapamycin; Nrf-2, NF-E2-related factor 2; VEGF, vascular endothelial growth factor.

diseases.[33] Researchers have found that THB exerts the most cytotoxic activity in p53 wild-type A549 and H460 cell lines in a dose and time-dependent manner. THB has been shown to hinder the proliferation of NSCLC by triggering apoptosis, as indicated by increasing the Bad, cleaved caspase-3 and cleaved PARP expression, and reducing the expression of Bcl-xl.[34] In addition, animal and cell studies have demonstrated that THB promotes apoptosis by inhibiting the steroid receptor coactivator-3 (SRC-3)-induced insulin like growth factor 1 receptor (IGF1R)−P13K-AKT signaling pathway. SRC1, SRC2 and SRC-3 are members of a transcription coactivator family. Elevated SRC-3 expression is frequently associated with tumor progression.[35,36] THB has also exhibited promising pharmacological safety, with low inhibition of normal lung epithelial cells, as well as no observable harm to the organs of A549-bearing mice.[34] THB is a low-toxicity natural product extract that may be employed as an adjuvant medication in lung cancer. Sesamin is a lignan abundant in *Sesamum indicum*.[37] Sesamin has antihypertension, antithrombosis, and antitumor pharmacodynamic activities.[38-41] Sesamin

modulates the AKT/P53 signaling pathway, mainly inhibits AKT activity, and downregulates cyclin D1 and CDK2 in A549 and H1792 lung cancer cells.[42] In a previous study, sesamin suppressed AKT/PI3K signaling by downregulating cyclooxygenase 2, leading to G_1 phase cell arrest, and downregulating Bcl-2, Bax and cyclin E1 gene expression.[43] Yang et al[44] showed that sesamin causes an increase in the production of ROS in A549 cells and loss of the mitochondrial membrane potential. Sesamin-treated A549 cells promote the expression of apoptosis-related proteins (cleaved caspase-3, caspase-9, cytochrome *c* and Bax/Bcl-2). Sesamin stimulated mitophagy in A549 cells via the ROS-mediated PTEN-induced kinase 1 (PINK1)/Parkin signaling pathway, increased Parkin levels in mitochondria and whole cells, and reduced Parkin levels in the cytoplasm. Cyclosporine A, a mitotic inhibitor, abolishes sesamin's inhibitory effect on A549.[44] Sesamin may therefore be a suitable NSCLC adjuvant. Jervine is a steroid alkaloid from *Veratrum rhizome*. Jervine exhibited a dose and time-dependent inhibition of proliferation and colony formation.[45] Jervine promotes the expression of LC3 to induce autophagy and

activates caspase-3 to promote apoptosis. Bafilmycina1, an autophagy inhibitor, can abolish the jervine-mediated suppression of human lung cancer cell proliferation.[45] Transformation of cytosolic LC3 (LC3-I) into autophagy, the vesicle-associated form (LC3-II) bound by phosphatidylethanolamine, is essential for inducing autophagy.[46] The AKT/mTOR and hedgehog signaling pathways are usually strongly suppressed in multiple cancer cells.[47,48] Jervine acts against NSCLC by suppressing hedgehog and AKT signaling. Treatment with jervine effectively suppressed the AKT/mTOR and hedgehog signaling pathways by decreasing the expression of AKT, patched 1, sonic hedgehog, GLI family zinc finger 1 and smoothened, frizzled class receptor. Notably, jervine inhibited tumor growth in A549 tumor-bearing mice.[45] Therefore, jervine may become a potential drug for lung cancer treatment.

Thymol Acts Against NSCLC by Arresting the Cell Cycle

Thymol can be found in various plants, including *Ocimum gratissimum* L. and *Satureja thymbra* L. Thymol is a naturally occurring monoterpene phenol. A previous study has demonstrated that thymol has important pharmacodynamic effects in antibacterial, antioxidant and analgesic applications.[49] In addition, researchers have found that thymol exerts cytotoxic effects in multiple types of cancer.[50-52] Balan et al[53] demonstrated that thymol's antiproliferative activity on A549 cells was dose and time-dependent, showing IC_{50} values of 745 μM after 24 hours. Thymol induced cell death by arresting the cell cycle. In the G_0/G_1 phase, the number of cells increased considerably. Moreover, Bax overexpression, Bcl-2 downregulation and apoptotic fragmented DNA were observed, which accelerated cell death. It is worth mentioning that thymol upregulates reactive oxygen species (ROS) levels and changes the mitochondrial membrane potential.[53] Elbe et al[54] reported the antitumor activity of thymol on NSCLC KLN205 cells. In the KLN205 cell line, thymol suppressed cell proliferation and promoted cell death. Notably, at 72 hours and 400 μM concentration, apoptosis increased at a higher rate than control in the cells. Koparal and Zeytinoğlu[55] found that A549 lung cancer cells treated with 500 and 1000 μM thymol exhibited certain apoptotic features and morphological changes after 24 hours. To summarize, thymol, as a natural chemical, could be used against NSCLC.

Ginseng Inhibits Angiogenesis and Relieves Drug Resistance

Ginseng is a herb that has been used for millennia in China and East Asia.[56] The steroid ginsenoside, an extract of ginseng, is the main active component responsible for its anticancer properties.[57,58] Zhang et al[59] used a multi-center, prospective, randomized, double-blind trial to assess the effectiveness of Rg3 ginsenoside in patients with advanced NSCLC. A total of 414 patients diagnosed with stage III-IV NSCLC were randomized to combined group (ginsenoside Rg3 + chemotherapy) and chemotherapy group (placebo + chemotherapy). The results showed that the combined treatment alleviated adverse side effects. The combined group had a median survival time of 12.03 months, which was longer than the chemotherapy group's median survival time (8.46 months) ($P < .05$). The Karnofsky Performance Scale scores for patients in the combined and chemotherapy groups were 78.95 ± 9.14 and 76.77 ± 9.15, respectively ($P < .05$). Previous research has demonstrated that the ginsenoside Rg3 in conjunction with chemotherapy may increase overall survival, improve symptoms and alleviate the bone marrow suppression.[59] Previous studies have demonstrated that ginsenoside Rg3 exerts antitumor effects by controlling exogenous DNA damage.[60,61] Proto-oncogenes and cancer suppressor genes play vital roles in DNA damage repair. The stress response of cells to DNA damage is critical for preserving genetic material integrity, avoiding gene mutations and sustaining cell function.[62,63] Liu et al[64] showed that ginsenoside Rg3 prevents the destruction of DNA integrity by stimulating the vaccinia-related kinase 1 (VRK1)/P53 binding protein 1 (bp1) signaling pathway. VRK1 is a serine-threonine kinase present in the nucleus, which is involved in DNA repair and cell death following DNA damage. P53 bp1 is a downstream protein associated with the VRK1-mediated DNA damage and repair mechanism. VRK1 can recognize the local distortion of chromatin by phosphorylating specific proteins such as P53 bp1, which triggers downstream cascade signaling.[65,66] Ginsenoside Rg3 has been shown to increase chemotherapeutic sensitivity. For instance, combined treatment with ginsenoside Rg3 and osimertinib reduces drug resistance in NSCLC cells[67]; ginsenoside Rg3 downregulates programed death-ligand 1 to reduce A549/DDP cisplatin resistance[68]; and ginsenoside Rg3 has the ability to specifically and effectively reverse icotinib resistance in HCC827 and PC-9 cells.[69] These findings suggest that ginsenoside Rg3 may be an effective anti-NSCLC agent.

Cinnamaldehyde (CA) Acts Against NSCLC by Inhibiting the Wnt/β-catenin Signaling Pathway

CA, an anticancer component found in *Cinnamomum cassia*,[70] is effective against a diversity of cancer types, including human oral squamous cell carcinoma and colon cancer.[71,72] Wu et al[73] reported that CA exerts cytotoxicity in NSCLC cells, particularly in the A549, YTMLC-90 and NCI-H1299 cell lines, in which the IC_{50} was 41.02, 32.30, and 10.50 g/ml, respectively. CA increased Bax gene and protein expression but decreased Bcl-2 and Bcl-xl expression. CA increases E-cadherin and inhibits N-cadherin to

block cell motility via reversing the epithelial-mesenchymal transition (EMT). Animal and cell studies demonstrated that CA promote apoptosis by inhibiting the Wnt/β-catenin signaling pathway, as evidenced by reduced expression of β-catenin. Tumor volume and weight decreased in A549-bearing mice following CA treatment.[73] A recent study showed that CA regulated the Wnt/β-catenin signaling pathway via circular RNA *Homo sapiens* circ 0043256, which induced NCI-H460 and A549 cell death.[74] Hong et al[75] reported that CA inhibits invasive by downregulating MMP-2 and MMP-9. Park and Baek[76]demonstrated that CA and hyperthermia arrest the cell cycle, increase ROS and up-regulate pro-apoptotic protein levels to generate significant cytotoxicity in A549. In addition, the Food and Drug Administration has approved CA as a food ingredient.[70]

Eupatolide and Piperlongumine Act Against NSCLC by Suppressing STAT3 Signaling

Eupatolide is a new type of terpenoid extracted from the Chinese medicinal plant *Inula helenium*.[77] Research has reported that eupatolide may have inflammatory, analgesic, and antimicrobial activity.[78] The action of eupatolide against neoplasms has gained the interest of researchers.[79] Cisplatin and 5-fluorouracil are 2 drugs commonly used for NSCLC treatment. Previous studies[80] reported that eupatolide markedly increases NSCLC cell chemosensitivity to cisplatin and 5-fluorouracil. Eupatolide may promote A549 and H1975 cell death by downregulating Bcl-2 and myeloid leukemia 1. In nude mice injected with A549 and H1975 cells, oral eupatolide therapy reduce tumor volume for 3 weeks. In addition, eupatolide suppresses STAT3 signaling to promote apoptosis in NSCLC cells.[80] Persistent stimulation of STAT3 signaling may cause cancer cells aberrant proliferation and malignant transformation.[81] Additionally, eupatolide was not toxic.[80] Thus, it is likely to be a potential drug for adjuvant antitumor therapy. Piperlongumine, which is isolated from *Piper longum* L., exhibits anticancer activity in numerous carcinomas.[82-84] Piperlongumine inhibits the phosphorylation and degradation of IκBα, reducing NF-κB p50 and p65 subunit phosphorylation in NSCLC cells. In addition, piperlongumine (15 μM) downregulates Bcl-2 and upregulates Bax, cleaved caspase-3 and cleaved caspase-8 in A549/NCI-H460. In A549 xenografts it was shown that cleaved caspase-3, cleaved caspase-8 and Bax levels increased, while Bcl-2 levels decreased.[85] Profilin-1 (PFN1) belongs to the actin-binding protein family. PFN1 has been demonstrated to affect cell migration and apoptosis. Using a wound-healing assay, Gagat et al[86] demonstrated that piperlongumine suppresses PFN1 to inhibit migration in A549. Piperlongumine dose-dependently inhibited proliferation and induced cell death. The concentration of piperlongumine at which IC50 was observed was 10.64 μM. Lewis et al[87] reported that

piperlongumine lowered phosphorylated STAT3 levels and decreased anti-apoptotic protein targets (Bcl-2, Bcl-xl, and cyclin D1). In addition, piperlongumine reduced STAT3 downstream transcriptional targets and suppressed tumor volume. These studies suggest that piperlongumine may become an active anticancer compound.

In addition to these herbal extracts, Ophiopogon saponin C1, kaempferol, and cordycepin are effective against NSCLC. Ophiopogon saponin C1 exerts antitumor effects by modulating kinase activity and blocking the cell cycle to alter the tumor microenvironment.[88] Kaempferol, a natural flavonoid, is mainly found in tea, grapes, berries, and cruciferous vegetables. This compound plays an antitumor role primarily by modulating the level of Bcl-2 family proteins that trigger apoptosis.[89] Cordycepin acts as an antitumor agent by blocking the cell cycle at G_0/G_1 and by affecting protein expression in the H1975 and PC9 cell lines.[90]

Herbal Prescriptions Commonly Used in NSCLC Treatment

Traditional herbal prescriptions are usually composed of >2 types of herbal medicine. The ingredients of herbal remedies are complex, but their rich active ingredients exert immunomodulatory and antitumor effects. Herbal prescriptions have been shown to act on different signaling pathways in vivo and in vitro to exert anti-NSCLC effects (Table 3).

Maimendong and Qianjin Weijing decoction are oriental prescriptions for treating "pulmonary carbuncles," as recorded in traditional Chinese medicine classic books over 1000 year ago. Maimendong and Qianjin Weijing decoction are composed of 8 Chinese medicinal herbs: *Ophiopogonis Radix, Ginseng Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Phragmites Rhizoma, Coicis Semen, Benincasa hispida*, and *Persicae Semen*. In modern pharmacological trials, Maimendong and Qianjin Weijing decoction was able to suppress cell proliferation and induce NSCLC cell death.[91,92] Jiang et al[93]showed that Maimendong and Qianjinweijing decoction acted on the Wnt signaling pathway to induce the expression of microRNA (miR)-149-3p and inhibit the expression of may-associated zinc-finger protein (MAZ), c-Myc and cyclin D1, thus inhibiting NSCLC cell metastasis. A study reported a significant inhibitory effect of Maimendong and Qianjin Weijing decoction combined with cisplatin on A549 xenografts in nude mice, mainly through inhibition of p-AKT and p-PTEN expression and down-regulated Bcl-2.[94] A clinical study revealed that Maimendong decoction combined with cisplatin was more effective than cisplatin alone in 19 patients with NSCLC.[95]

Jinfukang (JFK) decoction (JFKD) is an herbal prescription approved by the Food and Drug Adiministration for NSCLC therapy. JFK is composed of 12 herbs, including

Table 3. Effects of Herbal Prescriptions on Non-small Cell Lung Cancer.

Formula	Ingredients	Extraction method	Preclinical	Clinical	(Refs.)
MaiMenDong and QianJinWeiJing	Ophiopogonis Radix, Ginseng Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Phragmitis Rhizoma, Coicis Semen, Benincasa hispida, Persicae Semen	Water	Inactive Wnt/β-catenin signaling; Inhibit PI3K/AKT pathway	Attenuate the adverse toxicity of Cisplatin	Jiang et al[93], Xiong et al[94], Xia et al[95]
JinFuKang	Radix astragali, Radix glehniae, Radix asparagi, Fructus ligustri lucidi, Herba selaginellae, Rhizoma paridis yunnanensis, Folium epimedii, Herbal gynostemmatis, Fructus corni, Herba salviae chinensis, Radix Ophiopogon, Semen trigonella	70% ethanol	Block the G2 and M phases of the cell cycle; Active Fas and DR4	prolong survival in patients with stage II/III NSCLC (JinFuKang + Cisplatin)	Lu et al[96], Han[97], Liu et al[98], Jiao et al[99], Huang et al[100]
BuZhongYiQi	Astragali Radix, Glycyrrhizae Radix, Codonopsis Radix, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium, Cimicifugae Rhizoma, Bupleuri Radix, Atractylodis Macrocephalae Rhizoma	Water	Induce ROS accumulation Reduced Bcl-2, increased Bax levels; Upregulate LC3-II,ATG7 levels	Improve patient symptoms and systemic inflammation; reduce the adverse toxicity of paclitaxel	Yu et al[105], Ouyang et al[106], Satoh et al[107], Tatsumi et al[108]
WenXiaChangFu	Aconiti Lateralis RadixPraeparata, Ginseng Radix et Rhizoma, Angelicae Sinensis Radix, Rhei Radix et Rhizoma	Water	Suppress integrin β/PI3K/AKT signaling pathway; Block the cell cycle; mitigate drug resistance	No reports in English	Ji et al[109], Zhang et al[110], Ji et al[111], Wang et al[112]
LianJiaSanjie	Scutellariae Radix, Trionycis Carapax, Sarcandrae Herba, Ranunculus ternatus Thunb, Adenophorae Radix, Glehniae Radix, Pseudostellariae Radix, Ophiopogonis Radix, Asparagi Radix, Rubia cordifolia, Pinelliae Rhizoma, Hedyotidis Herba, Bombyx Batryticatus, Inula japonica	Water	Regulate EGRF/ p53 signaling pathway; mitigate drug resistance	No reports in English	Wang et al[113], Liu[114]
BuFei	Codonopsis pilosula, Schisandra chinensis, Rehmannia glutinosa, Astragalus, Aster and Cortex Mori.	Water	Inhibit PD-LI and IL-10 expression; Suppress Canonical Smad signaling pathway; Inhibit TGF-β1 mediated EMT	Extend the disease-free survival of patients with stage II-IIIA NSCLC	Pang et al[115], He et al[116], Zhao et al[117], McCulloch et al[118]

Abbreviations: PI3K, phosphatidylinositol 3-kinase; AKT, Protein Kinase B; Fas, Death receptor; DR, Death receptor; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2 Associated X Protein; LC3, MAPILC3; ATG, autophagy related gene; EGRF, epidermal growth factor receptor; P53, tumor protein 53; IL, interleukin; PD-LI, programed death-ligand I.

Radix astragali, Radix glehniae, Radix asparagi, Fructus ligustrum Lucidi, Herba selaginella, Rhizoma paradise yunnanensis, Folium epimedii, Herbal gynostemmatis, Fructus corni, Herba salviae chinensis, Radix Ophiopogon, and *Semen trigonella*. Lu et al[96] stated that JFKD prescriptions may be associated with Fas and DR4 activation to cause apoptosis. Research has shown that JFK prescriptions act as tumor inhibitors in human lung cancer cells by blocking cancer cells due to its inhibitory effect on DNA.[97] In addition, clinical reports have shown that JFKD combined with cisplatin chemotherapy prolongs survival in patients with stage II/III NSCLC, improves immune parameters and reduces cisplatin-related side effects.[98-100]

Buzhong Yiqi (BZYQ) decoction (BZYQD) first appeared in the book "Spleen and Stomach Theory" by Li Dongyuan >700 years ago, which focused on prescriptions for treating visceral ptosis, chronic gastrointestinal diarrhea, and other spleen and stomach diseases.[101] Previous studies reported that high concentrations of BZYQ can cause gastric cancer and ovarian neoplasm tumor cell death by regulating apoptosis.[102] BZYQ contains 8 herbs: *Astragali Radix, Glycyrrhizae Radix, Codonopsis Radix, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium, Cimicifugae Rhizoma, Bupleuri Radix*, and *Atractylodis Macrocephalae Rhizoma*. Gou et al[103] confirmed that BZYQD could reduce gastrointestinal damage by inhibiting the expression of inflammatory cytokines. Moreover, BZYQD reduces kidney damage in mice through antioxidant mechanisms.[104] Yu et al[105] demonstrated that BZYQ could reduce the resistance of the A549/DDP cell line to cisplatin, making the A549/DDP cell line more sensitive to chemotherapy. Previous clinical studies showed that BZYQ combined with conventional chemotherapy drug effectively improved patient symptoms and systemic inflammation. Additionally, BZYQ prescriptions can alleviate fatigue caused by the chemotherapeutic drug paclitaxel and improve lung cancer survival.[106-108]

WenXiaChangFu (WXC), a commercial herbal prescription, comprises *Aconiti Lateralis Radix Praeparata, Ginseng, Angelicae Sinensis Radix*, and *Rhei Radix et Rhizoma*. Ji et al[109] reported that WXC mitigated cisplatin resistance by inducing cell death. Previous studies have indicated that WCF acts on the A549 cell line, and in a nude mouse model, it can inhibit the integrin β/PI3K/AKT signaling pathway to reverse drug resistance.[110] Previous studies revealed that WXC prescriptions with cisplatin may effectively suppress tumors by block the cell cycle and induce apoptosis.[111,112]

Lianjia Sanjie decoction (LJSJD) is a composition of 14 herbs mainly used as a lung cancer adjuvant therapy, including *Scutellariae Radix, Trionycis Carapax, Sarcandrae Herba, Ranunculus terminates Thunb, Adenophorae Radix, Glehniae Radix, Pseudostellariae Radix, Ophiopogonis Radix, Asparagi Radix, Rubia cordifolia, Pinelliae Rhizoma,*

Hedyotidis Herba, Bombyx Batryticatus, and *Inula japonica*. Wang et al[113] showed that LJSJD prescriptions had a pronounced cytotoxic effect on A549, H460, H1650 and H1975 cells. Additionally, LJSJD prescriptions could inhibit EGFR mutations and stimulate the expression of P53. LJSJD prescriptions have been shown to mitigate gefitinib drug resistance in lung cancer cell lines.[114]

BuFei decoction (BFD) is a conventional Chinese medicine prescription formulated to treat lung cancer. The medicinal ingredients of BFD include *Codonopsis pilosula, Schisandra chinensis, Rehmannia glutinosa, Astragalus, Aster*, and *Cortex Mori*. Previous studies showed that BFD inhibits IL-10 and PD-L1 expression to interrupt the association between TAMs and NSCLC cells (A549, H1975).[115] He et al[116] showed that BFD blocks cancer cell metastasis by the Smad signaling pathway, thus inhibiting the TGF-β1-induced EMT process, thereby exerting an antitumor effect. In the clinic, BFD as an adjuvant therapy could mitigate tumor recurrence rates, modulate human immunological functions, and extend the disease-free survival of patients with stage II-IIIA NSCLC.[115,117,118]

In summary, the multicomponent and multitarget effects of traditional herbal prescriptions effectively prevent cancer and overcome drug resistance. The above studies have shown that herbal prescriptions have a potential as adjuvant cancer therapy. Clinical studies should be conducted to explore their mechanism of action.

Discussion

As NSCLC gradually progresses, the applications of traditional herbal medicine attract increasing attention. Whether in combination with chemotherapy drugs or by alleviating chemotherapy-related adverse side effects in patients with cancer, herbal medicine provides an optional adjuvant treatment for clinicians. Apoptosis is a form of cell death vital for the human body to maintain its proper function and is frequently a major factor in herbal anticancer treatment. Apoptosis occurs via nuclear fragmentation, cell contraction, cell membrane blistering, chromosome DNA breakage and chromatin concentration.[119,120] Internal pathways (also known as mitochondrial pathways) and exterior pathways (also called death receptor pathways) participate in the apoptotic process. The mitochondrial pathway primarily involves the Bcl-2 family. The pro-apoptotic Bcl-2 family of proteins can be transported to the mitochondrial outer membrane to secrete pro-apoptotic factors and activate caspase-9, which triggers caspase-3 activation and finally induces apoptosis. Conversely, anti-apoptotic proteins in the Bcl-2 family often act as inhibitors of apoptosis.[121] The exogenous apoptosis pathway activates caspase-8 by enhancing death receptor expression, which directly cleaves or activates downstream caspases to transmit apoptotic signals.[121] Autophagy involves autophagosomes phagocytizing proteins and

organelles, and then transporting them to lysosomes. Autophagy can promote tumor proliferation while also causing tumor cell death.[122] Previously, it was reported that puerarin may regulate LC3II/LC3I and autophagy related 5 expression by PI3K/AKT signaling pathways, ultimately inducing the cancer cells autophagic death.[123] Thus, apoptosis and autophagy may be beneficial in preventing and treating NSCLC. Cell proliferation and metastasis are linked to cancer-related mortality and poor prognosis. Tumor metastasis is the product of cell biological processes involving numerous aspects, such as cell adhesion, extracellular matrix degradation, tumor cell migration and invasion.[124] It has been shown that, in NSCLC, brain and liver are common tumor metastatic organs.[124] Herbal extracts have been reported to exhibit potential efficacy in inhibiting neoplasm metastasis. Marine-mediated inhibition neoplasm metastasis is generally associated with the migration-related gene paired box 2 (PAX2).[125] Patients with cancer often have high expression levels of the PAX2 gene. Overexpression of the PAX2 gene may contribute to tumorigenesis, but it may be a useful tumor marker.[125] The cell cycle is divided into 4 phases: G_1, S, G_2, and M. Inhibiting the cell cycle can block tumor progression.[126] Herbal extracts such as praeruptorin C block the cell cycle and induce cell death by controlling cyclin D1 and p21 proteins.[127] Polyphyllin D induces G0/G1 cell cycle arrest and downregulates cyclin D1 expressions by upregulating the level of sex-determining region Y-box 7 (SOX7) transcription factor.[128] Garg et al[129] reported that SOX7 acts as a tumor suppressor in lung tissue, especially in NSCLC cell lines (H23 and H1299). It was found that stimulating the high expression of SOX7 could significantly induce apoptosis and inhibit cell proliferation. Aberrant activation of signaling pathways is critical in tumor progression. Herbal medicine may selectively interfere with cancer cells at different stages by regulating different signaling pathways, thereby playing an auxiliary antitumor effect. The Wnt signaling pathway is one of the classical signaling pathways, and its mis-regulation is common in NSCLC. The Wnt signaling pathway is responsible for regulating various behaviors associated with tumor cells, including proliferation, invasion, metabolic activity, apoptosis, and inflammation. In orthotopic xenografts, Jiang et al[93] observed that Maimendong and Qianjinweijing prescriptions reduced Wnt target gene expression, particularly miR-149-3p, and thus had an anti-NSCLC effect. CA, the most cytotoxic component in *Cinnamomum cassia*, blocks NSCLC proliferation by regulating the Wnt signaling pathway.[73] AKT signaling pathway activation is often positively correlated with neoplasm occurrence. AKT signaling pathway is frequently aberrantly activated in lung cancer, leukemia, gastric cancer, and other cancer types, so inhibiting AKT signaling pathway could effectively prevent tumor proliferation and migration.[130] Therefore, targeting the AKT signaling pathway may provide potential anti-NSCLC effects. The NF-κB

signaling pathway is crucial in anti-cancer activity, inducing apoptosis, blocking the cell cycle and suppressing the inflammatory response.[131] The formula YangYinWenYang regulates inflammatory cytokine levels and inhibits NF-κB signaling pathway.[132] Zheng et al[85] found that piperlongumine, a potential anti-tumor herbal extracts, blocks NF-κB and DNA binding activity. In conclusion, the common pathways involved in anti-NSCLC are P13K/AKT, Wnt, and NF-κB signaling pathways, which can be inhibited by acting on different targets. Also, herbal medicine inhibits anti-apoptotic protein levels while inducing pro-apoptotic protein expression, leading to cancer cell apoptosis. In addition to the main signaling pathways mentioned above, some herbal extracts or prescriptions use different anti-tumor mechanisms. The herbal extracts also act on the STAT3 signaling pathway and Hedgehog signaling pathway to inhibit NSCLC by regulating these pathways' upstream and downstream related proteins. STAT3 plays a vital role in human malignancies. It regulates cell apoptosis, cell proliferation, and angiogenesis.[133] On the other hand, STAT3 signaling overexpression promotes drug resistance and induces cell metastasis.[134] Garg et al[134]summarized that several potential natural product-derived small molecules inhibit STAT3 signaling, such as formononetin, zerumbone, garcinol, and others, providing a reference for new drug discovery in the future. The herbal prescriptions inactivate the classical Smad signaling pathway by regulating the expression of TGF-β1. Figure 1 summarizes the study of herbal medicine treatment for NSCLC (Figure 1).

Conclusion

To summarize, herbal medicine has the potential to be used as adjunctive therapy for NSCLC. With the advancement in systems biology, a more profound and systematic knowledge of herbal treatment has been obtained. The practice of herbal medicine has progressively evolved into a medical system based on evidence rather than the practitioner's own experiences. Herbal medicines inhibit tumor progression and improve chemoradiotherapy sensitivity mainly through the P13K/AKT signaling pathway, Wnt signaling pathway, NF-κB signaling pathway. Additionally, some herbal extracts and prescriptions exert multi-target, pleiotropic effects by regulating related apoptosis proteins (Bad, Bax, Bcl-xl, Bcl-2), ROS levels, and upstream and downstream proteins affecting related pathways. They act to achieve network regulation and ultimately produce tumor-inhibiting effects. In NSCLC treatment, Chinese herbal medicine combined with radio-chemotherapy can improve efficacy, alleviate the toxicity and adverse side effect caused by radio-chemotherapy, and prolong progression-free survival. By reviewing and summarizing these drugs, it is helpful to discover that herbal medicine may be applied as a potential adjunct treatment to NSCLC in the future and provide
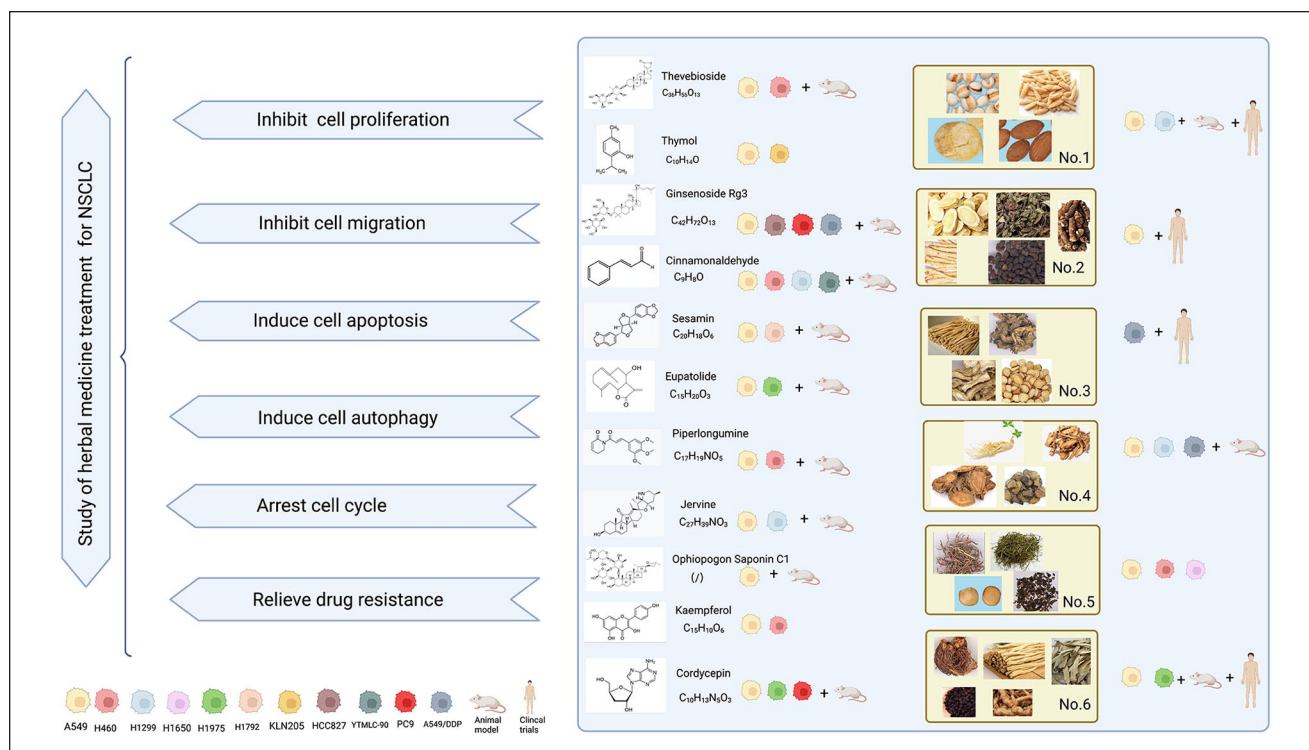
Figure 1. Study of herbal medicine treatment for non-small cell lung cancer. Animal experiments, clinical trials and molecular biology studies of herbal extracts and herbal prescriptions to inhibit the growth of NSCLC are graphically and vividly presented in this diagram. This figure was created with Biorender.com.

useful information for the development of effective new drugs. However, there are limitations in the published studies. Research on herbal medicines is still mainly based on cell and animal experiments. Clinical trials are rare in the literature; thus, further studies should be conducted to confirm their safety and efficacy. In conclusion, Chinese herbal medicine inhibits tumor growth through induces apoptosis of tumor cells, inhibits metastasis of cancer cells, reverses the resistance of conventional chemotherapeutic drugs and so on. Clinically, Chinese herbal medicine combined with traditional chemotherapeutic drugs may increase effectiveness and reduce toxicity.

Authors' Contributions

P-Y Y and LT designed the review. JH and J-X L wrote the manuscript. R-Z L, L-R M, PW, D-H X, L-Q L, L-L Y, YL, HZ and Y-H Z revised the manuscript. All authors approved the submitted version.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The

ORCID iDs

Jie Huang https://orcid.org/0000-0003-2782-2453

Jia-Xin Li https://orcid.org/0000-0002-7489-8840

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. *Lancet*. 2021;398:535-554.
3. Dawkins JBN, Webster RM. The small-cell lung cancer drug market. *Nat Rev Drug Discov*. 2020;19:507-508.
4. Gridelli C, Rossi A, Carbone DP, et al. Non-small-cell lung cancer. *Nat Rev Dis Primers*. 2015;1:15009.
5. Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: non-small cell lung cancer, version 2.2021. *J Natl Compr Canc Ne*. 2021;19:254-266.
6. Lachgar A, Tazi MA, Afif M, Er-Raki A, Kebdani T, Benjaafar N. Lung cancer: incidence and survival in Rabat, Morocco. *Morocco Rev Epidemiol Sante*. 2016;64:391-395.
7. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature*. 2018;553:446-454.

8. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med*. 2021;27:1345-1356.

9. Jiao L, Dong C, Liu J, et al. Effects of Chinese medicine as adjunct medication for adjuvant chemotherapy treatments of non-small cell lung cancer patients. *Sci Rep*. 2017;7:46524.

10. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362:2380-2388.

11. Lim SM, Kim HR, Lee JS, et al. Open-label, Multicenter, PHASE II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol*. 2017;35:2613-2618.

12. Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation–positive non-small cell lung cancer (NSCLC) patients. *J Clin Oncol*. 2013;31:8009-8009.

13. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated*EGFR*-mutated advanced non–small-Cell lung cancer. *N Engl J Med*. 2018;378:113-125.

14. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials. *Lancet Oncol*. 2020; 21:261-270.

15. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. *N Engl J Med*. 2015;372:2018-2028.

16. Spigel D, de Marinis F, Giaccone G, et al. IMpower110: interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. *Ann Oncol*. 2019;30:v915.

17. Antonia SJ, Gettinger SN, Chow LQM, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in first-line NSCLC: Interim phase I results. *J Clin Oncol*. 2014;32: 8023-8023.

18. Borghaei H, Langer CJ, Gadgeel S, et al. 24-month overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non–small cell lung cancer. *J Thorac Oncol*. 2019;14:124-129.

19. Theelen WSME, Peulen HMU, Lalezari F, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol*. 2019;5:1276-1282.

20. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. *Lancet*. 2017;389:299-311.

21. An X, Zhang Y, Duan L, et al. The direct evidence and mechanism of traditional Chinese medicine treatment of COVID-19. *Biomed Pharmacother*. 2021;137:111267.

22. Merarchi M, Dudha N, Das BC, Garg M. Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs. *Phytother Res*. 2021;35:5384-5396.

23. Li SG, Chen HY, Ou-Yang CS, et al. The efficacy of Chinese herbal medicine as an adjunctive therapy for advanced non-small cell lung cancer: a systematic review and meta-analysis. *PLoS One*. 2013;8:e57604.

24. Xu B, Zhang H, Wang Y, Huang S, Xu L. Mechanism of Xu Li's experiential prescription for the treatment of EGFR-positive NSCLC. *Evid-Based Compl Alt*. 2020;2020:8787153.

25. Lourenço AM, Ferreira LM, Branco PS. Molecules of natural origin, semi-synthesis and synthesis with anti-inflammatory and anticancer utilities. *Curr Pharm Des*. 2012;18:3979-4046.

26. Orlikova B, Legrand N, Panning J, Dicato M, Diederich M. Anti-inflammatory and anticancer drugs from nature. *Cancer Treat Res*. 2014;159:123-143.

27. Xu W, Yang G, Xu Y, et al. The possibility of traditional chinese medicine as maintenance therapy for advanced nonsmall cell lung cancer. *Evid-Based Compl Alt*. 2014;2014:278917.

28. Lee HY, Meng M, Liu Y, Su T, Kwan HY. Medicinal herbs and bioactive compounds overcome the drug resistance to epidermal growth factor receptor inhibitors in non-small cell lung cancer. *Oncol Lett*. 2021;22:646.

29. Lu Y, Sun C, Jiao L, Liu Y, Gong Y, Xu L. Chinese herbal medicine combined with first-generation EGFR-TKIs in treatment of advanced non-small cell lung cancer with EGFR sensitizing mutation: a systematic review and meta-analysis.. *Front Pharmacol*. 2021;12:698371.

30. Jin H, Park SB, Yoon JH, Lee JY, Kim EH, Yoon SW. Traditional herbal medicine combined with first-line platinum-based chemotherapy for advanced non-small-cell lung cancer: A PRISMA-compliant systematic review and meta-analysis. *Medicine*. 2021;100:e27163.

31. Horie S. Chemoprevention of prostate cancer: soy isoflavones and curcumin. *Korean J Urol*. 2012;53:665-672.

32. Sarkar FH, Li Y, Wang Z, Padhye S. Lesson learned from nature for the development of novel anti-cancer agents: implication of isoflavone, curcumin, and their synthetic analogs. *Curr Pharm Des*. 2010;16:1801-1812.

33. Rincón-Pérez J, Rodríguez-Hernández L, Ruíz-Valdiviezo VM, et al. Fatty acids profile, phenolic compounds and antioxidant capacity in elicited callus of *Thevetia peruviana* (Pers.) K. Schum. *J Oleo Sci*. 2016;65:311-318.

34. Yao C, Su L, Zhang F, et al. Thevebioside, the active ingredient of traditional Chinese medicine, promotes ubiquitin-mediated SRC-3 degradation to induce NSCLC cells apoptosis. *Cancer Lett*. 2020;493:167-177.

35. Jin J, Wang T, Wang Y, et al. SRC3 expressed in BMSCs promotes growth and migration of multiple myeloma cells by regulating the expression of Cx43. *Int J Oncol*. 2017;51: 1694-1704.

36. Dasgupta S, Rajapakshe K, Zhu B, et al. Metabolic enzyme PFKFB4 activates transcriptional coactivator SRC-3 to drive breast cancer. *Nature*. 2018;556:249-254.

37. Thuy TD, Phan NN, Wang CY, et al. Novel therapeutic effects of sesamin on diabetes-induced cardiac dysfunction. *Mol Med Rep*. 2017;15:2949-2956.

38. Noguchi T, Ikeda K, Sasaki Y, Yamamoto J, Yamori Y. Effects of vitamin E and sesamin on hypertension and cerebral thrombogenesis in stroke-prone spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol*. 2004;31 Suppl 2: S24-S26.

39. Akl M, Ayoub N, Sylvester P. Mechanisms mediating the synergistic anticancer effects of combined γ-Tocotrienol and sesamin treatment. *Planta Med*. 2012;78:1731-1739.

40. Deng P, Wang C, Chen L, et al. Sesamin induces cell cycle arrest and apoptosis through the inhibition of signal transducer and activator of transcription 3 signalling in human hepatocellular carcinoma cell line HepG2. *Biol Pharm Bull*. 2013;36:1540-1548.

41. Harikumar KB, Sung B, Tharakan ST, et al. Sesamin manifests chemopreventive effects through the suppression of NF-kappa B-regulated cell survival, proliferation, invasion, and angiogenic gene products. *Mol Cancer Res*. 2010;8:751-761.

42. Chen Y, Li H, Zhang W, et al. Corrigendum to "Sesamin suppresses NSCLC cell proliferation through cyclin D1 inhibition-dependent cell cycle arrest via Akt/p53 pathway" [Toxicology and applied pharmacology, 387 (2020) 114848]. *Toxicol Appl Pharmacol*. 2020;400:115048.

43. Fang Q, Zhu Y, Wang Q, Song M, Gao G, Zhou Z. Suppression of cyclooxygenase 2 increases chemosensitivity to sesamin through the Akt-PI3K signaling pathway in lung cancer cells. *Int J Mol Med*. 2019;43:507-516.

44. Yang S, Li X, Dou H, Hu Y, Che C, Xu D. Sesamin induces A549 cell mitophagy and mitochondrial apoptosis via a reactive oxygen species-mediated reduction in mitochondrial membrane potential. *Korean J Physiol Pharmacol*. 2020;24:223-232.

45. Lei W, Huo Z. Jervine inhibits non-small cell lung cancer (NSCLC) progression by suppressing Hedgehog and AKT signaling via triggering autophagy-regulated apoptosis. *Biochem Biophys Res Commun*. 2020;533:397-403.

46. Pan S-T, Zhou J, Yang F, Zhou S-F, Ren T. Proteomics reveals a therapeutic vulnerability via the combined blockade of APE1 and autophagy in lung cancer A549 cells. *BMC Cancer*. 2020;20:634.

47. Wei X, Liu W, Wang JQ, Tang Z. "Hedgehog pathway": a potential target of itraconazole in the treatment of cancer. *J Cancer Res Clin*. 2020;146:297-304.

48. Klein SD, Nguyen DC, Bhakta V, et al. Mutations in the sonic hedgehog pathway cause macrocephaly-associated conditions due to crosstalk to the PI3K/AKT/mTOR pathway. *Am J Med Genet A*. 2019;179:2517-2531.

49. Nagoor Meeran MF, Javed H, Al Taee H, Azimullah S, Ojha SK. Pharmacological properties and molecular mechanisms of thymol: prospects for its therapeutic potential and pharmaceutical development. *Front Pharmacol*. 2017;8:380.

50. Li C, Thompson MA, Tamayo AT, et al. Over-expression of thioredoxin-1 mediates growth, survival, and chemoresistance and is a druggable target in diffuse large B-cell lymphoma. *Oncotarget*. 2012;3:314-326.

51. Dashtaki A, Mahjoub S, Zabihi E, Pourbagher R. The effects of pre-treatment and post-treatment of thymol against tert-butyl hydroperoxide (t-BHP) cytotoxicity in MCF-7 cell line and fibroblast derived foreskin. *Rep Biochem Mol Biol*. 2020;9:338-347.

52. De La Chapa JJ, Singha PK, Lee DR, Gonzales CB. Thymol inhibits oral squamous cell carcinoma growth via mitochondria-mediated apoptosis. *J Oral Pathol Med*. 2018;47:674-682.

53. Balan DJ, Rajavel T, Das M, Sathya S, Jeyakumar M, Devi KP. Thymol induces mitochondrial pathway-mediated apoptosis via ROS generation, macromolecular damage and SOD diminution in A549 cells. *Pharmacol Rep*. 2021;73:240-254.

54. Elbe H, Yigitturk G, Cavusoglu T, Uyanikgil Y, Ozturk F. Apoptotic effects of thymol, a novel monoterpene phenol, on different types of cancer. *Bratisl Med J*. 2021;121:122-128.

55. Koparal AT, Zeytinoglu M. Effects of carvacrol on a human non-small cell lung cancer (NSCLC) cell line, A549. *Cytotechnology*. 2003;43:149-154.

56. Mancuso C, Santangelo R. Panax ginseng and Panax quinquefolius: from pharmacology to toxicology. *Food Chem Toxicol*. 2017;107:362-372.

57. Unlu A, Nayir E, Kirca O, Ay H, Ozdogan M. Ginseng and cancer. *J Buon*. 2016;21:1383-1387.

58. Majeed F, Malik FZ, Ahmed Z, Afreen A, Afzal MN, Khalid N. Ginseng phytochemicals as therapeutics in oncology: recent perspectives. *Biomed Pharmacother*. 2018;100:52-63.

59. Zhang Y, Wang XQ, Liu H, Liu J, Hou W, Lin HS. A multicenter, large-sample, randomized clinical trial on improving the median survival time of advanced non-small cell lung cancer by combination of Ginseng Rg3 and chemotherapy. *Zhonghua Zhong Liu Za Zhi*. 2018;40:295-299.

60. Zhang YH, Li HD, Li B, Jiang SD, Jiang LS. Ginsenoside Rg3 induces DNA damage in human osteosarcoma cells and reduces MNNG-induced DNA damage and apoptosis in normal human cells. *Oncol Rep*. 2014;31:919-925.

61. Poon PY, Kwok HH, Yue PYK, et al. Cytoprotective effect of 20S-Rg3 on benzo[a]pyrene-induced DNA damage. *Drug Metab Dispos*. 2012;40:120-129.

62. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7-34.

63. Bhattacharjee S, Nandi S. Choices have consequences: the nexus between DNA repair pathways and genomic instability in cancer. *Clin Transl Med*. 2016;5:45-52. doi:10.1186/s40169-016-0128-z

64. Liu T, Zuo L, Guo D, et al. Ginsenoside Rg3 regulates DNA damage in non-small cell lung cancer cells by activating VRK1/P53BP1 pathway. *Biomed Pharmacother*. 2019;120:109483.

65. Campillo-Marcos I, Lazo PA. Implication of the VRK1 chromatin kinase in the signaling responses to DNA damage: a therapeutic target? *Cell Mol Life Sci*. 2018;75:2375-2388.

66. Sanz-García M, Monsalve DM, Sevilla A, Lazo PA. Vaccinia-related kinase 1 (VRK1) is an upstream nucleosomal kinase required for the assembly of 53BP1 foci in response to ionizing radiation-induced DNA damage. *J Biol Chem*. 2012;287:23757-23768.

67. Tan Q, Lin S, Zeng Y, et al. Ginsenoside Rg3 attenuates the osimertinib resistance by reducing the stemness of non-small cell lung cancer cells. *Environ Toxicol*. 2020;35:643-651.

68. Jiang Z, Yang Y, Yang Y, et al. Ginsenoside Rg3 attenuates cisplatin resistance in lung cancer by downregulating PD-L1 and resuming immune. *Biomed Pharmacother*. 2017;96:378-383.

69. Wang XJ, Zhou RJ, Zhang N, Jing Z. 20(S)-ginsenoside Rg3 sensitizes human non-small cell lung cancer cells to

icotinib through inhibition of autophagy. *Eur J Pharmacol*. 2019;850:141-149.

70. Gruenwald J, Freder J, Armbruester N. Cinnamon and health. *Crit Rev Food Sci Nutr*. 2010;50:822-834.

71. Long M, Tao S, Rojo de la Vega M, et al. Nrf2-dependent suppression of azoxymethane/dextran sulfate sodium-induced colon carcinogenesis by the cinnamon-derived dietary factor cinnamaldehyde. *Cancer Prev Res*. 2015;8:444-454.

72. Chang WL, Cheng FC, Wang SP, Chou ST, Shih Y. *Cinnamomum cassiaessential* oil and its major constituent cinnamaldehyde induced cell cycle arrest and apoptosis in human oral squamous cell carcinoma HSC-3 cells. *Environ Toxicol*. 2017;32:456-468.

73. Wu C, Zhuang Y, Jiang S, et al. Cinnamaldehyde induces apoptosis and reverses epithelial-mesenchymal transition through inhibition of Wnt/β-catenin pathway in non-small cell lung cancer. *Int J Biochem Cell Biol*. 2017;84:58-74.

74. Tian F, Yu CT, Ye WD, Wang Q. Cinnamaldehyde induces cell apoptosis mediated by a novel circular RNA hsa_circ_0043256 in non-small cell lung cancer. *Biochem Biophys Res Commun*. 2017;493:1260-1266.

75. Hong SH, Ismail IA, Kang SM, Han DC, Kwon BM. Cinnamaldehydes in Cancer Chemotherapy. *Phytother Res*. 2016;30:754-767.

76. Park J, Baek SH. Combination therapy with cinnamaldehyde and hyperthermia induces apoptosis of A549 Non-Small cell lung carcinoma cells via regulation of reactive oxygen species and mitogen-activated protein kinase family. *Int J Mol Sci*. 2020;21:6229.

77. Boldbaatar A, Lee S, Han S, et al. Eupatolide inhibits the TGF-β1-induced migration of breast cancer cells via downregulation of SMAD3 phosphorylation and transcriptional repression of ALK5. *Oncol Lett*. 2017;14:6031-6039.

78. Adekenov SM. Sesquiterpene lactones with unusual structure. Their biogenesis and biological activity. *Fitoterapia*. 2017;121:16-30.

79. Lee J, Hwangbo C, Lee JJ, Seo J, Lee JH. The sesquiterpene lactone eupatolide sensitizes breast cancer cells to TRAIL through down-regulation of c-FLIP expression. *Oncol Rep*. 2010;23:229-237.

80. Ma X, Wu K, Xu A, Jiao P, Li H, Xing L. The sesquiterpene lactone eupatolide induces apoptosis in non-small cell lung cancer cells by suppressing STAT3 signaling. *Environ Toxicol Pharmacol*. 2021;81:103513.

81. Banerjee K, Resat H. Constitutive activation of STAT3 in breast cancer cells: a review. *Int J Cancer*. 2016;138:2570-2578.

82. Bezerra DP, Pessoa C, Moraes MOD, et al. *In vivo* growth inhibition of sarcoma 180 by piperlonguminine, an alkaloid amide from the *Piper* species. *J Appl Toxicol*. 2008;28:599-607.

83. Golovine K, Makhov P, Teper E, et al. Piperlongumine induces rapid depletion of the androgen receptor in human prostate cancer cells. *Prostate*. 2012;73:23-30.

84. Raj L, Ide T, Gurkar AU, et al. Selective killing of cancer cells by a small molecule targeting the stress response to ROS. *Nature*. 2011;475:231-234.

85. Zheng J, Son DJ, Gu SM, et al. Piperlongumine inhibits lung tumor growth via inhibition of nuclear factor kappa B signaling pathway. *Sci Rep*. 2016;6:26357.

86. Gagat M, Hałas-Wiśniewska M, Zielińska W, Izdebska M, Grzanka D, Grzanka A. The effect of piperlongumine on endothelial and lung adenocarcinoma cells with regulated expression of profilin-1. *Onco Targets Ther*. 2018;11:8275-8292.

87. Lewis KM, Bharadwaj U, Eckols TK, et al. Small-molecule targeting of signal transducer and activator of transcription (STAT) 3 to treat non-small cell lung cancer. *Lung Cancer*. 2015;90:182-190.

88. Zhang Y, Zhao Y, Wu Y, et al. Ophiopogon saponin C1 inhibits lung tumors by stabilizing endothelium permeability via inhibition of PKCδ. *Int J Biol Sci*. 2020;16:396-407.

89. Fouzder C, Mukhuty A, Kundu R. Kaempferol inhibits Nrf2 signalling pathway via downregulation of Nrf2 mRNA and induces apoptosis in NSCLC cells. *Arch Biochem Biophys*. 2021;697:108700.

90. Nakamura K, Shinozuka K, Yoshikawa N. Anticancer and antimetastatic effects of cordycepin, an active component of Cordyceps sinensis. *J Pharmacol Sci*. 2015;127:53-56.

91. Zhou Y, Zhan Z, Tang Y, Duan J. Zhang X.Mechanisms of proliferative inhibition by maimendong & qianjinweijing decoction in A549 cells. *Zhongguo Fei Ai Za Zhi*. 2010;13:477-482.

92. Fan Y, Ma Z, Zhao L, et al. Anti-tumor activities and mechanisms of traditional Chinese medicines formulas: a review. *Biomed Pharmacother*. 2020;132:110820.

93. Jiang Z, Ma Y, Tian T, et al. Maimendong and Qianjinweijing Tang (Jin formula) suppresses lung cancer by regulation of miR-149-3p. *J Ethnopharmacol*. 2020;258:112836.

94. Xiong F, Jiang M, Chen M, et al. Study on inhibitory effect of MaiMenDong decoction and WeiJing decoction combination with cisplatin on NCI-A549 xenograft in nude mice and its mechanism. *J Cancer*. 2017;8:2449-2455.

95. Xia K, Zeng Y, Hao W, et al. Clinic study of Maimendong Tang combining with EP regimen in treatment for patients with advanced non-small cell lung cancer. *J Liaoning Univ Tradit Chin Med*. 2015;42:1705-1707.

96. Lu J, Chen J, Kang Y, et al. Jinfukang induces cellular apoptosis through activation of Fas and DR4 in A549 cells. *Oncol Lett*. 2018;16:4343-4352.

97. Han M-Q. Effects of Yifei Kangliu Qral Liquid on cell cycle and protein-nucleic acid synthesis of experimental lung cancer. *Zhong Xi Yi Jie He Xue Bao*. 2003;1:205-208. Chinese.

98. Liu J, Pan M, Li Y, Ye D, Guo Y, Li Y. Clinical study of oral liquid Jin Fu Kang for the treatment of primary non-small cell lung cancer. *Tumor (Shanghai)*. 2001;21:463-465.

99. Jiao L, Wang Y, Xu L, You M. Lung cancer prevention and therapy using the JinFuKang herbal mixture. *Curr Pharmacol Rep*. 2015;1:346-353.

100. Huang X, Sun J, Sun J. Combined treatment with JFKD and gefitinib overcomes drug resistance in non-small cell lung cancer. *Curr Pharm Biotechnol*. 2021;22:389-399.

101. Chang YY, Tsai YT, Lai JN, Yeh CH, Lin SK. The traditional Chinese medicine prescription patterns for migraine patients in Taiwan: a population-based study. *J Ethnopharmacol*. 2014;151:1209-1217.

102. Zhu K, Fukasawa I, Furuno M, et al. Inhibitory effects of herbal drugs on the growth of human ovarian cancer cell lines through the induction of apoptosis. *Gynecol Oncol*. 2005;97:405-409.

103. Gou H, Gu L, Shang B, Xiong Y, Wang C. Protective effect of Bu-Zhong-Yi-Qi decoction, the water extract of Chinese traditional herbal medicine, on 5-fluorouracil-induced intestinal mucositis in mice. *Hum Exp Toxicol*. 2016;35: 1243-1251.

104. Xiong Y, Shang B, Xu S, Zhao R, Gou H, Wang C. Protective effect of Bu-Zhong-Yi-Qi decoction, the water extract of Chinese traditional herbal medicine, on 5-fluorouracil-induced renal injury in mice. *Ren Fail*. 2016;38:1240-1248.

105. Yu N, Xiong Y, Wang C. Bu-Zhong-Yi-Qi decoction, the water extract of Chinese traditional herbal medicine, enhances cisplatin cytotoxicity in A549/DDP cells through induction of apoptosis and autophagy. *Biomed Res Int*. 2017;2017:3692797.

106. Ouyang M, Liu Y, Tan W, et al. Bu-Zhong-Yi-Qi pill alleviate the chemotherapy-related fatigue in 4 T1 murine breast cancer model. *BMC Complement Altern Med*. 2014;14:497.

107. Satoh H, Ishikawa H, Ohtsuka M, Sekizawa K. Japanese herbal medicine in patients with advanced lung cancer: prolongation of survival? *J Altern Complement Med*. 2002; 8:107-108.

108. Tatsumi K, Shinozuka N, Nakayama K, Sekiya N, Kuriyama T, Fukuchi Y. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. *J Am Geriatr Soc*. 2009;57:169-170.

109. Ji XM, Wu ZC, Liu GW, et al. Wenxia Changfu Formula (温下肠腑方) induces apoptosis of lung adenocarcinoma in a transplanted tumor model of drug-resistance nude mice. *Chin J Integr Med*. 2016;22:752-758.

110. Zhang Y, Wu Z, Yu H, et al. Chinese herbal medicine Wenxia Changfu Formula reverses cell adhesion-mediated drug resistance via the integrin β1-PI3K-AKT pathway in lung cancer.. *J Cancer*. 2019;10:293-304.

111. Ji XM, Ouyang B, Liu H, et al. In vitro and in vivo inhibitory effect of the combination of Wenxia Changfu formula [see text] with cisplatin in non-small cell lung cancer. *Chin J Integr Med*. 2011;17:908-916.

112. Wang MR, Chen RJ, Zhao F, et al. Effect of Wenxia Changfu formula combined with cisplatin reversing non-small cell lung cancer cell adhesion-mediated drug resistance. *Front Pharmacol*. 2020;11:500137.

113. Wang Q, Acharya N, Liu Z, et al. Enhanced anticancer effects of Scutellaria barbata D. Don in combination with traditional Chinese medicine components on non-small cell lung cancer cells. *J Ethnopharmacol*. 2018;217:140-151.

114. Liu Z. Overcoming the drug resistance of epidermal growth factor receptor-tyrosine kinase inhibitors in lung cancer cell lines. 2018.

115. Pang L, Han S, Jiao Y, et al. Bu Fei Decoction attenuates the tumor associated macrophage stimulated proliferation, migration, invasion and immunosuppression of non-small cell lung cancer, partially via IL-10 and PD-L1 regulation. *Int J Oncol*. 2017;51:25-38.

116. He XR, Han SY, Li XH, et al. Chinese medicine Bu-Fei decoction attenuates epithelial-mesenchymal transition of non-small cell lung cancer via inhibition of transforming growth factor β1 signaling pathway in vitro and in vivo. *J Ethnopharmacol*. 2017;204:45-57.

117. Zhao X, Dai X, Wang S, et al. Traditional Chinese medicine integrated with chemotherapy for stage II-IIIA patients with non-small-cell lung cancer after radical surgery: a retrospective clinical analysis with small sample size. *Evid-Based Compl Alt*. 2018;2018:1-7.

118. McCulloch M, See C, Shu XJ, et al. *Astragalus*-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. *J Clin Oncol*. 2006;24:419-430.

119. Nagasaka A, Kawane K, Yoshida H, Nagata S. Apaf-1-independent programmed cell death in mouse development. *Cell Death Differ*. 2010;17:931-941.

120. Burgess DJ. Apoptosis: refined and lethal. *Nat Rev Cancer*. 2013;13:79.

121. Carneiro BA, El-Deiry WS. Targeting apoptosis in cancer therapy. *Nat Rev Clin Oncol*. 2020;17:395-417.

122. Behrends C, Sowa ME, Gygi SP, Harper JW. Network organization of the human autophagy system. *Nature*. 2010;466:68-76.

123. Hu Y, Li X, Lin L, Liang S, Yan J. Puerarin inhibits non-small cell lung cancer cell growth via the induction of apoptosis. *Oncol Rep*. 2018;39:1731-1738.

124. Ganesh K, Massagué J. Targeting metastatic cancer. *Nat Med*. 2021;27:34-44.

125. Yang J, He D, Peng Y, et al. Matrine suppresses the migration and invasion of NSCLC cells by inhibiting PAX2-induced epithelial-mesenchymal transition. *Onco Targets Ther*. 2017;10:5209-5217.

126. Hashimoto O, Shinkawa M, Torimura T, et al. Cell cycle regulation by the Wee1 inhibitor PD0166285, pyrido [2,3-d] pyimidine, in the B16 mouse melanoma cell line.. *BMC Cancer*. 2006;6:292.

127. Liu C-M, Shen H-T, Lin Y-A, et al. Antiproliferative and antimetastatic effects of praeruptorin C on human non-small cell lung cancer through inactivating ERK/CTSD signalling pathways. *Molecules*. 2020;25:1625.

128. Zheng B, Wang G, Gao W, Wu Q, Zhu W, Weng G. SOX7 is involved in polyphyllin D-induced G0/G1 cell cycle arrest through down-regulation of cyclin D1. *Acta Pharm*. 2020;70:191-200.

129. Hayano T, Garg M, Yin D, et al. SOX7 is down-regulated in lung cancer. *J Exp Clin Cancer Res*. 2013;32:17.

130. Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E. PI3K/AKT signaling pathway and cancer: an updated review. *Ann Med*. 2014;46:372-383.

131. Poma P, Labbozzetta M, D'Alessandro N, Notarbartolo M. NF-κB is a potential molecular drug target in triple-negative breast cancers. *OMICS*. 2017;21:225-231.

132. Zhao B, Hui X, Jiao L, et al. A TCM formula YYWY inhibits tumor growth in non-small cell lung cancer and enhances immune-response through facilitating the maturation of dendritic cells. *Front Pharmacol*. 2020;11:798.

133. Yuan J, Zhang F, Niu R. Multiple regulation pathways and pivotal biological functions of STAT3 in cancer. *Sci Rep*. 2015;5:17663.

134. Garg M, Shanmugam MK, Bhardwaj V, et al. The pleiotropic role of transcription factor STAT3 in oncogenesis and its targeting through natural products for cancer prevention and therapy. *Med Res Rev*. 2021;41:1291-1336.