



RESEARCH STATUS AND MOLECULAR MECHANISM OF THE TRADITIONAL CHINESE MEDICINE AND ITS RELATION IN ANTITUMOR THERAPY COMBINED STRATEGY BASED ON TUMOR MICROENVIRONMENT: A DATA BASE RESEARCH.

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Abstract:

Objectives: 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.

Methods: 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.

Results: 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.

Discussion: 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: 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.

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

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Introduction:

Cancer is one of the major non communicable chronic diseases that seriously affect human health(1) Although treatment methods and drug research and development continue to improve, many problems such as drug resistance and recurrence still hinder progress (2) 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(3) 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(4) *The tumor microenvironment (TME)* 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 and immunosuppression(5) 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 (6). 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 (6)

Methodology:

TCM Combined With Chemotherapy

The clinical studies on TCM combined with chemotherapy for anticancer treatment research have been mainly published in Chinese journals. The studied cancer types include lung cancer (7), digestive system cancer (gastric/liver/esophageal cancer) (8), gynecological cancer (ovarian cancer, choriocarcinoma, breast cancer) (9), and bladder cancer (10). The observed drugs are mainly compound herbal medicines, including classic prescriptions [Baihe Gujin decoction (7), Yanghe decoction (11), listed drugs [Shenqi Fuzheng injection (12), Kanglaite injection (13), compound Kushen injection (14), Aidi injection (15), Jinfukang oral liquid (16), Yifei Qinghua granules (17), a variety of self-made empirical formulas, and monomeric Chinese medicines or their components (matrine) (18). 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⁺ (19), interleukin-2 (IL-2) (19), interferon-gamma (INF- γ) (19), natural killer cells (NK) and cytotoxic T lymphocytes (CTL) (10), while downregulating IL-6, IL-10, transforming growth factor- β 1 (TGF- β 1), vascular endothelial growth factor (VEGF), matrix metalloproteinase-2 (MMP-2), MMP-9, Forkhead box protein 3 (Foxp3), and B7-H3, and Tregs. However, there are also inconsistencies between different research results for some indicators.

The observed drugs include Chinese medicine monomers [curcumin (21), ginsenoside Rg3, extracts [Ginseng and Astragalus], classic traditional compound prescriptions [Huangqin decoction PHY906, Shiquan Dabu decoction], listed compound drugs [Shexiang Baoxin pill], and self-made compound prescriptions. 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, oxaliplatin, 5-Fu] 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.

Cancers	Herbal medicine	Group and Number of cases	Effect of Combination	Refs.
Lung Cancer				
NSCLC	Baihe Gujin Decoction (Rehmannia, Rehmannia, Carlo, album AGLAOPHOTIS, lilium, Fritillaria, Ophiopogon, Bellflower, Scrophulariaceae, rudis Licoricia)	TCM + DC vs DC = 24 vs 24	DCR 89.6% vs 72.9% (p<0.05)	He and Huang (52)
NSCLC	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 = 15 vs 15	-	Wang et al. (53)
NSCLC	Jinfukang Oral Liquid (Astragalus, Ophiopogon japonicus, Adenophora glabra, Ligustrum lucidum, Cornus alba, etc)	TCM + G vs G = 30 vs 30	DCR 91.67% vs 75% (p<0.05)	Zhang et al. (54)
NSCLC	Yifei Qinghua Granule (American Ginseng, Adenophora, Astragalus, Ophiopogon japonicus, Patrinia vulgaris, Oldenlandia diffusa, Panax notoginseng, etc)	TCM + CT vs CT = 50 vs 50	DCR 81.19% vs 64.36% (p<0.05)	Wang et al. (55)
NSCLC	Yifei Xiaoai 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 = 16 vs 16	DCR 84.4% vs 68.9% (p<0.05)	Liu and Yang (56)
NSCLC	Shenqi Fuzheng Injection (Codonopsis, Astragalus)	TCM + TP vs TP = 20 vs 19	DCR 90.2% vs 76.3%, PFS 19m vs 13m, OS 43m vs 29m (p<0.05)	Chen et al. (57)
NSCLC	Kanglaite (Coix Oil) Injection	TCM + GP vs GP = 18 vs 18	DCR 91.67% vs 69.34% (p<0.05)	Wang et al. (58)
Digestive system cancer				
Gastric Cancer	Compound Kushen Injection (Sophora flavescens, Berberis uniseriale) Aidi Injection	TCM + FOLFOX vs	DCR 97.44% vs 87.18% (p<0.05)	Meng et al. (59)

	(Astragalus, Acanthopanax senticosus, Ginseng, Cantharidin)	FOLFOX = 19 vs 19		
Gastric Cancer	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, gingeriberi, Jujube)	TCM + FOLFOX vs FOLFOX = 25 vs 25	DCR 66% vs 38% (p<0.05)	Wang and Zhang (60)
Gastric Cancer	Yanghe Decoction (Muta Rehmannia, cornibus gum, eruca alba semina, ephedra, cinnamo, gingeriberi, Licoricia)	TCM + DOX vs DOX = 30 vs 30	DCR 85% vs 68.3% (p<0.05)	Tian et al. (61)
Hepatocellular Carcinoma	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 = 20 vs 20	ORR 35% vs 22.5% (p<0.05)	Wang and Jiao (62)
Esophageal Cancer	Buyi Zhiai Decoction (Ginseng, Poria, Astragalus, Carlo, album AGLAOPHOTIS, Rehmannia, Atractylodes, Licoricia, Shouwu, CISSANTHEMOS, dandelion, Taraxacum)	TCM + DDP vs DDP = 26 vs 26	-	Feng et al. (63)

Table:Influence of traditional Chinese medicine (TCM) Combined Chemotherapy (CT) on tumor microenvironment (TME)-Clinical Study.

TCM Combined With Targeted Therapy or Immunotherapy

They have achieved significant effects in clinical practice in recent years and have also triggered a change in the concept of anticancer treatment. 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) (23) and the AKT pathway in gastric cancer and pancreatic cancer cells (Astragalus polysaccharide) (24). YIV-906, which is based on PHY906, is a clinical observation drug that ensures >90% consistency in product quality. 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. 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 (25), ginsenoside Rg3, Glycyrrhiza uralensis water extract, and bisdemethoxycurcumin. Most of the compound prescriptions are classic medicines, including Gegen Qinlian decoction, Renshen Yangrong decoction, Shiquan Dabu decoction, Guipi decoction, and Buzhong Yiqi decoction. The components of Astragalus can downregulate PD-L1 on the tumor cell surface, which may be related to the AKT/mTOR/p70S6K pathway (25). *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.

Cancers	Formulation	Herbal medicine	Targeted therapy	Effect of Combination	Refs.
NSCLC	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 = 19 vs 19	DCR 56.4% vs 48.7% (p<0.05)	Li et al. (82)
Hepatocellular Carcinoma	Compound (Listed drug, injection)	Shenqi Fuzheng Injection (Codonopsis, Astragalus)	TCM + sorafenib vs sorafenib = 22 vs 22	DCR 97.7% vs 86.4% (p<0.05)	Lu et al. (83)
Ovarian cancer	Compound (Self-made, oral)	Yiqi Yangyin Decoction (Seres yam, Astragalus,	TCM + bevacizumab vs	/	Guli et al. (84)

		Habitat, Polygonatum, Scrophulariaceae, Ligustrum lucidum, Zingiber turmeric, Shanzi fungus Prunella vulgaris, Platycodon grandiflorum, Jujube)	bevacizumab = 21 vs 18		
HCC cells	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.	Yang et al. (85)
Gastric AGS cells	Monomer component	Astragalus polysaccharide (APS)	apatinib	Remarkable increase in apoptosis	Wu et al. (86)
Pancreatic cancer cell lines	Monomer component	Astragalus polysaccharide (APS)	apatinib	Enhanced inhibitory effects on cell migration and invasion, and increased cell apoptosis percentage	Wu et al. (87)
HepG2 xenografts	Compound (Classic, oral)	PHY906 (KD018)	sorafenib	potentiate the anti-hepatoma activity	Lam et al. (88)

Table:TCM Combined With Targeted Therapy

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. 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, and research on their mechanism of action is relatively lacking and limited to peripheral blood immune function detection

Cancer	Formulation	Herbal medicine	Local treatment	Effect of Combination	Refs.
NSCLC	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)	Teng et al. (100)
Lung cancer	Compound (Listed drug, oral)	Zilongjin Tablets	Post operation: TCM vs control = 30 vs 30	promote the recovery of immune function	Huang et al. (101)
Triple-negative Breast Cancer	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)	Wang et al. (102)
Primary liver cancer	Compound (Listed drug, injection)	Compound Danshen Injection	TCM + γ -knife vs γ -knife = 20 vs 20	/	Zhu and Yi (103)

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

Discussion:

The clinical application of TCM has a long history 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.

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