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Review

Traditional Chinese medicines for non-small cell lung cancer: Therapies and mechanisms

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ABSTRACT

The most common subtype of lung cancer is non-small cell lung cancer (NSCLC), which has a poor prognosis and seriously threatens the health of human beings. The multidisciplinary comprehensive treatment model has gradually become the mainstream of NSCLC treatment. Traditional Chinese medicine (TCM) can be used effectively either as an adjunctive therapy or alone throughout the NSCLC therapy, which has a significant impact on survival, quality of life, and reduction of toxicity. Therefore, this paper reviewed the theoretical basis, the latest clinical application, and combined treatment mechanisms in order to explore the advantage stage of TCM treatment and the synergistic therapeutic mechanisms.

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1. Introduction

Lung cancer has the highest fatality rate of all malignant tumors on a global scale which seriously threatens the quality of life and health of human beings (Siegel, Miller, Fuchs, & Jemal, 2022; Sung et al., 2021). About 85% of all new cases of lung cancer are non-small cell lung cancer (NSCLC) (Duma, Santana-Davila, & Molina, 2019). Due to the lack of effective early screening methods, most NSCLC patients are diagnosed at an advanced stage, and the 5-year survival rate for distant tumors is only 5% (Cronin et al., 2022). Targeted therapy and immunotherapy have significantly improved the survival in selected NSCLC patients, but their accessibility and effectiveness remain limited (Herbst, Morgensztern, & Boshoff, 2018). Therefore, a multidisciplinary comprehensive mode for the treatment of NSCLC is required to expand the clinical benefit.

Traditional Chinese medicine (TCM) has followed the individualized precision therapy concept for more than 2000 years. Rather than only being used at the terminal stage of NSCLC, TCM can be used effectively as a complementary therapy or alone throughout the NSCLC therapy (Xiang, Guo, Zhu, Chen, & Huang, 2019). TCM has a significant impact on improving the quality of life (QOL), reducing drug toxicity, preventing metastasis and recurrence, enhancing the efficacy of radiotherapy and chemotherapy, and prolonging the survival of tumor patients with the depth of modern medical research (Zhang, Zhang, & Li, 2021; Zhang, Liu, Jiang, & Mao, 2018). TCM-derived compound has a potential to be developed as a therapeutic candidate for lung cancer (Li, Liu, Yang, & Tian, 2022). Due to cultural differences, geographical limitations, and a lack of support for evidence-based clinical trials, TCM only serves patients in a small number of countries and regions around the world, so we urgently need to fully explore the TCM's potential role in treating NSCLC. This paper summarized the clinical role of TCM in each stage of NSCLC to explore the advantageous stage of TCM treatment. By reviewing the mechanism of "reducing toxicity and increasing efficiency" in the combined treatment of TCM, we provided evidence for the synergistic therapeutic mechanisms and development of more effective anti-cancer drugs.

2. TCM theory in NSCLC

TCM theory is based on classical knowledge that dates back several thousand years, along with plenty of clinical experience, which focuses on the macroscopic and external phenomena and emphasizes that the body is an organic whole. Pathological changes in the internal organs of the body can be observed through external symptoms (Wang, Long, & Wu, 2018). In TCM, lung cancer is classified as "lung accumulation, lung carbuncle, lung distension, chest pain" (Liu et al., 2022). As described in *The Yellow Emperor's Inner Canon*, a classic Chinese medicine book, lung cancer is caused by both internal (emotional disorders and poor diet) and external (exopathogens and environment) factors, and these pathogenic factors impair organ function and cause stasis of *qi*, blood, dampness, phlegm, leading to an accumulation of 'toxins'. After these long-lasting malfunctions, they may cause significant inflammation and eventually lead to cancer (Liu, Wang, Zhang, Fan, & Lin, 2015). The theory of TCM in NSCLC is an individualized treatment program based on the holistic concept and syndrome differentiation. Treatment aims to counterbalance these factors by "Fuzheng" which means strengthening the body's resistance and immunity and "Quxie" which means eliminating pathogenic factors. TCM has different purposes and methods in each stage of the treatment of NSCLC, such as supplementing *qi* and regenerating blood during chemotherapy, supplementing *qi* and nourishing *yin* during radiotherapy, resolving stasis and dispersing masses after radiochemotherapy, and so on (Liu et al., 2017; Qi et al., 2015), and TCM is often used in combination with modern medicine to play a better synergistic action and clinical efficacy.

3. Clinical applications

3.1. TCM and perioperative treatment

For resectable NSCLC, surgery is the main method and the 5-year overall survival (OS) is close to 70% (Lee, Lee, & Park, 2018). Therefore, preventing postoperative recurrence and metastasis, prolonging survival, reducing perioperative complications, and improving patients' quality of life are important goals of perioperative adjuvant therapy.

A multicenter, prospective, cohort study showed that in both stage II-IIIA NSCLC postoperative patients, TCM therapy acted as a preventative measure against cancer recurrence and metastasis (Wang et al., 2019). Zhang et al. found that TCM had better 1-, 2-, and 3-year disease-free survival (DFS, 99.1%, 97.0% and 93.7% *vs* 97.6%, 91.7% and 87.5%), demonstrating that the use of decotion could greatly lower the rate of postoperative recurrence (Zhang et al., 2021). A clinical study randomly divided 80 postoperative NSCLC patients into TCM combined treatment group and chemotherapy group. Yiqi Yangxue Decoction consists of nine herbs such as *Codonopsis Radix* (Dangshen in Chinese), *Angelicae Sinensis Radix* (Danggui in Chinese), *Paeoniae Radix Alba* (Baishao in Chinese), *Astragali Radix* (Huangqi in Chinese), *Spatholobi Caulis* (Jixueteng in Chinese), *Chuanxiong Rhizoma* (Chuanxiong in Chinese),*Citri Reticulatae Pericarpium Viride* (Qingpi in Chinese), *Citri Reticulatae Pericarpium* (Chenpi in Chinese), and *Glycyrrhizae Radix* et *Rhizoma* (Gancao in Chinese). The combination of Yiqi Yangxue Decoction can effectively promote rapid postoperative recovery in patients with NSCLC (Liang, Wang, Zheng, & Mei, 2022). A systematic review evaluating TCM combined with chemotherapy for the prevention of postoperative recurrence and metastasis in II-IIIA NSCLC is underway (Chen et al., 2019), and we expect higher-quality evidence.

TCM can reduce the complications of perioperative NSCLC patients, such as the risk of venous thromboembolism and chronic pain. The Chinese patent medicine Huisheng Oral Solution (HSOS) was prepared via extracting *Chuanxiong Rhizoma, Carthami Flos* (Honghua in Chinese), *Hirudo* (Shuizhi in Chinese), *Acori Tatarinowii Rhizoma* (Shichangpu in Chinese), and *Trogopterus Dung* (Wulingzhi in Chinese). A clinical trial showed that HSOS has a good short-term anticoagulant effect in patients during the perioperative period, which is a good safety profile and has a lower risk of bleeding compared to aspirin (Yang et al., 2017). Electroacupuncture can significantly reduce lung-related complications, and the mechanism may be related to regulating inflammation and reducing plasma levels of pro-inflammatory factors (Liu et al., 2016). TCM administration routes are diversified and combined with the syndrome differentiation and treatment of patients. Whether acupuncture, transcutaneous electrical acupoint stimulation, or oral and intravenous application of TCM, they both can reduce surgery-related complications, the recurrence and metastasis of the postoperative stage (Li et al., 2017; Tu et al., 2018).

3.2. TCM and first-line treatment of advanced NSCLC

The first-line treatment of advanced NSCLC includes chemotherapy, immunotherapy, gene-targeted therapy, vascular-targeted therapy, and combination therapy (Chen et al., 2020; Low, Walsh, Ang, Chan, & Soo, 2019). In recent years, the

combination therapy of TCM works synergistically and plays an important role in enhancing curative effects, reducing side effects, and overcoming drug resistance (Hu, Sun, Lau, Zhao, & Su, 2016; Xiang, Guo, Zhu, Chen, & Huang, 2019).

Various TCM injections combined with paclitaxel, platinum, vinca alkaloids, or gemcitabine chemotherapeutic drugs have achieved great results in synergy and toxicity reduction (Li, Zhu, Liu, Xu, & Li, 2022; Li et al., 2021; Ni et al., 2020). A number of systematic reviews have found that Kanglaite Injection (*Coicis Semen*, Yiyiren in Chinese), Kangai Injection [*Astragali Radix, Ginseng Radix* et *Rhizoma* (Renshen in Chinese), and *Sophorae Flavescentis Radix*, Kushen in Chinese], Kushen Injection [*Sophorae Flavescentis Radix* and *Smilacis Glabrae Rhizoma* (Tufuling in Chinese)], Javanica Oil Emulsion Injection (*Bruceae Fructus*, Yadanzi in Chinese), Aidi Injection [*Mylabris* (Banmao in Chinese), *Astragali Radix, Ginseng Radix* et *Rhizoma*, and *Acanthopanacis Senticosi Radix* et *Rhizoma Seu Caulis* (Ciwujia in Chinese)], and Xiaoaiping Injection (*Marsdeniae Tenacissimae Caulis*, Tongguanteng in Chinese) have been shown to play a synergistic effect. The synergistic effect of TCM injections with chemotherapy is now introduced as follows (Table 1).

For advanced NSCLC patients with gene mutation, Zhang et al. systematically reviewed 64 randomized controlled trials with 4384 patients. The results found that the combination therapy showed some value in prolonging the progress free surviva (PFS), improving the percentage of T lymphocytes, and overcoming drug resistance (Zhang, Liu, Jiang, & Mao, 2018). A total of 91 NSCLC patients with EGFR mutation were divided into control group (n = 30) and experimental group (n = 61). For 1988 NSCLC patients with epidermal growth factor receptor (EGFR) mutations, a cohort study showed that the OS and progression-free survival (PFS) can be significantly prolonged in the TCM adjuvant treatment group compared with the simple targeted drug treatment group, which are 18.7 *vs* 13.9 months and 12.5 *vs* 8.3 months (Li et al., 2019). The experimental group received EGFR-TKIs plus TCM. The result showed that the combined therapy had a certain effect to prolong mPFS (12.3 *vs* 8.9 months, P < 0.05) and mOS (28.2 *vs* 24.2 months, P < 0.05), especially for the patients with exon 21 deletion mutation (L858R) (Wang et al., 2021). At the same time, TCM could delay EGFR-tyrosine kinase inhibitors (EGFR-TKIs) related skin toxicity of any grade and reduce the incidence of grade 3 skin toxicity (Li et al., 2022).

Immunotherapy is now at the forefront of oncogenic driver negative NSCLC treatment. The Food and Drug Administration has approved Palivizumab, Nivolumab, and Atezolizumab as first-line treatment for advanced NSCLC (Reck, Remon, & Hellmann, 2022). Current studies have shown that TCM can improve the immune response of patients with NSCLC, increase cerebrospinal fluid and interleukin-2 levels, reduce tumor necrosis factor, and maintain their anti-tumor immune function (Zhang, Guan, Wang, & Li, 2018; Zhao et al., 2020). However, there are few studies on TCM combined with immunotherapy in advanced first-line NSCLC. It is necessary to further explore its efficacy and potential molecular biological mechanism.

3.3. TCM and maintenance treatment of advanced NSCLC

Maintenance treatment originated from Goldie and Goldman's hypothesis (Liao et al., 2017) and was recommended by National Comprehensive Cancer Network (NCCN) guidelines of NSCLC in 2009. Patients with advanced NSCLC receive maintenance therapy if there has not been tumor progression after 4–6 cycles of first-line therapy. TCM is used throughout the conventional therapeutic procedure and recommended as one of the maintenance regimens for advanced NSCLC (Xu et al., 2014). A multicenter, randomized, double-blind trial showed that maintenance chemotherapy with

Table 1
Meta-analysis results of TCM injections combined with chemotherapy in advanced NSCLC.

Participants		Inventions		Outcome	Effect estimate (RR)	P	Adverse drug reactions	Effect estimate (RR)	P	References
Treatment	Control	Treatments	Control							
1670	1602	Kushen Injection + PBC	PBC	ORR	1.30 [1.20, 1.40]	<0.00001	Severe toxicities	0.42 [0.37, 0.49]	<0.00001	Chen et al., 2020
793	781	Xiaoaiping Injection + PBC	PBC	ORR	1.27 [1.14, 1.40]	<0.00001	Leukopenia	0.49 [0.38, 0.64]	<0.00001	Feng et al., 2020
							Anemia	0.63 [0.46, 0.87]	0.004	
							Thrombocytopenia	0.53 [0.38, 0.73]	0.0001	
							Nausea and vomiting	0.57 [0.36, 0.90]	0.02	
2110	1971	Aidi Injection + PBC	PBC	ORR	1.26 [1.26, 1.36]	<0.00001	Severe toxicities	0.64 [0.58, 0.70]	<0.00001	Wang et al., 2018
1422	1415	Aidi Injection + DBC	DBC	ORR	1.30 [1.19, 1.42]	<0.00001	Neutropenia	0.70 [0.61, 0.79]	<0.00001	Xiao et al., 2018
							Trombocytopenia	0.63 [0.53, 0.75]	<0.00001	
							Gastrointestinal toxicity	0.76 [0.65, 0.89]	0.0006	
1122	1112	*Brucea javanica* oil emulsion + PBC	PBC	ORR	1.25 [1.14, 1.36]	<0.00001	Nausea and vomiting	0.67 [0.46, 0.98]	0.04	Xu et al., 2016
							Leukopenia	0.63 [0.52, 0.75]	<0.00001	
							Thrombocytopenia	0.78 [0.49, 1.23]	0.29	
1291	1286	Kanglaite Injection + PBC	PBC	ORR	1.41 [1.28, 1.56]	<0.00001	Nausea and vomiting	0.58 [0.42, 0.81]	0.001	Li et al., 2020
							Leukopenia	0.61 [0.44, 0.86]	0.004	
1128	1115	Kanglaite Injection + PBC	PBC	ORR	1.45[1.31, 1.60]	<0.00001	Severe toxicities	0.41 [0.33, 0.51]	<0.00001	Huang et al., 2020
1328	1290	Kangai Injection + PBC	PBC	ORR	1.36 [1.25, 1.49]	<0.00001	Gastrointestinal reactions	0.64 [0.54, 0.77]	<0.00001	Li et al., 2019
							Leukopenia	0.54 [0.46, 0.63]	<0.00001	
							Hemoglobin deficiency	0.52 [0.36, 0.76]	0.0007	
							Thrombocytopenia	0.65 [0.34, 1.24]	0.19	

Note: PBC: platinum-based chemotherapy; DBC: docetaxel-based chemotherapy; ORR: objective response rate; RR: relative risk.

TCM Formulas can prolong the PFS (HR = 0.55, P = 0.019) compared with the control group after first-line chemotherapy (Wang et al., 2018). Han et al. found that Chinese herbal medicine is well tolerated as maintenance therapy and may improve patients' QOL (Han et al., 2016). And several other randomized controlled studies (Jiang et al., 2016; Wang et al., 2017) showed similar PFS and therapy on time to progression (TTP) in the TCM and chemotherapy groups.

Toxicity is the main reason why patients with nonprogressive diseases refuse to maintain chemotherapy. Symptom burdens could also discontinue maintenance chemotherapy (Sztankay et al., 2017). On one hand, tonifying herbal medicine increases the number of T-lymphocyte subtypes and natural killer cells, boosting the human body's immunity to tumor cells (Liu et al., 2021). TCM formulas, on the other hand, have demonstrated anti-tumor effects *in vivo* or *in vitro* (Fan et al., 2020). In the management of NSCLC, the two aspects are frequently combined. Although TCM has not shown a great breakthrough in the non-small cell maintenance treatment stage, TCM can keep the body in balance to achieve a favorable living state (Xu et al., 2014). We believe that maintenance plus TCM therapy is a more feasible regimen.

In the perioperative treatment stage, TCM treatment has been proven to alleviate postoperative adverse reactions, and reduce the postoperative recurrence. In the advanced stage, TCM combined treatment works synergistically in prolonging survival, improving patients' quality of life, decreasing adverse reactions, and ensuring the continuation of maintenance therapy. However, the quality of clinical research is generally low and the sample size is small, which cannot reflect the curative effect of the TCM. We hope that the existing research can provide ideas for the transformation of high-quality evidence in the future.

4. Mechanism research

4.1. TCM combined with chemotherapy

Platinum-based drug resistance and cytotoxicity affect the efficacy of chemotherapy for NSCLC patients. TCM and chemotherapy act a synergistic role in increasing chemotherapy sensitivity and reducing toxic and side effects. The main mechanisms include synergistic enhancement of chemotherapy efficacy and overcoming drug resistance. These studies explored the potential mechanisms of TCM combined with chemotherapy in NSCLC (Table 2).

The synergistic effect of Chinese herbal medicine Feiyanning Granules combined with cisplatin (DDP) was that Feiyanning Granules inhibited protective autophagy induced by DDP in A549 cells (Zheng et al., 2021). Through the reciprocal interaction of PVT1 and miR181a-5p expression, Xiaoji Decoction improved the anti-cancer effect of DDP in NSCLC cells (Wu et al., 2020). Ke et al. found that the addition of Yi-qi-yang-yin-tian-sui Decoction to the DDP treatment could promote the apoptosis of tumor cells and reduce myelosuppression via up-regulating IL-7 (Ke et al., 2019). Danggui Buxue Decoction is a potential deoxycytidine kinase promoter that sensitizes the response of NSCLC patients to Gemcitabine (Sun et al., 2019).

In overcoming drug resistance, Yu Ping Feng San reversed drug resistance of DDP by elevating intracellular cisplatin in lung cancer cells (Du et al., 2021). In cisplatin-resistant A549/DDP cells, Shenmai Injection could enhance the cisplatin cytotoxicity via the AKT/mTOR/c-Myc pathway (Sun et al., 2020). Ophiopogonin B, extracted from Chinese herbal medicine *Ophiopogonis Radix* (Maidong in Chinese), induced cisplatin-resistant A549 cells pyroptosis via Caspase-1/GSDMD pyroptosis pathway (Cheng et al., 2022).

Table 2
Pharmacological effects of TCMs combined with chemotherapy in NSCLC.

TCM prescriptions	Medicinal materials contained	Chemotherapy	Cell lines	Effects	Mechanisms	References
Danggui Buxue Decoction	*Astragali Radix, Angelicae Sinensis Radix*	Gemcitabine	Human NSCLC A549 cells	Inhibit tumor growth	Regulate deoxycytidine kinase and P-glycoprotein	Sun et al., 2019
Qiyusanlong Decoction	*Astragali Radix, Polygonati Odorati Rhizoma, Scolopendra, Sclerotium Difflusum, Solanum Nigrum, Coicis Semen, Euphorbia Helioscopi, Curcumae Rhizoma, Fritillariae Cirrhosae Bulbus*	Cisplatin	Human NSCLC A549 cells	Repress lung tumor development	Regulate Wnt/β-catenin pathway	Tong et al., 2018
Shenmai Injection	*Ginseng Radix* et *Rhizoma Rubra, Ophiopogonis Radix*	Cisplatin	Cisplatin-Resistant A549/DDP cells	Enhance cisplatin cytotoxicity	Regulate AKTmTOR-c-Myc pathway	Sun et al., 2020
Yu Ping Feng San	*Astragali Radix, Atractylodis Macrocephalae Rhizoma, Saposhnikoviae Radix*	Cisplatin	Cisplatin-Resistant A549/DDP cells	Reverse drug resistance of cisplatin	Regulate ATP-binding cassette transporter and glutathione S-transferase	Du et al., 2021
Yiqi Yangyin Tiansui Decoction	*Cervi Cornus Colla, Turtle Shell, Panacis Quinquefolii Radix, Lycii Fructus, Asini Corii Colla, Ginseng Radix* et *Rhizoma, Astragali Radix, Angelicae Sinensis Radix, Notoginseng Radix* et *Rhizoma*	Cisplatin	Human NSCLC A549 cells	Inhibit tumor growth and reduce the chemotherapy-induced myelosuppression	Induce expressions of IL-7 and hematopoietic growth factors	Ke et al., 2019
Feiyanning Granules	*Astragali Radix, Ganoderma, Polygonati Rhizoma, Ligustri Lucidi Fructus, Atractylodis Macrocephalae Rhizoma, Corni Fructus, Paridis Rhizoma, Cremastrae Pseudobulbus Pleiones Pseudobulbus, Epimedii Folium*	Cisplatin	Human NSCLC A549 cells	Inhibit the protective autophagy induced by cisplatin	Decrease of autophagosome formation, lysosomalfusion, LC3B-II accumulation and SQSTM1 degradation	Zheng et al., 2021
Xiaoji Decoction	*Psoraleae Fructus, Astragali Radix, Coriolus, Scolopendra, Curcumae Longae Rhizoma, Rhei Radix Et Rhizoma*	Cisplatin	Human NSCLC A549 and H1975 cells	Inhibit tumor growth and induce a high magnitude of apoptosis	Decrease lncRNA PVT1 and increase miR181a-5p expressions	Wu et al., 2020

4.2. TCM combined with targeted therapy

Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI has become the first-line treatment due to its advantages of high specificity and low cytotoxicity in advanced NSCLC patients with EGFR mutations. First - and second-generation EGFR TKIs, including Gefitinib, Erlotinib, Icotinib, and Afatinib, produced a strong and relatively durable response in most lung cancer patients. However, 20%–40% of patients develop primary resistance (Wu & Shih, 2018). Furthermore, the adverse effects of EGFR-TKIs have an impact on patient's quality of life. EGFR-TKI-based combination regimens may be more advantageous.

TCM formulas Huanglian Jiedu Decoction (HJD) composes of *Gardeniae Fructus* (Zhizi in Chinese), *Scutellariae Radix* (Huangqin in Chinese), *Coptidis Rhizoma* (Huanglian in Chinese), and *Phellodendri Chinensis Cortex* (Huangbo in Chinese). HJD and Erlotinib inhibited tumor growth in Erlotinib-resistant xenografts, and Erlotinib resistance was alleviated via the STAT3/Bcl-2 signaling pathway (Zhou et al., 2021). Yangyin Jiedu Decoction (YYJDD) consists of *Glehniae Radix* (Gouqizi in Chinese), *Ophiopogonis Radix*, *Lilii Bulbus* (Baihe in Chinese), *Dendrobii Caulis* (Shihu in Chinese), *Citri Reticulatae Pericarpium* and *Codonopsis Radix*. YYJDD has the potential to overcome Gefitinib resistance via the PI3K/Akt pathway (Chen, Zhang, & Shu, 2021). TCM combination therapy may become a promising strategy for overcoming the resistance to EGFR-TKIs. With the cooling-heat TCM treatment principle, Yu et al. found that Tanreqing Injection [*Scutellariae Radix* (Huangqin in Chinese), *Saigae Tataricae Cornu* (Lingyangjiao in Chinese), *Lonicerae Japonicae Flos* (Jinyinhua in Chinese), and *Forsythiae Fructus* (Lianqiao in Chinese)] increased the efficacy of Gefitinib in the resistant NSCLC models. Warming-*yang* drug Shenfu Injection [*Codonopsis Radix* and *Aconiti Lateralis Radix Praeparata* (Fuzi in Chinese)], on the other hand, should be avoided (Yu et al., 2021).

In adverse reactions, Hu et al. used network pharmacology to explore the core TCMs for EGFR-TKI-associated diarrhea, which included *Corydalis Rhizoma* (Yanhusuo in Chinese), *Glycyrrhizae Radix* et *Rhizoma*, *Salviae Miltiorrhizae Radix* et *Rhizoma* (Danshen in Chinese), and *Euodiae Fructus* (Hu et al., 2021). The research provided data to support clinical studies on the use of TCM in the future.

4.3. TCM combined with immunotherapy

Despite some success with immunotherapy in NSCLC, only 30% of patients may benefit from immune checkpoint inhibitor therapy (Li et al., 2019). The study found that evodiamine is suitable for NSCLC patients in combination with immunotherapy, which can inhibit NSCLC by down-regulating the MUC1-C/PD-L1 axis (Jiang et al., 2020). Huang et al. found that ginseng polysaccharides (GPs) combined with αPD-1 monoclonal antibody may be a new strategy for making immunotherapy more effective. GPs enhanced CD8+ T cell function and reduced the suppressive effect of T regs to potentiate the antitumour effect of αPD-1 mAb (Huang et al., 2022). Apigenin and luteolin significantly inhibited lung cancer through KRAS mutant proliferation, and downregulated IFN-γ-induced PD-L1 expression (Jiang et al., 2021).

More and more clinical studies have demonstrated that immune checkpoint inhibitors in combination with other treatments can produce greater anti-tumor activity than monotherapy. Anti-angiogenic therapy and immunotherapy form a positive feedback loop, which helps to improve immunotherapy outcomes (Huinen, Huijbers, Van Beijnum, Nowak-Sliwinska, & Griffioen, 2021). A variety of Chinese herbs have been proved to normalize blood vessels (Tang et al., 2019; Zhou et al., 2021) and are expected to be a new immunotherapy regimen. It is worth further exploration and discussion to find the entry point of immunotherapy and how to play a synergistic therapeutic effect.

5. Conclusion

In this review, we document that TCM plays an important role in the perioperative stage and advanced stage of NSCLC. Combination therapy works primarily by increasing drug efficacy, overcoming drug resistance, reducing adverse drug effects, and enhancing patients' confidence during the whole course of treatment. At present, syndrome differentiation and holistic concept are still the main methods of TCM. We should continue to conduct in-depth research on the molecular biological mechanism of TCM, and carry out the multicenter, large sample, double-blind, randomized controlled trials to prove the high quality of clinical evidence. These findings may help future researchers investigate TCM's synergistic therapeutic mechanism and develop more effective anti-cancer drugs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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