



Research Status and Molecular Mechanism of the Traditional Chinese Medicine and Antitumor Therapy Combined Strategy Based on Tumor Microenvironment

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Treatment of malignant tumors encompasses multidisciplinary comprehensive diagnosis and treatment and reasonable combination and arrangement of multidisciplinary treatment, which is not a simple superimposition of multiple treatment methods, but a comprehensive consideration of the characteristics and specific conditions of the patients and the tumor. The mechanism of tumor elimination by restoring the body's immune ability is consistent with the concept of "nourishing positive accumulation and eliminating cancer by itself" in traditional Chinese medicine (TCM). The formation and dynamic changes in the tumor microenvironment (TME) involve many different types of cells and multiple signaling pathways. Those changes are similar to the multitarget and bidirectional regulation of immunity by TCM. Discussing the relationship and mutual influence of TCM and antitumor therapy on the TME is a current research hotspot. TCM has been applied in the treatment of more than 70% of cancer patients in China. Data have shown that TCM can significantly enhance the sensitivity to chemotherapeutic drugs, enhance tumor-suppressing effects, and significantly improve cancer-related fatigue, bone marrow suppression, and other adverse reactions. TCM treatments include the application of Chinese medicine monomers, extracts, classic traditional compound prescriptions, listed compound drugs, self-made compound prescriptions, as well as acupuncture and moxibustion. Studies have shown that the TCM functional mechanism related to the positive regulation of cytotoxic T cells, natural killer cells, dendritic cells, and interleukin-12, while negatively regulating of regulatory T cells, tumor-associated macrophages, myeloid-derived suppressive cells, PD-1/PD-L1, and other immune regulatory factors. However, the application of TCM in cancer therapy needs further study and confirmation. This article summarizes the existing research on the molecular mechanism of TCM regulation of the TME and provides a theoretical basis for further screening of the predominant population.

Moreover, it predicts the effects of the combination of TCM and antitumor therapy and proposes further developments in clinical practice to optimize the combined strategy.

Keywords: traditional Chinese medicine, cancer, immune ability, anti-tumor therapy, tumor microenvironment

INTRODUCTION

Cancer is one of the major noncommunicable chronic diseases that seriously affect human health (1–3). Although treatment methods and drug research and development continue to improve, many problems such as drug resistance and recurrence still hinder progress (4–9). The treatment of malignant tumors encompasses multidisciplinary comprehensive diagnosis and treatment (10–12) and reasonable combination and arrangement of multiple treatment methods including surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, endocrine therapy, interventional therapy (13–19). Multidisciplinary treatment is not a simple superimposition of multiple treatment methods, but a comprehensive consideration of the characteristics and specific conditions of the patients and the tumor, leading to a planned and reasonable choice (20). While pursuing prolonged survival (21), attention should also be given to improving the quality of life of the patients (22).

Due to its huge population, China accounts for about a quarter of the world's new tumors and deaths, leading to a serious disease burden (23–25). Traditional Chinese medicine (TCM) is a unique diagnosis and treatment method with thousands of years of history (26, 27). It is reported that most Chinese cancer patients have used TCM during the diagnosis and treatment process (28, 29). TCM is mostly used in the form of compound prescriptions in clinical oncology, including oral herbal medicines, granules or capsules, and injections (30). There are many pieces of research on Chinese medicine monomers and their active ingredients (31). Many researches have shown that TCM combined with antitumor therapy can achieve significant tumor suppression effects, reduce drug resistance, and improve adverse reactions and patient quality of life (32–36). In recent years, targeting the immune checkpoints CTLA-4, PD-1, and PD-L1 has led to breakthroughs in a variety of cancer types (37–39). The mechanism of tumor eradication by restoring the body's immune ability is consistent with the concept of “nourishing positive accumulation and eliminating cancer by itself” or “strengthening vital Qi to treat cancer” in TCM (40, 41).

Abbreviations: Non-small cell lung cancer, NSCLC; Chemotherapy, CT; Traditional Chinese medicine, TCM; Disease control rate, DCR; Interleukin 2, IL-2; Interleukin 10, IL-10; Interferon- γ , IFN- γ ; Gemcitabine, G; Matrix metalloprotein-2, MMP-2; Matrix metalloprotein-9, MMP-9; Natural killer cells, NK; Tumor necrosis factor α , TNF- α ; High sensitivity C-reactive protein, hs-CRP; Vascular endothelial growth factor, VEGF; Gemcitabine & cisplatin, GP; Paclitaxel & cisplatin, TP; Transforming growth factor β 1, TGF- β 1; Fluorouracil & Oxaliplatin & calcium folinate, FOLFOX; Doxorubicin, DOX; Hypoxia inducible factor-1 α , HIF-1 α ; Monocyte chemoattractant protein-1, MCP-1; Myeloid suppressor cells, MDSCs; Insulin-like growth factor-2, IGF-2; Fluorouracil & adriamycin & chloramphenicol, FAP; Cisplatin, DDP; Paclitaxel & cyclophosphamide, TC; Methotrexate & actinomycete D & calcium folinate & vincristine sulfate & cyclophosphamide, EMA-CO; Paclitaxel & gemcitabine, GT; Cisplatin & docetaxel, DC; Gemcitabine & Cisplatin, GP.

The tumor microenvironment (TME) (42, 43) is formed by the structural components such as tumor cells, endothelial cells, fibroblasts, immune cells, extracellular matrix, and secreted cytokines. It has three main roles: inhibiting the immune response, promoting angiogenesis, and growing cancer stem cells. Chronic inflammation (44, 45) and immunosuppression (46, 47) are the core features of the TME. Chronic inflammation leads to low oxygen levels, low pH, high pressure in the microenvironment, and the prolonged existence of inflammatory factors such as tumor necrosis factor (TNF) that maintain and continuously aggravate the inflammatory features of the TME. The hypoxic microenvironment increases hypoxia inducible factor (HIF) levels, induces the formation of new blood vessels, modifies the vascular endothelial growth factor (VEGF), and recruits bone marrow-derived endothelial progenitor cells to form new blood vessels. The TME enables a large number of regulatory T cells (Tregs) that penetrate and accumulate in tumor tissues, inhibit the differentiation and maturation of effector cells such as lymphocytes, macrophages, dendritic cells (DC), and isolate them from tumor tissues to inhibit immune responses. The immunosuppressive microenvironment is closely related to the “deficiency of vital Qi” in Chinese medicine (48). The “syndrome” of TCM involves multiple systems and levels of Western medicine. TCM treatment of cancer pays attention to overall regulation whether it is to strengthen the body (Fu Zheng) or eliminate evil (Qu Xie). Its advantage lies in regulating the tumor-host microenvironment, allowing normal immune cells to perform their duties, so that there is no environment for tumor cells to survive, and causing apoptosis or autophagy (49–51).

In this review, we mainly discuss, from the perspective of TME regulation, the studies on the combined application of TCM and anticancer treatments. Further screening of dominant populations and predictors will help optimize the joint strategy and provide a theoretical basis for clinical practice.

TCM COMBINED WITH CHEMOTHERAPY

Chemotherapy is still the cornerstone of anticancer therapy. As one of the most important treatments for advanced stage cancer, chemotherapy compatibility ensures the correct combination of chemotherapeutic drugs and the combination of chemotherapy and other types of treatment. There are many clinical and preclinical studies on the combination of TCM treatment and chemotherapy.

The clinical studies on TCM combined with chemotherapy for anticancer treatment research have been mainly published in Chinese journals (Table 1). The studied cancer types include lung cancer (52–58), digestive system cancer (gastric/liver/esophageal cancer) (59–63), gynecological cancer (ovarian

TABLE 1 | Influence of traditional Chinese medicine (TCM) Combined Chemotherapy (CT) on tumor microenvironment (TME)-Clinical Study.

Cancers	Formulation	Herbal medicine	Group and Number of cases	Effect of Combination	Upregulate	Downregulate	Refs.
Lung Cancer							
NSCLC	Compound (Classic, oral)	Baihe Gujin Decoction (Rehmannia, Rehmannia, Carlo, album AGLAOPHOTIS, liliun, Fritillaria, Ophiopogon, Bellflower, Scrophulariaceae, rudis Licoricia)	TCM + DC vs DC = 48	DCR 89.6% vs 72.9% (p<0.05)	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , IL-2, and INF- γ	CD8 ⁺ , IL-4, IL-10	He and Huang (52)
NSCLC	Compound (Self-made, oral)	Bushen Yifei Jiedu Decoction (Xianling lienis contegentem membranam, Ligustrum lucidum, Ganoderma lucidum, Cruda Astragalus, Radix Angelicae Ginseng, Pinellia, Atractylodes, Germen Stone, aesculus aesculus, Shansi Fungorum aurea Buckwheat, etc)	TCM + CT vs CT = 30 vs 30	/	/	Foxp3, B7-H3	Wang et al. (53)
NSCLC	Compound (Listed drug, Oral Liquid)	Jinfukang Oral Liquid (Astragalus, Ophiopogon japonicus, Adenophora glabra, Ligustrum lucidum, Cornus alba, etc)	TCM + G vs G = 60 vs 60	DCR 91.67% vs 75% (p<0.05)	/	MMP-9	Zhang et al. (54)
NSCLC	Compound (Listed drug, oral)	Yifei Qinghua Granule (American Ginseng, Adenophora, Astragalus, Ophiopogon japonicus, Patrinia vulgaris, Oldenlandia diffusa, Panax notoginseng, etc)	TCM + CT vs CT = 101 vs 101	DCR 81.19% vs 64.36% (p<0.05)	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , NK	CD8 ⁺ , IL-6, TNF- α , hs-CPR	Wang et al. (55)
NSCLC	Compound (Self-made, oral)	Yifei Xiaoi Decoction (Houttuynia, Cattus BRACHIUM, Mountain Conch, Codonopsis, Asparagus, Fritillaria, Populus tremula Reed Stein, Loquat Folium, Panax notoginseng, Citrus aurantium, STILIO, etc)	TCM + TP vs TP = 32 vs 32	DCR 84.4% vs 68.9% (p<0.05)	/	VEGF, MMP-2, MMP-9	Liu and Yang (56)
NSCLC	Compound (Listed drug, injection)	Shenqi Fuzheng Injection (Codonopsis, Astragalus)	TCM + TP vs TP = 41 vs 38	DCR 90.2% vs 76.3%, PFS 19m vs 13m, OS 43m vs 29m (p<0.05)	Th17	Treg	Chen et al. (57)
NSCLC	Compound (Listed drug, injection)	Kanglaite Injection (Coix Oil)	TCM + GP vs GP = 36 vs 36	DCR 91.67% vs 69.34% (p<0.05)	/	VEGF, P53, anti-Survivin antibody	Wang et al. (58)
Digestive system cancer							
Gastric Cancer	Compound (Listed drug, injection)	Compound Kushen Injection (Sophora flavescens, Berberis vulgaris uniseriale) Aidi Injection (Astragalus, Acanthopanax senticosus, Ginseng, Cantharidin)	TCM + FOLFOX vs FOLFOX = 39 vs 39	DCR 97.44% vs 87.18% (p<0.05)	hydrogen sulfide, CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺	IL-6, TGF- β 1	Meng et al. (59)
Gastric Cancer	Compound (Self-made, oral)	Buzhong Guben Yiwei Decoction (Atractylodes movent-frixum, Ginseng, Astragalus, Poria, tangerine cortices, Chuanxiong, Carlo, Fritillaria, Cyperus rotundus, album AGLAOPHOTIS, Bupleurum falcatum, amomi, Platycodon, lignei, Licoricia, gingiberi, Jujube)	TCM + FOLFOX vs FOLFOX = 50 vs 50	DCR 66% vs 38% (p<0.05)	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺	/	Wang and Zhang (60)
Gastric Cancer	Compound (Classic, oral)	Yanghe Decoction (Muta Rehmannia, cornibus gum, eruca alba semina, ephedra, cinnamo, gingiberi, Licoricia)	TCM + DOX vs DOX = 60 vs 60	DCR 85% vs 68.3% (p<0.05)	IFN- γ	HIF-1 α , IL-10, TGF- β 1, TNF- α , MCP-1, MDSCs, Tregs	Tian et al. (61)
Hepatocellular Carcinoma	Compound (Self-made, oral)	Chaihu Zaoxiu Decoction (Bupleurum falcatum, Fusarium oxysporum, Poria, rubrum AGLAOPHOTIS, album AGLAOPHOTIS, Rubia, Angelica, Turmeric, Cyperus rotundus: Scutellaria, Curcuma, totum cucumis, Cruda turtur, Polygonum cuspidatum, Licorice)	TCM + FAP vs FAP = 40 vs 40	ORR 35% vs 22.5% (p<0.05)	IL-2	MMP-2, MMP-9, VEGF, IGF-2	Wang and Jiao (62)
Esophageal Cancer	Compound (Self-made, oral)	Buyi Zhiai Decoction (Ginseng, Poria, Astragalus, Carlo, album AGLAOPHOTIS, Rehmannia, Atractylodes, Licoricia, Shouwu, CISSANTHEMOS, dandelion, Taraxacum)	TCM + DDP vs DDP = 53 vs 53	/	CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , IgA, IgG, IgM	CD8 ⁺	Feng et al. (63)
Gynecological cancer							

(Continued)

TABLE 1 | Continued

Cancers	Formulation	Herbal medicine	Group and Number of cases	Effect of Combination	Upregulate	Downregulate	Refs.
Ovarian Cancer	Compound (Listed drug, injection)	Shenqi Fuzheng Injection (Codonopsis, Astragalus)	TCM + TC vs TC = 55 vs 50	DCR 70.9% vs 50% ($p < 0.05$)	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺	/	Wei and Li (64)
Choriocarcinoma	Compound (Self-made, oral)	Fuzheng Yiliu Formula (Astragalus, Ligustrum lucidum, Oldenlandia diffusa, Scutellaria barbata, Fritillaria, Salvia, muta Rehmannia, Codonopsis, rubrum AGLAOPHOTIS, futurist awards, Poria, Atractylodes, Carlo, Polygonatum, Zihe, Gynostemma, Pinellia, Licoricia, aurantiaco cortices, three-lens)	TCM + EMA-CO vs EMA-CO = 46 vs 46	DCR 73.91% vs 47.83% ($p < 0.05$)	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺	CD8 ⁺	Zhang et al. (65)
Triple-negative Breast Cancer	Compound (Self-made, oral)	Huangqi Jiedu Decoction (Astragalus, Scutellaria barbata, Coix semen Oldenlandia diffusa, Radix Angelicae Scrophulariaceae, Gentianaceae, Ligustrum lucidum, solanum, Atractylodes, Poria Cocos, Ophiopogon japonicus: Fungorum Shanzi, Fritillaria, Licorice)	TCM + GT vs GT = 51 vs 51	DCR 78.4% vs 58.8% ($p < 0.05$)	IL-2, IFN- γ , IL-2/IL-6, IFN- γ /IL-6	IL-6	Yang et al. (66)
Breast Cancer	Compound (Listed drug, injection)	Shenqi Fuzheng Injection (Codonopsis, Astragalus)	TCM + D vs DEC = 50 vs 50	DCR 84% vs 64% ($p < 0.05$)	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , CD80, CD83, CD86	CD8 ⁺	Lu et al. (67)
Cervical Cancer	Monomer (Listed drug, injection)	Matrine Injection	TCM + DC vs DC = 35 vs 35	DCR 94.29% vs 71.43% ($p < 0.05$)	IL-18, IFN- γ , CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺	IL-6	Du et al. (68)
Others Bladder Cancer	Monomer (Listed drug, injection)	Matrine Injection	TCM + GP vs GP = 39 vs 42	DCR 97.43% vs 87.5% ($p = 0.034$), PFS 12.64m vs 10.37m, OS 18.63m vs 15.09m ($p < 0.001$)	CTL, NK	Treg	Han et al. (69)

cancer, choriocarcinoma, breast cancer) (64–68), and bladder cancer (69). The observed drugs are mainly compound herbal medicines, including classic prescriptions [Baihe Gujin decoction (52), Yanghe decoction (61)], listed drugs [Shenqi Fuzheng injection (57, 64, 67), Kanglaite injection (58), compound Kushen injection (59), Aidi injection (59), Jinfukang oral liquid (54), Yifei Qinghua granules (55)], a variety of self-made empirical formulas (53, 56, 60, 62, 63, 65, 66), and monomeric Chinese medicines or their components (matrine) (68, 69). The results consistently show that TCM can help improve the sensitivity to chemotherapeutic drugs, enhance tumor-suppressing effects, and significantly improve cancer-related fatigue, bone marrow suppression, and other adverse reactions. The quality of life self-report scores also show significant improvement. Regarding the regulation of tumor immune function, clinical studies mainly detected immune-related factors in peripheral blood. The results concluded that TCM combined with chemotherapy can upregulate CD3⁺, CD4⁺, and CD4⁺/CD8⁺ (52, 55, 59, 60, 64, 65, 67, 68), interleukin-2 (IL-2) (52, 62, 66), interferon-gamma (INF- γ) (52, 61, 66, 68), natural killer cells (NK) (55, 69), and cytotoxic T lymphocytes (CTL) (69), while downregulating IL-6 (55, 59, 66, 68), IL-10 (52, 61), transforming growth factor- β 1 (TGF- β 1) (59, 61), vascular endothelial growth factor (VEGF) (58, 62), matrix metalloproteinase-2 (MMP-2), MMP-9 (54, 56, 62), Forkhead box protein 3 (Foxp3), and B7-H3 (53), and Tregs (57, 61, 69). However, there are also inconsistencies between different research results for some indicators.

Experimental studies were conducted through *in vivo* and *in vitro* research (Table 2). Cell and animal experiments present more in-depth research on the mechanism of TCM improvement of chemotherapeutic efficacy. The observed drugs include Chinese medicine monomers [curcumin (70–73), ginsenoside Rg3 (74)], extracts [Ginseng and Astragalus (75)], classic traditional compound prescriptions [Huangqin decoction PHY906 (76, 77), Shiquan Dabu decoction (78)], listed compound drugs [Shexiang Baoxin pill (79)], and self-made compound prescriptions (80, 81). The most representative ones are curcumin, PHY906, and tonic Chinese medicines. The combination of curcumin and chemotherapy has been proven to overcome multidrug resistance [FOLFOX (70), oxaliplatin (71, 73), 5-Fu (72)] through a number of *in vivo* and *in vitro* studies. The effect of this combined therapy may upregulate Bax, caspase-3, and PARP and downregulate EGFRs (such as IGF-1R), Bcl-2, survivin, HSP70, Nrf2, Bcl-2/Bax, NF- κ B, p-p65, and TGF- β /Smad2/3. PHY906 is derived from the classic formula prescription Huangqin decoction; however, instead of the separation and purification of the possible active compounds, it is taken as a whole. In-depth research via animal experiments, clinical trials, and quality control of PHY906 have been conducted. Results showed that PHY906 could significantly increase the antitumor activity of CPT-11, decreasing toxicity in normal tissues while promoting cell death within the TME, and that its effect may be upregulated by IRF-1, IRF-5, CCL-2/MCP-1, and CCL-5/RANTES. Tonic Chinese medicines include monomers, water extracts, the classic compound Shiquan Dabu

decoction, or self-made prescriptions, and their mechanism of action may be related to the regulation of macrophage polarization, the reduction of epithelial cell-mesenchymal transition, and cell stemness.

TCM COMBINED WITH TARGETED THERAPY OR IMMUNOTHERAPY

Unlike the destructive antitumor effects of traditional chemotherapy, new molecular targeted therapies target specific molecular changes in cancer (16). They have achieved significant effects in clinical practice in recent years and have also triggered a change in the concept of anticancer treatment. The immunotherapeutic approach involves the restart and maintenance of the tumor immune cycle, the restoration of the body's normal antitumor immune response, and the control and elimination of cancer, by means such as monoclonal antibody immune checkpoint inhibitors, therapeutic antibodies, tumor vaccines, cell therapy, and small molecule inhibitors. Among them, PD-1 inhibitors lead the treatment of malignant tumors into a new era of immunotherapy (17, 38, 39). There are currently many studies on the combined application of TCM and targeted drugs or immunotherapy, focusing on improving efficacy, reversing drug resistance, and reducing adverse reactions. Some research results describing the impact of TCM combined with targeted drugs (Table 3) and immunotherapy (Table 4) on the TME have been released; however, there are still more treatment aspects that need further clarification.

In addition to evaluating the immune function of peripheral blood, some studies involved the detection of tumor-specific markers and tumor tissue-related factors to evaluate the invasion ability of tumors. Clinical studies on non-small-cell lung carcinoma (NSCLC) (82), hepatocellular carcinoma (83), and ovarian cancer (84) use compound preparations, including classic traditional formula Xuefu Zhuyu decoction (82) and listed compound herbal medicine Shenqi Fuzheng injection (83). During *in vitro* and *in vivo* studies, apart from observing the effects on tumor cell proliferation, the related signaling pathways were explored, including the NF- κ B and p38 MAPK signaling cascades mediated by TNFR1 in hepatocellular carcinoma cells (compound Kushen injection) (85) and the AKT pathway in gastric cancer and pancreatic cancer cells (Astragalus polysaccharide) (86, 87). YIV-906, which is based on PHY906 (88), is a clinical observation drug that ensures >90% consistency in product quality (89). It is also the first Chinese medicinal project to be awarded a grant from the PO1 program of the National Cancer Center of the United States. Animal experiments show that PHY906 may potentiate sorafenib action and that its mechanism of action involves an increase in hMCP1 expression, enhanced infiltration of macrophages into tumors with a higher M1/M2 expression pattern, and upregulation of AMPK α -P and ULK1-S555-P. Computer simulation methods have also been used in the analysis of its mechanism of action and key components (90).

TABLE 2 | Influence of traditional Chinese medicine (TCM) Combined Chemotherapy (CT) on tumor microenvironment (TME) - Experimental Study.

Cells	Type	Formulation	Herbal medicine	Chemo	Effect of Combination	Upregulate	Downregulate	Refs.
HCT-116 and HT-29; LoVo-xenograft; HCT-8/5-Fu cells	In vitro and in vivo	Monomer	Curcumin	FOLFOLX/Oxa/5-Fu	Confirmed the reversal effect on multidrug resistance	Bax, caspase-3, and PARP	EGFRs and IGF-1R; Bcl-2, survivin, HSP70; Nrf2, Bcl-2/Bax; NF- κ B; p-p65, TGF- β /Smad2/3	Patel et al. (70) Guo et al. (71) Zhang et al. (72) Yin et al. (73)
SPC-A1, H1299, A549 cell lines	In vitro and in vivo	Monomer	Ginsenoside Rg3	DDP	Increase the sensitivity to DDP	/	NF- κ B, EMT and stemness	Wang et al. (74)
A549 cells and Lewis lung carcinoma (LLC1)	In vitro and in vivo	Compound extract	WEGA (Water extract of ginseng and astragalus)	DDP	Effectively inhibited the transplanted tumor growth and improved weight loss and immunosuppressive	inhibited A549 cell proliferation, M1 macrophage markers	M2 TAMs markers	Chen et al. (75)
Colon 38 tumors	In vivo	Compound (Classic)	PHY906 (Glycyrrhiza uralensis Fisch, Paeonia lactiflora Pall, Scutelleriabaicalensis Georgi, and Ziziphus jujuba Mill)	CPT-11	Increased the antitumor activity of CPT-11 while decreasing animal weight loss caused by CPT-11; decrease toxicity in normal tissues while promoting cell death within the tumor microenvironment	IRF-1, IRF-5, CCL-2/MCP-1 and CCL-5/ RANTES	/	Lam et al. (76) Wang et al. (77)
B6F10 Melanoma cells	In vitro and in vivo	Compound (Classic)	Shiquan Dabu Decoction (Ginseng, calami similiter ducentos quinquaginta, Chuanxiong, Rehmannia, Poria, Atractylodes, Licoricia, Astragalus, Carlo, etc)	DDP	Inhibit the proliferation of melanoma, promote apoptosis and the proliferation of mouse spleen lymphocytes, enhance the anti-tumor effect	IL-4	IL-1 β	Zhang et al. (78)
Murine LLC cells	In vitro and in vivo	Compound (Listed drug)	Shexiang Baoxin Pill (Artificial Moschus, Cortex cinnamomic, Borneolum, Radix ginseng, Calculus bovis, Styra, Venenum Bufonis)	GEM	Enhance the effective treatment performance while minimizing the toxic side effects	tumor angiogenesis, blood perfusion, vascular permeability, and vessel dilation	a-SMA, collagen	Yang et al. (79)
Lewis lung carcinoma (LLC1)	In vitro and in vivo	Compound (Self-made)	JC-001 (Bupleurum chinense DC, Gentiana scabra Bge., Rheum palmatum L., Clematis montana Buch.-Ham., Carthamus tinctorius L., Prunus persica (L.) Batsch, Angelicadahurica (Fisch. ex Hoffm.) Benth. et Hook. f., Siegesbeckia orientalis L., Glycyrrhiza uralensis Fisch. and Solanum incanum L.)	DDP	JC-001 suppressed foci formation and reduced the viability of LLC1 cells in vitro, increased the chemosensitivity to CDDP in vivo	IL-2, IL-10, TNF- α and INF- γ , enhanced the Th1 response	IL-17A, TGF- β	Chuang et al. (80)
CNE2 cells nasopharyngeal carcinoma	In vivo	Compound Granules	Qi-Boosting Toxin-Resolving Granules (Rudis Astragalus, Coptis, Oldenlandia diffusa, etc)	DDP	Apoptotic rate was significantly higher	INF- γ , Foxp3	IL-17, TGF- β , ROR- γ t mRNA	Hu et al. (81)

TABLE 3 | Influence of TCM Combined Targeted therapy.

Cancers	Type	Formulation	Herbal medicine	Targeted therapy	Effect of Combination	Upregulate	Downregulate	Refs.
NSCLC	Clinical	Compound (Classic, oral)	Xuefu Zhuyu Decoction (Angelica, peach kernel, chuanxiong, safflower, red peony root, achyranthes, bupleurum, citrus aurantium, platycodon, habitat, mountain mushroom, oldenlandia diffusa, shuyangquan, gecko, licorice)	TCM + gefitinib/erlotinib vs gefitinib/erlotinib = 39 vs 39	DCR 56.4% vs 48.7% (p<0.05)	T cell, Th, Tc	Protease activated receptor (PAR)-1 expression in tumor tissue	Li et al. (82)
Hepatocellular Carcinoma	Clinical	Compound (Listed drug, injection)	Shenqi Fuzheng Injection (Codonopsis, Astragalus)	TCM + sorafenib vs sorafenib = 44 vs 44	DCR 97.7% vs 86.4% (p<0.05)	CD4 ⁺	CD8 ⁺ , CXCR3, miR-103	Lu et al. (83)
Ovarian cancer	Clinical	Compound (Self-made, oral)	Yiqi Yangyin Decoction (Seres yam, Astragalus, Habitat, Polygonatum, Scrophulariaceae, Ligustrum lucidum, Zingiber turmeric, Shanzi fungus Prunella vulgaris, Platycodon grandiflorum, Jujube)	TCM + bevacizumab vs bevacizumab = 43 vs 37	/	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , NK IL-2, INF- γ	CD4 ⁺ CD25 ⁺ , IL-6, IL-10, VEGF, CD133, DDX4	Guli et al. (84)
HCC cells	in vitro and in vivo	Compound (Listed drug, injection)	Compound Kushen Injection (Sophora flavescens, Berberis vulgaris uniseriale)	sorafenib	Enhanced the anticancer activity of sorafenib at a subclinical dose with no obvious side effects.	triggering TNFR1, mediated NF- κ B and p38 MAPK signaling cascades	/	Yang et al. (85)
Gastric AGS cells	in vitro	Monomer component	Astragalus polysaccharide (APS)	apatinib	Remarkable increase in apoptosis	/	p-AKT, MMP-9	Wu et al. (86)
Pancreatic cancer cell lines	in vitro	Monomer component	Astragalus polysaccharide (APS)	apatinib	Enhanced inhibitory effects on cell migration and invasion, and increased cell apoptosis percentage	/	p-AKT, p-ERK, MMP-9	Wu et al. (87)
HepG2 xenografts	in vivo	Compound (Classic, oral)	PHY906 (KD018)	sorafenib	potentiate the anti-hepatoma activity	hMCP1, M1/M2, AMPK α -P and ULK1-S555-P, ERK1/2-P	/	Lam et al. (88)

TABLE 4 | Influence of traditional Chinese medicine (TCM) Combined Immunotherapy.

Cancers	Type	Formulation	Herbal medicine	Immunotherapy	Effect of Combination	Upregulate	Downregulate	Refs.
WEHI-3 leukemia or EL4 lymphoblast cells	in vitro	Monomer component	PG2 (A polysaccharide isolated from the radix of Astragalus membranaceus)	/	via the protein kinase B (Akt)/mammalian target of rapamycin (mTOR)/ribosomal protein S6 kinase beta-1 (p70S6K) pathway	/	PD-L1 on the cell surface	Chang et al. (91)
Diffuse large B cell lymphoma	in vitro	Monomer component	Ginsenoside Rg3	PD-1 inhibitor	enhances the anti-tumor effect and proliferation of T cells, inhibiting apoptosis, increasing the secretion of cytokine	IL-2, IFN- γ	/	Guo et al. (92)
TC-1	in vivo	Monomer	Glycyrrhiza uralensis water extract	HPV dendritic cell-based vaccine	dose-dependently promoted DC maturation and cytokine secretion through TLR4 signaling pathway	CD4+ and CD8+ T cells	iTregs: CD4+CD25-Fopx3+	Alpire et al. (93)
MB79 bladder cancer	in vivo	Monomer component	Bisdemethoxycurcumin	α -PD-L1	significantly prolonged survival of intraperitoneal metastasized bladder cancer bearing mice	intratumoral CD8 ⁺ T-cell infiltration, IFN- γ in the blood	intratumoral MDSCs	Shao et al. (94)
CT26 colon cancer	in vivo	Compound (Classic)	Gegen Qinlian Decoction	anti-mouse PD-1	Gut microbiota analysis revealed that combination significantly enriched for s: Bacteroides_acidifaciens and s:uncultured_organism_g:norank_f: Bacteroidales_S24-7_group.	CD8+ T cells in peripheral blood, IFN- γ , IL-2,	PD-1	Lv et al. (95)
CT26 colon cancer	in vivo	Compound (Classic)	ninjin'yoeito (NYT, Renshen Yangrong Decoction)	tumor vaccine	synergistically enhances the effects of the prophylactic tumor vaccine	CD8+ T cells	Tregs: CD4+CD25-Fopx3+	Takaku et al. (96)
B16 melanoma cancer	in vivo	Compound (Classic)	Juzentaihoto (JTT, Shiquan Dabu Decoction)	anti-PD-1 antibody	significantly suppressed B16 cell metastasis	IL-12, IFN- γ , NK	/	Ishikawa et al. (97)
Advanced stage cancer	Clinical	Compound (Classic, oral)	Guipi Decoction	NK cell	TCM symptoms improved (shortness of breath, over fatigued, tiredness)	CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , NK	/	Lu and Peng (98)
Castration-resistant prostate cancer	Clinical	Compound (Classic, oral)	Hochu-ekki-to (Buzhong Yiqi Decoction) and Keishi-bukuryo-gan (Guizhi Fuling Pills)	Personalized Peptide Vaccine (PPV)	well tolerated without severe adverse events.		Mo-MDSC, IL-6	Koga et al. (99)

Whether tonic herbal medicine be used in combination with immunotherapy is one of the issues that Chinese cancer patients are extremely concerned about; moreover, it is a very controversial issue for cancer clinicians. Research on the combination of TCM and immunotherapy mainly includes *in vivo* and *in vitro* studies, while clinical studies are rarely conducted. The TCM studied mostly include tonic drugs or their components: Astragalus (91), ginsenoside Rg3 (92), Glycyrrhiza uralensis water extract (93), and bisdemethoxycurcumin (94). Most of the compound prescriptions are classic medicines, including Gegen Qinlian decoction (95), Renshen Yangrong decoction (96), Shiquan Dabu decoction (97), Guipi decoction (98), and Buzhong Yiqi decoction (99). The components of Astragalus can downregulate PD-L1 on the tumor cell surface, which may be related to the AKT/mTOR/p70S6K pathway (91). *In vivo* studies have shown that TCM combinations have a positive effect on therapeutic curative potential and tumor inhibition. Some studies also explored the intestinal flora; however, in clinical observation, the main observed effect remains the improvement of symptoms. Both TCM treatment and immunotherapy have systematic and complex characteristics. Determining whether TCM affects the efficacy or the adverse effects of immunotherapy by regulating the TME and related factors necessitates further research.

TCM COMBINED WITH LOCAL TREATMENT

Malignant tumors require different treatment strategies according to the different stages of the disease. Additionally, local treatment plays an important role in the treatment of cancer. Early radical surgery is the most effective way to obtain a curative effect and long-term survival. Radiotherapy and interventional therapy can obtain survival benefits and symptom improvement through the control of local lesions. The combined citation of TCM and local treatment have been clinically observed to reduce perioperative complications, promote the recovery of immune function, reduce recurrence and metastasis, and improve long-term prognosis. The TCM involved are mostly listed drugs (Table 5), and research on their mechanism of action is relatively lacking and limited to peripheral blood immune function detection.

DISCUSSION

The clinical application of TCM has a long history, and its treatment principles and philosophy have a unique system. With the continuous improvement of research methods, our understanding of TCM is deepening. The study of herbal medicine monomers and their components is relatively easy to explain; however, compound prescription and compatibility are more characteristic of TCM holistic thinking. TCM has its advantages and specifics in the treatment of cancer. In addition to reducing the side effects of antitumor treatment and improving the symptoms and patient quality of life, it also

TABLE 5 | Influence of traditional Chinese medicine (TCM) Combined Local treatment (Peri-operation, γ -knife, interventional therapy).

Cancer	Type	Formulation	Herbal medicine	Local treatment	Effect of Combination	Upregulate	Downregulate	Refs.
NSCLC	Clinical	Compound (Listed drug, injection)	Aidi Injection	Neoadjuvant Chemo: TCM + Neo-Chemo vs Neo-Chemo = 35 vs 20	Decreased blood loss in operation: 530.15 ± 104.55 ml vs 615.49 ± 114.08 ml (P<0.05); Increased curative effect: 45.71% vs 30.00% (P<0.05); Decreased leucopenia: 37.14% vs 60.00% (P<0.05)	/	CD4 ⁺ , CD25 ⁺	Teng et al. (100)
Lung cancer	Clinical	Compound (Listed drug, oral)	Zilongjin Tablets	Post operation: TCM vs control = 30 vs 30	promote the recovery of immune function	IgA, IgG, CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , NK	/	Huang et al. (101)
Triple-negative Breast Cancer	Clinical	Compound (Self-made, oral)	Shenghe Powder	Post operation Chemo-Radio Therapy(CRT): TCM + CRT vs CRT = 84 vs 84	5-year survival rate: 76.2% vs 64.3% (P<0.05); Recurrence and metastasis rate: 25.0% vs 39.3% (P<0.01)	CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , NK; miR-34a,	LDHA	Wang et al. (102)
Primary liver cancer	Clinical	Compound (Listed drug, injection)	Compound Danshen Injection	TCM + γ -knife vs γ -knife = 20 vs 20	/	IgA, IgG, IgM, CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ ,	/	Zhu and Yi (103)
Primary liver cancer	Clinical	Compound (Listed drug, oral)	Jinlong Capsule	TCM + intervention vs intervention = 30 vs 30	facilitates the cellular immunity recovery	keep stable: CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , NK; SIL-2R, TSGF	/	Yuan et al. (104)

“supports the healthy Qi” and restores the body’s own immune system. It can improve efficacy and prolong survival in the comprehensive treatment of cancer.

Many studies on the monomers or components of herbal medicine have confirmed that they affect related factors in the TME; however, their effects in a more complex system are relatively unexplored. This review summarizes and analyzes the influence and effect of TCM in combination with antitumor therapy, including chemotherapy, targeted therapy, immunotherapy, the perioperative period, radiotherapy, and interventional therapy. Relevant Chinese medicines include marketed drugs (injections, oral liquids, and tablets), traditional prescriptions, and self-developed experiential prescriptions, as well as many Chinese medicinal monomers or ingredients. Tonic drugs are the main active agents, including multiple treatments such as replenishing Qi, invigorating the spleen, promoting blood circulation, eliminating phlegm, clearing heat, and dispelling stagnation. It is well known that the immune system of body, plays defensive, protective and eliminative roles on tumor cells. For example, NK cells can directly recognize and eradicate tumor cells; Dendritic cells (DCs) can activate adaptive immunity; macrophages (M) can kill tumor cells by generating cytotoxicity, which related to the production of effector molecules and accompanying phagocytosis. Clinical studies have shown that adding TCM to the treatment strategy can significantly improve patient symptoms without increasing adverse reactions, with a tendency to prolong survival. The detection of peripheral blood-related immune factors suggests that TCM has a regulatory effect on immune function and that it can promote a healthy Th1/Th2 balance and regulate the polarization of macrophages. Peripheral blood is the most commonly used medium for disease diagnosis and has been widely accepted by patients for noninvasive molecular diagnosis. In addition, compared with the tumor tissue sample, the dynamic change of microenvironment is ignored, and the peripheral blood can be sampled for many times regularly, which is convenient for monitoring. In relevant *in vivo* and *in vitro* studies, possible mechanisms of action have been discussed, including the classical NF- κ B, AKT, and TLR4 signaling pathways and the intestinal flora. However, TCM treatment still needs to go

through top-level design, good quality control, reverse verification, and in-depth research that can reproduce results to demonstrate the role of TCM in the comprehensive treatment of tumors and clarify its therapeutic mechanism.

CONCLUSIONS

Cancer treatment has multiple stages and high complexity, and the optimal approach includes multidisciplinary comprehensive diagnosis and treatment. TCM has its unique advantages and characteristics that are different from other types of antineoplastic treatment, and these should not be ignored. However, current research results cannot clearly explain the dominant population and mechanism of effect of TCM combined with antitumor therapy; however, the impact on the TME may be the core principle of this approach. More evidence-based experimental research is still needed to provide a basis for formulating better combined strategies for cancer treatment.

AUTHOR CONTRIBUTIONS

YZ, YL, and WS conceptualized and designed the review. YZ and YL wrote the manuscript. JW, CY, and WS revised the manuscript. All authors contributed to the article and approved the submitted version.

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

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