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REVIEW

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Traditional Chinese medicine in lung cancer treatment

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Abstract

Lung cancer remains a major global health challenge and one of the leading causes of cancer-related deaths worldwide. Despite significant advancements in treatment, challenges such as drug resistance, side effects, metastasis and recurrence continue to impact patient outcomes and quality of life. In response, there is growing interest in complementary and integrative approaches to cancer care. Traditional Chinese medicine (TCM), with its long history, abundant clinical experience, holistic perspective and individualized approach, has garnered increasing attention for its role in lung cancer prevention and management. This review provides a comprehensive overview of the advances in TCM for lung cancer treatment, covering its theoretical foundation, treatment principles, clinical experiences and evidence supporting its efficacy. We also provide a systematic summary of the preclinical mechanisms, through which TCM impacts lung cancer, including the induction of cell death, reversal of drug resistance, inhibition of metastasis and modulation of immune responses. Additionally, future prospects for TCM in lung cancer treatment are discussed, offering insights into its expanded application and integration with modern medicine to address this challenging disease.

Keywords Traditional Chinese medicine, Chinese herbal medicine, Lung cancer, Clinical trials, Combination therapy, Drug resistance, Cancer metastasis, Cancer immunology

Background

Lung cancer remains a significant global health challenge, with the highest incidence and mortality rates worldwide [1]. Cigarette smoking is the primary risk factor for lung cancer-related deaths, although genetics, radon exposure and environmental factors also contribute to its development [2]. Lung cancer is primarily categorized into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all cases, including adenocarcinoma, squamous cell carcinoma and large cell carcinoma [3]. Currently, advances in lung cancer treatment are driven by earlier detection, more precise staging and improved disease management [1]. Minimally invasive surgical procedures are effective for early-stage lung cancer, whereas concurrent radio/chemo-therapy with platinum-based regimens or stereotactic body radiotherapy is the standard treatment for patients with inoperable tumours [4, 5]. Breakthroughs in identifying oncogenic mutations have led to the development of targeted therapies, including tyrosine kinase inhibitors that improve treatment effectiveness and tackle drug resistance [6]. Immune checkpoint inhibitors have recently become the first-line treatment for advanced NSCLC patients without targetable mutations or with KRAS mutations, further improving therapeutic outcomes in lung cancer

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patients [7–10]. Additionally, antibody-drug conjugates and bispecific antibodies are being integrated into treatment guidelines, while emerging therapies, including circulating tumour DNA detection, T-cell engineering, cellular therapies and cancer vaccines, hold promise for future treatment options [11–14]. However, challenges such as drug resistance, treatment toxicity, high costs and limited access to diagnostics and therapies require sustained attention and intervention [3, 15].

TCM is increasingly recognized for its promising potential as a complementary therapy in lung cancer treatment [16]. Unlike conventional cancer treatments, which primarily focus on targeting and eliminating tumour cells, TCM adopts a holistic approach. It embraces the concept of "living with the tumour" and seeks to improve not only disease progression but also the patient's quality of life (QOL) [17]. Clinical studies have demonstrated that TCM can be effective both as a standalone treatment and in combination with conventional therapies, enhancing treatment outcomes, alleviating side effects and boosting immune function in lung cancer patients [18–21]. Additionally, numerous preclinical studies have uncovered the molecular pathways through which TCM combats lung cancer [22–24]. For example, TCM induces various cell death mechanisms, including apoptosis [25], autophagy [26], pyroptosis [27] and ferroptosis [28], to target lung cancer cells. When combined with conventional treatments such as chemotherapy or targeted therapy, TCM has been shown to reverse resistance by modulating drug resistance-related pathways, such as ATP-binding cassette (ABC) transporters, glycolysis and epidermal growth factor receptor (EGFR) [29–31]. Furthermore, TCM inhibits lung cancer metastasis by regulating premetastatic niche formation, angiogenesis and epithelial-mesenchymal transition (EMT) [32–35]. TCM also enhances the efficacy of immune checkpoint inhibitors by modulating immune cell populations [36]. These promising findings underscore the potential of TCM in lung cancer treatment and highlight the need for further research to fully explore its therapeutic role.

While several reviews have summarized the therapeutic role of TCM in lung cancer, a comprehensive review that covers its multifaceted role is still lacking. This review introduces the TCM approach to symptom typing, etiology and treatment principles for lung cancer, alongside a summary of clinical experiences and case studies. It also systemically reviews the mechanisms by which TCM influences lung cancer treatment in preclinical studies, including the induction of cell death, reversal of drug resistance, inhibition of metastasis and modulation of immune responses. Furthermore, we analyse the future prospects of TCM in lung cancer treatment, aiming to identify emerging therapeutic strategies, optimize clinical outcomes and personalized treatment approaches. This review provides a comprehensive overview of TCM's advances in lung cancer treatment, offers theoretical support and insights into its expanded application and highlights the importance of integrating ancient medical wisdom with modern medicine to overcome this challenging disease.

Experience with TCM in treating lung cancer

TCM has a millennia-long history and is deeply rooted in a unique theoretical framework and extensive clinical practice. TCM views the human body as a holistic and interconnected system, emphasizing macroscopic phenomena and external manifestations [37]. References to conditions resembling lung cancer can be traced back over two thousand years to the "Classic of Questioning", where terms like "Fei ji" or "Xi ben" were used to describe symptoms, such as coughing, chest pain, hemoptysis, asthma, chills and fever, symptoms now recognized as indicative of lung cancer. Similarly, the "Pulse Classics" by Shuhe Wang highlighted advanced-stage symptoms such as pain under the ribs, back pain and a floating pulse. In TCM, lung cancer is categorized under various terms, such as lung carbuncle, lung distension and lung gangrene [38].

The "Yellow Emperor's Inner Canon" attributes the pathogenesis of lung cancer to internal factors such as emotional disturbances, poor diet, stress, anxiety and improper lifestyle, as well as external influences like pathogens, environmental hazards and physical or poison exposure [39]. These factors disrupt the balance of Yin and Yang, impair organ function, lead to Qi and blood deficiency and obstruct meridian flow, culminating in the accumulation of dampness, phlegm and toxic heat [40, 41]. Prominent TCM practitioners have proposed detailed theories and treatment principles for lung cancer. Professor Shiqing Jiang proposed that the interplay between phlegm blockage and weakness in body resistance and blood stasis was the primary pathological mechanism, advocating for treatments that strengthen the body's foundational Qi while addressing specific pathological manifestations. Similarly, Professor Huawei Liu highlighted the convergence of phlegm, dampness, blood stasis and toxicity, along with impaired lung Qi transformation, in the progression of lung cancer. His therapeutic approach focuses on dissipating phlegm, eliminating dampness, resolving blood stasis and detoxifying to restore normal lung Qi circulation. Additionally, Jiaxiang Liu's "Fu zheng" therapy underscores strengthening the body's vital Qi to combat lung cancer, aiming to enhance immunity, inhibit tumour growth and alleviate

symptoms while improving overall patient resilience and QOL [41].

TCM employs a personalized and holistic approach, viewing the body as an interconnected system where the organs and their functions influence one another. For example, the lung-intestinal axis, which links lung function and digestive health, is considered to have a special relationship due to their shared role in regulating the body's Qi, fluid balance and immune function. By targeting both the lungs and intestines, TCM aims to restore harmony between these organs, offering a comprehensive treatment strategy for lung cancer that is tailored to each patient's unique constitution. This approach optimizes respiratory and digestive health, regulates Qi, strengthens immune responses and promotes overall well-being. Moreover, TCM emphasizes syndrome differentiation and customizes treatments to individual clinical presentations, such as Qi deficiency, which may be addressed through tonifying Qi; Yin deficiency, through nourishing Yin; and phlegm syndrome, through reducing phlegm. TCM treatments aim to restore balance by addressing both internal and external pathogenic factors *via* strategies such as "Fu zheng" (strengthening the body's resistance and immunity) and "Qu xie" (eliminating pathogenic factors) [42]. Numerous Chinese medicine formulas have been developed and utilized in the treatment of lung cancer (Table 1). For instance, Jin fu kang oral liquid exemplifies these principles and is widely used as an adjuvant therapy for NSCLC patients presenting with Qi-Yin deficiency patterns [43].

Building on ancient practices, TCM increasingly incorporates modern methodologies, including randomized double-blind clinical trials and experimental science, to elucidate its mechanisms and foster its integration with modern medicine. Research has shown that TCM plays distinct roles at various stages of NSCLC treatment, including supplementing Qi and regenerating blood during chemotherapy, nourishing Yin and supplementing Qi during radiotherapy, resolving stasis and dispersing masses after radio/chemo-therapy [37]. Additionally, TCM complements modern treatments by enhancing synergistic effects and improving clinical outcomes. In early- to middle-stage disease, it reduces toxicity and alleviates symptoms, while in advanced-stage disease, it enhances QOL and mitigates treatment-related side effects. Throughout the treatment process, TCM improves overall efficacy, delays drug resistance and supports general health. As research progresses, the complex mechanisms underlying TCM efficacy in lung cancer treatment continue to be elucidated.

Clinical evidence of TCM in lung cancer treatment

Although an increasing number of studies have demonstrated the clinical significance of TCM as a standalone treatment for lung cancer, it is still primarily used as part of a comprehensive treatment approach in most cases to enhance overall lung cancer management. The clinical evidence supporting the use of TCM in lung cancer treatment is burgeoning, with numerous studies highlighting its potential to improve treatment efficacy, enhance patient QOL and reduce adverse effects associated with conventional therapies [18–21]. This section focuses on TCM practices that have been validated by substantial clinical data, including extensive multicenter randomized controlled trials (RCTs), meta-analyses and cohort studies. By analysing the clinical outcomes associated with these TCM interventions (Table 2), we aim to explore the opportunities and challenges of TCM, further leveraging its strengths and avoiding its weaknesses to better treat lung cancer patients (Fig. 1).

Enhancing treatment efficacy

Platinum-based chemotherapy remains the standard first-line therapy for patients with various types of lung cancer. Commonly used platinum-based chemotherapy regimens include cisplatin combined with gemcitabine, cisplatin with paclitaxel, carboplatin with pemetrexed and carboplatin with gemcitabine or paclitaxel. TCM is often combined with platinum-based chemotherapy, which is administered in cycles to enhance therapeutic efficacy [103, 104]. A systematic review and network meta-analysis, which included 92 RCTs involving 7,728 patients, evaluated 10 Chinese herbal injections for advanced NSCLC. Kang ai injection, Kang lai te injection, Ai di injection and Compound ku shen injection clearly improved the anti-cancer efficacy and safety of platinum-based chemotherapy. For example, Ai di injection combined with cisplatin and gemcitabine showed a high objective response rate (ORR) of 79.0% compared with that of chemotherapy alone (11.5%) [105]. Another systematic review and meta-analysis encompassing 23 RCTs with 1,574 NSCLC patients examined the efficacy of integrating Shen fu injection with six different platinum-based chemotherapy regimens. The results showed that Shen fu injection combined with platinum-based chemotherapy improved tumour response, boosted Karnofsky performance status (KPS) scores and increased the percentages of CD3+, CD4+ and CD4+/CD8+ T lymphocytes in NSCLC patients. These results suggest that, compared with chemotherapy alone, Shen fu injection combination treatment results in a better disease control rate, improved QOL and strengthened immune function [18]. A retrospective review of clinical data from

Table 1 Chinese medicine formulas for lung cancer treatment

Formula name	Major composition	Original source	Ref
Jin fu kang oral solution	*Astragali* Radix, *Glehniae* Radix, *Asparagi* Radix, *Ligustri Lucidi* Fructus, *Selaginellae* Herba, *Paridis* Rhizoma, *Epimedii* Folium, *Gynostemma pentaphyllum* (Thunb.) Makino, *Corni* Fructus, *Salvia chinensis* Benth., *Ophiopogonis* Radix, *Trigonellae* Semen	A formula developed by Jiaxiang Liu based on TCM theory of "promoting the health energy to expel pathogenic factors"	[43]
Kang ai injection	*Astragali* Radix, *Ginseng* Radix et Rhizoma, kushenin	Changbaishan Pharmaceutical Co., Ltd.	[44]
Kang lai te injection	*Coicos* Semen	An empirical formula developed by Dapeng Li	[45]
Ai di injection	*Mylabris*, *Astragali* Radix, *Ginseng* Radix et Rhizoma, *Acanthopanacis Senticosi* Radix et Rhizoma seu Caulis	Guizhou Yibai Pharmaceutical Co., Ltd.	[46]
Compound ku shen injection	*Sophorae Flavescentis* Radix, *Heterosmilax japonica* Kunth	A modified formula based on Min Du's anti-tumour formula	[47]
Shen fu injection	*Ginseng* Radix et Rhizoma, *Aconiti Lateralis* Radix Praeparata	"Yan's Prescriptions for Rescuing Lives"	[18, 48]
Liu jun zi decoction	Raw *Astragali* Radix, *Codonopsis* Radix, *Atractylodis* Rhizoma, *Poria*, *Pinelliae* Rhizoma, *Citri Reticulatae* Pericarpium, *Platycodonis* Radix, *Amygdalus Communis* Vas	"Yi Xue Zheng Zhuan"	[49, 50]
Er chen and Tao hong four substances decoction	*Citri Reticulatae* Pericarpium, *Pinelliae* Rhizoma, *Poria*, *Glycyrrhizae* Radix et Rhizoma, *Persicae* Semen, *Carthami* Flos, *Angelicae Sinensis* Radix, *Paeoniae* Radix Alba, *Rehmanniae* Radix Praeparata, *Chuanxiong* Rhizoma	"Tai Ping Hui Min He Ji Ju Fang" (Er chen decoction) and "The Golden Mirror of Medicine" (Tao hong four substances decoction)	[49]
Qian jin wei jing decoction	*Phragmitis* Rhizoma, *Coicos* Semen, *Persicae* Semen, *Benincasae* Semen	"Prescriptions worth a Thousand in Gold for Every Emergency"	[49]
Pulse-Engendering powder	*Ginseng* Radix et Rhizoma, *Ophiopogonis* Radix, *Schisandrae Chinensis* Fructus	"Yi Xue Qi Yuan"	[49]
Sha shen mai dong decoction	*Pseudostellariae* Radix, *Ophiopogonis* Radix, *Adenophorae* Radix, *Anemarrhenae* Rhizoma, raw *Astragali* Radix, *Ligustri Lucidi* Fructus, *Paeoniae* Radix Alba, *Angelicae Sinensis* Radix, *Eriobotryae* Folium, *Atractylodis Macrocephala* Rhizoma, *Asini Corii Colla*, roasted *Glycyrrhizae* Radix et Rhizoma	"Systematized Identification of Warm Diseases"	[49]
Bo er ning capsules	*Astragali* Radix, *Ligustri Lucidi* Fructus, *Bulbus Tulipae*, *Portulacae* Herba, *Paridis* Rhizoma, *Solanum nigrum* L., *Perillae* Fructus, *Gallus gallus domesticus* Brisson, *Rhei* Radix et Rhizoma, *Borneolum*, *Bombyx batryticatus*	Livzon Pharmaceutical Group Inc.	[51, 52]
Zhen qi fu zheng capsules	*Astragali* Radix, *Ligustri Lucidi* Fructus	Developed by Yan Sun	[51]
Xiang sha liu jun zi decoction	*Ginseng* Radix et Rhizoma, *Atractylodis Macrocephala* Rhizoma, *Poria*, *Glycyrrhizae* Radix et Rhizoma, *Citri Reticulatae* Pericarpium, *Pinelliae* Rhizoma, *Amomi* Fructus, *Aucklandiae* Radix	"Gu Jin Ming Yi Fang Lun"	[53]
Xiao chai hu decoction	*Bupleuri* Radix, *Scutellariae* Radix, *Ginseng* Radix et Rhizoma, *Pinelliae* Rhizoma, *Glycyrrhizae* Radix et Rhizoma, *Zingiberis* Rhizoma Recens, *Jujubae* Fructus	"Treatise on Exogenous Febrile Disease"	[53]
Mai men dong decoction	*Ophiopogonis* Radix, *Pinelliae* Rhizoma, *Glycyrrhizae* Radix et Rhizoma, *Jujubae* Fructus, *Ginseng* Radix et Rhizoma, *Oryzae* Semen	"Synopsis of Golden Chamber"	[54]

Table 1 (continued)

Formula name	Major composition	Original source	Ref
Bai he gu jin decoction	*Rehmanniae* Radix Praeparata, *Rehmanniae* Radix, *Angelicae Sinensis* Radix, *Paeoniae* Radix Alba, *Glycyrrhizae* Radix et Rhizoma, *Platycodonis* Radix, *Scrophulariae* Radix, *Fritillariae Thunbergii* Bulbus, *Ophiopogonis* Radix, *Lilii* Bulbus	"Shen Zhai Yi Shu"	[55]
Yi qi qing du prescription	*Codonopsis* Radix, *Atractylodis Macrocephala* Rhizoma, *Poria*, *Glycyrrhizae* Radix et Rhizoma, *Astragali* Radix, *Aurantii* Fructus, *Scutellariae Barbatae* Herba, *Hedyotis diffusa* Willd., *Fagopyri Dibotryis* Rhizoma, *Sarcandrae* Herba, *Paridis* Rhizoma	A formula developed by professor Monian Xiong based on prescription included the changed Si jun zi decoction and excluded toxin herbs corresponding to different parts of malignancy	[56]
Modified Shen ling bai zhu powder	*Lablab* Semen Album, *Nelumbinis* Semen, *Codonopsis* Radix, *Poria*, *Coicos* Semen, *Citri Reticulatae* Pericarpium, *Atractylodis Macrocephalae* Rhizoma, *Platycodonis* Radix, *Glycyrrhizae* Radix et Rhizoma, *Amomi* Fructus, *Dioscoreae* Rhizoma	"Tai Ping Hui Min He Ji Ju Fang"	[57]
Modified Ba zhen decoction	*Astragali* Radix, *Angelicae Sinensis* Radix, *Cnidii* Rhizoma, *Ginseng* Radix et Rhizoma, *Sanguisorba* Radix, *Paeoniae* Radix Alba, *Rhemanniae* Radix Preparata, *Atractylodis Macrocephala* Rhizoma, *Poria*, *Glycyrrhizae* Radix et Rhizoma, *Salvia Miltiorrhiza* Radix et Rhizoma, *Cervi Cornu Pantotrichun*, *Bupleuri* Radix, *Cimicifugae* Rhizoma, *Schizonepetae* Herba, *Zingiberis* Rhizoma Recens	A formula based on "Rui Zhu Tang Jing Yan Fang"	[58]
Bu zhong yi qi decoction	*Astragali* Radix, *Atractylodis Macrocephala* Rhizoma, *Citri Reticulatae* Pericarpium, *Cimicifugae* Rhizoma, *Bupleuri* Radix, *Ginseng* Radix et Rhizoma, *Glycyrrhizae* Radix et Rhizoma, *Angelicae Sinensis* Radix	"Pi Wei Lun"	[59]
Shen yi capsules	Ginsenoside Rg3	Jilin Yatai Pharmaceutical Co., Ltd.	[60]
Yi fei qing hua granules	*Astragali* Radix, *Codonopsis* Radix, *Glehniae* Radix, *Ophiopogonis* Radix, *Agrimoniae* Herba, *Bistortae* Rhizoma, *Patrinia scabiosaefolia* Fisch. Ex Link., *Hedyotis diffusa* Willd., *Fritillariae Cirrhosae* Bulbus, *Platycodonis* Radix, *Armeniacae* Semen Amarum, *Glycyrrhizae* Radix et Rhizoma	Guang'anmen Hospital of China Academy of Chinese Medical Sciences and Beijing Huashen Pharmaceutical Co., Ltd.	/
Yang fei formula	*Adenophorae* Radix, *Asparagi* Radix, *Ophiopogonis* Radix, *Schisandrae Chinensis* Fructus, *Fritillariae Thunbergii* Bulbus, *Toad Skin* Cutis Bufonis, raw *Pinelliae* Rhizoma, *Poria*, *Polyporus*	"Pu Ji Fang"	[61]
Dang gui bu xue decoction	*Astragali* Radix, *Angelicae Sinensis* Radix	"Nei Wai Shang Bian Huo Lun"	[62]
Yu ping feng formula	*Astragali* Radix, *Atractylodis Macrocephalae* Rhizoma, *Saposhnikoviae* Radix	"Dan Xi Xin Fa"	[29]
Fei yan ning	*Astragali* Radix, *Ganoderma*, *Polygonati* Rhizoma, *Ligustri Lucidi* Fructus, *Epimedii* Folium, *Atractylodis Macrocephalae* Rhizoma, *Corni* Fructus, *Paridis* Rhizoma, *Cremastrae* Pseudobulbus *Pleiones* Pseudobulbus, *Salvia chinensis* Benth.	Shanghai University of Traditional Chinese Medicine Affiliated Longhua Hospital	[63]
Jie geng decoction	*Platycodonis* Radix, *Glycyrrhizae* Radix et Rhizoma	"Shang Han Lun"	[64]
Bu fei decoction	*Codonopsis* Radix, *Schisandrae Chinensis* Fructus, *Rehmanniae* Radix Preparata, *Astragali* Radix, *Asteris* Radix et Rhizoma, *Mori* Cortex	"Yong Lei Qian Fang"	[65]

Table 1 (continued)

Formula name	Major composition	Original source	Ref
Fei ji recipe	Raw *Astragali* Radix, *Glehniae* Radix, *Liriope* spicata, *Asparagi* Radix, *Poria*, *Selaginellae* Herba, Salvia *chinensia* Benth, *Houttuyniae* Herba, *Paridis* Rhizoma	Shanghai University of Traditional Chinese Medicine Affiliated Longhua Hospital	[66]
Yi qi yang yin tian sui prescription	*Cervi Cornu*, turtle shell of *Pelochelys bibroni* (Owen), *Panacis Quinquefolii* Radix, *Lycii* Fructus, *Asini Corii Colla*, *Ginseng* Radix et Rhizoma, *Astragali* Radix, *Angelicae Sinensis* Radix, *Stahlianthus involucratus* (King ex Bak.) Craib ex Loesener	Not identified	[67]
Si jun zi decoction	*Ginseng* Radix et Rhizoma, *Poria*, *Atractylodis Macrocephalae* Rhizoma, *Glycyrrhizae* Radix et Rhizoma	"Tai Ping Hui Min He Ji Ju Fang"	[68]
Shuang shen granules	*Notoginseng* Radix et Rhizoma, *Panacis Quinquefolii* Radix, *Cordyceps*	Main ingredient of Yi fei qing hua granules (Guang'anmen Hospital of China Academy of Chinese Medical Sciences)	[69]
Zeng sheng ping	*Sophorae Tonkinensis* Radix et Rhizoma, *Bistortae* Rhizoma, *Prunellae* Spica, *Sonchus brachyotus* L., *Dictamni* Cortex, *Dioscorea bulbifera* L.	Developed by Cancer Institute of Chinese Academy of Medical Sciences based on the experience of Guiqing Yu and Daizhao Zhang	[70]
Brucea javanica Oil emulsion injection	*Bruceae* Fructus	Shenyang Pharmaceutical University	[71]
Xiao ai ping injection	*Marsdenia tenacissima* (Roxb.) Moon	Nanjing Sanhome Pharmaceutical Co. Ltd.	[72]
Astragalus polysaccharide injection	*Astragali* Radix	Shanxi Traditional Chinese Medicine Institute	[73]
Lentinan injection	*Lentinula edodes* Mushroom	Not identified	[74]
Elemene injection	*Curcuma wenyujin* Y. H. Chen & C. Ling	Developed by Tian Xie based on "Molecular Compatibility Theory"	[75]
Er chen decoction plus San ren decoction	*Pinelliae* Rhizoma, dried *Citri Reticulatae* Pericarpium, *Poria*, *Glycyrrhizae* Radix et Rhizoma, Agastache rugosa (Fisch.et Mey.), *Armeniacae* Semen Amarum, Talcum, *Amomi* Fructus Rotundus, *Lophatheri* Herba, *Coicos* Semen, *Magnoliae Officinalis* Cortex	Chongqing Medical University	[76]
Wan dai decoction	Raw *Atractylodis Macrocephalae* Rhizoma, *Citri Reticulatae* Pericarpium, *Dioscoreae* Rhizoma, *Paeoniae* Radix Alba, *Plantaginis* Semen, *Atractylodis* Rhizoma, *Ginseng* Radix et Rhizoma, *Bupleuri* Radix, *Schizonepetae* Herba, *Glycyrrhizae* Radix et Rhizoma	"Fu Qing Zhu Nv Ke"	[77]
Tan re qing injection	*Forsythiae* Fructus, *Scutellariae* Radix, *Lonicerae Japonicae* Flos, *Capra hircus* Linnaeus, *Selenarctos Thibetanus* Cuvier	Shanghai Kaibao Pharmaceutical Co., Ltd.	[78]
Xuan fu dai zhe decoction	*Inulae* Flos, *Haematitum*, *Pinelliae Preparatum* Rhizoma, *Zingiberis* Rhizoma Recens, *Codonopsis* Radix, *Glycyrrhizae Preparata* Radix, *Jujube* Fructus	"Shang Han Lun"	[79]
Ba zhen decoction	*Ginseng* Radix et Rhizoma, *Atractylodis Macrocephalae* Rhizoma, *Poria*, *Angelica Sinensis* Radix, *Chuanxiong* Rhizoma, *Paeoniae* Radix Alba, *Rehmanniae* Radix, *Glycyrrhizae* Radix et Rhizoma	"Rui Zhu Tang Jing Yan Fang"	[80]
Liu wei di huang decoction	*Rehmanniae* Radix, *Rehmanniae* Radix Praeparata, *Corni* Fructus, *Dioscoreae* Rhizoma, *Alismatis* Rhizoma, *Moutan* Cortex, *Poria*	"Jing Yue Quan Shu"	[81]
Shen ling cao oral liquid	*Panacis Quinquefolii* Radix, *Ganoderma*, *Cordyceps*, *Rosa rugosa* Thunb.	China Resources Jiangzhong Pharmaceutical Group Co., Ltd.	[82]
He wei granules	*Hordei* Fructus Germinatus	Not identified	[83]

Table 1 (continued)

Formula name	Major composition	Original source	Ref
He wei granules	*Pinelliae* Rhizoma, *Zingiberis* Rhizoma Recens, *Ginseng* Radix et Rhizoma, *Scutellariae* Radix, *Coptidis* Rhizoma, *Glycyrrhizae* Radix et Rhizoma, *Jujubae* Fructus	Derived from the modified formulation Banxia Xiexin Decoction	[84]
Yi qi granules	*Astragali* Radix, *Codonopsis* Radix and *Atractylodis Macrocephalae* Rhizoma	Not identified	[83]
Jie du granules	*Prunellae* Spica, *Cremastrae* Pseudobulbus *Pleiones* Pseudobulbus, *Paridis* Rhizoma, *Fritillariae Thunbergii* Bulbus	Not identified	[83]
Xiao ji decoction	*Coriolus*, *Psoraleae* Fructus, *Hedyotis diffusa* Willd., *Astragali* Radix, *Scorpio*, *Scolopendra*, *Rhei* Radix et Rhizoma	Developed by Weisheng Liu	[85]
Ze qi decoction	*Euphorbia helioscopia* L., *Pinelliae* Rhizoma, *Salvia chinensis* Benth., *Cynanchi Stauntonii* Rhizoma et Radix, *Zingiberis* Rhizoma Recens, *Cinnamomi* Ramulus, *Scutellariae* Radix, *Ginseng* Radix et Rhizoma, *Glycyrrhizae* Radix et Rhizoma	"Jin Gui Yao Lve"	[86]
Yi fei san jie formula	*Hedysarum Multijugum* Maxim, *Atractylodis Macrocephalae* Rhizoma, *Saposhnikoviae* Radix, *Sinapis* Semen, *Fritillariae Thunbrgii* Bulbus, *Mori* Cortex, *Curcumae* Rhizoma, *Notoginseng* Radix et Rhizoma	A modified formula based on Yu ping feng formula	[87]
Qi dong ning	*Astragali* Radix, *Ophiopogonis* Radix, *Paridis* Rhizoma, *Ligustri Lucidi* Fructus, *Gynostemma pentaphyllum* (Thunb.) Makino	Optimized formula of Jin fu kang developed by Cancer Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine	[88, 89]
Fang ji huang qi decoction	*Stephaniae Tetrandrae* Radix, *Astragali* Radix, *Atractylodis Macrocephalae* Rhizoma, *Glycyrrhizae* Radix et Rhizoma, *Zingiberis* Rhizoma Recens, *Jujubae* Fructus	"Jin Gui Yao Lve"	[90]
Qing re huo xue formula	*Scutellariae* Radix, *Paeoniae* Radix Rubra	Huashan Hospital of Fudan University	[91]
Hedyotis diffusa injection	*Hedyotis diffusa* Willd.	Not identified	[92]
Jin fu an decoction	*Coicos* Semen, *Phragmites communis* Trin., *Pseudostellariae* Radix, *Salviae Miltiorrhizae* Radix et Rhizoma, *Arisaematis* Rhizoma, *Fritillariae Thunbergii* Bulbus, *Persicae* Semen, *Cremastrae* Pseudobulbus *Pleiones* Pseudobulbus	Derived from "Bei Ji Qian Jin Yao Fang" by Deng Tietao, who modified it by incorporating elements from Qian jin wei jing decoction	[93]
Xie bai formula	*Mori* Cortex, *Lycii* Cortex, *Glycyrrhizae* Radix et Rhizoma with honey, *Oryzae* Semen	"Xiao Er Yao Zheng Zhi Jue"	[94]
Shen mai injection	*Ginseng* Radix et Rhizoma Rubra, *Ophiopogonis* Radix	"Yi Xue Qi Yuan"	[30]
Fu zheng kang ai formula	*Pseudostellariae* Radix, *Astragali* Radix, *Hedyotis diffusa* Willd., *Solanum nigrum* L., *Salvia chinensis* Benth., *Cremastrae* Pseudobulbus *Pleiones* Pseudobulbus, *Coicos* Semen, *Akebiae* Caulis, *Rubus parviflolius* L., *Atractylodis Macrocephalae* Rhizoma, *Curcumae* Rhizoma, *Glycyrrhizae* Radix et Rhizoma	Guangdong Kangmei Pharmaceutical Company Ltd.	[95]
Huang lian jie du decoction	*Gardeniae* Fructus, *Phellodendri Chinese* Cortex, *Scutellariae* Radix, *Coptidis* Rhizoma	"Wai Tai Mi Yao"	[96]

Table 1 (continued)

Formula name	Major composition	Original source	Ref
Xiao ai jie du recipe	*Hedyotis diffusa* Willd., *Cremastrae* Pseudobulbus *Pleiones* Pseudobulbus, *Scolopendra*, *Akebiae* Caulis, *Pseudostellariae* Radix, *Ophiopogonis* Radix	Developed by Zhongying Zhou	[97, 98]
Tian men dong decoction	*Asparagi* Radix, *Cimicifugae* Rhizoma, *Peucedani* Radix, *Scutellariae* Radix, *Glycyrrhizae* Radix et Rhizoma	"Shengji Zonglu"	[99]
Yi qi formula	*Astragali* Radix, *Codonopsis* Radix, *Atractylodis Macrocephalae* Rhizoma, *Poria*, *Epimedii* Folium, *Trigonellae* Semen, *Psoraleae* Fructus	Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine	[100]
Yang yin formula	*Glehniae* Radix, *Adenophorae* Radix, *Asparagi* Radix, *Ophiopogonis* Radix, *Lilii* Bulbus, *Ligustri Lucidi* Fructus	Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine	[100]
Ruan jian jie du formula	*Prunellae* Spica, *Arisaematis* Rhizoma, *Amorphophallus konjac* K.Koch, *Cremastrae* Pseudobulbus *Pleiones* Pseudobulbus, *Euphorbia helioscopia* L., *Selaginellae* Herba, *Salvia chinensis* Benth., *Paridis* Rhizoma, *Jujubae* Fructus	Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine	[100]
Modified Bu shen yi qi formula	*Epimedii* Folium, *Astragali* Radix, *Rehmanniae* Radix, *Scutellariae* Radix, *Paeoniae* Radix Alba	Department of Integrative Medicine, Huashan Hospital	[101]
Yang yin wen yang formula	*Paridis* Rhizoma, *Gynostemma pentaphyllum* (Thunb.) Makino, *Liriope graminifolia* (L.) Baker, *Trigonellae* Semen	Optimized formula of Jin fu kang	[102]

Table 2 Clinical evidence of TCMs in lung cancer treatment

TCMs	Type of lung cancer	Study detail (*N*=total participants)	Main findings of TCMs	Ref/Trial ID
Decoctions composed of 10–20 Chinese herb varieties	Stage IIIB/IV NSCLC after 4–6 cycles of platinum-based first-line induction therapy	-An open-label RCT -*N*=99 -Control group received BSC versus experimental group treated with BSC in combination with decoctions -Corresponding fixed prescription composition of 3–5 herbs for each syndrome -Decoctions orally 200 mL twice daily	-Increased 3-month PFS probability in experimental group ($P<0.01$) -Improved QOL (physical well-being, emotional well-being, functional well-being, lung cancer symptom domain and total score of the FACT-L 4.0) ($P<0.05$)	[103]
4 TCM oral formulas	Stage IB/II/IIIA NSCLC	-*N*=314 -Control group received vinorelbine plus NP/NC versus intervention group treated with TCM in combination with NP/NC -NP regimen: cisplatin 75 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1&8 weekly, every 4 weeks for 4 cycles -NC regimen: carboplatin (AUC=5) on day 1 and vinorelbine 25 mg/m^2 on days 1&8 weekly, every 4 weeks for 4 cycles -TCM treatment: 160 mL orally twice daily	-Less adverse events in intervention group (0.57% vs 4.02%, $P=0.037$) -Less grade 3/4 transient severe hematological toxic effects in intervention group during the 2nd chemotherapy cycle: hemoglobin reduction (11.9% vs 22.5%) and total bilirubin increased (42.1% vs 46.2%)	[104] NCT01441752
Ai di injection, Kang lai te injection, Compound ku shen injection, Kang ai injection, Brucea javanica Oil emulsion injection, Shen qi fu zheng injection, *Astragalus* polysaccharide injection, Lentinan injection, Elemene injection	Stage III/IV NSCLC	-92 RCTs -*N*=7,728 -Control group received GP regimen chemotherapy alone versus experimental group treated with GP regimen chemotherapy in combination with CHIs	-ORR: improved ORR in GP+CHIs; GP+ Ai di injection (79.0%) showed the highest ORR -Adverse reactions: lower rates of leukopenia in GP+CHIs; GP+ Kang ai injection (4.4%) showed the lowest risk -MST: GP+Kang lai te injection ($P<0.05$) was the only combination that showed a significant difference -KPS: higher score in GP+CHIs; SUCRA of KPS: GP+ *Astragalus* polysaccharide injection (74.6%) showed the highest rank	[105]

Table 2 (continued)

TCMs	Type of lung cancer	Study detail (*N*=total participants)	Main findings of TCMs	Ref/Trial ID
Shen fu injection	Stage III and IV NSCLC	-23 RCTs -*N*=1,574 -Intravenous injection of Shen fu injection 30–100 mL/day for 1–3 weeks on 2–4 cycles -Control group received platinum-based chemotherapy alone versus experimental group treated with platinum-based chemotherapy plus Shen fu injection	-Improved objective tumour response in Shen fu injection+platinum-based chemotherapy (*P*=0.001) -Improved DCR in Shen fu injection+platinum-based chemotherapy (*P*=0.02) -Improved KPS in Shen fu injection+platinum-based chemotherapy (*P*<0.00001) -Reduced chemotherapy toxicity of white blood cell, hemoglobin, platelet and vomiting in Shen fu injection+platinum-based chemotherapy ($P \leq 0.0002$) -Enhanced immune function (increased percentages of CD3+, CD4+ and CD4+/CD8+ T lymphocytes) in Shen fu injection+platinum-based chemotherapy (*P*<0.00001)	[18]
Liu jun zi decoction, Er chen and Tao hong four substances decoction, Qian jin wei jing decoction, Pulse-Engendering powder combined with Sha shen mai dong decoction	Limited-stage SCLC after the first-line chemoradiotherapy	-*N*=67 -Control group received platinum-based chemotherapy (cisplatin + etoposide or carboplatin + etoposide) versus experimental group treated with platinum-based chemotherapy in combination with Chinese medicine	-Prolonged mPFS in experimental group (19 months) compared with control group (9 months) -Prolonged median OS in experimental group (34 months) compared with control group (18.63 months)	[49]
Astragalus-containing TCMs	Advanced NSCLC previously untreated by chemotherapy alone	-Seventeen randomized studies with scores on the Jadad quality scale of 2 or more -*N*=1,552 -Control group received platinum-based chemotherapy alone versus experimental group treated with platinum-based chemotherapy in combination with *Astragalus*-containing TCMs	-Increased OS in experimental group (*P*=0.011) -Increased one-year, two-year and three-year survival rates in experimental group (all *P*<0.001) -Improved performance status in experimental group (*P*<0.001) -Improved tumour ORR (*P*<0.001) -Reduced toxicities in experimental group (anemia, neutropenia, thrombocytopenia, fatigue, poor appetite, nausea, vomiting)	[51]

Table 2 (continued)

TCMs	Type of lung cancer	Study detail (*N*=total participants)	Main findings of TCMs	Ref/Trial ID
Kang lai te injection, Ai di injection, Brucea javarica oil emulsion	Advanced NSCLC	-64 RCTs -*N*=4,384 -Control group received EGFR-TKI alone versus experimental group treated with CHM+EGFR TKI	-Prolonged PFS (*P*<0.0001), MST (*P*<0.0001) in treatment with CHM+EGFR TKI -Improved one-year survival rate (*P*=0.002), two-year survival rate (*P*=0.005), ORR (*P*<0.0001), KPS score (P<0.0001) in treatment with CHM+EGFR TKI -Decreased probability of severe toxicities (*P*<0.0001) in treatment with CHM+EGFR TKI -Increased percentage of CD3+ T lymphocyte (*P*<0.0001) and CD4+ T lymphocyte (*P*<0.0001) in treatment with CHM+EGFR TKI	[106]
Traditional Chinese medicinal herbs	Advanced NSCLC	-19 studies -*N*=1,274 -Control group received EGFR-TKI alone versus treatment group treated with TCM plus EGFR-TKI	-Increased ORR (*P*=0.0002), DCR (P<0.0001), one-year survival rate (*P*=0.04), two-year survival rate (*P*=0.002) in treatment group -Improved or stable KPS score (*P*<0.00001) in treatment group -Reduced toxicity in treatment group: rash (*P*=0.03), nausea and vomiting (*P*=0.02), diarrhea (*P*=0.02)	[107]
TCM formulas including Xiang sha liu jun zi decoction, Xiao chai hu decoction, Mai men dong decoction, Sheng mai formula and Bai he gu jin decoction	EGFR-mutated advanced lung adenocarcinoma	-A cohort study -*N*=1,988 -Control group received gefitinib or erlotinib versus experimental group treated with TCM plus gefitinib or erlotinib	-Reduced mortality risk by 68% in addition of TCM for at least 180 days -Reduced risk of disease progression by 59% in addition of TCM for at least 180 days	[53]
TCM	Stage III B-IV NSCLC with exon 19 deletion mutation or exon 21 deletion mutation	-A cohort study -*N*=91 -Control group received EGFR-TKIs (gefitinib, erlotinib and icotinib) versus experimental group treated with TCM plus EGFR-TKIs	-Prolonged mPFS in experimental group (12.3 versus 8.9 months) (*P*=0.02) -Increased mOS in experimental group (28.2 versus 24.2 months) (*P*=0.02) -Increased DCR in experimental group (93.3% versus 80.1%) (*P*=0.77) -Less grade 3–4 treatment-related adverse events in experimental group (11.48% versus 26.67%)	[108]
Er chen decoction, San ren decoction, Qian jin wei jing decoction, Sheng mai formula, Sha shen mai dong decoction and Liu jun zi decoction	Stage IIIA, IIIB or IV NSCLC with exon 19 deletion mutation or exon 21 deletion mutation	-*N*=153 -Control group received EGFR-TKIs (gefitinib and erlotinib) versus experimental group treated with TCM plus EGFR-TKIs -Gefitinib 250 mg/day or erlotinib 150 mg/day orally -TCM three times a day orally for two weeks	-Prolonged mPFS in experimental group (13 versus 8.8 months) (*P*=0.001) - Prolonged mPFS of L858 mutant NSCLC in experimental group (14 versus 9.5 months) (*P*=0.015) -No additional adverse effects in experimental group (*P*=0.956)	[76]

Table 2 (continued)

TCMs	Type of lung cancer	Study detail (*N*=total participants)	Main findings of TCMs	Ref/Trial ID
Wan dai decoction and TCM fumigation and washing	SCLC with chronic vaginitis after Sintilimab treatment	-*N*=80 -Control group received Wan dai decoction versus observation group treated with Wan dai decoction combined with TCM fumigation and washing	-Reduced vulvar pruritus subsidence time, leukorrhea recovery time, TCM symptom scores and pH values in observation group ($P<0.001$); -Reduced levels of C-reactive protein, tumour necrosis factor and interleukin-6 in observation group ($P<0.001$); -Improved levels of immunoglobulin G, secretory immunoglobulin A and total effective rate in observation group ($P<0.001$)	[77]
Tan re qing injection	Lung cancer with pulmonary infection after chemotherapy	-18 RCTs -*N*=1,438 -Control group received antibiotics alone versus experimental group treated with Tan re qing injection in combination with antibiotics	-Improved clinical efficacy, defervescence time, lung rale disappearance time, cough disappearance time and average hospitalization time in experimental group -Reduced white blood cell, C-reactive protein, procalcitonin levels and adverse reactions in experimental group	[109]
Ginseng and its ingredients (ginsenosides and polysaccharides)	NSCLC	-28 RCTs -*N*=2,503 -Control group received chemotherapy alone versus experimental group treated with ginseng, ginsenosides or polysaccharides plus chemotherapy	-Improved ORR, DCR and QOL in experiment group ($P<0.00001$) -Increased CD3+, CD4+ and CD4+/CD8+ T lymphocytes in experiment group -Improved one- ($P=0.0008$) and two-year survival rates ($P=0.002$) in experiment group	[110]
Sheng mai injection	Stage III and IV NSCLC	-15 RCTs -Control group received platinum-based chemotherapy (cisplatin + vinorelbine and cisplatin + gemcitabine) versus experimental group treated with Sheng mai injection in combination with chemotherapy	-Improved KPS in experiment group (RR 2.36; 95% CI 1.50-3.96) -Reduced grade 3/4 myelosuppression (RR 0.61; 95% CI 0.46-0.81) and gastrointestinal reactions (RR 0.64; 95% CI 0.46-0.90) in experiment group	[19]
Various TCM prescriptions	NSCLC	-20 RCTs -*N*=1,669 -Control group received chemotherapy alone versus experimental group treated with TCM in combination with chemotherapy	-Improved QOL ($P<0.00001$), clinical efficacy ($P<0.00001$) and KPS score ($P<0.00001$) in experimental group -Reduced incidence of leukopenia ($P<0.0001$), thrombocytopenia ($P<0.00001$), hemoglobin reduction ($P<0.00001$), myelosuppression ($P<0.001$), nausea and vomiting ($P<0.00001$), diarrhea ($P<0.00001$), liver damage ($P<0.00001$) and kidney damage ($P=0.03$) in experimental group	[111]

Table 2 (continued)

TCMs	Type of lung cancer	Study detail (*N*=total participants)	Main findings of TCMs	Ref/Trial ID
Kang ai injection, Xuan fu dai zhe decoction, Ba zhen decoction, Liu wei di huang decoction, Zhen qi fu zheng capsules	Stage IIIA, IIIB, or IV NSCLC	-A prospective, open-label RCT -*N*=75 -Control group received platinum-based chemotherapy alone versus treatment group treated with TCM in combination with chemotherapy	-Improved QOL score ($P<0.05$) in treatment group -Declined deterioration in physical well-being and lung cancer symptoms in treatment group ($P<0.05$) -Lower incidence of platelet reduction in treatment group ($P=0.028$) after 2 cycles of treatment	[112]
Yi qi qing du prescription	Intermediate-stage and advanced NSCLC	-A RCT -*N*=300 -Control group received platinum-based chemotherapy alone or Yi qi qing du prescription alone versus treatment group treated with Yi qi qing du prescription in combination with chemotherapy	-Improved ORR and DCR in treatment group ($P<0.05$) -Increased CD3+ ($P=0.01$), CD4+ ($P=0.044$) and CD8+ ($P=0.009$) T lymphocytes in treatment group	[56]
Compound ku shen injection	NSCLC	-25 RCTs -*N*=2,460 -Control group received platinum-based chemotherapy alone versus treatment group treated with Compound ku shen injection in combination with chemotherapy	-Notably modulated levels of peripheral blood CD3+, CD4+ and CD8+ T lymphocytes and CD4+/CD8+ T cell ratio in treatment group -Increased serum levels of immunoglobulins such as IgA, IgG and IgM in treatment group	[113]
Kang ai injection	Stage III-IV NSCLC	-19 RCTs -*N*=1,389 -Control group received platinum-based chemotherapy alone versus treatment group treated with Kang ai injection in combination with chemotherapy	-Increased ratio of CD3+ cells ($P<0.00001$), CD4+ cells ($P<0.00001$), NK cells ($P<0.00001$) and CD4+ /CD8+ ($P<0.00001$)	[114]
Modified Shen ling bai zhu powder	NSCLC	-A prospective RCT -*N*=85 -Control group received imodium versus experimental group received modified Shen ling bai zhu powder	-Increased diarrhea remission rate in experimental group ($P<0.05$) -Decreased symptom scores in experimental group after treatment ($P<0.05$) -Less abdominal fullness and appetite loss in experimental group ($P<0.05$)	[57]
Shen ling cao oral liquid	Stage IIA-IIIA NSCLC	-A multicenter RCT -*N*=516 - Control group received conventional chemotherapy alone versus treatment group received Shen ling cao oral liquid combined with conventional chemotherapy	-Lower reduction in mean global QOL -Improved physical function, role function and emotional function -Improved lung cancer-related symptoms such as fatigue, nausea/vomiting and appetite loss -Improved performance status during the 6-month follow-up period ($P<0.05$)	[82] NCT03712969

Table 2 (continued)

TCMs	Type of lung cancer	Study detail (*N*=total participants)	Main findings of TCMs	Ref/Trial ID
TCM including Bu zhong yi qi decoction, Shen yi capsules and Yi fei qing hua granules	Stage I, II or IIIA NSCLC after radical resection and conventional postoperative treatment	-A multi-center prospective cohort study -*N*=503 -Control group received TCM therapy for less than 1 month versus treatment group received continuous TCM therapy for more than 6 months or until disease progression -TCM prescribed according to the principles of syndrome differentiation	-Higher DFS rate in treatment group after a three-year follow-up (HR=0.417, 95% CI: 0.307-0.567) -Lower rates of recurrence and metastasis in treatment group (HR=0.225, 0.119 and 0.083, respectively) after longer durations of TCM therapy (6–12 months, 12–18 months, >24 months) -Reduced lower cancer relapse rate in treatment group (35.9% versus 66.7%) in stage IIIA postoperative patients	[115]
3 herbal formulas based on their functions (Benefiting Qi and detoxication formula, Benefiting Yin and detoxication formula, Benefiting Qi and Yin and detoxication formula)	Completely resected stage IIIA NSCLC	-A NCT -*N*=75 -Observation group (did not receive any anti-cancer treatment) after adjuvant chemotherapy (adjuvant radiotherapy allowed for stage IIIA-N2) versus TCM group treated with different oral decoctions based on Qi-Yin syndrome differentiation -TCM orally 150 mL twice daily	-Improved one-year DFS in TCM group (82.1% versus 61.9%) (*P*=0.06) -Reduced proportion of CTLA-4+ Tregs in TCM group (*P*=0.046)	[116]
TCM	Stage IB-IIIA lung adenocarcinoma after radical surgery	-A multicenter, randomized, double-blind, placebo-controlled trial -*N*=233 -Control group received adjuvant chemotherapy and placebo versus treatment group received adjuvant chemotherapy + TCM	-Prolonged DFS (HR 0.53, 95% CI 0.28-0.99, *P*=0.046) in stage IB lung adenocarcinoma patients in treatment group	[117] NCT01441752
Yang fei formula	Advanced lung cancer	-*N*=119 -Combination of Yang fei formula and percutaneous cryoablation treatment	-Prolonged OS from the time of diagnosis and cryoablation (19 months and 10 months) compared to data previously published	[61]
He wei granules, Yi qi granules and Jie du granules	Early-stage NSCLC	-A prospective, double-blind RCT -*N*=180 - Control group received chemotherapy + placebo versus treatment group received chemotherapy + TCM	-Prolonged median time to disease deterioration in treatment group (*P*<0.001)	[83] NCT03372694

Abbreviation: AUC Area under the curve, *BSC* Best supporting care, *CHI* Chinese herbal injection, *CHM* Chinese herbal medicine, *CI* confidence interval, *CTLA-4* Cytotoxic T lymphocyte-associated antigen-4, *DCR* Disease control rate, *DFS* Disease-free survival, *EGFR* Epidermal growth factor receptor, *FACT-L* Functional assessment of cancer therapy-lung, *GP* Cisplatin and gemcitabine, *HR* hazard ratio, *KPS* Karnofsky Performance status, *mOS* Median overall survival, *mPFS* Median progression-free survival, *MST* Median survival time, *NC* Carboplatin, *NK* Natural killer, *NP* Cisplatin, *NSCLC* Non-small-cell lung cancer, *OS* Overall survival, *ORR* Objective response rate, *PFS* Progression-free survival, *QOL* Quality of life, *RCT* Randomized controlled trial, *RR* risk ratio, *SCLC* Small-cell lung cancer

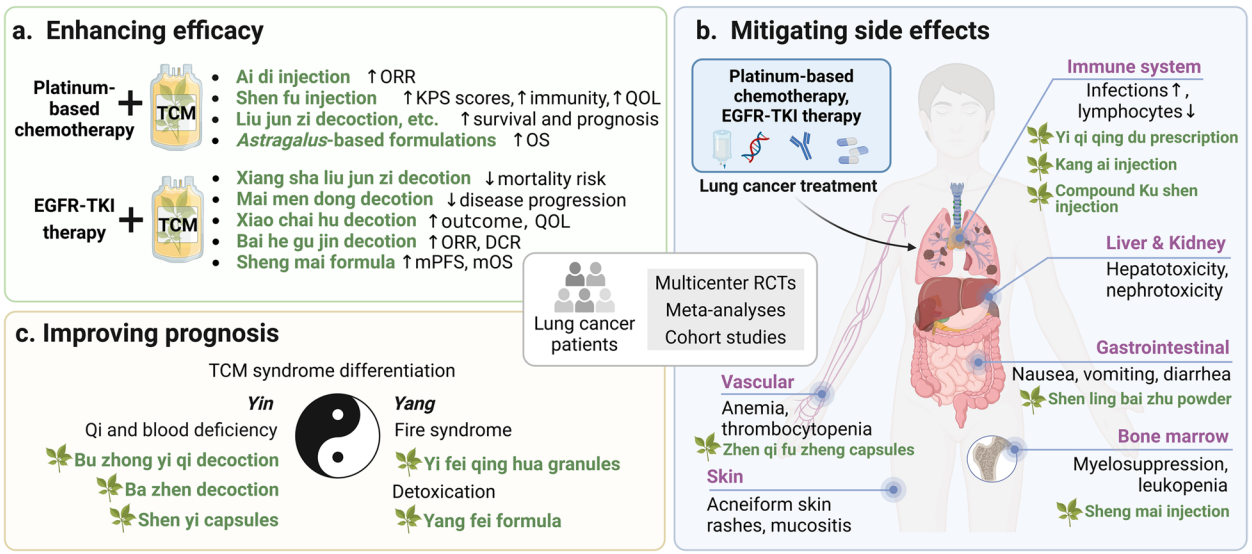

Fig. 1 Clinical evidence of TCM in lung cancer treatment. TCM has garnered substantial evidence from clinical studies, including extensive multicenter RCTs, meta-analyses and cohort studies. These studies underscore the effectiveness of TCM in (**a**) enhancing therapeutic outcomes when combined with platinum-based chemotherapy or EGFR-TKI therapy; (**b**) mitigating side effects induced by conventional treatments across various systems, including vascular, skin, immune system, liver and kidney, gastrointestinal and bone marrow; and (**c**) improving prognosis through TCM syndrome differentiation, addressing conditions such as Qi and blood deficiency, Yin and Yang dysregulation and fire syndrome

67 patients with limited-stage SCLC revealed that the concurrent use of TCM (Liu jun zi decoction, Er chen and Tao hong four-substance decoction, Qian jin wei jing decoction and Pulse-Engendering powder combined with Sha shen mai dong decoction) alongside platinum-based chemotherapy (cisplatin + etoposide or carboplatin + etoposide) improved patient prognosis, reduced disease progression and extended survival compared with chemotherapy alone [49]. Moreover, *Astragalus membranaceus* Fisch. ex Bunge is a key herb for tonifying Qi in anti-tumour Chinese herbal formulations, including Jin fu kang oral solution, Bo er ning capsules, Ai di injection, Zhen qi fu zheng capsules, Kang ai injection and other herbal formulas containing *Astragali* Radix. A systematic review and meta-analysis ($N = 1{,}552$) evaluated the efficacy of *Astragalus*-based TCM when combined with platinum-based chemotherapy, considering syndrome differentiation. The analysis found that adding *Astragalus*-based TCM to platinum-based chemotherapy significantly improved overall survival, with a hazard ratio (HR) of 0.61 (95% confidence interval (CI): 0.42 to 0.89, $P = 0.011$). This combination therapy also increased the one-year, two-year and three-year survival rates, with relative ratios (RR) of 0.73, 0.3344 and 0.30, respectively (all $P < 0.001$) and improved performance status (RR: 0.43, 95% CI: 0.34 to 0.55, $P < 0.001$) and tumour response rate (RR: 0.7982, 95% CI: 0.715 to 0.89, $P < 0.001$). Notably, tailoring treatment to specific TCM assessments and corresponding syndrome differentiation further enhanced the impact of these therapies, suggesting a promising direction for future research [51].

Lung cancer, particularly NSCLC, is commonly associated with mutations in EGFR, which play a critical role in disease progression and the response to treatment. Combining TCM with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) holds substantial potential for improving the management of lung cancer, including enhancing therapeutic outcomes and boosting patient's QOL [106]. A meta-analysis ($N = 1{,}274$) revealed that integrating TCM with EGFR-TKI therapy (gefitinib and erlotinib) notably enhanced the ORR, disease control rate (DCR) and both one-year and two-year survival rates, as well as maintaining or improving KPS scores, compared with EGFR-TKI monotherapy [107]. A cohort study involving 1,988 patients with EGFR-mutated advanced lung adenocarcinoma treated with gefitinib or erlotinib found that the addition of TCM, particularly formulas such as Xiang sha liu jun zi decoction, Xiao chai hu decoction, Mai men dong decoction, Sheng mai formula and Bai he gu jin decoction, for at least 180 days, significantly reduced mortality risk by 68% (adjusted HR = 0.32, 95% CI 0.21–0.50, $P < 0.0001$). Additionally, the use of TCM reduced the risk of disease progression by 59% (adjusted HR = 0.41, 95% CI 0.29–0.58, $P < 0.0001$) compared with patients not using TCM [53]. Another cohort study consistently demonstrated that, for NSCLC patients with EGFR mutations, the combination

of EGFR-TKIs (gefitinib, erlotinib and icotinib) and TCM effectively extended both median progression-free survival (mPFS) and median overall survival (mOS) compared with EGFR-TKIs alone, with particularly notable benefits observed in patients harboring the *exon* 21 deletion (L858R) mutation [108]. This finding is consistent with another study that the combination of TCM and EGFR-TKIs (gefitinib and erlotinib) was especially effective in extending the mPFS for patients with the L858R mutation and did not lead to an increase in adverse effects [76].

Mitigating side effects

The aggressive nature of chemotherapeutic agents often results in significant side effects that severely impact patients' QOL. Platinum-based chemotherapy is particularly associated with adverse effects such as nausea, vomiting, nephrotoxicity and peripheral neuropathy. In this context, TCM offers a valuable complementary strategy for alleviating these negative effects in lung cancer patients [18, 51, 77, 105, 109, 110, 118]. For instance, the addition of Sheng mai injection to platinum-based chemotherapy regimens (cisplatin + vinorelbine or cisplatin + gemcitabine) significantly reduced the incidence of grade III/IV myelosuppression and gastrointestinal adverse reactions [19]. A meta-analysis of 20 RCTs involving 1,669 NSCLC patients demonstrated that various TCM prescriptions combined with platinum-based chemotherapy markedly decreased the frequency of leukopenia, thrombocytopenia, anaemia and myelosuppression, alongside reductions in nausea, vomiting, diarrhoea and hepatic and renal impairment [111]. Similarly, NSCLC patients at stages IIIA, IIIB or IV treated with Kang ai injection and Zhen qi fu zheng capsules experienced significantly lower rates of thrombocytopeia than those who underwent platinum-based chemotherapy alone [112].

One of the most severe adverse effects of chemotherapy is its profound impairment of the immune system, leading to decreased white blood cell counts (myelosuppression), increased susceptibility to infections, fatigue and a reduced overall QOL. This immunosuppression necessitates supportive care strategies, such as TCM, to help patients maintain their immune defenses during treatment. An RCT involving 300 patients with intermediate-stage or advanced NSCLC demonstrated that platinum-based chemotherapy significantly decreased CD3+ T lymphocyte counts. In contrast, patients treated with a combination of the Yi qi qing du prescription and platinum-based chemotherapy exhibited significantly higher counts of CD3+, CD4+ and CD8+ T lymphocytes [56]. Similarly, a meta-analysis of 25 RCTs including 2,460 NSCLC patients revealed that concurrent administration of Compound ku shen injection with platinum-based chemotherapy notably enhanced peripheral blood T lymphocyte levels, including those of CD3+, CD4+ and CD8+ T cells, as well as the CD4+/CD8+ T-cell ratio. Furthermore, this combined therapy increased serum immunoglobulin levels, such as IgA, IgG and IgM [113]. Another meta-analysis ($N = 1,389$) demonstrated that combining Kang ai injection with platinum-based chemotherapy significantly improved immune parameters, including increased proportions of CD3+ T cells, CD4+ T cells, natural killer (NK) cells and an elevated CD4+/CD8+ T-cell ratio [114].

Patients receiving EGFR-TKI therapy frequently experience side effects such as diarrhea, acneiform skin rashes, mucositis and paronychia. Among these, diarrhea is the most severe gastrointestinal issue, affecting 21–95% of NSCLC patients treated with EGFR-TKIs. A prospective, randomized controlled trial ($N = 85$) demonstrated that modified Shen ling bai zhu powder effectively alleviated EGFR-TKI-induced diarrhea in NSCLC patients, outperforming Imodium in reducing diarrhea while avoiding significant adverse reactions [57]. Similarly, combining TCM with EGFR-TKIs (gefitinib and erlotinib) has been shown to reduce the incidence of severe side effects, including skin rashes, nausea, vomiting and diarrhea [107].

Improving the prognosis of postoperative lung cancer patients

Postoperative recurrence remains a major concern for patients with NSCLC, representing a significant challenge for clinical management and patient outcomes. It is noteworthy that TCM has gained significant attention as a potential postoperative supportive treatment strategy. TCM exhibits significant advantages in prolonging patients' disease-free survival (DFS) postoperatively, which refers to the time interval between the date of enrollment and the date of disease recurrence or metastasis [82]. A multicenter prospective cohort study conducted in China evaluated the impact of TCM on DFS in postoperative NSCLC patients. Patients with stage I, II or IIIA NSCLC, who underwent radical resection and received standard postoperative treatment according to the National Comprehensive Cancer Network (NCCN) guidelines were divided into a TCM treatment group and a control group. The TCM prescribed was tailored according to the principles of syndrome differentiation. Patients with Qi and blood deficiency or spleen and stomach weakness, were given modified Ba zhen decoction or Bu zhong yi qi decoction, respectively, while those with severe Qi deficiency received Shen yi capsules. Conversely, Yi fei qing hua granules were prescribed for patients diagnosed with a fire syndrome.

After a three-year follow-up, the TCM group exhibited a significantly higher DFS rate than the control group, with an HR of 0.417 (95% CI: 0.307–0.567). Notably, longer durations of TCM therapy (6–12 months, 12–18 months, > 24 months) were associated with lower rates of recurrence and metastasis (HR = 0.225, 0.119 and 0.083, respectively). Among stage IIIA postoperative patients, the TCM treatment group had a significantly lower cancer relapse rate (35.9%) compared to the control group (66.7%) [115]. In another clinical trial (N = 75), patients with completely resected stage IIIA NSCLC who received oral decoctions of three Chinese herbal formulas on the basis of their functions (Benefiting Qi and detoxication formula, Benefiting Yin and detoxication formula, Benefiting Qi and Yin and detoxication formula), showed extended DFS. This approach significantly reduced the risk of disease recurrence and metastasis. Moreover, it decreased the prevalence of CTLA-4-positive regulatory T cells (Tregs), suggesting an enhancement of immune function by mitigating peripheral immune escape [116]. Additionally, combining TCM prescription based on syndrome differentiation with adjuvant chemotherapy after radical surgery significantly prolonged DFS (HR = 0.53, 95% CI 0.28–0.99, P = 0.046) in stage IB lung adenocarcinoma patients (N = 233), compared with the chemotherapy + placebo group [117].

In addition to enhancing DFS, TCM also demonstrates value in prolonging OS and delaying disease progression following surgical intervention. The Yang fei formula has been shown to extend the lifespan of elderly patients with advanced lung cancer who have undergone percutaneous cryoablation treatment [61]. Moreover, a prospective, randomized, controlled and double-blind study (N = 180) demonstrated the potential of staged TCM treatment to prolong the median time to disease deterioration in early-stage NSCLC patients undergoing postoperative adjuvant chemotherapy [83]. Overall, these clinical findings reveal that combining conventional therapies with TCM can provide a synergistic anti-cancer effect.

Ongoing clinical trials

Several ongoing clinical trials are exploring the potential role of TCM in lung cancer treatment, particularly in combination with conventional therapies. For example, the trial NCT05834413 is evaluating the efficacy of TCM as a postoperative adjuvant therapy in patients with driver gene-negative lung cancer, specifically examining its effects during the chemotherapy and immunotherapy phases. Similarly, the NCT06445881 trial is assessing whether the addition of modified Si jun zi decoction to chemotherapy and immunotherapy during the neoadjuvant phase can improve clinical outcomes, such as the R0 resection rate, ORR and safety, in patients with resectable and potentially resectable NSCLC. Another study, NCT06674252, is a multicenter, randomized, double-blind, placebo-controlled trial investigating the effectiveness of Jia wei bu fei decoction in improving clinical symptoms and QOL in elderly postoperative lung cancer patients. Interestingly, trial NCT06143436 aimed to explore relationships among TCM constitutions, pattern identification and lung cancer characteristics in Taiwanese patients, offering valuable insights into disease patterns from a TCM perspective. These trials provide promising evidence to further support the integration of TCM into modern lung cancer treatment regimens.

Although numerous clinical studies have highlighted the therapeutic potential of TCM in treating lung cancer, significant limitations remain, such as small sample sizes, a lack of control groups and patient population heterogeneity. To address these challenges, it is crucial to design pragmatic studies with clearly defined and feasible sampling time points. Strict recruitment criteria, considering participants' overall health and treatment history, are essential to ensure that evaluations of TCM's anti-cancer efficacy in lung cancer are clinically relevant. Despite promising results, the evolving research landscape necessitates the establishment of comprehensive guidelines and continued investigations to solidify the role of TCM in lung cancer management. Only through high-quality, methodologically sound trials can the true potential of TCM be realized in contemporary oncology practice.

Preclinical investigations of TCM in lung cancer treatment

TCM induces programmed cell death in lung cancer

Programmed cell death is a tightly regulated process governed by specific genetic and molecular pathways that play pivotal roles in anti-tumour therapies by eliminating cancer cells and overcoming resistance mechanisms. TCM has been shown to induce various forms of programmed cell death in cancer cells, including apoptosis, autophagy, ferroptosis, pyroptosis and necroptosis [25, 26, 119–121]. This section highlights the principal forms of programmed cell death extensively studied in the context of the effects of TCM on lung cancer (Table 3). We detail their underlying mechanisms, emphasize the key molecular targets involved and underscore their application as cytotoxic agents to enhance therapeutic efficacy against lung cancer (Fig. 2).

Apoptosis

TCM has significant potential for inducing apoptosis in lung cancer cells through various biological pathways [21, 86, 87, 123–125, 127–142, 146, 147, 216–220, 222, 226, 227], including the caspase cascade [148, 225, 228], endoplasmic reticulum (ER) stress [149, 150, 152],

Table 3 TCM induces cell death in lung cancer treatment

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
Apoptosis	Ginsenoside Rh2	*Panax ginseng* C.A.Mey.	Induction of apoptosis *via* HIF-1α/PDK4 axis in NSCLC cells	[25]
	Halofuginone	*Dichroa febrifuga* Lour.	Induction of ROS accumulation and apoptosis in NSCLC cells	[122]
	Andrographolide	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	Activation of the mitochondrial-dependent apoptosis pathway in H1975 cells	[123]
			Induction of Noxa-dependent apoptosis by transactivating ATF4 in A549 and H1299 cells	[124]
	Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Induction of mitochondrial-dependent apoptosis *via* EGFR-AKT-Mcl1 axis for NSCLC tumour in vitro and in vivo	[125]
	Tanshinone	*Salvia miltiorrhiza* Bunge	Induction of apoptosis through PTEN-mediated inhibition of PI3K/AKT pathway in Glc-82 cells and Glc-82 xenografts	[126]
	Fu zheng kang ai formula	12 TCMs	Promotion of lung cancer cell apoptosis through STAT3/Bcl-2/caspase-3 signalling pathways	[127]
	Berberine hydrochloride	*Coptis chinensis* Franch.	Promotion of apoptosis of NSCLC cells *via* the suppression of the MMP-2 and Bcl-2/Bax signalling pathways	[128]
	Bufalin	*Bufo bufo gargarizans* Cantor	Induction of apoptosis through intrinsic mitochondria-dependent way and the Fas-mediated extrinsic pathway in NCI-H460 cells	[129]
			Induction of apoptosis in A549 and H460 NSCLC cells through Axl downregulation	[130]
			Induction of apoptosis *via* degradation of Mcl-1 through GSK-3β activation in H1975 cells	[131]
	Matrine	*Sophora flavescens* Aiton	Induction of cell cycle arrest and apoptosis with recovery of the expression of miR-126 in A549 cells	[132]
	Xiao ji decoction	7 TCMs	Induction of apoptosis through AKT signalling pathway in A549 cells	[133]
	Xanthatin	*Xanthium sibiricum* Patr.	Induction of G2/M cell cycle arrest and apoptosis *via* disrupting NF-κB pathway in A549 cells	[134]
	Acetone extract of *Bupleurum scorzonerifolium*	*Bupleurum scorzonerifolium* Willd.	Induction of apoptosis and inhibition of telomerase in A549 cells	[135]
	Berberine chloride	*Berberis aristate* Sims	Induction of DNA damage and apoptosis by deregulating Sin3A/TOP2B pathway for NSCLC in vitro and in vivo	[136]
	Ze qi decoction	9 TCMs	Induction of mitochondrial apoptosis and G0/G1 cell cycle arrest through p53 pathway in A549 and H460 cells	[86]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Astragaloside IV	*Astragalus membranaceus* Fisch. ex Bunge	Induction of apoptosis indicated by decreased Bcl-2, increased Bax and cleaved caspase-3 in NSCLC cells	[137]
	Nuciferine	*Nelumbo nucifera* Gaertn.	Induction of apoptosis through downregulation of the ratio of Bcl-2/Bax in A549 cells	[138]
	Vasicinone	*Adhatoda vasica* Nees	Induction of apoptosis through Fas death receptors and Bcl-2 regulated signalling in A549 cells	[139]
	Deguelin	*Derris trifoliata* Lour.	Induction of mitochondrial-dependent apoptosis in H460 cells	[140]
	Polysaccharide from *Glehnia littoralis*	*Glehnia littoralis* F.Schmidt	Induction of apoptosis and cell cycle arrest in A549 cells	[141]
	Triptolide	*Tripterygium wilfordii* Hook.f.	Induction of apoptosis by reversing hypermethylation of WIF-1 in A549 and H460 cells	[142]
			Induction of AKT/Bcl-2-mediated mitochondrial-dependent apoptosis through decreasing Caveolin-1 by miR-204-5p and Sirt-1/Sirt-3 in A549 and H460 cells	[143]
			Induction of apoptosis by decreasing miR-21 levels while upregulating PTEN protein expression level in PC-9 cells	[144]
			Induction of apoptosis and cell cycle arrest by enhancing the activation of p53 upregulated modulator of apoptosis, caspase 9 and caspase 3 and suppressing Bcl-2 through increased binding of RPL23 to MDM2 in vitro and in vivo	[145]
	Yi fei San jie formula	8 TCMs	Alleviated tumour progression *via* suppressing PRMT6-YBX1-CDC25A axis in A549, NCI-H1975 and Calu-3 cells	[87]
	Acacetin	*Vachellia farnesiana* (L.) Wight & Arn.	Inhibition of cell growth *via* upregulating miR-34a in A549 and H460 cells and in A549-xenografted nude mice model	[146]
	Gambogic acid	*Garcinia hanburyi* HooK.f.	Induction of apoptosis and ROS in LLC model	[147]
	Berberine	*Coptis chinensis* Franch.	-Induction of caspase cascade apoptotic pathway by modulation of histone deacetylase in A549 cells -Inhibition of the progression of NSCLC *via* the PI3K/AKT pathway targeting KIF20A and CCNE2 in H1299, A549 cells and H1299 nude mice model	[148]
	Lathyrol	*Euphorbia lathyris* L.	Promotion of ER stress-induced apoptosis in lung cancer cells by targeting SERCA2	[149]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Licochalcone A	*Glycyrrhiza* species	Induction of apoptosis *via* PARP/Bcl-2 pathway and ER stress in H460 and A549 cells	[150]
			Induction of apoptosis through increasing miR-144-3p in H292 cells	[151]
	Polygonatum Rhizoma and *Scutellaria baicalensis*	*Polygonatum sibiricum* Delar. ex Redoute, *Scutellaria baicalensis* Georgi	Induction of apoptosis through downregulation of PON3-induced mitochondrial damage and endoplasmic reticulum stress in A549 cells	[152]
	Sinomenine hydrochloride	*Sinomenium acutum* (Thunb.) Rehd. et Wils.	Induction of apoptosis by activating the AMPK-mTOR pathway	[153]
	Eriodictyol	*Dracocephalum rupestre* Hance	Induction of mitochondrial-mediated apoptosis by regulating the Bcl-2/Bax signalling pathway, G2/M cell cycle arrest and inhibition of mTOR/PI3K/AKT signalling pathway in A549 cells	[154]
	Salvianolic acid F	*Salvia miltiorrhiza* Bunge	Promotion of apoptosis by inhibiting downstream PI3K/AKT signalling pathway activation in KRAS-overexpressing lung cancer cells and KRAS G12D lung tumours	[155]
	HQi-sRNA-2	*Scutellaria baicalensis* Georgi	Suppression of tumour progression *via* targeting COX-2/PTGS2 and downregulating the PI3K and AKT signalling pathways in NSCLC mice	[156]
	Raddeanin A	*Anemonoides raddeana* (Regel) Holub	Promotion of autophagy-induced apoptosis by inactivating PI3K/AKT/mTOR pathway in A549 cells	[157]
	Fangchinoline	*Stephania tetrandra* S. Moore	Induction of apoptosis through the PI3K/AKT/mTOR signalling pathway in A549 mice	[158]
	Belamcanda chinensis extract	*Belamcanda chinensis* (L.) Redouté	Inhibition of cell proliferation and induction of apoptosis by inhibiting the MAPK (Ras/Raf) and AKT pathways in SPC-A1, NCI-H460 cells and SPC-A1 xenograft model	[159]
	Dioscin-6′-O-acetate	*Dioscorea althaeoides* R. Knuth.	Induction of apoptosis by ROS-mediated PI3K/AKT, MAPK and NF-κB signalling pathways in lung cancer cells	[160]
	Isoorientin	*Patrinia* Juss.	Induction of apoptosis and cell cycle arrest *via* the ROS-regulated MAPK, STAT3 and NF-κB signalling pathways in A549 cells	[161]
	Moracin N	*Morus alba* L.	Induction of autophagy and mitochondrial-dependent apoptosis through ROS generation in A549 and PC9 cells	[162]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Ethyl acetate extract from *Celastrus orbiculatus* Thunb.	*Celastrus orbiculatus* Thunb.	-Activation of apoptosis, Hippo signalling and inhibition of YAP nuclear translocation in NSCLC cells -Activation of Hippo signalling by associated with ROS-mediated phosphorylation of MOB1 protein	[163]
	Tubeimoside I	*Fritillaria* genus	-Induction the leakage of cathepsin B by increased lysosomal membrane permeability resulting from excessive ROS accumulation -Promotion of cytosolic cytochrome C-mediated caspase-dependent mitochondrial apoptosis through enhancement of Bax-mediated mitochondrial outer membrane permeability by cathepsin B in lung cancer cells	[164]
	Qi dong ning	5 TCMs	Induction of apoptosis *via* triggering P53/DRP1-mediated mitochondrial fission and increased ROS in A549 and NCI-H460 cells	[88]
	Aconiti Lateralis Radix Praeparata	*Aconitum carmichaelii var. truppelianum* (Ulbr.) W.T.Wang & P.K.Hsiao	Inhibition of cell proliferation and induction of apoptosis along with reduced MMP and increased ROS in NCI-H1975 cells	[165]
	Dihydrotanshinone	*Salvia miltiorrhiza* Bunge	Induction of Porimin-dependent oncosis by ROS-mediated mitochondrial dysfunction in A549 cells and LLC xenograft mice	[166]
	Elemene	*Curcuma wenyujin* Y.H.Chen & C.Ling	Induction of cell apoptosis and reduced MMP *via* inhibiting glutathione synthesis and increased ROS in A549 and PC9 cells	[167]
	Rabdoternin E	*Isodon ternifolius* (D.Don) Kudô	Induction of apoptosis and ferroptosis of A549 cells by activating the ROS/p38 MAPK/JNK signalling pathway	[168]
	Total flavonoids from *Adinandra nitida* Merr. ex Li leaves	*Adinandra nitida* Merr. ex H.L.Li	Induction of apoptosis *via* ROS-dependent p53 activation and disruption of NADPH homeostasis in A549 cells and A549 xenograft nude mice	[169]
	Ginsenoside Rd	*Panax ginseng* C.A.Mey.	Reduced cell proliferation by p53-mitochondrial apoptotic pathway in NCI–H460 and 95-D cells	[170]
	Formosanin C	*Paris yunnanensis* Franch.	-Induction of intrinsic apoptosis by increasing oxidative stress and disrupting mitochondrial function in NSCLC cells -Blockage of MCT4/CD147-mediated lactate export leading to excessive calcium accumulation, increasing ROS accumulation	[171]
	Ginkgo biloba exocarp extracts	*Ginkgo biloba* L.	Induction of extrinsic apoptosis by activating the FasL/Fas death receptor pathway in LLC cells	[172]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	TXA9	*Streptocaulon juventas* (Lour.) Merr.	Induction of extrinsic apoptosis by activating the Fas death receptor pathway in A549 cells	[173]
	The lyophilized extract of *Venenum Bufonis*	*Bufo bufo gargarizans* Cantor	Promotion of extrinsic apoptosis by activating DR4 signalling in A549 cells	[174]
	Ovatodiolide	*Anisomeles indica* (L.) Kuntze	Induction of G2/M cell cycle arrest and extrinsic apoptosis *via* DR5 activation and ROS-dependent ATM/ATR signalling pathways	[175]
	Baicalein	*Scutellaria baicalensis* Georgi	Suppression of mTOR signalling and promotion of apoptosis by regulating glutamine metabolism in H1299 and A549 cells	[176]
Autophagy	Kaempferol	*Hedyotis diffusa* Willd.	Promotion of autophagy through Met-and its downstream PI3K/AKT/mTOR signalling pathway in NSCLC cells	[26]
	Cantharidin	*Mylabris phalerata* Pallas	Activation of autophagy through downregulation of p62 expression and upregulation of microtubule-associated proteins 1A/1B LC3B and Beclin-1 expression in A549 cells	[177]
	Cepharanthine	*Stephania cepharantha* Hayata	Regulation of autophagy *via* activating the p38 signalling pathway in A549 cells	[178]
	Flavonoids and steroidal saponins from *Ophiopogon japonicus*	*Ophiopogon japonicus* (Thunb.) Ker Gawl.	Induction of autophagy through PI3K/AKT/mTOR signalling pathway in A549 cells	[179]
	Baicalin	*Scutellaria baicalensis* Georgi	MCOLN3-mediated lysosomal dysfunction and autophagy blockage in A549, H1299 and PC-9 cells	[180]
	Cycloastragenol	*Astragalus membranaceus* Fisch. ex Bunge	Induction of apoptosis and protective autophagy through AMPK/ULK1/mTOR axis in H1299 and A549 cells	[181]
	α-Hederin	*Clematis ganpiniana* (H.Lév. & Vaniot) Tamura	Induction of incomplete autophagic injury by interfering with the lysosomal acidification in H1299 and A549 cells	[182]
	13-Oxyingenol-dodecanoate	*Euphorbia kansui* Liou ex S.B.Ho	Inhibition of growth by targeting ULK1 and autophagy-related pathways in A549 and H460 cells	[183]
	β-elemene	*Curcuma wenyujin* Y.H.Chen & C.Ling	Autophagy induction through maturation of miR-127-3p by inhibiting CBX8 activity and subsequently inactivating the AKT/mTOR/P70S6K signalling cascade *via* MAPK4 in NSCLC cells	[184]
	Chelerythrine	*Chelidonium majus* L., *Macleaya cordata* (Willd.) R.Br. and *Sanguinaria canadensis* L.	Promotion of autophagy and induction of LC3-II expression *via* Beclin 1-dependent initiation of autophagosome formation in A549 and NCI-H1299 cells	[185]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Isodeoxyelephantopin	*Elephantopus scaber* L.	Enhancement autophagy flux by increasing LC3-II, ATG3 and Beclin1	[186]
	Melittin	*Apis cerana* Fabr.	Induction of hyperautophagy through upregulation of CTSB in A549 and HCC1833 cells and NSCLC animal models	[187]
	Ailanthone	*Ailanthus altissima* (Mill.) Swingle	Inhibition of ULK1-driven autophagy initiation through upregulation of lncRNA GAS5 by suppressing UPF1-dependent nonsense-mediated mRNA decay in NSCLC cells and subcutaneous mice models	[188]
	Aloperine	*Sophora alopecuroides* L.	Inhibition of late-stage autophagy by blocking the fusion of autophagosomes with lysosomes *via* VPS4A and STX17 in H1299 cells	[189]
	Fang ji huang qi decoction	6 TCMs	Inhibition of autophagy through disrupted cathepsin maturation in NSCLC cells	[90]
	Ginkgo biloba exocarp extracts	*Ginkgo biloba* L.	Induction of autophagy involving AMPK/mTOR/P70S6k signalling pathway in LLC cells	[190]
Ferroptosis	Dihydroartemisinin	*Artemisia annua* L.	-Sensitizing cells to ferroptosis by inducing the lysosomal degradation of ferritin to increase free iron levels -Promotion the binding of IRPs to mRNAs containing IRE sequences to disrupt the IRP/IRE-mediated regulation of iron homeostasis	[119]
			Ferroptosis-triggered ER stress and DNA damage initiating from GPX4 reduction and lipid peroxide accumulation in LLC cells, A549 cells and LLC-bearing mice	[191]
	Andrographolide	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	Induction of ferroptosis through GPX4 and SLC7A11 downregulation along with decreased GSH, increased ROS and intracellular iron levels for NSCLC in vitro and in vivo	[28]
	Sarcandra glabra	*Sarcandra glabra* (Thunb.) Nakai	Induction of ferroptosis by regulating HMOX1, GPX4 and FTL in LLC cells	[192]
	Sappanone A	*Caesalpinia sappan* L.	Induction of ferroptosis by regulating Nrf2/GPX4/xCT pathway in NSCLC cells	[193]
	Timosaponin AIII	*Anemarrhena Asphodeloides* Bunge	Induction of ferroptosis through targeting and facilitating HSP90 mediated GPX4 ubiquitination and degradation in NSCLC cells	[194]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Erianin	*Dendrobium chrysotoxum* Lindl.	Induction of ferroptosis along with ROS accumulation, lipid peroxidation and GSH depletion *via* Ca^{2+}/CaM signalling pathway in lung cancer cells	[195]
	Asiatic acid	*Centella asiatica* (L.) Urb.	Induction of SRC-mediated ferroptosis through GPX4 downregulation in H358 and H23 cells	[196]
	Qing re huo xue formula	2 TCMs	Induction of ferroptosis and apoptosis through GPX4 suppression and P53 & GSK-3β/Nrf2 signal pathways in NSCLC mice	[91]
	Sophora alopecuroide-Taraxacum decoction	*Sophora alopecuroides* L. and *Taraxacum mongolicum* Hand.-Mazz.	Inhibition of NSCLC *via* inducing ferroptosis by GSH decrease and modulating tumour immune microenvironment in H1299, A549, LLC cells and LLC mice	[197]
	Hedyotis diffusa injection	*Hedyotis diffusa* Willd.	Induction of ferroptosis *via* the Bax/Bcl-2/VDAC2/3 axis in lung cancer cells	[92]
	Curcumenol	*Curcuma wenyujin* Y.H.Chen & C.Ling	Induction of ferroptosis *via* lncRNA H19/miR-19b-3p/FTH1 axis in vitro and in vivo	[198]
Pyroptosis	Dihydroartemisinin	*Artemisia annua* L.	Induction of pyroptosis through cGAS/STING/NLRP3 signalling pathway *via* mtDNA damage and translocation resulting from TOM70 inhibition in vitro and in vivo	[120]
	Sodium new houttuyfonate	*Houttuynia cordata* Thunb.	-Induction of pyroptosis through TCONS-14,036/miR-1228-5p/PRKCDBP pathway in NSCLC cells -Promotion of pyroptosis through activating the NLRP3 inflammasome, resulting in increasing the cleavage of caspase 1, IL-1β and GSDMD in NSCLC cells	[27]
Necroptosis	Acetylshikonin	*Lithospermum erythrorhizon* Siebold & Zucc.	Induction of necroptosis *via* the RIPK1/RIPK3-dependent pathway in H1299 and A549 cells	[199]
DNA damage	Quercetin	Various TCMs	Promotion of DNA damage *via* SIRT5/PI3K/AKT pathway in NSCLC cells	[200]
	Oridonin	*Rabdosia rubescens* (Hemsl.) H.Hara	Increased DNA damage and apoptosis in H460 cells	[201]
Cellular senescence	Andrographolide	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	Induction of senescence *via* p53/p21 and Skp2/p27 in vitro and in vivo	[202]
	Yangyinjiedu	5 TCMs	Induction of G2/M cell cycle arrest and senescence in 95-D, A549, H460 and H1975 cells	[89]
Cell cycle-dependent cell death	Emodin	*Cassia obtusifolia* L., *Aloe vera* Mill., *Polygonum multiflorum* Thunb., *Rheum palmatum* L.	Induction of G1/G0 cell cycle arrest through hyaluronan synthase 2-HA-CD44/receptor for hyaluronic acid-mediated motility interaction-dependent signalling pathway in NSCLC cells	[203]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Trichosanthes kirilowii	*Trichosanthes kirilowii* Maxim.	Induction of G2/M arrest, necrosis and apoptosis in NSCLC cells	[204]
	Magnolol	*Magnolia officinalis* Rehder & E.H.Wilson	-Induction of the mitotic phase arrest and inhibition of G2/M progression *via* inhibiting the polymerization of microtubule -Activation of apoptosis through a p53-independent pathway -Induction of autophagy *via* down-regulation of the AKT/mTOR pathway in NSCLC cells	[205]
	Agrimol B	*Agrimonia pilosa* Ledeb.	Induction of G0 arrest through c-MYC, SKP2 and p27 in lung cancer cells	[206]
	Lycorine	*Lycoris radiata* (L'Hér.) Herb.	Inhibition of proliferation partially *via* regulating the miR-186/CDK1 axis in NSCLC cells	[207]
	Piperlongumine	*Piper longum* L.	Decreased cell proliferation and expression of cell cycle-associated proteins by inhibiting AKT pathway in A549 cells	[208]
	Oridonin	*Rabdosia rubescens* (Hemsl.) H.Hara	Promotion of G2/M arrest by facilitating ATM activation in A549 cells	[209]
	Astragalus polysaccharide	*Astragalus membranaceus* Fisch. ex Bunge	Inhibition of NF-κB activity and decreased p50, CyclinD1 and Bcl-xL protein in vitro and in vivo	[210]
	Ailanthone	*Ailanthus altissima* (Mill.) Swingle	Induction of cell cycle arrest through repression of DNA replication during S phase *via* downregulating RPA1 in NSCLC cells	[211]
	Jin fu an decoction	10 TCMs	Suppression of proliferation, induction of cell cycle arrest and reduced migration and invasion ability in A549 cells	[93]
	Diosbulbin C	*Dioscorea bulbifera* L.	Inhibition of cell proliferation by inducing G0/G1 phase cell cycle arrest in A549 and NCI-H1299 cells	[212]
	Camellia nitidissima C. W. Chi	*Camellia petelotii* (Merr.) Sealy	Induction of cell apoptosis, G0/G1 and S cell cycle arrest, increased intracellular ROS levels in A549 and SK-MES-1 cells	[213]
	Camellia oleifera bud ethanol extract	*Camellia oleifera* C.Abel	Inhibition of proliferation of A549 cells by inducing cell cycle arrest at the G1 phase	[214]
Mitochondrial dysfunction	Demethylzeylasteral (T-96)	*Tripterygium wilfordii* Hook.f.	Disrupting interaction of LRPPRC with mt-mRNA and inhibiting OXPHOS complex synthesis, mitochondrial aerobic respiration and ATP production	[215]
Apoptosis and ferroptosis	Dihydroisotanshinone I	*Salvia miltiorrhiza* Bunge	Induction of apoptosis and ferroptosis through GPX4 inhibition in A549 cells in vitro and in vivo	[216]

Table 3 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
Apoptosis and cell cycle arrest	Homoisoflavanone-1	*Polygonatum odoratum* (Mill.) Druce	Induction of apoptosis in A549 cells by regulating the mitochondria-caspase-dependent and ER stress pathways and G2/M arrest by activating the p38/p53 signalling pathway	[21]
	Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Induction of apoptosis and cell cycle arrest by regulating CCNA2-CDK2 complex and AURKA/PLK1 pathway in A549 and NCI-H1975 cells	[217]
Apoptosis and autophagy	Scutellarin	*Erigeron breviscapus* (Vaniot) Hand.-Mazz.	Induction of apoptosis and autophagy in NSCLC cells through ERK1/2 and AKT signalling pathways in vitro and in vivo	[218]
	Honokiol	*Magnolia officinalis* Rehder & E.H.Wilson	Induction of apoptosis, G1 arrest and autophagy *via* AMPK-mTOR signalling pathway in KRAS mutant NSCLC cells	[219]
	Polygonatum odoratum lectin	*Polygonatum odoratum* (Mill.) Druce	Initiation of apoptosis through inhibiting AKT-NF-κB pathway and autophagy *via* suppressing AKT-mTOR pathway in A549 cells	[220]
			Induction of apoptosis and autophagy by regulation of miR-1290 and miR-15a-3p in A549 cells	[221]
	Cucurbitacin E and myricetin	*Citrullus colocynthis* (L.) Schrad.	-Induction of apoptosis and G0/G1 cell cycle arrest in A549 cells -Inhibition of autophagy *via* activation of the PI3K/AKT/mTOR signalling pathway in A549 cells	[222]
	Marsdenia tenacissima extract	*Marsdenia tenacissima* Wight & Arn.	-Induction of apoptosis partially through activation of ERK signalling pathway -Autophagy suppression through impairing lysosomal function, blocking autophagosome–lysosome fusion and increasing expression of LC3-II and p62 in H1975 and A549 cells	[223]
Autophagy and pyroptosis	Sophflarine A	*Sophora flavescens* Aiton	-Induction of autophagy by increasing ROS accumulation through inhibition of the PI3K/AKT/mTOR signalling in A549 cells -Induction of pyroptosis *via* activating the NLRP3/caspase-1/GSDMD signalling pathway	[224]
Apoptosis and pyroptosis	Alcohol-precipitated fraction of fig fruit latex	*Ficus carica* L.	Promotion of apoptosis and pyroptosis *via* the Caspase/Gasdermin/AKT signalling pathway for NSCLC in vitro and in vivo	[225]

Abbreviation: *AKT* Protein Kinase B, *ATF4* Activating transcription factor 4, *ATM* Ataxia telangiectasia-mutated gene, *AURKA* Aurora Kinase A, *Axl* Anexelekto, *Bcl-2* B-cell lymphoma-2, *Bax* Bcl-2-associated X protein, *CCNA2* Cyclin A2, *CDK* Cyclin dependent kinase, *cGAS* Cyclic GMP-AMP synthase, *CTSB* Cathepsins B, *DR* Death receptor, *ER* Endoplasmic reticulum, *ERK* Extracellular regulated protein kinases, *GPX4* Glutathione Peroxidase 4, *HIF* Hypoxia-inducible factor, *IRPs* iron-regulatory proteins, *IRE* iron-responsive element, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *LC3B* Light chain 3B, *lnc* Long non-coding, *LRPPRC* Leucine-rich pentatricopeptide repeat-containing protein, *Mcl-1* Myeloid cell leukemia 1, *MCOLN3* Mucolipin TRP Cation Channel 3, *MDM2* Mouse double minute 2 protein, *MET* Mesenchymal-epithelial transition factor, *miR* MicroRNA, *MMP-2* Matrix metallopeptidase 2, *mt-mRNA* mitochondrial DNA-encoded mRNA, *mTOR* Mammalian target of rapamycin, *NF-κB* Nuclear factor kappa B, *NLRP3* Nucleotide-binding oligomerization domain-like receptor protein 3, *NSCLC* Non-small-cell lung cancer, *OXPHOS* Oxidative phosphorylation, *Noxa (PMAIP1)* Phorbol-12-myristate-13-acetate-induced protein 1, *PDK4* Pyruvate dehydrogenase kinase 4, *PI3K* Phosphatidylinositol 3-kinase, *PLK1* Polo-like kinase 1, *PTEN* Phosphatase and tensin homolog, *RPL23* Ribosomal protein L23, *ROS* Reactive oxygen species, *Sin3A* SIN3 transcription regulator family member A, *STAT3* Signal transducer and activator of transcription 3, *STING* Stimulator of interferon genes, *TOP2B* DNA Topoisomerase II beta

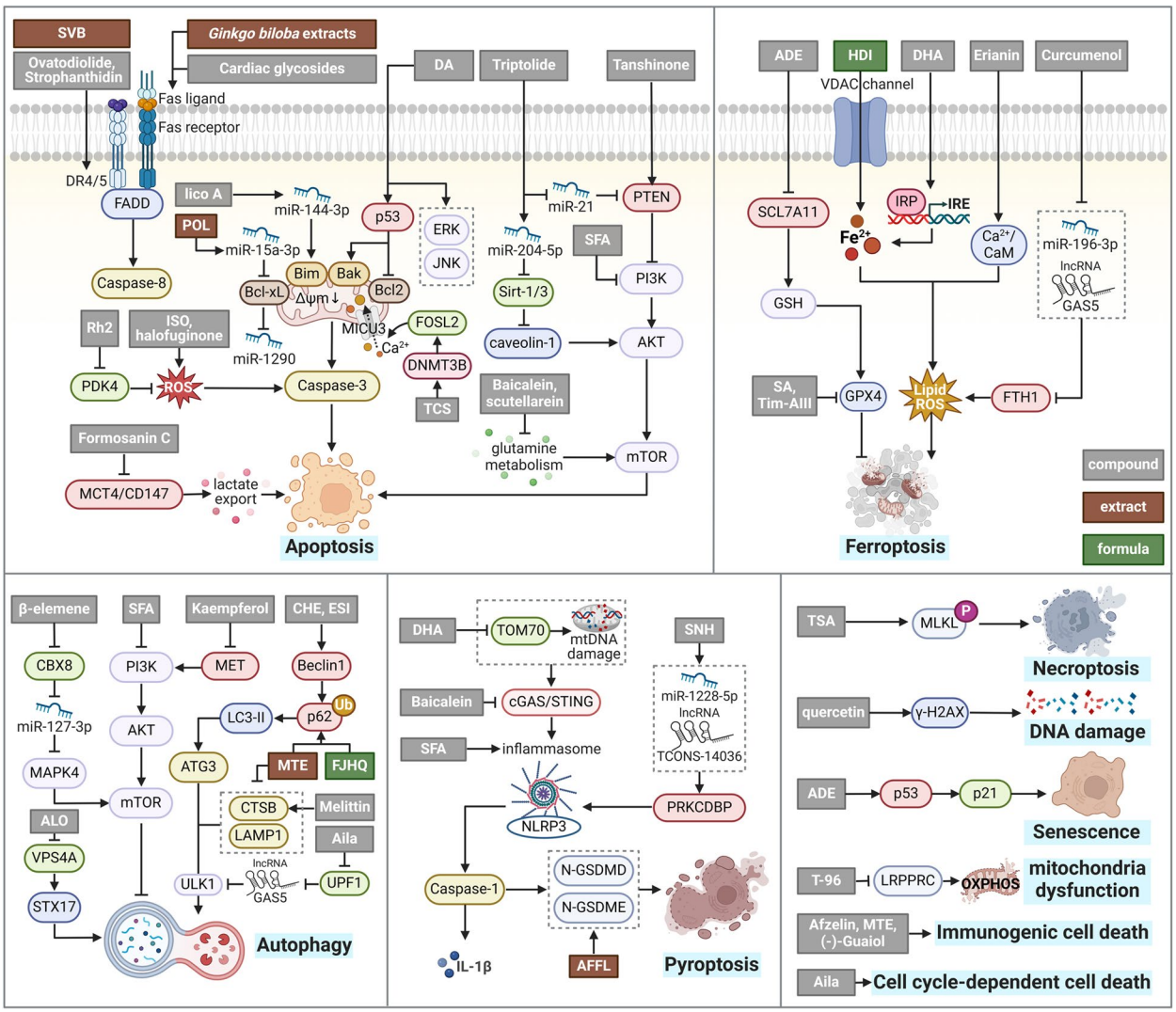

Fig. 2 The underlying mechanisms of TCM-induced cell death in lung cancer. A wide variety of TCMs, including both formulas and isolated bioactive components, can initiate diverse cell death mechanisms in lung cancer cells. These mechanisms include: apoptosis, autophagy, ferroptosis, pyroptosis, necroptosis, senescence and DNA damage. "↑" indicates activation, stimulation or promotion, whereas "⊥" indicates inhibition, suppression or decrease. Formula abbreviation: FJHQ-Fang ji huang qi decoction, HDI-*Hedyotis diffusa* injection

AMPK signalling [153] and the PI3K/AKT signalling pathway [126, 154–159, 229]. For example, Dioscin-6′-O-acetate (DA), derived from the rhizomes of *Dioscorea althaeoides* R. Knuth., significantly increases p53 protein expression and activates caspase-3 in lung cancer cells. Concurrently, DA markedly downregulates the anti-apoptotic proteins Bcl-2 and activates upstream signalling pathways, such as phosphorylated c-Jun N-terminal protein kinase (JNK) and ERK, collectively driving apoptosis in lung cancer cells [160]. The methanol extract of *Salvia miltiorrhiza* Bunge, known as tanshinone, has been shown to upregulate phosphatase and tensin homologue (PTEN) protein expression and inhibit the phosphorylation of AKT at Thr 308 and Ser 473. This suppression of the PI3K/AKT pathway induces apoptosis in NSCLC cells and significantly reduces tumour growth in nude mice bearing Glc-82 xenografts [126].

Mitochondrial-dependent apoptosis, also known as intrinsic apoptosis, involves alterations in the mitochondrial membrane potential, the release of pro-apoptotic factors like cytochrome c and the activation of caspases. This process often requires the balance between pro-apoptotic and anti-apoptotic proteins from the Bcl-2 family, which modulate mitochondrial outer membrane permeabilization. Mitochondrial-dependent apoptosis is tightly linked to reactive oxygen species (ROS) levels,

with elevated ROS leading to mitochondrial dysfunction and triggering the apoptotic cascade. A variety of TCMs induce mitochondrial-dependent apoptosis in lung cancer through ROS-related mechanisms [88, 122, 147, 161–170]. For instance, Formosanin C, a diosgenin derived from the rhizoma of *Paris yunnanensis*, induces intrinsic apoptosis in NSCLC cells by increasing oxidative stress and disrupting mitochondrial function. It also blocks MCT4/CD147-mediated lactate export and excessive calcium accumulation, further enhancing its pro-apoptotic effect [171]. Isoorientin (ISO) is a C-glycosyl flavone that can be extracted from various TCMs such as *Patrinia*. With prolonged ISO treatment, there is a corresponding increase in intracellular ROS levels in A549 cells, while pre-treatment with N-acetylcysteine (NAC), an antioxidant that neutralizes ROS, effectively mitigates ISO-induced apoptosis in these cells [161]. Similarly, halofuginone derived from *Dichroa febrifuga* Lour., increases ROS levels and induces apoptosis in NSCLC, an effect that can also be significantly inhibited by NAC [122]. The ginsenoside Rh2 downregulates the protein expression of mitochondrial pyruvate dehydrogenase kinase 4 (PDK4), a key regulator of cellular energy metabolism, increasing mitochondrial oxidative phosphorylation and ROS accumulation, which in turn encourages lung cancer cells to undergo apoptotic processes [25]. In addition to inducing intrinsic apoptosis, certain TCMs have also been shown to trigger apoptosis through extrinsic pathways, although such research remains limited. For instance, extracts from the exocarp of *Ginkgo biloba* [172] and TXA9 from *Streptocaulon juventas* [173] induce extrinsic apoptosis in lung cancer cells by activating the FasL-Fas death receptor pathway. Similarly, *Venenum bufonis* from the skin secretions of *Bufo bufo gargarizans* Cantor [174], Strophanthidin from *Lepidii* Semen and *Antiaris toxicaria* [230] and ovatodiolide isolated from *Anisomeles indica* [175] promote extrinsic apoptosis by activating the DR4 and DR5 signalling pathways in lung cancer cells.

Many microRNAs (miRs) are known to target genes that play pivotal roles in apoptosis. Triptolide induces mitochondrial apoptosis by downregulating caveolin-1 (CAV-1) mRNA and protein expression, resulting in the activation of the AKT/Bcl-2 signalling axis. Further investigation identified microRNA 204-5p (miR-204-5p) as a critical negative regulator of CAV-1, with its levels significantly elevated following triptolide treatment. Notably, the pro-apoptotic effects of triptolide are markedly diminished when cells are pre-treated with Sirt-1/Sirt-3 siRNA or its inhibitors, such as EX-527 and nicotinamide [143]. In another study, triptolide was shown to induce apoptosis by decreasing miR-21 levels while upregulating the PTEN protein expression level. This effect could be counteracted by artificially increasing miR-21 expression in human NSCLC PC-9 cells [144]. Similarly, licochalcone A (lico A), a flavonoid compound derived from the root of the *Glycyrrhiza* species, induces apoptosis through increasing miR-144-3p. Suppression of miR-144-3p significantly reversed the pro-apoptotic effects of lico A, whereas overexpression of miR-144-3p amplified these effects [151]. Additionally, *Polygonatum odoratum* lectin (POL) was found to modulate miRNA levels, reducing miR-1290 and increasing miR-15a-3p levels in A549 cells. Further downregulation of miR-1290 or upregulation of miR-15a-3p enhances the proapoptotic effects of POL [221].

Glutamine metabolism plays a critical role in maintaining cellular homeostasis and regulating apoptosis. Its function in promoting cell survival and inhibiting apoptosis underscores its importance, particularly in lung cancer. Recent findings revealed that baicalein, a bioactive component of *Scutellaria baicalensis* Georgi, suppresses lung cancer tumour growth in xenograft model and inhibits proliferation while promoting apoptosis in lung cancer cells. Baicalein significantly influences amino acid metabolism, particularly those related to glutamine, in H1299 and A549 cell lines. Mechanistically, baicalein negatively interacts with glutamine transporters and glutaminase, inhibiting their activation. Additionally, baicalein suppresses the activation of the mTOR signalling pathway, another key downstream effector of glutamine metabolism, as evidenced by a reduction in both mTOR and p-mTOR protein levels [176]. In line with the effects observed with baicalin, scutellarein, another key compound extracted from *Scutellaria baicalensis* Georgi, has demonstrated similar outcomes. Scutellarein suppresses lung cancer cell growth in both in vitro and in vivo models by reducing glutamine metabolism and triggering apoptosis [231].

Autophagy

Autophagy is a fundamental cellular process that governs the degradation and recycling of cellular components, including damaged organelles, misfolded or aggregated proteins and lipid droplets, which plays a critical role in cancer cell survival. Interestingly, autophagy exhibits a dual role in lung cancer development and progression. In the early stages of tumour formation, autophagy acts as a tumour suppressor by removing damaged organelles and reducing genomic instability [232, 233]. This process is vital for maintaining cellular homeostasis and preventing malignant transformation. However, in established tumours, autophagy often supports cancer progression by enabling cancer cells to adapt to metabolic stressors, such as nutrient deprivation and hypoxia, thereby promoting tumour growth and survival [234, 235]. This

adaptive mechanism is particularly significant in the tumour microenvironment, where limited resources and high cell turnover necessitate metabolic flexibility. TCM offers a rich source of natural products and formulations that modulate autophagy, either by inducing or inhibiting it, to influence lung cancer outcomes [177–183, 190].

Autophagy is a multifaceted process with distinct stages that is leveraged by TCMs to induce autophagic cell death, presenting a promising therapeutic approach for treating lung cancer. The initiation phase, often triggered by signals such as nutrient deprivation or cellular stress, is critically regulated by the AKT/mTOR signalling pathway, which suppresses autophagy under normal conditions but allows its activation in response to stress [234, 236]. TCMs inhibit AKT/mTOR activation, serving as an effective mechanism for inducing autophagic cell death. For example, sophoridine A (SFA), extracted from the roots of *Sophora flavescens* Aiton, suppresses NSCLC cell proliferation by triggering autophagy through inhibition of the PI3K/AKT/mTOR signalling cascade [224]. Kaempferol combats NSCLC by stimulating autophagy in NSCLC cells, primarily through significant suppression of Met expression at both the protein and mRNA levels, which leads to inhibition of the PI3K/AKT/mTOR signalling pathway. Moreover, overexpression of Met counteracts the effects of kaempferol on NSCLC cell viability and autophagy, highlighting the role of Met in mediating the effect of kaempferol [26]. Additionally, β-elemene promotes the maturation of miR-127-3p by inhibiting CBX8 activity, which subsequently inactivates the AKT/mTOR/P70S6K signalling cascade *via* MAPK4, leading to autophagy induction in NSCLC cells [184]. Following autophagy initiation, the phagophore forms and proteins like LC3 (microtubule-associated protein 1 light chain 3) are recruited and lipidated to become LC3-II, elongating the structure to form autophagosomes. Certain TCMs have been shown to promote these processes. For instance, chelerythrine (CHE), extracted from *Chelidonium majus* L., *Macleaya cordata* (Willd.) R.Br. and *Sanguinaria canadensis* L., increases the expression of the autophagy marker LC3-II in NSCLC cells. This effect is significantly reversed by silencing beclin 1, indicating that CHE induces beclin 1-dependent initiation of autophagosome formation. Furthermore, the induction of LC3-II by CHE is enhanced when combination with chloroquine (CQ), an autophagy inhibitor, suggesting that CHE promotes autophagy flux [185]. In the late stage of autophagy, autophagosomes fuse with lysosomes, where the autophagic substrates are degraded for reuse by proteases. By monitoring the formation of autophagolysosomes in mCherry-EGFP-LC3-transfected H1299 cells, it was demonstrated that isodeoxyelephantopin (ESI), derived from *Elephantopus scaber* L., significantly enhances autophagy flux. This is accompanied by a dose-dependent increase in the expression of autophagy markers, including LC3-II, ATG3 and beclin1 [186]. Melittin, which is extracted from *Apis cerana* Fabr., inhibits the proliferation of A549 and HCC1833 cells and reduces the tumour volume in NSCLC animal models by inducing hyperautophagy through the upregulation of cathepsin B (CTSB). This effect is reversed by the CTSB-specific inhibitor CA-074 Me and the autophagy inhibitor 3-MA [187].

Conversely, various TCMs can impede the progression of lung cancer by modulating excessive autophagy at different stages, thereby preventing cancer cells from relying on this process for survival. For instance, ailanthone (aila), the primary active constituent extracted from the stem bark of *Ailanthus altissima* (Mill.) Swingle, increases the expression of long non-coding RNA GAS5 by suppressing UPF1-dependent nonsense-mediated mRNA decay. This upregulation of GAS5 inhibits ULK1-driven autophagy initiation, thereby suppressing the growth and metastasis of NSCLC cells in vitro and in a subcutaneous tumour model [188]. Guo et al. demonstrated that aloperine (ALO), a quinolizidine alkaloid derived from *Sophora alopecuroides* L., acts as a novel inhibitor of late-stage autophagy by blocking the fusion of autophagosomes with lysosomes. This disruption halts autophagic flux, leading to the accumulation of p62 and the induction of NSCLC cell death. Mechanistically, ALO facilitates the formation of unsealed autophagosomes by interacting with VPS4A, which prevents the recruitment of STX17 to the autophagosome membrane, thereby inhibiting autophagosome-lysosome fusion [189]. Additionally, the *Marsdenia tenacissima* extract (MTE) disrupts autophagic flux in NSCLC cells, leading to increased expression of LC3-II and p62, a process further intensified by the autophagy inhibitor bafilomycin A1. MTE also impairs lysosomal function, as indicated by reduced expression of LAMP1 and CTSB and blocks the fusion of autophagosomes with lysosomes [2]. Furthermore, Fang ji huang qi decoction induces the formation of autophagosomes in NSCLC cells and elevates protein lev6els of p62 and LC3-II in a concentration- and time-dependent manner, suggesting a blockade of autophagic flux. Co-localization studies indicated that, rather than hindering autophagosome–lysosome fusion, Fang ji huang qi decotion disrupted cathepsin maturation, thereby inhibiting the autophagic process [90].

Overall, autophagy acts as a double-edged sword in cancer, functioning both as a tumour suppressor and a tumour promoter depending on the context. This dual role underscores the need for careful consideration when TCM is used to modulate autophagic pathways. The

timing and context of herbal therapy application are crucial for determining its effectiveness in cancer treatment.

Ferroptosis

Ferroptosis is a form of regulated cell death primarily driven by iron overload and oxidative stress. Elevated ROS levels lead to lipid peroxidation in cellular membranes, a hallmark of this process. The canonical ferroptosis pathway involves the transport of cystine into the cell *via* the system xc- antiporter, where it is reduced to cysteine by glutathione (GSH) and/or thioredoxin reductase 1 (TXNRD1). Cystine is then used for GSH biosynthesis, which plays a critical role in reducing phospholipid hydroperoxides (PL-OOH) to non-toxic alcohols through the action of glutathione peroxidase 4 (GPX4) [237]. When this antioxidant defense is compromised, the accumulation of lipid peroxides reaches a threshold that leads to membrane rupture, oxidative damage and ultimately cell death through ferroptosis.

GPX4 is a key regulator that inhibits ferroptosis by reducing lipid hydroperoxide levels and preventing membrane damage. As a substrate, GSH is essential for the protective mechanism of GPX4. Depletion of GSH disrupts this defense, leading to lipid peroxide accumulation and triggering ferroptotic cell death [238]. In most contexts, TCM promotes ferroptosis in lung cancer by inhibiting GSH/GPX4 signalling, eliminating cancer cells dependent on iron and lipid metabolism [28, 91, 119, 191–197, 239]. For instance, sappanone A (SA) isolated from the *Caesalpinia sappan* L. and timosaponin AIII (Tim-AIII) derived from *Anemarrhena asphodeloides* Bunge have been shown to induce ferroptosis in NSCLC cells by inhibiting GPX4-related signalling pathways [193, 194]. Andrographolide (ADE), a key component of *Andrographis paniculata* (Burm.f.) Wall. ex Nees, suppresses NSCLC tumour growth by inducing ferroptosis both in vitro and in vivo. ADE downregulates the expression of ferroptosis-associated proteins GPX4 and SLC7A11, increases ROS and intracellular iron levels and decreases GSH. These effects can be neutralized by the ferroptosis inhibitor ferrostatin-1 [28]. Moreover, Jiang and colleagues demonstrated that dihydroartemisinin (DHA), an active metabolite of artemisinin, induces the lysosomal degradation of ferritin, leading to increased free iron levels within cells and enhancing their vulnerability to ferroptosis. Additionally, DHA interacts with intracellular free iron, promoting the binding of iron-regulatory proteins (IRPs) to mRNAs containing iron-responsive element (IRE) sequences. This disrupts the IRP/IRE-mediated regulation of iron homeostasis, further elevating free iron levels. Notably, in both in vitro and mouse xenograft models of lung cancer, ferroptosis induced by GPX4 knockout was further enhanced by DHA, suggesting its potential to overcome cancer cell resistance to GPX4-mediated ferroptosis [119]. Furthermore, Chen et al. demonstrated that erianin, derived from *Dendrobium chrysotoxum* Lindl., triggers ferroptosis in lung cancer cells, which is characterized by ROS accumulation, lipid peroxidation and GSH depletion. The Ca^{2+}/CaM signalling pathway plays a pivotal role in erianin-induced ferroptosis and its inhibition significantly mitigates the ferroptotic cell death caused by erianin [195].

While the GSH-GPX4 axis is recognized as the primary regulator of ferroptosis in mammals, TCMs can also initiate GPX4-independent ferroptotic pathways in lung cancer cells. *Hedyotis diffusa* injection has been found to suppress the proliferation of lung adenocarcinoma cells by inducing ferroptosis, as evidenced by increased intracellular Fe^{2+} intensity, elevated intracellular lipid ROS and malondialdehyde (MDA) level. Mechanistically, *Hedyotis diffusa* injection inhibits Bcl-2 and enhances Bax, which activates the opening of VDAC2/3 channels, in turn promoting ion transport. This action facilitates the accumulation of ROS within intracellular compartments, ultimately leading to the induction of ferroptosis in lung adenocarcinoma cells [92]. In addition, Sui's group demonstrated that Curcumenol, a key component of *Curcuma wenyujin* Y.H.Chen & C.Ling, induces lung cancer cell death primarily through ferroptosis in both in vitro and in vivo models. Curcumenol treatment significantly downregulates long non-coding RNA H19 (lncRNA H19) in lung cancer cells. Ectopic expression of lncRNA H19 counteracts the anti-tumour effects of curcumenol, whereas its knockdown enhances ferroptosis triggered by curcumenol. Mechanistically, lncRNA H19 acts as a competing endogenous RNA (ceRNA), binding to miR-19b-3p and upregulating the transcription of its target gene, ferritin heavy chain 1 (FTH1), a key regulator of ferroptosis induction [198].

Pyroptosis

Pyroptosis, an inflammatory form of programmed cell death, plays a complex and significant role in tumour pathogenesis by influencing the balance between cell death and survival within the tumour microenvironment. Pyroptosis can suppress tumour growth by directly eliminating malignant cells and enhancing anti-tumour immunity. Pyroptosis can be triggered through pattern recognition receptors (PRRs) like the NLRP3 inflammasome, or through the release of pro-inflammatory cytokines, such as IL-1β and IL-18 and danger-associated molecular patterns (DAMPs), which recruit and activate immune cells, including macrophages, dendritic cells and cytotoxic T cells, to attack tumours. Moreover, key

markers such as gasdermins, inflammatory cytokines and cleaved caspases are vital for understanding the dynamics of pyroptosis and its role in tumour immunity [240].

Sophflarine A, a newly discovered water-soluble alkaloid derived from the roots of *Sophora flavescens* Aiton, triggers pyroptosis in NSCLC cells. Sophflarine A activates NLRP3 and caspase-1, leading to the cleavage of full-length GSDMD into its N-terminal fragment, which forms pores in the cell membrane. This process also facilitates the conversion of pro-IL-1β into its mature form, which further promotes inflammation and enhances the immune response against tumour cells [224]. Similarly, the alcohol-precipitated fraction of fig fruit latex (AFFL) triggers the cleavage of GSDMD and GSDME, resulting in the release of their N-terminal domains, which accumulate and puncture the cell membrane, consequently facilitating pyroptosis in NSCLC cells [225]. Additionally, sodium new houttuyfonate (SNH), a key derivative of *Houttuynia cordata* Thunb., inhibits NSCLC cell growth by triggering pyroptosis. This effect is mediated through the upregulation of TCONS-14,036, a newly identified lncRNA that functions as a ceRNA. TCONS-14,036 binds to microRNA-1228-5p, leading to the upregulation of PRKCDBP, a putative tumour suppressor. Elevated PRKCDBP levels activate the NLRP3 inflammasome, initiating pyroptosis *via* the cleavage of caspase 1, IL-1β and GSDMD in NSCLC cells [27]. Furthermore, DHA inhibits TOM70, causing damage to mitochondrial DNA (mtDNA) and its translocation from the mitochondria to the cytoplasm. This disrupts mitochondrial function and activates the cGAS/STING/NLRP3 signalling pathway. Both in vitro and in vivo studies have shown that mtDNA translocation triggers pyroptosis in malignant cells and enhances their immunogenicity. The presence of DHA not only induces cell death but also potentially strengthens the immune response against lung cancer [120].

Other cell death mechanisms

In lung cancer research, in addition to the cell death mechanisms mentioned above, various other forms of cell death induced by TCMs have been investigated, including necroptosis [121, 199], DNA damage [200, 201], immunogenic cell death [223, 241, 242] and cellular senescence [72, 72]. Tanshinol A (TSA) stimulates the phosphorylation of mixed lineage kinase domain-like protein (MLKL), a necroptosis marker, leading to its translocation to the cell membrane and an increase in cytosolic calcium levels, eventually causing necroptosis in lung cancer cells [121]. Additionally, quercetin promoted DNA damage in NSCLC cells, as evidenced by upregulated γ-H2AX protein expression and increased occurrence of DNA fragmentation. Furthermore, quercetin disrupts DNA repair mechanisms, including homologous recombination and non-homologous end-joining, which contributes to mitotic catastrophe in NSCLC cells [200]. Some TCMs also induce cellular senescence, a form of non-programmed cell death [89, 202]. For instance, ADE increases the proportion of senescent cancer cells, which exhibit a flattened morphology and positive staining for SA-β-gal activity in human lung adenocarcinoma. At the molecular level, ADE activates the p53 pathway, leading to the upregulation of p21, which in turn induces senescence in A549 cells [202]. Moreover, numerous TCMs have been shown to arrest lung cancer cells at various stages of the cell cycle, thereby inducing cell cycle-dependent cell death [93, 145, 203–214]. For example, aila, a principal bioactive constituent derived from the stem bark of *Ailanthus altissima* (Mill.) Swingle, reduces BrdU incorporation into newly synthesized DNA in NSCLC cells in a dose-dependent manner, suggesting that aila inhibits DNA replication during S phase [211]. Interestingly, a recent study revealed that the absence of mitochondrial calcium uptake protein 3 (MICU3) is associated with the progression of lung cancer. Trichosanthin (TCS), extracted from the Chinese herb *Trichosanthes kirilowii* Maxim., has been shown to promote calcium influx into mitochondria, inducing a distinct form of cancer cell death. This effect is mediated by the activation of MICU3 transcription, which involves the DNA methyltransferase DNMT3B and the transcription factor FOSL2 [243]. Moreover, Fan et al. identified that cGAS-mediated sensing of mtDNA plays a crucial role in the development of lung cancer associated with the genetic loss of *Kras* and *p53*. Baicalein prevents mtDNA release and cGAS activation and functions as a novel cGAS inhibitor. It inhibits cGAS by facilitating a liquid-to-solid phase transition of cGAS, which may suppress lung tumourigenesis driven by cGAS overactivity [244]. A recent study identified Demethylzeylasteral (T-96), a small molecule from *Tripterygium wilfordii* Hook.f., as a novel inhibitor of leucine-rich pentatricopeptide repeat-containing protein (LRPPRC), which regulates the stability of mitochondrial DNA-encoded mRNA (mt-mRNA) and plays a crucial role in the synthesis of the OXPHOS complex. T-96 directly binds to the RNA-binding domain of LRPPRC, disrupting its interaction with mt-mRNA and causing instability in both LRPPRC and mt-mRNA. This ultimately impairs OXPHOS complex synthesis and inhibits mitochondrial aerobic respiration and ATP production in lung cancer cells [215]. In conclusion, TCM provides a multifaceted approach to lung cancer treatment by targeting various cell death pathways. Understanding these mechanisms may lead to innovative strategies

that enhance treatment efficacy and improve patient QOL.

Combining TCM with conventional cancer therapy to overcome resistance

Lung cancer, particularly NSCLC, presents substantial therapeutic challenges due to the development of chemoresistance. Resistance mechanisms in lung cancer cells involve the overexpression of drug efflux transporters, mutations in critical signalling pathways such as the EGFR and AKT pathways and the activation of compensatory pathways such as the nuclear factor erythroid 2-related factor 2 (Nrf2) and hypoxia-inducible factor-1α (HIF-1α) pathways. Autophagy and metabolic reprogramming also contribute to cell survival under therapeutic stress. Recent studies have highlighted the potential of TCMs to reverse these resistance mechanisms, offering promising adjuncts to conventional therapies (Table 4). This section explores the involvement of transporters and key molecular pathways in drug resistance, alongside the therapeutic potential of TCMs in overcoming these challenges (Fig. 3).

ABC transporters

Drug efflux mediated by ABC transporters is a key mechanism underlying chemoresistance in cancer cells. These membrane-bound transporters actively extrude chemotherapeutic drugs, reducing intracellular drug concentrations and diminishing therapeutic efficacy [292]. In NSCLC, the overexpression or hyperactivation of ABC transporters, including P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs, such as MRP-1, MRP-2 and MRP-3) and breast cancer resistance protein (BCRP), has been closely linked to acquired resistance to multiple chemotherapeutic agents [293].

Efforts to overcome ABC transporter-mediated multidrug resistance have focused on the use of inhibitors that suppress transporter activity, thereby reducing drug efflux and sensitizing lung cancer cells to chemotherapy [245]. For instance, rosmarinic acid (RA) has been shown to downregulate the mRNA and protein expression of P-gp by activating the phosphorylation of JNK in cisplatin-resistant A549-DDP cells. The combination of RA and cisplatin synergistically reduces cisplatin efflux, reverses P-gp-mediated resistance and promotes mitochondria-mediated apoptosis. Compared with cisplatin alone, this combination significantly enhances the inhibition of NSCLC xenograft tumour growth in vivo [246]. Similarly, Dang gui bu xue decoction not only inhibits P-gp activity in A549 cells but also reverses gemcitabine-induced upregulation of P-gp protein expression in tumour tissues of LLC-bearing mice (a murine Lewis lung carcinoma model). As a result, the combination of dang gui bu xue decoction and gemcitabine significantly enhances anti-tumour efficacy compared with gemcitabine alone in an LLC-bearing mouse model [247]. Yu ping feng formula, a well-known Chinese herbal formula composed of *Astragali* Radix, *Atractylodis Macrocephalae* Rhizoma, *Saposhnikoviae* Radix, also enhances the cytotoxicity of cisplatin in A549-DDP cells by inhibiting drug efflux. Yu ping feng formula significantly suppresses the activity and expression of P-gp and BCRP in A549-DDP cells while exerting minimal effects on A549 cells. Additionally, Yu ping feng formula reduces the ATPase activity of efflux transporters, including P-gp ATPase, BCRP ATPase and MRPs ATPase, particularly MRP2, which is crucial for cisplatin efflux. Further analysis identified prim-O-glucosylcimifugin, a major component of Yu ping feng formula, as a key active ingredient in reversing cisplatin resistance [29]. Another study also found that Yu ping feng formula pretreatment markedly reduces the cisplatin-induced mRNA expression levels of MRP1, MRP2, MRP3 and BCRP in A549-DDP cells, thereby increasing intracellular cisplatin levels [248].

Copper transporter

Copper transporters are a class of membrane transport proteins responsible for maintaining cellular copper homeostasis. They efficiently regulate the absorption, distribution, utilization and storage of copper ions (Cu^{2+}) while preventing toxic accumulation [294]. Copper transporter 1 (CTR1), a high-affinity copper importer, has been shown to mediate the uptake of cisplatin, as the drug shares similarities with Cu^{2+}. This allows cisplatin to utilize CTR1 as a transporter to enter cells [295]. In lung cancer cells, reduced expression or activity of CTR1 limits its cisplatin uptake, decreasing its intracellular concentration and contributing to cisplatin resistance [296].

Studies have demonstrated that the green tea polyphenol (−)-epigallocatechin-3-gallate (EGCG) not only upregulates CTR1 expression but also facilitates its translocation from the peri-nucleus to the cytoplasm, promoting its movement to cell surface for metal transport. Moreover, microRNA hsa-mir-98-5p has been found to target the 3′ UTR of CTR1 mRNA, thereby downregulating CTR1 expression. However, EGCG increases the expression of lncRNA nuclear enriched abundant transcript 1 (NEAT1), which acts as a molecular sponge for miR-98-5p, alleviating its inhibitory effect on CTR1. This interaction sensitizes cisplatin-resistant NSCLC cells to cisplatin and improves treatment outcomes in an A549 xenograft mouse model [294]. Further investigations revealed that EGCG increases ROS production in lung cancer cells and xenografts, which in turn upregulates CTR1 expression [250]. Additionally, curcumin has been shown to enhance cisplatin uptake in A549 cells

Table 4 Combining TCM with conventional cancer therapy in lung cancer treatment

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
ATP-binding cassette transporters	Ginsenoside Rb1	*Panax ginseng* C.A.Mey.	Enhanced cisplatin-sensitivity of A549/DDP cells in vitro and in vivo through the dual-inhibition on two efflux pumps of ABCB1 and PTCH1	[245]
	Rosmarinic acid	*Salvia rosmarinus* Spenn.	-Downregulation of P-gp by activating the phosphorylation of JNK in cisplatin-resistant A549-DDP cells -Synergistic effects on reducing cisplatin efflux, reversing P-gp-mediated resistance, promoting mitochondria-mediated apoptosis -Enhanced inhibition of NSCLC xenograft tumour growth combined with cisplatin compared to cisplatin alone	[246]
	Dang gui bu xue decoction	2 TCMs	-Inhibition of P-gp activity in A549 cells and reversion of gemcitabine-induced upregulation of P-gp protein expression in LLC mice -Enhanced anti-tumour efficacy combined with gemcitabine in LLC mice compared to gemcitabine alone	[247]
	Yu ping feng formula	3 TCMs	-Enhanced cytotoxicity of cisplatin in A549-DDP cells by inhibiting drug efflux -Suppression of P-gp and BCRP in A549-DDP cells with minimal effects on A549 cells	[29]
			-Reduced ATPase activity of efflux transporters, particularly MRP2 -Identified Prim-O-glucosylcimifugin as a key active ingredient in reversing cisplatin resistance -Reduced cisplatin-induced mRNA levels of MRP1, MRP2, MRP3 and BCRP and increased intracellular cisplatin levels in A549-DDP cells	[248]
Copper transporter	Green tea polyphenol (–)-epigallocatechin-3-gallate	Green tea	Sensitized cisplatin-resistant NSCLC cells to cisplatin through NEAT1/has-miR-98-5p/CTR1in an A549 xenograft mouse model	[249]
			Upregulation of CTR1 expression by increased ROS production in lung cancer cells and xenografts	[250]
	Curcumin	*Curcuma longa* L.	-Enhanced cisplatin uptake in A549 cells and A549 xenograft tumours by promoting Cu chelation and upregulating CTR1 through Cu^{2+}-Sp1-CTR1 feedback loop *Curcuma longa*	[251]
Autophagy	Xie bai formula	4 TCMs	Enhanced sensitivity of NSCLC cells to gefitinib by inhibiting Beclin-1 mediated autophagosome formation in PC-9 cell line invitro and in vivo	[94]
	Ailanthone	*Ailanthus altissima* (Mill.) Swingle	Increased cisplatin-induced apoptosis and autophagy in cisplatin-resistant A549 cells through the PI3K/AKT/mTOR pathway	[252]

Table 4 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Fei yan ning	10 TCMs	Enhanced cisplatin's anti-cancer effects by inhibiting cisplatin-induced protective autophagy in A549 cells	[63]
	Andrographis	Andrographis paniculata (Burm.f.) Wall. ex Nees	Reversed cisplatin-induced autophagy and enhanced cisplatin-mediated apoptosis in A549 and LLC cells	[253]
			Suppressed autophagy and reversed cisplatin resistance through AKT/mTOR signalling pathway activation by downregulating PTEN in lung cancer cells	[254]
	Pristimerin	*Euonymus alatus* (Thunb.) Siebold	Enhanced lung cancer cell chemosensitivity to cisplatin by inhibiting the miR-23a/AKT/GSK3β signalling pathway and autophagy	[255]
	Oridonin	*Rabdosia rubescens* (Hemsl.) H.	Protective effect against cisplatin-induced nephrotoxicity	[256]
			Inhibition of cell proliferation and metastasis through EGFR/ERK/MMP-12 signalling pathway in gefitinib-resistant NSCLC cells	[257]
	Bu zhong yi qi decoction	8 TCMs	Activated autophagy with increased LC3 puncta, LC3-II and ATG7 proteins levels when co-administrated with cisplatin in A549-DDP cells	[258]
	Curcumin	*Curcuma longa* L.	-Sensitized cytotoxicity to gefitinib by inducing robust autophagy in gefitinib-resistant H157 and H1299 cells -Stronger autophagic cell death and autophagy-mediated apoptosis through suppression of EGFR activity by Sp1/HADC1 and ERK/MEK, AKT/S6K pathways in cotreatment with gefitinib group	[259]
	Scutellarin	*Erigeron breviscapus* (Vaniot) Hand.-Mazz.	Enhanced cytotoxicity to cisplatin through induction of autophagy by inhibiting c-met/AKT signalling pathway in A549 xenograft mouse model	[260]
	Sun-Bai-Pi Extract	*Morus alba* L.	Improved killing effects by inducing autophagy in A549 cells when combined with cisplatin	[261]
Glycolysis	Shen mai injection	2 TCMs	Enhanced cisplatin-induced cytotoxicity in cisplatin-resistant A549-DDP cells through decreased glucose uptake and lactate output by suppressing glycolytic enzymes *via* AKT-mTOR-c-Myc pathway	[30]
	Melittin	*Apis cerana* Fabr.	Re-sensitized A549/DDP cells to cisplatin by suppressing aerobic glycolysis both in vitro and in vivo through downregulation of HSF1 and PDK3	[262]
EGFR	Fu zheng kang ai formula	12 TCMs	Reverse gefitinib resistance through regulating p-ERK1/2-EZH2-Snail/EGFR pathway in lung adenocarcinoma	[95]

Table 4 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Aqueous extracts of *Taxus mairei* (Lemée & H.Lév.) S.Y.Hu	*Taxus mairei* (Lemée & H.Lév.) S.Y.Hu	Enhanced osimertinib sensitivity by ERK/SREBP-2/HMGCR-mediated cholesterol biosynthesis in EGFR-mutant NSCLC cells.	[263]
	Griffithazanone A	*Goniothalamus yunnanensis* W. T. Wang	-Enhanced the efficacy of gefitinib and osimertinib, reversed osimertinib resistance -Regulating the ASK1/JNK/p38 and BAD/Bcl-2 pathways in A549 cells by targeting PIM1	[264]
	Oridonin	*Rabdosia rubescens* (Hemsl.) H.Hara	Inhibition of cell proliferation and metastasis through EGFR/ERK/MMP-12 signalling pathway in gefitinib-resistant NSCLC cells	[257]
	Aucklandia lappa DC. extract	*Aucklandia lappa* DC.	Enhanced gefitinib efficacy by downregulating EGFR expression in transgenic *Caenorhabditis elegans* (jgIs25) model system	[265]
	Shikonin	*Lithospermum erythrorhizon* Siebold & Zucc.	Promotion of proteasomal degradation of EGFR and deactivation of EGFR by suppressing its phosphorylation at Tyr1173 and Tyr1068 in gefitinib-resistant NSCLC cells	[31]
Nrf2 pathway	Tangeretin	Peel of *Citrus* species	Reversed multidrug resistance to paclitaxel and osimertinib through suppression of Nrf2/P-gp in lung cancer cells and paclitaxel-resistant A549/T cell-derived xenograft models	[266]
	Triptolide	*Tripterygium wilfordii* Hook.f.	Enhanced chemosensitivity to cisplatin in A549 cells and xenograft tumour models through inhibition of Nrf2	[267]
	3′,4′,5′,5,7-Pentamethoxyflavone	*Rutaceae* Juss.	Sensitized cytotoxicity to cisplatin by inhibition of Nrf2 pathway in cisplatin-resistant A549 cells	[268]
	Pedunculoside	*Ilex rotunda* Thunb.	Inhibition of EMT and improved gefitinib sensitivity through regulating MAPK and Nrf2 pathways in gefitinib-resistant A549 cells and B16-F10 mouse model	[269]
	Jie geng decoction	2 TCMs	Reversed cisplatin resistance through the Nrf2 pathway in DDP-resistant A549 cells	[64]
HIF-1α	Oroxylin A	*Scutellaria baicalensis* Georgi	Reversed hypoxia-induced cisplatin resistance through inhibiting HIF-1α-mediated XPC transcription by directly binding to HIF-1α and reduced binding of HIF-1α to HRE3 on the promotor region of XPC in NSCLC cells	[270]

Table 4 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Polyphyllin I	*Paris polyphylla* Sm.	-Resensitized of gefitinib-resistant PC9 cells to gefitinib resistance in vitro and in vivo *via* HIF-1α degradation promotion of formation of the HIF-1α/VHL complex -Inhibition of angiogenesis by downregulating the VEGF/VEGFR2/p38 pathway	[271]
	Ononin	*Astragalus membranaceus* Fisch. ex Bunge	Promotion of radiosensitivity by suppressing excessive activation of the HIF-1α/VEGF pathway in lung cancer	[272]
AKT pathway	Baicalin	*Scutellaria baicalensis* Georgi	Enhanced activity of TRAIL by promoting p38 MAPK activation and reduced TRAIL-associated resistance in A549 and H2009 cells	[273]
			Enhanced cisplatin's anti-cancer effects by inhibiting proliferation and invasion through downregulation of p-AKT levels and MARK2 expression in both cisplatin-sensitive and cisplatin-resistant lung cancer cells	[274]
	Cordycepin	*Cordyceps*	Enhanced cisplatin's inhibitory effects on cell proliferation and promotion of apoptosis partially through inhibition of the AKT pathway in both parental and cisplatin resistant A549 cell lines	[275]
	Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Synergistic effect on inhibiting NSCLC *via* downregulation of the PI3K/AKT signalling pathway when combined with cisplatin in vitro and in vivo	[276]
NF-κB pathway	Triptolide	*Tripterygium wilfordii* Hook.f.	Reversed Taxol resistance by inhibiting the NF-κB and NF-κB-regulated drug-resistant genes in Taxol-resistant A549 cells	[277]
ER stress	Honokiol	*Magnolia officinalis* Rehder & E.H.Wilson	Synergistic killing effect with paclitaxel through paraptosis *via* ER stress, ER dilation and mitochondrial Ca2 + overloadin H1650, H1299 cells and H1299 xenograft tumours	[278]
STAT3	Huang lian jie du decoction	4 TCMs	Inhibited growth and improved sensitivity of EGFR-mutated NSCLC cells through inhibition of STAT3 in vitro and in vivo when combined with erlotinib	[96]
	L-Theanine	Green Tea	Mitigated chemoresistance to cisplatin by regulating STAT3/NOTCH1-BMAL1 signalling pathway in cisplatin-resistant lung cancer cells	[279]
	Tan re qing injection	5 TCMs	Improvement sensitivity to gefitinib through increasing ROS and suppressing the phosphorylation of STAT3 in NSCLC models	[280]

Table 4 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
JNK pathway	Huaier aqueous extract	*Trametes robiniophila* Murr.	Inhibition of cisplatin resistance by suppressing the phosphorylation and nuclear translocation of JUN by binding and inhibiting the kinase activity of JNK	[281]
FOXO3 pathway	Shen qi fu zheng injection	2 TCMs	Inhibited lactic acid-induced cisplatin resistance in NSCLC via FOXO3/FBXO22/p53 signalling pathway	[282]
Chk1	Betulinic acid	*Celastrus orbiculatus* Thunb.	Enhanced chemoresistance to gemcitabine by promoting Chk1 degradation in H1299 cells	[283]
miR-155-5p/SIRT1 pathway	Andrographis	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	Reduced cisplatin resistance in vitro and synergistic effect with cisplatin in vivo *via* miR-155-5p/SIRT1 pathway	[284]
Ferroptosis	α-Hederin	*Clematis ganpiniana* (H.Lév. & Vaniot) Tamura	Induction of DDIT3/ATF3-mediated ferroptosis and reversing cisplatin chemoresistance in NSCLC cells	[285]
Pyroptosis	Ophiopogonin B	*Ophiopogon japonicus* (Thunb.) Ker Gawl.	Alleviated cisplatin resistance by inducing Caspase-1/GSDMD dependent pyroptosis in cisplatin-resistant A549 cells	[286]
Apoptosis and cell cycle arrest	Fruit Hull of *Gleditsia sinensis*	*Gleditsia sinensis* Lam.	Enhanced anti-tumour effect of cisplatin through increased apoptosis and cell cycle arrest by increasing p21 in LLC in vitro and in vivo	[287]
	Tanshinone IIA	*Salvia miltiorrhiza* Bunge	-Inhibition of malignant biological behaviors and inducing apoptosis and cell cycle arrest when combined with adriamycin in A549 cells	[288]
SIRT6	Astragaloside IV	*Astragalus membranaceus* Fisch. ex Bunge	Enhanced Gefitinib chemosensitivity potentially *via* regulation of SIRT6 in A549, HCC827 and NCI-H1299 cells	[289]
ADAM9	Resveratrol	*Veratrum album* L.	Decreased cancer progression *via* ADAM9 degradation and synergistic effects in combination with dasatinib or 5-FU	[290]
PVT1 and miR-181a-5p	Xiao ji decoction	8 TCMs	Synergistic impact on regulating the expression of PVT1, miR-181a-5p and SP1 when combined with cisplatin	[291]

Abbreviation: *ABCB1* ATP-binding cassette subfamily B member 1, *AKT* Protein Kinase B, *Bax* Bcl-2-associated X protein, *Bcl-2* B-cell lymphoma-2, *BCRP* Breast cancer resistance protein, *CTR1* Copper transport protein 1, *DDP* Cisplatin, *EGFR* Epidermal growth factor receptor, *EMT* Epithelial-mesenchymal transition, *ERK* Extracellular regulated protein kinases, *HIF-1α* Hypoxia inducible factor-1α, *HRE3* Hypoxia response element 3, *HSF1* Heat shock factor 1, *JUN* c-Jun, *JNK* c-Jun-N-terminal protein kinase *LLC* Lewis lung cancer, *MAPK* Mitogen-activated protein kinase, *MET* Mesenchymal-epithelial transition factor, *miR* MicroRNA, *MMP* Matrix metallopeptidase, *MRP* Multidrug resistance protein, *NEAT1* Nuclear enriched abundant transcript 1, *Nrf2* Nuclear factor erythroid 2-related factor 2, *NSCLC* Non-small lung cancer, *PDK3* Pyruvate dehydrogenase kinase 3, *P-gp* P-glycoprotein, *PI3K* Phosphatidylinositol 3-kinase, *PVT1* Plasmacytoma variant translocation 1, *Sp1* Specificity protein 1, *STAT3* Signal transducer and activator of transcription 3, *TCM* Traditional Chinese medicine, *TRAIL* Tumour necrosis factor-related apoptosis-inducing ligand, *VEGF* Vascular endothelial growth factor, *XPC* Xeroderma pigmentosum group C

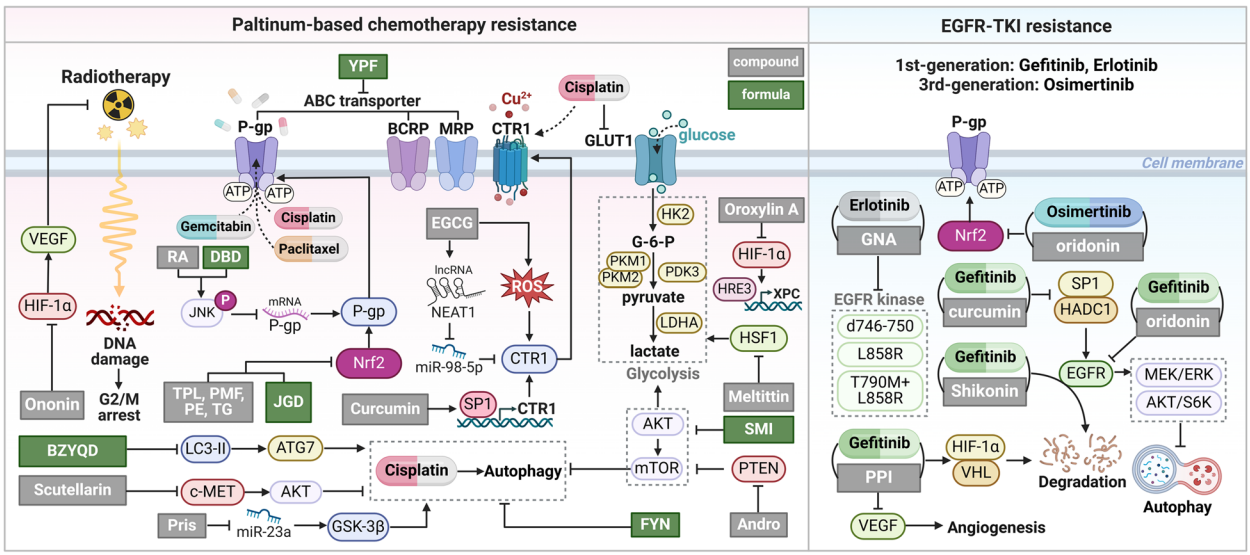

Fig. 3 TCM reverses resistance to conventional cancer therapies in lung cancer. Standard therapies for lung cancer include radiotherapy; platinum-based chemotherapy, such as cisplatin; and EGFR-TKIs targeted therapies, such as gefitinib, erlotinib and osimertinib. However, resistance to these treatments often develops through various mechanisms, including drug efflux, autophagy, glycolysis and signalling pathways such as the EGFR, Nrf2, HIF-1α and AKT pathways. TCM has shown the potential to overcome these resistance mechanisms, thereby enhancing the efficacy of conventional lung cancer therapies and achieving synergistic anti-cancer effects. "↑" indicates activation, stimulation or promotion, whereas "⊥" indicates inhibition, suppression or decrease. Formula abbreviation: YPF-Yu ping feng formula, DBD-Dang gui bu xue decoction, FYN-Fei yan ning, SMI-Sheng mai injection, BZYQD-Bu zhong yi qi decoction, JGD-Jie geng decoction

and A549 xenograft tumours by promoting copper chelation and upregulating CTR1 expression at the cell membrane. This effect is mediated by the ability of curcumin to increase the binding of transcription factor specificity protein 1 (Sp1) to both the CTR1 and Sp1 promoter, thereby enhancing CTR1 transcription. This mechanism is regulated by the Cu^{2+}-Sp1-CTR1 feedback loop, which contributes to increased chemosensitivity to cisplatin [251].

Autophagy

Autophagy exhibits a complex dual role in the sensitization of lung cancer to chemotherapy. It can facilitate tumour growth and survival by enabling cancer cells to adapt to chemotherapy-induced stress, maintain homeostasis and develop resistance [297]. Conversely, autophagy can enhance chemotherapy-induced cell death by promoting autophagic cell death in certain instances [234]. The impact of autophagy on chemotherapy efficacy depends on factors such as cancer type, stage and the signalling pathways involved. This duality allows autophagy to shift from a protective mechanism to a pro-death pathway, thereby enhancing the therapeutic effects of chemotherapy.

Targeting autophagic pathways with inhibitors has shown promise in enhancing chemotherapy sensitivity in cancers where autophagy supports cell survival [94, 252]. For instance, cisplatin induces protective autophagy in lung cancer cells, reducing drug sensitivity in A549 cells. Fei yan ning, a Chinese herbal medicine, significantly enhances the anti-cancer effects of cisplatin by inhibiting cisplatin-induced protective autophagy in A549 cells [63]. Similarly, andrographis (Andro), a diterpene lactone derived from *Andrographis paniculata* (Burm.f.) Wall. ex Nees, reversed cisplatin-induced autophagy in A549 and Lewis lung cancer (LLC) cells, enhancing cisplatin-mediated apoptosis. The combination of Andro and cisplatin inhibits tumour growth and lung metastasis more effectively than cisplatin alone in both subcutaneous and orthotopic LLC implantation mouse models [253]. Mechanistically, Andro activates the AKT/mTOR signalling pathway by downregulating PTEN, suppressing autophagy and reversing cisplatin resistance in lung cancer cells [254]. Pristimerin (Pris), a naturally occurring triterpenoid quinone compound extracted from *Euonymus alatus* (Thunb.) Siebold, enhances lung cancer cell chemosensitivity to cisplatin by inhibiting the miR-23a/AKT/GSK3β signalling pathway and suppressing autophagy. In vivo studies confirmed that Pris synergizes with cisplatin to inhibit xenograft tumour growth [255].

Interestingly, autophagy inducers also potentiate chemotherapy by promoting autophagic cell death [252, 256]. Bu zhong yi qi decoction, a traditional Chinese herbal formula, activates autophagy when co-administrated

with cisplatin, as evidenced by increased LC3 puncta and elevated levels of LC3-II and ATG7 proteins in A549-DDP cells. Notably, 3-MA, an autophagy inhibitor, abolishes the growth-inhibitory effects of Bu zhong yi qi decoction and cisplatin co-treatment, confirming the role of autophagy in the observed therapeutic synergy [258]. Curcumin sensitizes gefitinib-resistant NSCLC cell lines (H157 and H1299) to gefitinib by inducing robust autophagy. Co-treatment with curcumin and gefitinib results in greater rates of autophagic cell death and autophagy-mediated apoptosis than either treatment alone. Mechanistically, this combination suppresses EGFR activity by disrupting the interaction between Sp1 and HADC1 and inhibits the ERK/MEK and AKT/S6K pathways, contributing to the induction of autophagy [259]. Scutellarin, a flavone derived from *Erigeron breviscapus* (Vaniot) Hand.-Mazz., enhances cisplatin-induced autophagy by inhibiting c-met/AKT signalling pathway. This autophagy induction amplifies the anti-tumour effects of cisplatin, as demonstrated in an A549 xenograft mouse model [260].

Glycolysis

Enhancing glycolysis, also known as the Warburg effect, is a crucial strategy employed by lung cancer cells to reprogram their metabolism and adapt to therapeutic stress. In this process, cancer cells preferentially metabolize glucose anaerobically, even under normoxic conditions [298]. Compared with their parental A549 cells, cisplatin-resistant A549-DDP cells exhibit increased glucose consumption, lactate production and elevated levels of key glycolytic enzymes, including hexokinase 2 (HK2), pyruvate kinase M1/2 (PKM1/2), glucose transporter 1 (GLUT1) and lactate dehydrogenase A (LDHA). The combination of sheng mai injection with cisplatin effectively decreases glucose uptake and lactate output in A549-DDP cells by suppressing the expression of these glycolytic enzymes, primarily through inhibition of the AKT-mTOR-c-Myc pathway. This metabolic reprogramming enhances cisplatin-induced cytotoxicity in resistant cells [30]. Melittin, a major component of *Apis cerana* Fabr., has demonstrated potent anti-cancer effects across various cancer types. Recent studies revealed that melittin effectively re-sensitizes A549-DDP cells to cisplatin by suppressing aerobic glycolysis both in vitro and in vivo. Mechanistically, melittin downregulates the expression of heat shock factor 1 (HSF1) and pyruvate dehydrogenase kinase 3 (PDK3), two key regulators of glycolysis. Notably, the inhibitory effects of melittin on glycolysis are further enhanced when melittin is combined with an HSF1 inhibitor, providing a promising strategy to overcome cisplatin resistance in lung cancer [262].

EGFR

EGFR mutations are frequently observed in lung cancer, particularly in NSCLC, which is commonly treated with EGFR-TKIs as targeted therapies. While EGFR-TKIs are initially effective, resistance often develops, limiting their long-term efficacy [299]. To address this challenge and improve treatment outcomes, there is growing interest in combining EGFR-TKIs with complementary therapeutic strategies, such as TCMs [95, 263, 264]. Gambogenic acid (GNA), a small molecule derived from the TCM herb gamboge, significantly inhibits the kinase activity of both wild-type and mutated EGFR, including EGFR (d746-750), EGFR (L858R) and EGFR (T790M + L858R). GNA not only potentiates the therapeutic efficacy of erlotinib in vitro but also sensitizes erlotinib-resistant tumours in xenograft nude mice and PDX model [300]. Similarly, oridonin effectively suppresses the EGFR/ERK/MMP-12 signalling pathway in gefitinib-resistant NSCLC cells, thereby inhibiting cell proliferation and metastasis [257]. Additionally, *Aucklandia lappa* DC. extract enhances gefitinib efficacy by downregulating EGFR expression at both the mRNA and protein levels. This effect was evaluated using the vulval development of the transgenic *Caenorhabditis elegans* (jgIs25) model system [265]. Additionally, shikonin, a major active component of *Lithospermum erythrorhizon* Siebold & Zucc., promotes the proteasomal degradation of EGFR in gefitinib-resistant NSCLC. Furthermore, shikonin significantly deactivates EGFR by suppressing its phosphorylation at Tyr1173 and Tyr1068, underscoring its potential anti-tumour properties in gefitinib-resistant NSCLC [31].

Nrf2 pathway

Mutations in the Kelch-like ECH associated protein 1 (Keap1)/Nrf2 signalling pathway have been identified in NSCLC in recent years. These genetic alterations impair Keap1 function, leading to constitutive Nrf2 activation and promoting cancer chemoresistance [301]. Tangeretin (TG), a flavonoid derived from the peel of *Citrus* species, effectively reverses multidrug resistance to both paclitaxel and osimertinib (a third-generation EGFR-TKI) in lung cancer cells and A549/T (paclitaxel-resistant) cell-derived xenograft models. Mechanistic studies revealed that TG suppresses the Nrf2 pathway and its downstream target P-gp, resulting in increased paclitaxel concentrations within tumours [266]. Triptolide (TPL), an abietane-type diterpenoid extracted from *Tripterygium wilfordii* Hook.f., significantly inhibits the expression and transcriptional activity of Nrf2 in NSCLC. Consequently, TPL enhances the chemosensitivity of lung cancer cells to cisplatin in both A549 cells and xenograft tumour models [267]. Similar effects have been observed with 3',4',5',5,7-pentamethoxyflavone, a natural flavonoid

extracted from *Rutaceae* plants [268], pedunculoside, a triterpene saponin extracted from *Ilex rotunda* Thunb [269], and Jie geng decoction (an ancient traditional Chinese herbal decoction) [64]. These substances act as effective adjuvant sensitizers to enhance the efficacy of chemotherapeutic drugs by downregulating the Nrf2 signalling pathway.

HIF-1α

Hypoxia in the tumour microenvironment is a key factor driving cisplatin resistance in lung cancer, primarily through HIF-1α. HIF-1α activates DNA repair mechanisms, anti-apoptotic pathways and drug efflux pumps, enabling cancer cells to evade cisplatin-induced cell death and reducing treatment efficacy [302]. Oroxylin A, a main bioactive flavonoid derived from *Scutellariae* Radix, significantly reverses hypoxia-induced cisplatin resistance by directly binding to the bHLH-PAS domain of HIF-1α. This interaction prevents HIF-1α from binding to the hypoxia response element 3 (HRE3) on the promoter region of xeroderma pigmentosum group C (XPC), a critical DNA repair protein implicated in cisplatin resistance. By inhibiting HIF-1α-mediated XPC transcription, oroxylin A effectively counteracts hypoxia-induced cisplatin resistance in NSCLC [270]. Polyphyllin I (PPI), a compound extracted from the rhizomes of *Paris polyphylla* Sm., has demonstrated the ability to overcome gefitinib resistance in lung adenocarcinoma. PPI promotes the formation of the HIF-1α/VHL complex, leading to HIF-1α degradation. This process inhibits angiogenesis by downregulating the vascular endothelial growth factor (VEGF)/VEGFR2/p38 pathway, thereby resensitizing gefitinib-resistant PC9/GR cells to gefitinib in both in vitro and in vivo models [271]. The overexpression of HIF-1α is associated with resistance to radiotherapy, leading to tumour radiotherapy failure. Ononin, a compound derived from *Astragalus membranaceus* Fisch. ex Bunge, enhances radiosensitivity in lung cancer by suppressing the excessive activation of the HIF-1α/VEGF pathway [272].

AKT pathway

The AKT signalling pathway is frequently hyperactivated in lung cancer cells, enabling them to evade apoptosis induced by cisplatin or targeted therapies like gefitinib [303]. Baicalin, a flavone glycoside derived from the *Scutellaria* genus, synergistically enhances the anticancer effects of cisplatin by inhibiting proliferation and invasion of both cisplatin-sensitive and cisplatin-resistant human lung cancer cells. Mechanistically, baicalin effectively decreases phosphorylated AKT levels and downregulates MARK2 mRNA and protein expression, which are significantly elevated in cisplatin-resistant lung cancer cells [274]. Similarly, compared with cisplatin alone, cordycepin, the primary active compound of *Cordyceps*, significantly enhances the inhibitory effects of cisplatin on cell proliferation and promotes apoptosis in both parental and cisplatin-resistant A549 cell lines. These synergistic effects are partially attributed to the inhibition of the AKT pathway [275].

Together, although the action mechanisms of these TCMs vary, they collectively reverse drug resistance in various drug-resistant lung cancer cell lines and tumour-bearing mouse models. In addition to the pathways discussed above, other mechanisms regulated by TCMs to enhance drug efficacy include modulation of NF-κB-regulated drug-resistant genes [277], induction of ER stress [278], inhibition of signal transducer and activator of transcription 3 (STAT3) [96, 279, 280], blockade of JNK signalling [281], inhibition of FOXO3 pathway [282], destabilization of Chk1 [283], suppression of miR-155-5p [284], promotion of ferroptosis [285] and activation of caspase-1/GSDMD-dependent pyroptosis [286]. The multifaceted components and diverse actions of TCMs warrant further investigation, providing valuable insights into novel strategies for overcoming drug resistance in lung cancer.

TCM inhibits lung cancer metastasis

Metastasis is a primary driver of lung cancer-associated mortality, commonly involving the bone, brain and liver, each governed by distinct molecular mechanisms. This complex process is mediated by cellular and molecular interactions within the tumour microenvironment. While chemotherapy and targeted therapies can achieve substantial tumour reduction, their inability to fully eliminate metastatic cells allows for potential relapse. Immunotherapy shows potential but is constrained by heterogeneity in immune responses and tumour microenvironment dynamics. TCM offers a complementary approach by potentially mitigating key processes in metastasis (Table 5), such as anoikis resistance, EMT and pre-metastatic niche formation and provides additional avenues for managing lung cancer metastasis [97, 188, 304–318] (Fig. 4).

Anoikis

Metastatic lung cancer cells can develop resistance to anoikis, a form of detachment-induced programmed cell death, enabling their survival in circulation and facilitating metastasis to distant sites [342]. Circulating tumour cells (CTCs), which detach from the primary tumour and enter the bloodstream, play a critical role in lung cancer dissemination. Polyphyllin VII, a bioactive compound derived from *Paris polyphylla* Sm., exhibits significant cytotoxic effects on the

Table 5 TCM inhibits lung cancer metastasis

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
Anoikis	Polyphyllin VII	*Paris polyphylla* Sm.	-Inhibition of colony formation, migration and invasion in CTC-TJH-01 cell line -Induction of anoikis primarily *via* suppressing the EGFR-MEK/ERK signalling pathway -Reduced lung metastasis, EGFR protein levels and CTCs in immunodeficient mouse models	[319]
	Jin fu kang	11 TCMs	Inhibition of aggregation and invasiveness through plakoglobin protein downregulation by modulating the EGFR-mediated cytoskeletal regulation in CTC-TJH-01 cells	[320]
	Imperatorin	*Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav.	-Sensitized cells to anoikis through downregulation of Mcl-1 and upregulation of Bax *via* upregulation of p53 in H23, H292 and A549 cells -Enhanced detachment-induced apoptosis and inhibition of anchorage-independent growth	[321]
EMT	*Cinnamomum cassia* extracts	*Cinnamomum cassia* (L.) D.Don	Inhibition of metastasis by reversion of TGF-β1-induced EMT in A549 and H1299 cells and suppression of tumour growth in A549 tumour in vivo	[306]
	Ligustrazine	*Ligusticum striatum* DC.	-Inhibition of invasion and proliferation through promotion of PTEN expression in H1299 cells -Inhibition of tumour formation by increasing PTEN levels and blocking the Wnt/β-catenin pathway in vivo	[307]
	Triptolide	*Tripterygium wilfordii* Hook.f.	Inhibition of EMT and induction of apoptosis in gefitinib-resistant A549 cells	[310]
			Suppression of growth and metastasis by inhibiting β-catenin-mediated EMT in NCI-H1299 cells	[322]
	Celastrus orbiculatus Thunb. extract	*Celastrus orbiculatus* Thunb.	-Inhibition of NSCLC invasion and metastasis through mitochondrial-induced ROS accumulation *via* targeting DJ-1 -Inhibition of EMT process in vitro and in vivo	[317]
	β-Elemene	*Curcuma wenyujin* Y.H.Chen & C.Ling	Inhibition of EMT by targeting ALDH3B2/RPSA axis in PC-9 and NCI-H1373 cells	[323]
	Huaier Granule extract	*Trametes robiniophila* Murr.	Suppression of metastasis by downregulating EMT-related proteins, including N-cadherin, β-catenin, slug, snail, MMP-9, TCF8/ZEB1 and claudin-1 in A549 and NCI-H1650 cells	[324]
	6,6′-Bieckol	*Ecklonia kurome* Okam.	Inhibition of TGF-β-induced EMT by down-regulating Snail1 and Twist1 in A549 and H1299 cells	[325]
	Osthole	*Cnidium monnieri* Cusson	Inhibition of TGF-β-induced EMT by suppressing NF-κB mediated Snail activation in cells	[326]

Table 5 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Cinnamaldehyde	*Cinnamomum cassia* (L.) D.Don	Induction of apoptosis and reversed EMT through inhibition of Wnt/β-catenin pathway in A549, YTMLC-90 and NCI-H1299 cells	[327]
	Vinblastine and vincristine	*Catharanthus roseus* (L.) G.Don	Inhibition of ERK-ZEB1-mediated EMT in pemetrexed-resistant CL1 and A549 cells by vinblastine and in pemetrexed-resistant A549 mice by vincristine	[33]
	Paeonol	*Paeonia lactiflora* Pall.	Suppression of metastasis of lung cancer cells through downregulation of ZEB2 by upregulating miR-126-5p expression	[328]
	Dioscin	*Phyllanthus amarus* Schumach. & Thonn.	Inhibition of A549 lung cancer migration and invasion through suppression of TGF-β1-induced EMT	[329]
	WSG	*Ganoderma lucidum* L.	Reduction in metastatic lung nodules and prolonged survival in LLC mice through degradation of EGFR, TGFβRI and TGFβRII *via* proteasomal pathway	[32]
	Angelica	*Angelica sinensis* (Oliv.) Diels	Suppression of metastasis by regulating MMPs/TIMPs and TGF-β1 in A549 cells	[330]
	Ginsenoside Rg3	*Panax ginseng* C.A.Mey.	Inhibition of EMT and invasion of lung cancer by down-regulating FUT4 mediated EGFR inactivation and blocking MAPK and NF-κB signal pathways	[331]
	Hedyotis diffusa polysaccharide	*Hedyotis diffusa* Willd.	Inhibition of metastatic potential by inhibiting EMT *via* EGFR/AKT/ERK signalling pathways in A549 cells	[332]
	Isobavachalcone	*Psoralea corylifolia* L.	Inhibition of TGF-β1 induced EMT in A549 cells	[333]
	Xanthotoxol	*Angelica dahurica (Hoffm.)* Benth. & Hook.f. ex Franch. & Sav.	Induction of cell cycle arrest, facilitated apoptosis and inhibition of EMT processes through down-regulating the PI3K-AKT pathway and ECM components	[334]
Premetastatic niches formation	*Astragalus* polysaccharide	*Astragalus membranaceus* Fisch. ex Bunge	Suppression of lung premetastatic niches formation and reduced MDSC recruitment by inhibiting the S1PR1/STAT3 signalling pathway	[34]
ECM remodelling	Isoorientin	*Patrinia* Juss.	Preventation of migration by inhibiting activity and expression of MCT1/4 and MMP-2/9 in A549 cells	[335]
	Bufalin	*Bufo bufo gargarizans*	Inhibition of migration and invasion and MMP-2 downregulation in gefitinib resistant NCI-H460 cells	[336]
			Inhibition of malignant development by regulating the circ_0046264/miR-522-3p axis and MMP-9 downregulation in A549 and H460 cells	[337]

Table 5 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Fucoxanthin	*Causonis japonica* (Thunb.) Raf.	-Suppression of metastasis and improved the sensitivity to gefitinib in vitro and in vivo -Suppression of MMP-2 in A549, H1299 and H446 cells	[338]
	Cantharidin	*Mylabris phalerata* Pallas	Degradation of ECM components and inhibition of migration and invasion *via* MMP-2 downregulation in A549 cells	[339]
	Solasodine	*Solanum melongena* L.	Inhibit of cell invasion at non-toxic concentrations through decreased mRNA expression of MMP-2/9 and EMMPRIN and increased expression of TIMP-1/2 and RECK *via* miR-21 downregulation in A549 cells	[340]
	Sinomenine	*Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson	Inhibition of migration and invasion by downregulating expression of miR-21 and MMPs in A549 and H1299 cells	[341]
Angiogenesis	*Brucea javanica* oil	*Brucea javanica* (L.) Merr.	Enhanced efficacy of Anlotinib by inhibiting angiogenesis in a mouse model of liver-metastasis of SCLC	[312]
	Delphinidin	*Consolida ajacis* (L.) Schur, *Styphnolobium japonicum* (L.) Schott, *Viscum coloratum* (Kom.) Nakai	Inhibition of angiogenesis through the suppression of HIF-1α and VEGF expression in A549 cells	[35]
Autophagy	Ailanthone	*Ailanthus altissima* (Mill.) Swingle	Inhibition of cell growth and metastasis through targeting UPF1/GAS5/ULK1 signalling pathway in NSCLC cells	[188]
STAT pathway	Glycyrrhizin	*Glycyrrhiza glabra* L.	Suppression of cell growth, metastasis and invasion by JAK/STAT/HMGB1 signalling pathway in HCC827 cells	[304]
	Honokiol	*Magnolia officinalis* Rehder & E.H.Wilson	Prevention of metastasis *via* inhibiting the phosphorylation of STAT3 in PC9-BrM3 and H2030-BrM3 cells	[305]
	Fu zheng kang ai formula	12 TCMs	Inhibition of metastasis through STAT3/MMP-9 pathway in A549, PC9 and H1650 cells	[311]
AKT pathway	Dioscin	*Phyllanthus amarus* Schumach. & Thonn.	Inhibition of proliferation, invasion and migration with decreased p-AKT1, MMP and PCNA in vitro and in vivo	[308]
P38/MAPK pathway	Xiao ai jie du recipe	9 TCMs	Inhibition of proliferation and metastasis by blocking the P38/MAPK pathway in A549 cells	[97]
	Cantharidin	*Mylabris phalerata* Pallas	Inhibiton of migration and invasion *via* UPA and MAPK signalling pathways in NCI-H460 cells	[314]
FAK	Triptolide	*Tripterygium wilfordii* Hook.f.	-Inhibition of migration through suppression of FAK and inhibition of invasion in H460, A549 and H358 cells -Inhibition of metastatic tumour formation in H358 mice	[309]
p120ctn/Kaiso pathway	Jin fu an decoction	10 TCMs	Inhibition of invasion and metastasis *via* p120ctn-mediated induction of Kaiso in H1650 cells	[313]

Table 5 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
Cytoskeletal remodel	Triptonodiol	*Tripterygium wilfordii* Hook.f.	Inhibition of migration and invasion by inhibiting cytoskeletal remodelling in H1299 and A549 cells	[315]
miR-7-5p/c-Myc/LDHA axis	Sulforaphane	*Cruciferous* species	Inhibition of metastasis by regulating the miR-7-5p/c-Myc/LDHA axis in the acidic tumour microenvironment in A549 and H1975 cells	[316]

Abbreviation: *AKT* Protein kinase B, *Bax* Bcl-2-associated X protein, *CTC* Circulating tumour cell, *ECM* Extracellular matrix, *EGFR* Epidermal growth factor receptor, *EMMPRIN* Extracellular matrix metalloproteinase inducer, *EMT* Epithelial-mesenchymal transition, *ERK* Extracellular regulated protein kinases, *FAK* Focal adhesion kinase, *FUT4* Fucosyltransferase 4, *GAS5* Growth arrest-special transcript 5, *HIF-1α* Hypoxia-inducible factor-1α, *HMGB1* High mobility group box-1 protein, *HRE* hypoxia-responsive element, *LDHA* Lactate dehydrogenase A, *MAPK* Mitogen-activated protein kinase, *Mcl-1* Myeloid cell leukemia 1, *MCT* Monocarboxylate transporter, *MDSC* Myeloid-derived suppressor cell, *MEK* Mitogen-activated protein, *miR* microRNA, *MMP* Matrix metallopeptidase, *NF-κB* Nuclear factor kappa B, *NSCLC* Non-small-cell lung cancer, *PTEN* Phosphatase and tensin homolog, *RECK* Reversion-inducing cysteine-rich protein with Kazal motifs, *ROS* Reactive oxygen species, *S1PR1* Sphingosine-1-phosphate receptor 1, *SCLC* Small-cell lung cancer, *STAT3* Signal transducer and activator of transcription 3, *TGF* Transforming growth factor, *TIMP* Tissue inhibitors of metalloproteinases, *TKI* Tyrosine kinase inhibitor, *ULK1* Unc-51 like autophagy activating kinase 1, *UPA* Urokinase-type plasminogen activator, *UPF1* Up-frameshift protein 1, *VEGF* Vascular endothelial growth factor, *ZEB* Zinc finger E-box binding homeobox

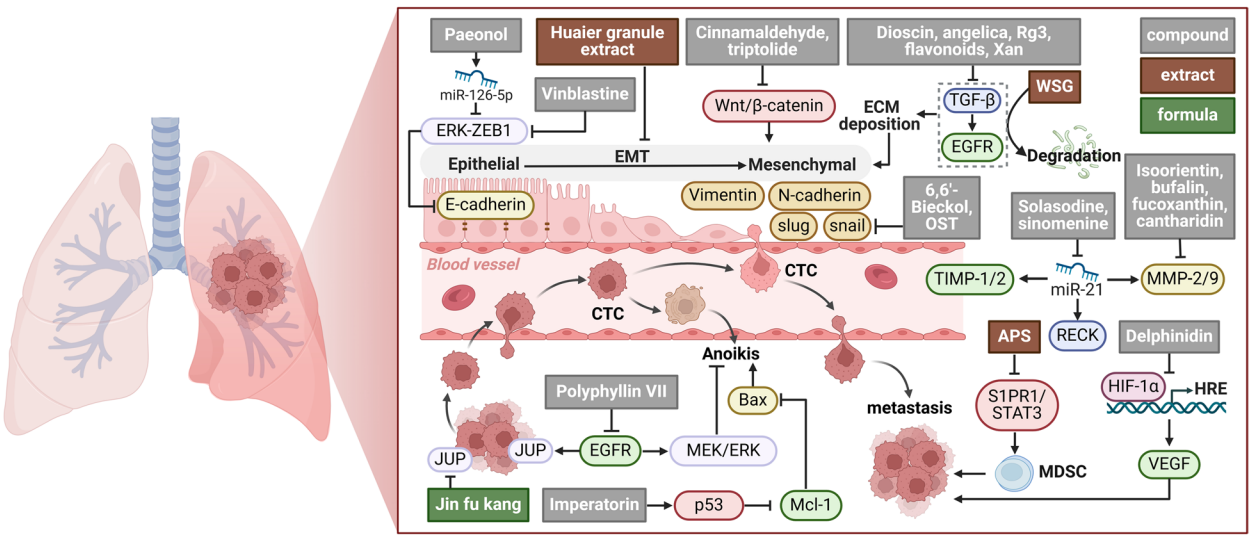

Fig. 4 TCM inhibits lung cancer metastasis. TCM provides a complementary approach to potentially suppress lung cancer metastasis through several key processes: **a** targeting CTCs and overcoming anoikis resistance; **b** reversing EMT; and (**c**) preventing the formation of pre-metastatic niche, disturbing ECM remodelling and inhibiting angiogenesis. "↑" indicates activation, stimulation or promotion, whereas "⊥" indicates inhibition, suppression or decrease

CTC-TJH-01 cell line (an established lung cancer CTC line), effectively inhibiting colony formation, migration and invasion. Notably, polyphyllin VII induces anoikis primarily by suppressing the EGFR-MEK/ERK signalling pathway, an effect that can be reversed by EGFR overexpression. In vivo studies using immunodeficient mouse models further demonstrated that polyphyllin VII markedly reduces lung metastasis, which is correlated with decreased EGFR protein levels and a reduced number of CTCs, highlighting its potential as an anti-metastatic agent through anoikis induction [319]. Similarly, Jin fu kang, a Chinese herbal prescription, inhibits the aggregation and invasiveness of lung cancer CTCs, primarily by modulating the EGFR-mediated cytoskeletal regulation pathway, leading to the down-regulation of plakoglobin protein expression [320]. Imperatorin, a furanocoumarin isolated from *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., also sensitizes lung cancer cells to anoikis at sub-toxic concentrations. In human lung cancer cell lines (H23, H292 and A549), imperatorin enhances detachment-induced apoptosis, as confirmed by its inhibitory effect on anchorage-independent growth in vitro.

Mechanistically, imperatorin upregulates p53 protein expression, leading to the downregulation of Mcl-1 and upregulation of Bax, thereby promoting anoikis [321].

Epithelial-mesenchymal transition (EMT)

EMT is a pivotal process in lung cancer metastasis, enabling epithelial cells to acquire mesenchymal traits such as increased mobility and invasiveness, which are crucial for cancer dissemination. EMT is characterized by the downregulation of epithelial markers, such as E-cadherin and the upregulation of mesenchymal markers like N-cadherin and vimentin, along with the activation of EMT-inducing transcription factors. Numerous TCMs have been reported to inhibit EMT, potentially limiting lung cancer metastasis through various critical signalling pathways [323]. For example, Huaier granule extract suppresses lung cancer cell metastasis by downregulating EMT-related proteins, including N-cadherin, β-catenin, slug, snail, MMP-9, TCF8/ZEB1 and claudin-1 [324]. Additionally, 6,6′-bieckol from *Ecklonia kurome* Okam. [325] and osthole (OST) from *Cnidium monnieri* Cusson [326] inhibit EMT by suppressing snail activation. Other compounds such as cinnamaldehyde from *Cinnamomum cassia* (L.) D.Don [327] and triptolide from *Tripterygium wilfordii* Hook.f [322]. prevent NSCLC metastasis by blocking Wnt/β-catenin pathway-mediated EMT. Interestingly, Chiu et al. demonstrated that pemetrexed-resistant lung cancer cells exhibit enhanced EMT driven by the ERK-ZEB1 pathway. Vinblastine effectively inhibits ERK-ZEB1-mediated EMT by using a mouse model, and vincristine show potential to overcome pemetrexed resistance and metastasis in pemetrexed-resistant lung adenocarcinoma sublines [33]. Additionally, paeonol, the main active component of *Paeonia lactiflora* Pall., suppresses the viability and metastasis of human lung cancer cells by up-regulating miR-126-5p expression, which subsequently downregulates its target gene ZEB2, a key EMT inducer that represses E-cadherin expression [328].

Transforming growth factor-beta1 (TGF-β1) is a potent inducer of EMT in lung cancer cells, primarily by upregulating EGFR ligands such as amphiregulin and enhancing EGFR pathway activity. This, in turn, amplifies EMT through increased extracellular matrix (ECM) deposition. Various active components from TCM have been reported to effectively reverse this process. Notable examples include dioscin from *Phyllanthus amarus* Schumach. & Thonn. [329], a water-soluble polysaccharide from *Geranium lucidum* L. (WSG) [32], angelica from *Angelica sinensis* (Oliv.) Diels [330], ginsenoside Rg3 [331], *Hedyotis diffusa* polysaccharide [332], flavonoids from the fruits of *Psoralea corylifolia* L. [333] and xanthotoxol (Xan) [334]. For instance, WSG has been shown to facilitate the degradation of EGFR, TGFβRI and TGFβRII *via* proteasomal pathways, resulting in a significant reduction in metastatic lung nodules and prolonged survival in LLC-bearing mice [32].

Premetastatic niches formation, ECM remodelling and angiogenesis

The formation of premetastatic niches, tissue sites primed to support metastatic cell growth, represents a promising therapeutic strategy against tumour metastasis. Primary tumours release pro-inflammatory cytokines and chemokines that recruit myeloid-derived suppressor cells (MDSCs) to distant tissues, aiding metastatic cells even before their arrival. Notably, *Astragalus* polysaccharide (APS) has been shown to suppress the formation of the lung premetastatic niches and reduce MDSC recruitment by inhibiting the S1PR1/STAT3 signalling pathway [34].

Structural changes in the ECM are essential for tumour cell invasion and metastasis, as ECM remodelling enables epithelial cells to detach from adhesive junctions and migrate. The enzymatic cleavage of laminin-5 by matrix metalloproteinases (MMPs) is crucial for the invasive activity of cancer cells. MMP-2, which often acts with MMP-9, degrades the ECM and basement membrane, promoting EMT and enhancing cancer invasiveness [343]. A variety of TCMs including isoorientin [335], bufalin [336, 337], fucoxanthin [338] and cantharidin [339], have been reported to regulate MMP-2 and MMP-9, thereby inhibiting migration and invasion of lung cancer. For example, Shen and colleagues identified two potent compounds derived from TCM, solasodine from *Solanum melongena* Wall. [340] and sinomenine from *Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson [341], both of which significantly inhibit lung cancer cell invasion at non-toxic concentrations. Both compounds work by decreasing the mRNA expression of MMP-2, -9 and extracellular matrix metalloproteinase inducer (EMMPRIN), while increasing the expression of tissue inhibitors of metalloproteinases-1, -2 (TIMP-1, -2) and reversion-inducing cysteine-rich protein with Kazal motifs (RECK). Notably, miR-21, which is overexpressed in lung cancer cells and promotes invasion by targeting RECK, is significantly downregulated by solasodine and sinomenine. Furthermore, silencing miR-21 has similar effects on regulating MMP-2, -9, EMMPRIN, RECK and TIMP-1, -2, suggesting that targeting miR-21 could be a promising therapeutic strategy for inhibiting lung cancer metastasis [340, 341].

In lung cancer, angiogenesis is often dysregulated, with pro-angiogenic factors such as VEGF being overexpressed, thereby driving tumour progression and enhancing metastatic potential. For example, delphinidin, a

polyphenol from the anthocyanidin group abundant in various pigmented fruits and vegetables, has been shown to effectively suppress VEGF expression at both the mRNA and protein levels by downregulating HIF-1α, a key transcription factor for VEGF. Furthermore, delphinidin inhibits VEGF by reducing hypoxia-responsive element (HRE) promoter activity and preventing HIF-1α from binding to the HRE promoter [35].

TCM modulates cancer immunology

Despite the promising outcomes of current immunotherapies in cancer treatment, challenges remain, including limited patient response rates, transient efficacy and immune-related adverse events. TCM adopts a holistic approach by strengthening the body's natural defenses (Zheng Qi) to combat external pathogens (Xie Qi), aligning with the principle of "supporting the righteous and dispelling evil". Certain TCM herbs, such as *Astragalus membranaceus* Fisch. ex Bunge and *Ganoderma lucidum* L., are known to modulate immune function, potentially enhancing immunity in the context of lung cancer treatment [344–346]. Integrating TCM with immunotherapy holds the potential to improve patient outcomes by addressing the complexities of tumour-induced immune evasion and supporting immune homeostasis (Table 6). This section highlights the role of TCM in cancer immunology, focusing on its regulatory effects on immune cells and its ability to enhance the efficacy of immune checkpoint inhibitors (Fig. 5).

TCM regulates immune cells

T cells play a pivotal role in therapeutic response to antitumour treatments and their composition and functionality are often significantly altered in individuals with lung cancer [375]. Studies have reported an increase in exhausted T cells in lung cancer patients, a state characterized by diminished cytotoxic activity and reduced effectiveness against cancer cells [376]. TCM has been shown to support T cell function, potentially improving therapeutic outcomes in lung cancer patients [99, 100, 347–352]. For example, Cai et al. demonstrated that TCS enhances immune responses in tumour-bearing immunocompetent mice. TCS treatment increases the population of IFN-γ-producing CD8+ T cells and stimulates the secretion of Th1-type cytokines, including IFN-γ and IL-2. Furthermore, the CD44+ CD62L- phenotype within the lymph nodes and spleen significantly increased the number of memory T cells, both CD4+ and CD8+ T cells, in TCS-treated mice. These findings suggest that TCS provides specific immune protection against LLC cells and promotes the generation of memory T cells, which are crucial for sustaining long-term immunity. Notably, in mice that had been treated with TCS and survived for more than 100 days, tumour growth was completely inhibited when a second injection of LLC cells was administered into the left inguinal region. In contrast, in control mice without TCS treatment, the second LLC tumours grew [36]. Additionally, bioactive components of TCMs, including cantharidin, licorice and resveratrol, have demonstrated the potential to enhance T-cell counts, improve antigen presentation, promote T-cell infiltration and boost T-cell cytotoxic activity [348–350].

In lung cancer, NK cell numbers and functionality are often impaired due to the presence of immunosuppressive cytokines from tumour cells, which hinder NK cell activation and cytotoxicity [377]. TCM formulations, such as Yu ping feng formula, have been shown to significantly suppress LLC tumour growth and prolong survival in tumour-bearing mice. This effect is achieved by enhancing NK cell infiltration into tumours, increasing NK cell populations in the spleen and strengthening NK-cell-mediated cytotoxicity. Notably, these antitumour effects of Yu ping feng formula can be reversed by treatment with the anti-NK1.1 antibody PK136 [353]. Additionally, a study by Yao et al. demonstrated that Rocaglamide (RocA), a compound derived from *Aglaia odorata* Lour., potentiates NK-cell-mediated elimination of NSCLC cells both in vitro and in vivo. Since autophagy contributes to tumour cell resistance to NK-cell-mediated killing, RocA effectively suppresses autophagy by inhibiting ULK1 translation, which restores NK-cell-derived granzyme B levels in NSCLC cells. This action enhances NK-cell-mediated killing and highlights the potential of RocA as an agent for NK-cell-based cancer immunotherapy by inhibiting autophagic immune resistance [355]. Furthermore, Tanshinone IIA (TIIA) enhances the NK-cell-mediated killing of NSCLC cells by increasing the expression of ULBP1 and DR5 on the cell surface, which are crucial ligands for activating NK cell functions, thereby increasing the susceptibility of NSCLC cells to NK-cell-mediated lysis [36].

The balance between M1 and M2 macrophages is critical for maintaining immune homeostasis. M1 macrophages, which produce pro-inflammatory cytokines and ROS to defend against pathogens and tumour cells, can trigger chronic inflammation and tissue damage if excessively activated. In contrast, excessive M2 polarization promotes immunosuppression and facilitates tumour progression. Therefore, preserving the equilibrium between M1 and M2 macrophages is crucial for optimizing anti-cancer therapies. Currently, macrophage-based immunotherapies aim to reduce the presence of M2 macrophages or reprogram them into the M1 phenotype, thereby inhibiting the spread and metastasis of lung cancer [378, 379]. TCMs also show therapeutic benefits in this regard [101, 357]. For example, Yu

Table 6 TCM modulates cancer immunology

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
T cell	Fei yan ning	12 TCMs	Lower CD4(+)/CD25(+) regulatory T cell ratio and Foxp3 mRNA expression in LLC mouse model	[347]
	Cantharidin	*Mylabris phalerata* Pallas	Decreased percentage of CD4+ Tregs and enhanced percentage of CD8+ T cells, CD4+ T effective cells in tumour infiltrating lymphocytes from mice	[348]
	Licorice extract powder	*Glycyrrhiza uralensis* Fisch. ex DC.	Increased antigen presentation and improved CD8+ T cell infiltration in NSCLC mice	[349]
	Resveratrol	*Veratrum album* L.	Activation of cytotoxic CD8 + T cells in lung squamous cell carcinoma	[350]
	Salidroside	*Rhodiola rosea* L.	Regulating tumour microenvironment of NSCLC *via* Hsp70/Stub1/Foxp3 pathway in Tregs	[351]
	Tian men dong decoction	5 TCMs	Suppression of tumour-infiltrating G-MDSCs *via* IL-1β-mediated signalling in LLC model in vivo and ex vivo	[99]
	Yi qi formula, Yang yin formula, Ruan jian jie du formula	22 TCMs	YQ exerted significant anti-tumour effects and immune regulation effects on LLC mice by relieving T cell exhaustion and regulating the immune microenvironment	[100]
	Jin fu kang	12 TCMs	Inhibition of metastasis by regulating T cell receptors in LLC mice	[352]
	Trichosanthin	*Trichosanthes kirilowii* Maxim.	-Increased population of IFN-γ-producing CD4+ and CD8+ effector T cells and stimulation of Th1-type cytokine secretion in LLC mice -Increased memory T cells in LLC mice	[36]
NK cell	Yu ping feng formula	3	Enhanced NK cell infiltration, increased NK cell populations in the spleen and strengthened NK cell-mediated cytotoxicity in LLC mice	[353]
			-Promotion of M1 macrophage polarization through increasing the STAT1 phosphorylation -Increased percentage and cytotoxicity of CD4+ T cells in LLC mice	[354]
	Rocaglamide	*Aglaia odorata* Lour.	Enhanced NK cell-derived granzyme B levels through suppression of autophagy by inhibiting ULK1 translation	[355]
	Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Enhanced NK cell-mediated killing of NSCLC cells through increasing expression of ULBP1 and DR5 on the cell surface	[356]
Macrophage	Yu ping feng	3 TCMs	-Promotion of M1 macrophage polarization through increasing the STAT1 phosphorylation -Increased percentage and cytotoxicity of CD4+ T cells in LLC mice	[354]
	Modified Bu shen yi qi formula	5 TCMs	Enhanced anti-tumour immunity by reducing the chemotactic recruitment of M2-TAMs and PMN-MDSCs in LLC mice	[101]

Table 6 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Cinobufagin	*Bufo bufo gargarizans* Cantor	Enhanced production of pro-inflammatory cytokines by M1 macrophages and reduced anti-inflammatory factors produced by M2 macrophages	[357]
	Ginsenoside Rh2	*Panax ginseng* C.A.Mey.	Converting tumour-associated macrophages from the pro-tumourigenic M2 phenotype to the anti-tumour M1 phenotype	[358]
	Sophoridine	*Sophora alopecuroides* L.	Increased expression of pro-inflammatory cytokines and the M1 surface markers CD86 through inducing macrophages M1 polarization *via* activating MAPKs signalling pathway	[359]
	Astragaloside IV	*Astragalus membranaceus* Fisch. ex Bunge	Blocking the M2 polarization of macrophages partially through the AMPK signalling pathway	[360]
	ZnF3	*Antrodia cinnamomea*	-Induction of M1 type macrophage polarization -Stimulating activation macrophage through AKT/mTOR pathway	[361]
T cell and NK cell	*Astragalus membranaceus* polysaccharides	*Astragalus membranaceus* Fisch. ex Bunge	Stimulation of NK and T cells through activation of lineage$^-$CD11c$^+$dendritic cells in the mesenteric lymph nodes in mice	[344]
T cell and MDSCs	*Ganoderma lucidum* polysaccharide	*Ganoderma lucidum* L.	-Inhibition and differentiation of immunosuppressive cells MDSCs *via* a CARD9-NF-κB-IDO pathway in both spleen and tumour tissues from an LLC mouse model -Increased CD4+ and CD8+T cells with increased production of IFN-γ and IL-12 in the spleen of LLC mouse model	[345]
Macrophage and dendritic cell	*Astragalus* polysaccharide	*Astragalus membranaceus* Fisch. ex Bunge	-Increased M1/M2 macrophage polarization ratio in vitro and in vivo -Promotion of dendritic cell maturation in NSCLC patients-derived sample ex vivo	[346]
Dendritic cell	Yang yin wen yang formula	5 TCMs	Enhanced dendritic cell maturation by activating MAPK and TLR4-NF-κB pathways	[102]
PD-1/PD-L1 pathway	Si jun zi decoction	4 TCMs	Inhibition tumour growth by reducing the expression of PD-L1 through TLR4/MyD88/NF-κB pathway in A549 cells and LLC mice	[362]
	Moracin N	*Morus alba* L.	Enhanced T cell-mediated immunity through regulating the PD-L1/PD-1 signalling pathway in A549 cells	[363]
	Bu fei decoction	6 TCMs	Inhibition of the protein and mRNA expressions of PD-L1 in vitro and in vivo	[65]
	Evodiamine	*Tetradium ruticarpum* (A.Juss.) T.G.Hartley	Decreased protein and mRNA levels of IFN-γ-induced PD-L1 in NSCLC cells	[364]

Table 6 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
	Ginsenoside Rg3	*Panax ginseng* C.A.Mey.	-Reduced PD-L1 glycosylation by EGFR signalling pathway suppression in NSCLC cells -Promotion of GSK3β-mediated degradation of PD-L1 -Promotion the activation and cytotoxicity of T cells through inhibiting PD-L1 glycosylation under coculture condition	[365]
	Gentiopicroside	*Gentiana manshurica* Kitag.	Decreased PD-L1 levels *via* inhibition of USP22 activity in lung cancer cells	[366]
	Andrographolide	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	Enhanced P62-mediated selective autophagic degradation of PD-L1 through inhibition of STAT3 phosphorylation in NSCLC cells	[367]
	Shen mai injection	2 TCMs	Enhanced NK cell infiltration, increased Granzyme A secretion by NK cells and reduced inhibitory receptors on NK and T cells in NSCLC mice when combined with a PD-1 inhibitor	[368]
	Aloperine	*Sophora alopecuroides* L.	-Boosted NK cell cytotoxicity, increased percentages of Granzyme B + NK cells and Perforin + NK cells in tumours and spleens of mice with LLC-derived subcutaneous tumours -Promotion of anti-tumour effect in these mice when combined with an anti-PD-L1/TGF-β bispecific antibody	[189]
	Tetrandrine	*Stephania tetrandra* S.Moore	Enhanced CD8+T cell infiltration and cytotoxic activity *via* STING pathway in NSCLC-bearing mice when combined with an αPD-1 monoclonal antibody	[369]
	Ginseng polysaccharides	*Panax ginseng* C.A.Mey.	-Increased populations of activated CD8 + T cells and decreased populations of Foxp3 + regulatory T cells in peripheral circulation in lung cancer mice when combined with an αPD-1 monoclonal antibody -Altered gut microbiota composition in non-responder mice toward a responder-like pattern and reinstated therapeutic response to the αPD-1 monoclonal antibody	[370]
IDO enzyme	Fei ji Recipe	9 TCMs	-Decreased the IDO protein level and the percentages of CD4+ CD25+ T-cells and Foxp3+ T-cells in a mouse LLC orthotopic transplant model -Reduced T cell apoptosis by inhibiting IDO expression and kynurenine production in the coculture system	[66]
	Atractylenolide III	*Atractylodes chinensis* Koidz.	Inhibition of IFN-γ-induced IDO expression through the Jak3/STAT3 signalling pathway in LLC mice	[371]

Table 6 (continued)

Mechanism	TCM compound/extract/formula	TCM source	Mediated pathway	Ref
Modulation gut microbiota	Kaempferol	*Kaempferia galanga* L.	Inhibition of xenograft LLC models through modulation of gut microbiota in activating immune cell function	[372]
Mitigating cisplatin-induced immunotoxicity	Isovitexin	bamboo leaves, *Tetrastigma hemsleyanum* Diels & Gilg, *Vitex trifolia* L.	Enhanced reduced immune function induced by cisplatin in A549 xenograft mouse model	[373]
	A water-soluble glucose-rich polysaccharide from *Ganoderma lucidum* (WSG)	*Ganoderma lucidum* L.	Reduced the cytotoxicity of cisplatin-induced in macrophages	[374]
	Yi qi yang yin tian sui prescription	9 TCMs	Counteracted the cisplatin-induced decrease in IL-7 levels in the bone marrow	[67]

Abbreviation: *EGFR* Epidermal growth factor receptor, *G-MDSC* Granulocytic-myeloid-derived suppressor cell, *IDO* Indoleamine-2,3-dioxygenase, *LLC* Lewis lung cancer, *MDSC* Myeloid-derived suppressor cell, *NK* Natural killer, *NSCLC* Non-small-cell lung cancer, *PD-1* Programmed cell death protein 1, *PD-L1* Programmed cell death ligand 1, *PMN-MDSC* Polymorphonuclear-myeloid-derived suppressor cell, *STAT3* Signal transducer and activator of transcription 3, *TAM* Tumour-associated macrophage, *TCM* Traditional Chinese medicine, *Treg* Regulatory T cell, *ULK1* Unc-51 like autophagy activating kinase 1

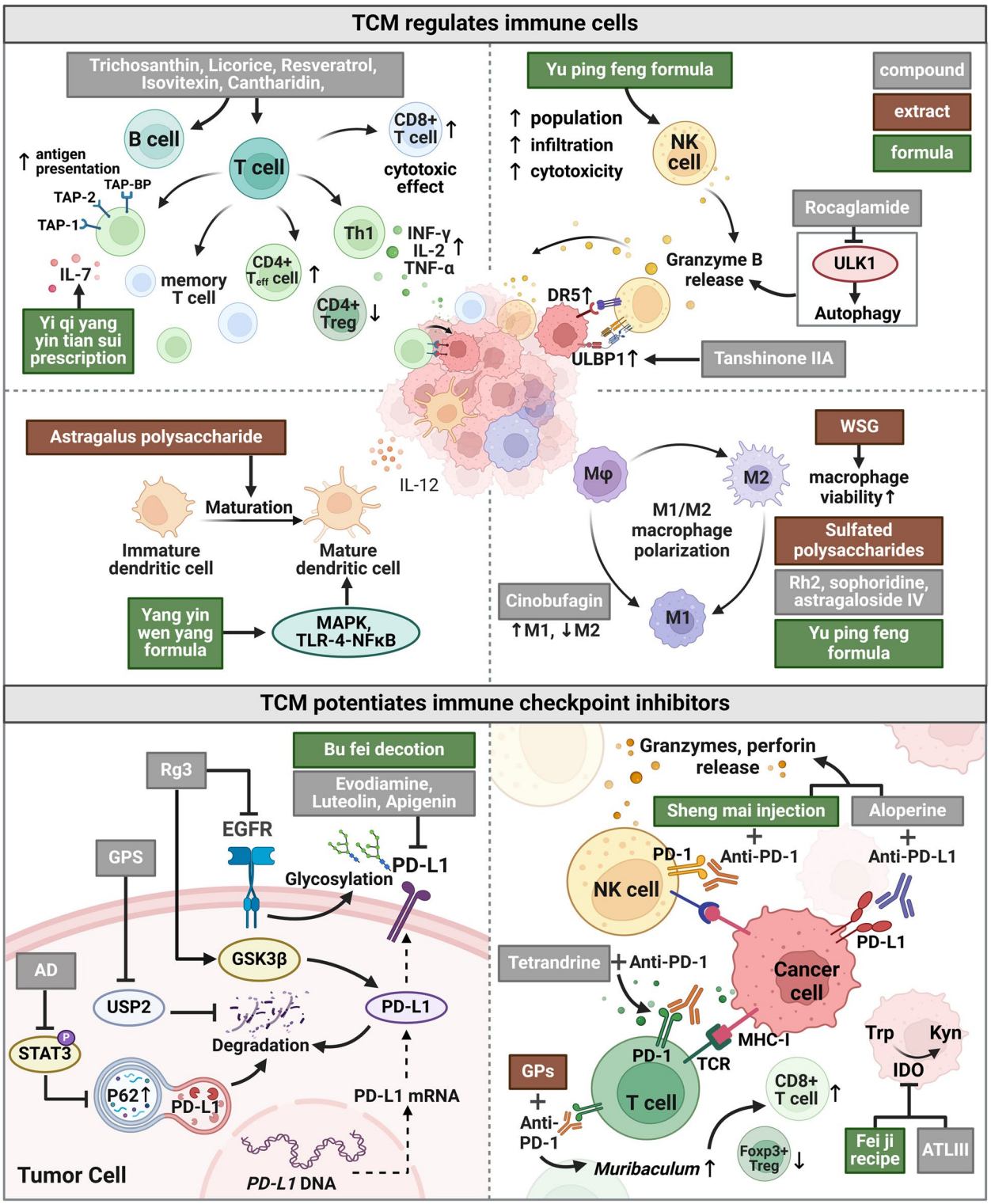

Fig. 5 TCM modulates immunology in lung cancer treatment. Combining TCM with immunotherapy could improve patient outcomes by addressing tumour-induced immune evasion and maintaining immune system balance. Key mechanisms include: **a** regulating immune cells; **b** enhancing the efficacy of immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors and IDO inhibitors; and (**c**) strengthening immune function to mitigate the adverse effects of standard cancer therapies. "↑" indicates activation, stimulation or promotion, whereas "⊥" indicates inhibition, suppression or decrease

ping feng formula significantly suppresses LLC tumour growth in a subcutaneous xenograft model and prolongs survival in tumour-bearing mice by promoting M1 macrophage polarization [354]. Cinobufagin has also been shown to enhance the production of pro-inflammatory cytokines by M1 macrophages while reducing anti-inflammatory factors produced by M2 macrophages, ultimately attenuating lung cancer cell progression and metastasis [357]. Similarly, active components from TCM, including ginsenoside Rh2 [358], sophoridine [359], astragaloside IV [360] and sulfated polysaccharides from *Antrodia cinnamomea* [361], effectively reprogram tumour-associated macrophages (TAMs) from the pro-tumourigenic M2 phenotype to the anti-tumour M1 phenotype, thereby suppressing lung cancer cell growth and migration. Besides, APS not only reprograms macrophage phenotypes, but also promotes dendritic cell maturation in NSCLC patient-derived samples ex vivo [346]. Similarly, the TCM Yang yin wen yang formula [102] enhances dendritic cell maturation by activating MAPK and TLR4-NF-κB pathways. The ability of TCM to modulate immune cells underscores its potential as an immunotherapeutic agent for lung cancer treatment, emphasizing the need for further investigations into its clinical application.

TCM potentiates immune checkpoint inhibitors

Immune checkpoints are regulatory pathways in the immune system that maintain self-tolerance and prevent excessive immune activation. However, tumours exploit these pathways to evade immune surveillance, making them key targets in cancer immunotherapy. Among these, the programmed cell death protein 1 (PD-1) pathway is one of the most extensively studied in T cells. When PD-1 binds to its ligands, PD-L1 or PD-L2, it suppresses T-cell activation and proliferation. Tumour cells often overexpress PD-L1, thereby reducing the effectiveness of T-cell-mediated anti-tumour immunity and enabling immune evasion. Inhibitors targeting PD-1, such as nivolumab and pembrolizumab, block this interaction and restore T-cell activity, enhancing the ability of the immune system to fight tumours [380, 381]. TCM has shown promise in modulating multiple immune checkpoint-related pathways, including the PD-1/PD-L1 axis and indoleamine-2,3-dioxygenase-1 (IDO) signalling. By inhibiting these pathways, TCM can strengthen the immune response against lung cancer cells, highlighting its potential as an adjunct to current immunotherapies.

Evidence suggests that TCM can decrease PD-L1 expression in lung cancer cells, thereby disrupting the PD-1/PD-L1 interaction and enhancing T cell-mediated immune responses [362, 363]. For instance, Bu fei decoction, a classical TCM formula, has been shown to inhibit both the protein and mRNA expression of PD-L1 in A549 and H1975 cells, as well as in an NSCLC xenograft model in athymic nude mice [65]. Similarly, Leung's team discovered that evodiamine (EVO), an alkaloid derived from *Euodia ruticarpa* (A.Juss.) Benth., decreases both the protein and mRNA levels of PD-L1 in NSCLC cells [364]. In addition, certain TCM compounds have demonstrated the ability to promote PD-L1 degradation in lung cancer cells, thereby significantly enhancing T cell-mediated cytotoxicity. For instance, ginsenoside Rg3 inhibits PD-L1 glycosylation by suppressing the EGFR signalling pathway, which subsequently triggers GSK3β-mediated degradation of PD-L1, leading to reduced PD-L1 expression [365]. Gentiopicroside (GPS), the main bioactive secoiridoid glycoside of *Gentiana manshurica* Kitag. decreases PD-L1 levels by inhibiting the activity of USP22, a deubiquitinating enzyme implicated in PD-L1 stabilization, in lung adenocarcinoma [366]. Moreover, Wang and colleagues revealed that ADE, the primary bioactive component of *Andrographis paniculata* (Burm.f.) Wall. ex Nees, enhances p62-mediated selective autophagic degradation of PD-L1 by binding to and downregulating STAT3 phosphorylation, effectively inhibiting NSCLC cell growth [367].

More importantly, studies have investigated the combination of these TCMs with immune checkpoint inhibitors, such as PD-L1 blockade, demonstrating synergistic anti-tumour effects. These combinations have been shown to enhance tumour growth suppression and prolong survival in lung cancer-bearing mice by augmenting the efficacy of cancer immunotherapy. For instance, single-cell RNA sequencing revealed that sheng mai injection combined with a PD-1 inhibitor enhanced NK cell infiltration, increased Granzyme A secretion by NK cells and blocked inhibitory receptors on NK and T cells, thereby improving anti-tumour efficacy and extending survival in an NSCLC mouse model [368]. Similarly, aloperine, an alkaloid isolated from *Sophora alopecuroides* L., significantly boosted NK cell cytotoxicity, increasing the percentages of Granzyme B+NK cells and Perforin+NK cells in tumours and spleens of mice with LLC-derived subcutaneous tumours. When combined with an anti-PD-L1/TGF-β bispecific antibody, aloperine markedly improved tumour growth suppression in these mice [189]. Furthermore, tetrandrine combined with an αPD-1 monoclonal antibody, synergistically enhanced CD8+T-cell infiltration and cytotoxic activity, leading to reduced tumour growth and prolonged survival in NSCLC-bearing mice [369].

Interestingly, studies revealed that TCM could activate immune cell function in lung cancer by modulating the gut microbiota [372]. For example, Huang's team identified gut microbiota as an important regulator influencing

the anti-cancer efficacy of combining TCM with anti-PD-1 immunotherapy. Their study showed that the combination of ginseng polysaccharides (GPs) and αPD-1 monoclonal antibody enhances the therapeutic response by increasing activated CD8+ T-cell populations and decreasing Foxp3+ regulatory T-cell populations in the peripheral circulation. Furthermore, this combination therapy significantly altered the gut microbiota composition in non-responder mice, shifting it toward a responder-like pattern and reinstating the therapeutic response to the αPD-1 monoclonal antibody. These findings highlight GPs as a novel class of prebiotics that could enhance the efficacy of anti-PD-1 immunotherapy in NSCLC patients [370].

Indoleamine 2,3-dioxygenase 1 (IDO1) is a key enzyme in the catabolism of tryptophan (Trp) *via* the kynurenine (Kyn) pathway and plays a critical role in inducing immune tolerance, making it an important immune checkpoint. Fei ji recipe, a classical herbal formula comprising nine Chinese herbs, suppresses lung cancer growth by inhibiting IDO expression and Kyn production, thereby reducing T-cell apoptosis in a mouse LLC orthotopic transplant model [66]. Additionally, atractylenolide III (ATLIII), derived from the rhizome of *Atractylodes chinensis* Koidz., directly binds to Jak3, inhibiting IFN-γ-induced IDO expression through the Jak3/STAT3 signalling pathway [371].

TCM improves immune function to mitigate chemotherapy-induced adverse effects

TCM complements chemotherapy in patients with lung cancer by enhancing immunity and reducing inflammation, thus playing a vital role in improving patients' QOL during treatment. For example, cisplatin significantly reduced T-cell and B-cell proliferation, IL-2 and TNF-α production and NK cell activity. However, isovitexin alone or in combination with cisplatin, notably increased these immune markers, demonstrating its ability to mitigate cisplatin-induced immunotoxicity in an A549 xenograft mouse model [373]. Additionally, cisplatin treatment reduces macrophage viability, whereas WSG from *Ganoderma lucidum* L. significantly enhances macrophage viability under cisplatin treatment [374]. Furthermore, cisplatin reduces both the protein and mRNA levels of IL-7 in the bone marrow, but Yi qi yang yin tian sui prescription effectively counters this reduction [67]. These findings suggest that TCM can alleviate chemotherapy-induced immune dysfunction, thereby mitigating its adverse effects.

Overall, TCM serves as a valuable adjunct to cancer treatment by effectively modulating immune responses. When integrated with immunotherapy, it has the potential to enhance immune function, synergistically amplify the anti-tumour effects and mitigate chemotherapy-induced adverse effects in the fight against lung cancer. Continued research into the specific immunological mechanisms underlying TCM will further elucidate its role in modern oncology.

Discussion and future perspectives

The role of TCM in lung cancer treatment is widely recognized and has been effectively integrated into standardized cancer therapies. Clinical trials and preclinical studies investigating the efficacy and underlying mechanisms of TCM in lung cancer have garnered significant attention. Although TCM is currently primarily employed as an adjuvant therapy to chemotherapy or as a maintenance treatment post-surgery [261, 273, 276, 287–291, 382–384], the ongoing discovery of its anti-tumour mechanisms is expected to broaden its clinical application [385]. Future research could focus on promising directions such as targeting tumour heterogeneity, addressing precancerous conditions, exploring the lung-intestinal axis and utilizing advanced drug delivery systems. These advancements hold the potential to enhance TCM-based therapies and pave the way for its evolution in lung cancer treatment.

Targeting tumour heterogeneity

Tumour heterogeneity, characterized by diverse cellular traits and behaviors within tumours, is a key feature of cancer that significantly impacts progression, treatment efficacy and patient outcomes. This heterogeneity encompasses genetic, phenotypic and microenvironmental variations among cancer cells, resulting in subpopulations with varying treatment sensitivities [386]. Despite its critical importance, tumour heterogeneity appears to be overlooked in lung cancer treatment. Recent studies have explored the effects of TCM on cancer stem cells (CSCs), a distinct subpopulation within tumours known for their self-renewal and differentiation abilities. CSCs play a pivotal roles in tumour initiation, metastasis and recurrence [387]. Aberrant activation of the Sonic Hedgehog (SHH) signalling pathway is a defining feature of CSCs, with proteins such as Smoothened (SMO), GLI family zinc finger 1 (GLI1) and sex determining region Y-box 2 (SOX2) being frequently hyperactivated. Several TCM-derived compounds, including β-elemene [388], chelerythrine chloride [389], curcumin [390] and As_2O_3 [391], have been demonstrated to inhibit CSC activity by targeting the SHH pathway in lung cancer. For instance, *Scutellaria barbata* D.Don extract (SBE) suppresses stemness-related characteristics of NSCLC cells by disrupting the SOX2/SMO/GLI1 axis. By directly interacting with and inhibiting SOX2, SBE effectively

downregulates the SHH cascade, reducing stemness-prone phenotypes [392]. Similarly, aberrant activation of NOTCH3 signalling promotes CSC-related stemness and is linked to NSCLC pathogenesis. EVO from *Euodia ruticarpa* (A.Juss.) Benth., significantly reduces CSC stemness by inhibiting NOTCH3 signalling. This effect is achieved through the activation of DNA methyltransferases (DNMTs), which induce NOTCH3 methylation [393]. While research on CSCs is progressing, investigations into other tumour subpopulations remain limited. For example, dormant cancer cells are in an inactive or quiescent state, avoiding proliferation but retaining the potential to reactivate. These cells are resistant to conventional chemoradiotherapy and immune evasion, contributing to cancer metastasis and recurrence. Dormant cancer cells have been identified in various cancer types, including lung cancer [394]. However, to the best of our knowledge, studies on the therapeutic efficacy of TCM in targeting dormant lung cancer cells are limited. Expanding research to include diverse tumour subpopulations and identifying the role of TCM in targeting these cells, is essential for developing more comprehensive and effective therapeutic strategies.

Addressing precancerous conditions

The concept of "treatment before disease" in TCM theory is highly valuable for promoting early intervention in lung cancer treatment. Early intervention through TCM can strengthen the body's resistance, balance internal systems and reduce the risk of tumour formation, offering a proactive strategy for cancer management, particularly for high-risk individuals. By addressing the disease before it progresses to malignancy, this approach can yield more effective results, potentially preventing tumour development and improving patient outcomes. Lung inflammation, pulmonary fibrosis and chronic lung diseases such as chronic obstructive pulmonary disease (COPD) are considered common precancerous conditions of the lung [395]. Chronic inflammation in the lungs creates a conducive environment for the emergence and proliferation of abnormal cell clones, which can evade immune surveillance and eventually progress to invasive lung carcinomas [396]. Several TCMs have demonstrated therapeutic potential in alleviating lung inflammation [397–400]. For example, *Euphorbia helioscopia* L. inhibits lung tumourigenesis in mice induced by treatment with lipopolysaccharide and the tobacco carcinogen nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by alleviating T-cell exhaustion caused by chronic inflammation. This effect is linked to the suppression of STAT3 activation and the preservation of T-cell stemness [401]. The ethanolic extract of *Tussilago farfara* L. reduces lung inflammation caused by cigarette smoke through activation of the Nrf2 pathway, inhibition of NF-κB and modulation of the NLRP3 inflammasome [402]. In addition, pulmonary fibrosis is a significant risk factor for lung cancer, with the risk being approximately eight times greater in patients with pulmonary fibrosis than in the general population [403]. Extracts of *Pseudostellaria heterophylla* (Miq.) Pax have shown protective effects against bleomycin-induced pulmonary fibrosis by regulating the STING signalling pathway [404]. Astragalus IV reverses EMT associated with the progression of pulmonary fibrosis by suppressing FOXO3a hyperphosphorylation and downregulation [405]. Furthermore, tanshinone IIA inhibits the development of pulmonary fibrosis through modulation of the Keap1/Nrf2 signalling pathway [406]. Overall, incorporating TCMs into preventive strategies that focus on health maintenance and disease preemption can provide effective approaches to address the complex challenges of lung cancer treatment.

Emphasizing on the lung-intestinal axis

The concept of "lung and large intestine interconnection" in TCM posits that the lung, one of the five "zang" organs and the large intestine, one of the six "fu" organs, share an interior-exterior relationship, wherein they mutually reinforce and influence each other. This interconnection is now explained by the fact that the intestine, home to the richest diversity of gut microbiota, shares a common embryonic origin and structural similarities with the respiratory tract. Increasing clinical and preclinical evidence has highlighted the potential of TCM in this context [372]. For example, an observational study found that Si jun zi decoction significantly increased microbial abundance and diversity, enriched probiotic microbes and regulated microbial functions in postoperative NSCLC patients [68]. Additionally, Shuang shen granules restore balance to the gut microbiota and mitigate metabolic disturbances, slowing the progression of lung metastasis [407]. Zeng sheng ping prevents lung cancer by maintaining the integrity of the intestinal barrier and restoring the balance of the intestinal microecology [70]. The future of research in this area is promising, with the potential to uncover new microbial targets for lung cancer prevention and treatment. Further studies employing advanced experimental designs, comprehensive microbial profiling and precise research models are needed to better understand the interactions between TCM and the gut microbiota. These insights could guide TCM-based drug discovery and offer novel therapeutic approaches.

Utilizing cutting-edge drug delivery systems

In recent years, the development of innovative drug delivery systems for TCM has led to significant advances, offering benefits such as enhanced biocompatibility,

targeted delivery, controlled release, increased therapeutic efficacy and minimal side effects. Among these, nanocarrier-based drug delivery systems have emerged as particularly promising [408]. For example, Chen and colleagues engineered a biotin-modified MoS2 nanosheet system, termed MoS2-PEG-Biotin-curcumin/erythrosine, for the targeted co-delivery of curcumin and erythrosine to lung cancer cells. This system demonstrated notable physiological stability, low toxicity, high biocompatibility and efficient tumour-targeting properties [409]. Similarly, Wang et al. developed Rg1 carbon nanodots, which exhibit excellent water solubility and biocompatibility and significantly inhibit proliferation, migration and induce apoptosis in NSCLC A549 cells [410]. In addition to nanocarrier systems, other cutting-edge drug delivery approaches are also being explored to enhance the effectiveness of TCM in lung cancer treatment [411–413]. For instance, glycyrrhizic acid (GA) was encapsulated in liposomes formed by blending saponin and lecithin, with platycodin and ginsenoside replacing cholesterol to form saponin liposomes (RP-lipo). This formulation, named PR-lipo@GA, retained the morphological features and drug release patterns of standard liposomes while exhibiting superior targeting of lung cancer cells and enhanced in vitro anti-tumour efficacy [414]. Another innovative system involves the use of a topotecan-loaded crosslinked cyclodextrin metal-organic framework (TPT@CL-MOF), which improves local bioavailability of topotecan (TPT), a semisynthetic derivative of camptothecin. This system provides high TPT loading capacity, sustained release, excellent protection against hydrolysis and an extended half-life. Upon intravenous administration, TPT@CL-MOF preferentially accumulated in the lungs, significantly reducing the number of metastatic lung nodules at lower doses, with no observed side effects, thus showcasing its potential as a promising therapeutic for lung cancer [415]. Collectively, these novel drug delivery systems for TCM offer multiple advantages, including enhanced efficacy, safety and patient adherence to therapeutic protocols. As research progresses, the integration of these innovative drug delivery systems with TCM holds significant promise for improving treatment outcomes in lung cancer patients.

Abbreviations

ABC	ATP-binding cassette
ADE	Andrographolide
AFFL	Alcohol-precipitated fraction of fig fruit latex
Aila	Ailanthone
ALO	Aloperine
Andro	Andrographis
APS	*Astragalus* polysaccharide
ATLIII	Atractylenolide III
BCRP	Breast cancer resistance protein
CAV-1	Caveolin-1
ceRNA	Competing endogenous RNA
CHE	Chelerythrine
COPD	Chronic obstructive pulmonary disease
CQ	Chloroquine
CSC	Cancer stem cell
CTC	Circulating tumour cell
CTR1	Copper transporter 1
CTSB	Cathepsin B
Cu^{2+}	Copper ion
DA	Dioscin-6′-O-acetate
DAMP	Danger-associated molecular pattern
DCR	Disease control rate
DFS	Disease-free survival
DHA	Dihydroartemisinin
DNMT	DNA methyltransferase
ECM	Extracellular matrix
EGCG	(−)-epigallocatechin-3-gallate
EGFR	Epidermal growth factor receptor
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EMMPRIN	Extracellular matrix metalloproteinase inducer
EMT	Epithelial-mesenchymal transition
ER	Endoplasmic reticulum
ESI	Isodeoxyelephantopin
EVO	Evodiamine
FTH1	Ferritin heavy chain 1
GA	Glycyrrhizic acid
GLI1	GLI family zinc finger 1
GLUT1	Glucose transporter 1
GNA	Gambogenic acid
GP	Ginseng polysaccharide
GPS	Gentiopicroside
GPX4	Glutathione peroxidase 4
GSH	Glutathione
HIF-1α	Hypoxia-inducible factors-1α
HK2	Hexokinase 2
HR	Hazard ratio
HRE	Hypoxia-responsive element
HSF1	Heat shock factor 1
IDO	Indoleamine-2,3-dioxygenase-1
IRE	Iron-responsive element
IRP	Iron-regulatory protein
ISO	Isoorientin
JNK	c-Jun N-terminal protein kinase
Keap1	Kelch-like ECH associated protein 1
KPS	Karnofsky Performance Status
Kyn	Kynurenine
LC3	Microtubule-associated protein 1 light chain 3
LDHA	Lactate dehydrogenase A
LLC	Lewis lung cancer
lico A	Licochalcone A
lncRNA	Long non-coding RNA
LRPPRC	Leucine-rich pentatricopeptide repeat-containing protein
MDA	Malondialdehyde
MDSC	Myeloid-derived suppressor cell
MICU3	Mitochondrial calcium uptake protein 3
miR	MicroRNA
MLKL	Mixed lineage kinase domain-like protein
MMP	Matrix metalloproteinase
mOS	Median overall survival
mPFS	Median progression-free survival
MRP	Multidrug resistance associated protein
mtDNA	Mitochondrial DNA
MTE	*Marsdenia tenacissima* extract
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NEAT1	Nuclear enriched abundant transcript 1
NK	Natural killer
Nrf2	Nuclear factor erythroid 2-related factor 2
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OST	Osthole
PD-1	Programmed cell death protein 1

PDK	Pyruvate dehydrogenase kinase
P-gp	P-glycoprotein
PKM	Pyruvate kinase M
PL-OOH	Phospholipid hydroperoxide
POL	*Polygonatum odoratum* lectin
PPI	Polyphyllin I
Pris	Pristimerin
PRR	Pattern recognition receptor
PTEN	Phosphatase and tensin homologue
QOL	Quality of life
RA	Rosmarinic acid
RCT	Randomized controlled trial
RECK	Reversion-inducing cysteine-rich protein with Kazal motifs
RocA	Rocaglamide
ROS	Reactive oxygen species
RR	Relative ratio
SA	Sappanone A
SBE	*Scutellaria barbata* D.Don extract
SCLC	Small-cell lung cancer
SFA	Sophoridine A
SHH	Sonic Hedgehog
SMO	Smoothened
SNH	Sodium new houttuyfonate
SOX2	Sex determining region Y-box 2
Sp1	Specificity protein 1
STAT3	Signal transducer and activator of transcription 3
TAM	Tumour-associated macrophage
TCM	Traditional Chinese medicine
TCS	Trichosanthin
TIMP	Tissue inhibitors of metalloproteinase
TG	Tangeretin
TGF-β1	Transforming growth factor-beta1
TIIA	Tanshinone IIA
Tim-AIII	Timosaponin AIII
TPL	Triptolide
TPT	topotecan
TPT@CL-MOF	Topotecan-loaded crosslinked cyclodextrin metal-organic framework
TRAIL	Tumour necrosis factor-related apoptosis-inducing ligand
Treg	Regulatory T cell
Trp	Tryptophan
TSA	Tanshinol A
TXNRD1	Thioredoxin reductase 1
VEGF	Vascular endothelial growth factor
WSG	Water-soluble polysaccharide from *Geranium lucidum* L.
Xan	Xanthotoxol
XPC	Xeroderma pigmentosum group C

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Authors' contributions
Z.X.: Writing - original draft, Conceptualization. R.D.: Writing - original draft, Data Curation, Funding aquisition. Y.Z.: Writing - review & editing, Visualization. X.J.: Writing - review & editing, Visualization. M.L.: Writing - review & editing, Supervision, Funding acquisition. H.X.: Supervision, Project administration, Conceptualization.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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