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# Traditional Chinese Medicine in Oncotherapy: The Research Status

Huijuan Tang, Peng Shu, Shenlin Liu, Xu Zhang, and Monica Mattioli-Belmonte

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REVIEW



## Traditional Chinese Medicine in Oncotherapy: The Research Status

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### ABSTRACT

In China, traditional Chinese medicine (TCM) plays a vital role in the comprehensive treatment of cancer. As an auxiliary and supplement of major treatment modalities for cancer such as surgery, chemotherapy, and radiotherapy, both clinical observations and biomolecular research have confirmed the therapeutic efficacy of TCM in cancer.

### ARTICLE HISTORY

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### Introduction

GLOBOCAN announced that in 2018 there were 18.1 million new cancer cases, 9.6 million cancer deaths, and 43.8 million people living with cancer (within 5 years of diagnosis) worldwide. Of this, 48.4% (8.8 million) of new cancer cases, 57.3% (5.5 million) of the cancer deaths, and 39.7% (17.4 million) of the 5-year prevalent cancer cases occurred in Asia (1). China is a developing country with a large population and a high incidence rate of cancer; therefore, cancer remains a major burden for the Chinese population.

Cancer treatment using traditional Chinese medicine (TCM) has a long history in China and is now well integrated into current healthcare systems. The occurrence of the tumor is believed to be caused by the imbalance between the healthy body and the malignant factors: either the body is not enough strong, or the malignant factors are too potent.

In TCM, treatment is based on the differentiation of syndromes. According to syndrome differentiation, TCM mainly emphasizes the treatment of “Yin and Yang balance”: the balance between “strengthening the body resistance to eliminate pathogenic factors,” and “detoxifying and removing blood stasis” (2). Based on the TCM theory, Chinese medicines therefore used for treating cancer are divided into two main categories: “strengthening the body resistance” and “attacking pathogen,” as shown in Figure 1.

Conversely, the development of modern medical research has made it possible for researchers to



explore the mechanism of TCM from a pharmacological perspective. At present, the main recognized mechanisms of TCM in cancer treatment are cytotoxicity, anti-metastasis, anti-angiogenesis, the reversal of multiple drug resistance (MDR), inducing differentiation, regulating immunity, toxicity reducing, and efficacy enhancing (for chemotherapy and radiotherapy) (Figure 2).

### Clinical Investigation

In clinical practice, TCM usually uses a combination of several medicines as a formula. Therefore, in most clinical investigations, the prescriptions were compounds rather than single drugs. Tables 1 and 2 summarize some main single Chinese medicines and formulas commonly used in oncotherapy, with relative references.

### Chinese Medicine Formulas

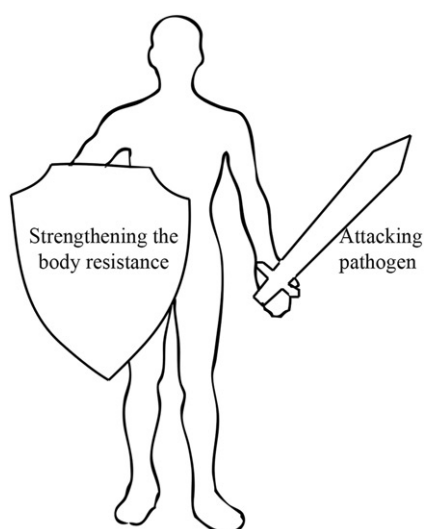
The good curative effect of Chinese medicine formulas has been verified in numerous clinical observations. In a multicenter, prospective cohort study (34), *Yiqi Huayu Jiedu Decoction* along with chemotherapy treated 201 cases of gastric cancer patients (stages II and III), compared with 196 patients with chemotherapy alone, found that the group using a combination of TCM and chemotherapy had a 39.1% lower risk of recurrence. Another study showed that *Yangzhengxiaoji Capsule* could improve the syndromes of Chinese medicine and increase the clinical

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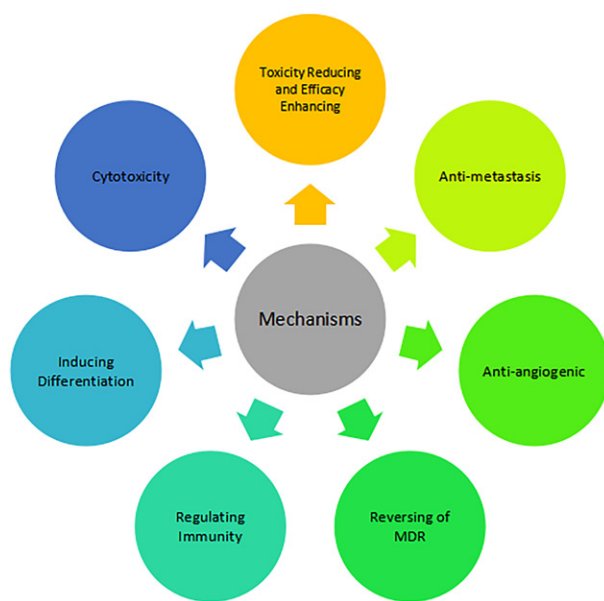
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**Figure 1.** Chinese herbs for oncotherapy classified according to the TCM theory. Chinese medicines are divided into two main categories: “strengthening the body resistance” and “attacking pathogen” based on the TCM theory. Medicines used as “strengthening the body resistance” strengthen the human body, to make it like a shield against disease; others used as “attacking pathogen” act as a weapon to help the body drive away disease.



**Figure 2.** The main mechanisms of Chinese herbs for oncotherapy.

efficacy of patients with advanced digestive tract malignancies (35). There remains a wealth of evidence for the role of Chinese medicine formulas in western biomedicine and TCM.

### Strengthening the Body Resistance

The good curative effect of “strengthening the body resistance” medicines, when used as an auxiliary for chemotherapy, has been found in modern medicine to

be mainly related to reducing toxicity, increasing efficiency, and regulating immunity. The contribution of TCM in alleviating adverse reactions is unquestionable; *Yiguan Decoction* and *Xiangsha Liujunzi Decoction* combined with western medicine can relieve vomiting, anorexia, and fatigue adverse reactions caused by chemotherapy (36).

Regarding TCM effects on regulating immunity, routine chemoradiotherapy combined with *Yiqi Yangyin Decoction* can effectively reduce tumor load and optimize the antitumor immune function in patients with advanced non-small-cell lung cancer (37). Another clinical study found that docetaxel–cisplatin (DC) chemotherapy combined with *Yiqi Guben Decoction* in the treatment of advanced non-small-cell lung cancer could effectively reduce the serum tumor marker levels, the inflammatory stress, and improve immune function (38).

In view of the outstanding performance of TCM in this area, some of the effective compounds have even been approved for mass production as adjuvant drugs for chemoradiotherapy, such as *Shenqi Fuzheng Injection* (39).

### Attacking Pathogen

The most representative example of “attacking pathogen” medicine against the tumor is the remarkable efficacy of arsenic in the treatment of leukemia. Other representative TCM patent prescriptions of “attacking pathogen” in clinical observation, such as *Aidi Injection*, not only improve the efficacy of cisplatin regimen but also have the function of reducing adverse events and preventing the overexpression of P-glycoprotein (P-gp) induced by chemotherapy of cisplatin regimen (40). Recent studies suggest that treating advanced gastric cancer with *sodium cantharidinate* could improve the quality of life and decrease bone marrow suppression and gastrointestinal side effects (41). *Xiaoaping Injection* as a retention enema in the treatment of colorectal cancer (CRC) can significantly improve the clinical efficacy and relieve clinical symptoms of patients (42).

### Mechanism of Action

#### Cytotoxicity

Many Chinese herbs used in TCM, like *Oldenlandia diffusa*, *Scutellaria baicalensis*, *Solanum lyratum*, *Paris polyphylla*, contain cytotoxic components. Their components mainly inhibit cell proliferation and induce apoptosis. For example, after spongioblastoma

**Table 1.** Single Chinese medicines commonly used in formulas for oncotherapy.

Name	Classified	Study type	Disease	Anticancer activity	Ref.
<i>Astragalus mongholicus</i>	Strengthening the body resistance	Mechanism research	Multiple	Cytotoxicity, antimetastasis, anti-angiogenesis, regulating immunity	(3–7)
<i>Panax ginseng</i>	Strengthening the body resistance	Mechanism research	Multiple	Cytotoxicity, antimetastasis, anti-angiogenesis, regulating immunity, toxicity reducing and efficacy enhancing	(8–11)
<i>Curcuma longa</i>	Attacking pathogen	Mechanism research	Multiple	Cytotoxicity, antimetastasis, anti-angiogenesis	(12–15)
<i>Scolopendra subspinipes</i>	Attacking pathogen	Mechanism research	Multiple	Cytotoxicity, anti-angiogenesis	(16–18)
<i>Agrimonia eupatoria</i>	Strengthening the body resistance and attacking pathogen	Mechanism research	Multiple	Cytotoxicity, regulating immunity	(19, 20)
<i>Solanum nigrum</i>	Attacking pathogen	Mechanism research	Colorectal cancer	Cytotoxicity, antimetastasis, regulating immunity	(21, 22)

**Table 2.** Chinese medicine formulas commonly used for oncotherapy.

Name	Components	Classified	Study Type	Disease	Anticancer activity	Ref.
Dahuang Zhechong pill	<i>Rheum palmatum</i> , <i>Scutellaria baicalensis</i> , <i>Glycyrrhiza uralensis</i> , the seed of <i>Prunus persica</i> , the seed of <i>Amygdalus communis</i> , <i>Rehmannia glutinosa</i> , <i>Paeonia lactiflora</i> , <i>Toxicodendron vernicifluum</i> , <i>Tabanus mandarinus</i> , <i>Hirudo medicinalis</i> , <i>Eupolyphaga sinensis</i> , <i>Holotrichia diomphalia</i>	Attacking pathogen	Clinical Investigation and mechanism research	Multiple	Cytotoxicity, anti-angiogenesis, regulating immunity, reversal of MDR, toxicity reducing and efficacy enhancing	(23–28)
Da Huangqi Decoction	<i>Astragalus mongholicus</i> , <i>Panax ginseng</i> , <i>Cinnamomum cassia</i>	Strengthening the body resistance	Clinical Investigation and mechanism research	Lung cancer	Antimetastasis	(29, 30)
Jianpi Liqi Decoction	<i>Codonopsis pilosula</i> , <i>Atractylodes macrocephala</i> , <i>Wolfiporia cocos</i> , <i>Akebia trifoliata</i> , <i>Oldenlandia diffusa</i>	Strengthening the body resistance and attacking pathogen	Clinical Investigation	Liver cancer	Benefiting the survival of patients	(31)
Jianpizaoshi Myogenic Decoction	<i>Astragalus mongholicus</i> , the seed of <i>Coix lacryma-jobi</i> , <i>Dioscorea opposita</i> , <i>Psoralea corylifolia</i> , <i>Scutellaria baicalensis</i> , <i>Phellodendron amurense</i> , <i>Bletilla striata</i> , <i>Sophora flavescens</i> , <i>Lithospermum erythrorhizon</i>	Strengthening the body resistance and attacking pathogen	Clinical Investigation	Enteritis caused by radiotherapy	Toxicity reducing for radiotherapy	(32)
Qiyu Sanlong Decoction	<i>Astragalus mongholicus</i> , <i>Polygonatum odoratum</i> , <i>Scolopendra subspinipes</i> , <i>Pheretima</i> , <i>Solanum nigrum</i> , <i>Oldenlandia diffusa</i> , the seed of <i>Coix lacryma-jobi</i> , <i>Euphorbia helioscopia</i> , <i>Curcuma longa</i> , <i>Fritillaria cirrhosa</i>	Strengthening the body resistance and attacking pathogen	Mechanism research	Lung cancer	Cytotoxicity	(33)

U87MG cells transformation induced by *paclitaxel* (from *Taxus chinensis*), the spindle appeared, the number of centrosomes changed, and the nuclear crumbled (43). *Tripterine* (from *Tripterygium wilfordii*) can activate DR-5/p53/Bax/caspase-9/caspase-3 and DR-5/FADD/caspase-8/lysosomal/cathepsin B/caspase-3 signaling pathway to inhibit osteosarcoma MG63 cells (44). *Saikosaponin-d* (from *Bupleurum chinense*) can inhibit the proliferation of HeLa cell though blocking of the cell cycle at the G1 phase and induce apoptosis (45).

### Antimetastasis

Even when the effects of chemotherapy and radiation are significant, many patients will lose their lives due to

recurrence and metastasis. Research has found that *geranyl lignin* (from the *Citrus limon*) through matrix metalloproteinase (MMP) pathway could inhibit the expression of MMP-2 and MMP-9 protein levels and reduce the hydrolysis of the extracellular matrix, and the extracellular matrix has powerful resistance to invasion and metastasis in liver cancer (46). FAM46C plays a critical role in migration and invasion of hepatocellular carcinoma cells via TGF- $\beta$ /Smad signaling. *Norcantharidin* (a *cantharidin* derivative, from *Lytta vesicatoria*) could antimetastatic by upregulating FAM46C expression and regulating TGF- $\beta$ /Smads signaling pathway that prevents the expression of EMT-related transcription factors (47). *Berberine* (from *Coptis chinensis*) can significantly inhibit the extracorporeal and internal

migration of HCT-116 cells in CRC by regulating the Ras-ERK signaling pathway (48).

### Anti-angiogenic

There are currently many adverse reactions and contraindications of using anti-angiogenesis drugs in western medicine. More and more, clinicians are considering alternative TCM medicine options. *Curcumin* (from *Curcuma longa*) has been found to inhibit vascular shape by regulating the vascular endothelial growth factor (VEGF)-VEGFR2 signaling pathway to improve the hematopoietic defect induced by VEGF (49). *Scutellaria baicalensis*, capable of inhibiting gastric cancer cells Y705 phosphorylation loci of STAT3 activation, indirectly plays an inhibitory role of the VEGF expression and can directly prevent the angiogenesis induced by VEGF (50).

### Reversing MDR

At present, there is no optimal solution to the multi-drug resistance (MDR). *Evodiamine* (from *Tetradium rutilcarpum*) can inhibit the proliferation of oxaliplatin resistance colon cancer cells, promote apoptosis, inhibit the phosphorylation of NF- $\kappa$ B, and then reverse the drug resistance (51). *Resveratrol* (from *Polygonum cuspidatum*) can reverse the drug resistance of CRC cells by inhibiting EMT, activating NF-kappa B, and enhancing colon cells sensitivity to 5-fluorouracil (52).

### Inducing Differentiation

There is sparse research on TCM mechanism of induction of cell differentiation. For example, *shikonin* (from *Lithospermum erythrorhizon*) and *glycyrrhizin* (from *Glycyrrhiza uralensis*) seem capable of inducing leukemia HL-60 cell differentiation (53, 54). In the case of *glycyrrhizin*, NADPH oxidase plays an important role in this process (54).

### Regulating Immunity

Regulating immunity is a crucial aspect of TCM in the treatment of cancer. *Soybean sterol B* (from *Glycine max*) can significantly inhibit the growth and metastasis of subcutaneous tumors in a mouse model of osteosarcoma (LM8 tumor mice) and induce the immune response of mice against tumor (55). Polysaccharide extracted from *Astragalus mongholicus* and *Codonopsis pilosula* can effectively enhance the

dendritic cell-based vaccine 4T1 preventing breast cancer metastasis in mice; enhance the expression of CD40, CD80, and CD86 markers; and effectively modulate the specific cellular function of dendritic cells (56).

### Reducing Toxicity and Enhancing the Efficacy

Adverse reactions of radiotherapy and chemotherapy seriously affect the quality of life of oncologic subjects. TCM can reduce toxicity and enhance the efficacy of chemotherapy and radiotherapy (57). After observing 191 patients with advanced lung cancer treated with platinum-containing chemotherapy regimen along with or without *Shengbai* oral solution (composed of *Epimedium brevicornu*, *Psoralea corylifolia*, processed *Aconitum carmichaelii*, *Lycium barbarum*, *Astragalus mongholicus*, *Milletia dielsiana*, *Rubia cordifolia*, *Angelica sinensis*, *Phragmites australis*, *Ophiopogon japonicus*, and *Glycyrrhiza uralensis*), it has been shown that the latter could decrease bone marrow suppression caused by chemotherapy in these patients and reduce the amount of G-CSF used in these subjects (58). However, at present, there is little research on the molecular mechanism underpinning TCM capability to reduce the toxicity of chemoradiotherapy and enhance the efficacy.

### Forecast

More progress needs to be made in the study of the antitumor activity of TCM. The development of evidence-based medicine has improved knowledge of this matter. But the collection of clinical data is still not perfect, and the epidemiological survey is not developed in China, especially in the field of TCM; therefore, the research of the role of TCM in oncotherapy lacks large clinical database. At the same time, as new research directions are being explored, TCM will continue to contribute to oncotherapy developments.

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### Authors' Contributions

Conceptualization, Monica Mattioli-Belmonte and Huijuan Tang; Writing—Original Draft Preparation, Huijuan Tang; Writing—Review & Editing, Monica Mattioli-Belmonte; Supervision, Monica Mattioli-Belmonte.

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## Disclosure Statement

The authors declare no conflict of interest.

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