

**Review****Chinese herbal medicines as adjuvant treatment during chemo- or radio-therapy for cancer****Fanghua Qi<sup>1,2</sup>, Anyuan Li<sup>1,\*</sup>, Yoshinori Inagaki<sup>2</sup>, Jianjun Gao<sup>2</sup>, Jijun Li<sup>1</sup>, Norihiro Kokudo<sup>2</sup>, Xiao-Kang Li<sup>3</sup>, Wei Tang<sup>2,\*</sup>**<sup>1</sup> Department of Traditional Chinese Medicine, Shandong Provincial Hospital affiliated with Shandong University, Ji'nan, China;<sup>2</sup> Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;<sup>3</sup> Division of Radiation Safety and Immune Tolerance, National Research Institute for Child Health and Development, Tokyo, Japan.**Summary**

Numerous studies have indicated that in cancer treatment Chinese herbal medicines in combination with chemo- or radio-therapy can be used to enhance the efficacy of and diminish the side effects and complications caused by chemo- and radio-therapy. Therefore, an understanding of Chinese herbal medicines is needed by physicians and other health care providers. This review provides evidence for use of Chinese herbal medicines as adjuvant cancer treatment during chemo- or radio-therapy. First, Chinese herbal medicines (*e.g.* Astragalus, Turmeric, Ginseng, TJ-41, PHY906, Huachansu injection, and Kanglaite injection) that are commonly used by cancer patients for treating the cancer and/or reducing the toxicity induced by chemo- or radio-therapy are discussed. Preclinical and clinical studies have shown that these Chinese herbal medicines possess great advantages in terms of suppressing tumor progression, increasing the sensitivity of chemo- and radio-therapeutics, improving an organism's immune system function, and lessening the damage caused by chemo- and radio-therapeutics. Second, clinical trials of Chinese herbal medicines as adjuvant cancer treatment are reviewed. By reducing side effects and complications during chemo- and radio-therapy, these Chinese herbal medicines have a significant effect on reducing cancer-related fatigue and pain, improving respiratory tract infections and gastrointestinal side effects including diarrhea, nausea, and vomiting, protecting liver function, and even ameliorating the symptoms of cachexia. This review should contribute to an understanding of Chinese herbal medicines as adjuvant treatment for cancer and provide useful information for the development of more effective anti-cancer drugs.

**Keywords:** Chinese herbal medicine, adjuvant treatment, chemotherapy, radiotherapy

**1. Introduction**

Cancer has emerged as a major global public health problem (1). Its incidence and mortality rates continue to rise. A report released by the World Health

Organization (WHO) shows that in 2008 an estimated 12.7 million people were diagnosed with cancer and 7.6 million people died from cancer worldwide. The WHO predicts that by 2030 an estimated 21.4 million new cases of cancer and 13.2 million cancer deaths will occur annually around the world (2). Surgery, chemotherapy, and radiotherapy are still the major conventional cancer therapies. However, these therapies have numerous limitations and drawbacks: *i)* given poor diagnosis and other factors, most cancer patients are diagnosed too late to undergo surgery; *ii)* most cancers have a postoperative survival rate of less than 5 years and recurrence is quite common in patients who have had a resection; *iii)* although chemotherapy and radiotherapy are effective against cancer, they also have serious side effects and

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complications (*e.g.* fatigue, pain, diarrhea, nausea, vomiting, and hair loss); and *iv*) since some cancers are relatively chemo- or radio-resistant and highly refractory to cytotoxic chemotherapy or radiotherapy, systemic cytotoxic chemotherapy and radiotherapy are minimally effective at improving patient survival (3,4). Therefore, more effective therapies or combination therapies must soon be developed to treat cancer.

Over the past few years, use of complementary and alternative medicine (CAM) has become increasingly popular among cancer patients in Western countries with a prevalence as high as 80% (5,6). Traditional Chinese medicine (TCM) and herbal medicines in particular have been used in the treatment of cancer for thousands of years in China, Japan, and other Asian countries. These medicines are widely accepted as current forms of CAM in cancer treatment in the United States and Europe (7,8). As recent pre-clinical and clinical studies have shown, TCM combined with conventional Western medicine (chemotherapy and radiotherapy) can provide effective supportive care for cancer patients. TCM has great advantages in terms of increasing the sensitivity of chemo- and radio-therapeutics, reducing the side effects and complications associated with chemotherapy and radiotherapy, and improving patient quality of life and survival time (9).

Therefore, an understanding of Chinese herbal medicines is needed by physicians and other health care providers. This review provides evidence for use of Chinese herbal medicines as adjuvant cancer treatment during chemo- or radio-therapy. First, some Chinese herbal medicines (*e.g.* Astragalus, Turmeric, Ginseng, TJ-41, PHY906, Huachansu injection, and Kanglaite injection) that are commonly used by cancer patients to treat the cancer and/or reduce the toxicity induced by chemo- or radio-therapy are discussed. Second, clinical trials of Chinese herbal medicines as adjuvant cancer treatment to reduce the side effects and complications during chemo- and radio-therapy are reviewed. This review should contribute to an understanding of Chinese herbal medicines as adjuvant treatment for cancer and provide useful information for the development of more effective anti-cancer drugs.

## 2. Chinese herbal medicines commonly used as adjuvant treatment in cancer therapy

Chinese herbal medicines have been used in the treatment of a variety of diseases in China, Japan, South Korea, and other Asian countries for thousands of years (10). The biological ingredients of herbal medicines are mainly extracted from plants, animal parts, shells, insects, and even stones and minerals (11). The herbal medicines in current use are usually classified as single

herbs, compound formulations (a combination of several herbs), and Chinese medicine preparations (12). In recent decades, a large number of herbal medicines including single herbs, traditional herbal formulations, and Chinese medicine preparations have been used by cancer patients around the world, and especially in China. Numerous basic and clinical studies have been conducted in order to identify effective anticancer agents in Chinese herbal medicines and ascertain their properties as relate to the treatment of cancer. Several herbal medicines have been found to have potentially beneficial effects on cancer progression and may ameliorate chemotherapy- or radiotherapy-induced complications and side effects (9,13). Therefore, the anticancer pharmacology of the Chinese herbal medicines most commonly used as adjuvant treatment in cancer therapy must be understood.

### 2.1. Single herbs

Several single herbs have been found to have a potentially beneficial effect at treating cancer. A brief outline on the oncologic pharmacology of the most commonly used ingredients is presented below (Table 1).

Radix Astragali (*Astragalus propinquus*, huangqi) has been used in China for thousands of years. It is traditionally considered to be a tonic that can improve the functioning of the lungs, adrenal glands, and the gastrointestinal tract, increase metabolism, promote healing, and reduce fatigue (14). Currently, much of the pharmacological research has shown that *Astragalus* has potent immunomodulatory properties that include increasing the production of interferon, tumor necrosis factor (TNF), activating lymphocytes, natural killer cells, and macrophages (15). *Astragalus* has also been shown to be an adjunct anticancer agent that increases resistance to the immunosuppressive effects of chemotherapy drugs while stimulating macrophages to produce interleukin (IL)-6 and TNF (16). *Astragalus* in combination with recombinant IL-2 is capable of enhancing the anticancer activity of recombinant IL-2-generated lymphokine-activated killer (LAK) cells on murine renal carcinoma cells and reducing the severe side effects of recombinant IL-2 therapy (*e.g.* acute renal failure, capillary leakage syndrome, myocardial infarction, and fluid retention) in the treatment of cancer patients (17).

Turmeric (*Curcuma longa*, jianghuang), a rhizomatous herbaceous perennial plant of the ginger family (Zingiberaceae), has a long history of use in Asia as a treatment for inflammatory conditions. Curcumin, a yellow natural polyphenol, is the primary active constituent of turmeric and has been noted to have numerous pharmacological activities including anti-inflammatory, antioxidant, and anticancer properties (18). Pre-clinical cancer research using curcumin has shown that it inhibits carcinogenesis

**Table 1. Single herbs commonly used in cancer treatment**

Common name	Other names	Latin name	Major active ingredients	Biological activity	Evidence of anticancer activity	Ref.
Radix astragali	Huang qi; Milk vetch	<i>Astragalus membranaceus</i>	Polysaccharides, saponins, flavonoids	Immunomodulatory, anticancer, antiviral	<i>Precinical:</i> Stimulates the production of IL-6 and TNF and enhances the activity of LAK cells  <i>Clinical:</i> Potentiates the activity of chemotherapeutic agents, prolongs survival, reduces the adverse toxicity of chemo- or radio-therapy	15-17
Turmeric	Jianghuang	<i>Curcuma longa</i>	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Anti-inflammatory, antioxidant, anticancer	<i>Precinical:</i> Inhibits carcinogenesis and modulates chemo-resistance and radio-resistance  <i>Clinical:</i> Potentiates the anti-tumor effect of chemotherapeutic agents	18-21
Ginseng	Rensen; Panax	<i>Panax Ginseng</i>	Triterpene glycosides, ginsenosides	Immune-modulation, vasorelaxation, antioxidation, anti-inflammation, anticancer	<i>Precinical:</i> Inhibits cancer growth and potentiates the anti-tumor effect of chemotherapeutic agents  <i>Clinical:</i> Potentiates the anti-tumor effect of chemotherapeutic agents and attenuates the adverse toxicity of chemo- or radio-therapy	22-25
Garlic	Dasuan	<i>Allium sativum</i>	Allicin, alliin	Anti-bacterial, anti-hypertensive, anti-thrombotic, anticancer, immuno-stimulant, hyperglycemic	<i>Precinical:</i> Inhibit cancer growth by inducing differentiation and apoptosis and scavenging carcinogen-induced free radicals  <i>Clinical:</i> Garlic reduces the incidence of stomach, esophageal, and colorectal cancer	26-28
Mylabris	Banmao	<i>Mylabris phalerata</i>	Cantharidin	Anticancer	<i>Precinical:</i> Inhibit cancer growth by inducing cell apoptosis and regulating the immune system  <i>Clinical:</i> No reports in English	29,30
Toad venom	Chansu	<i>Bufo bufo gargarizans</i> Cantor	Bufadienolides	Cardiotonic, antimicrobial, local anesthetic, analgesic, anticancer	<i>Precinical:</i> Inhibits cancer growth by inhibition of cell proliferation and induction of cell apoptosis  <i>Clinical:</i> No reports in English	12,31-33

in a number of cancers (*e.g.* colorectal, pancreatic, gastric, prostate, and hepatic) and at various stage of carcinogenesis (*e.g.* proliferation, angiogenesis, and metastasis) (19). Curcumin has also been found to be a chemo-sensitizer that enhances the activity of other anticancer agents in the treatment of chemo-resistant and multidrug-resistant (MDR) cancer (20). Furthermore, curcumin has a radio-sensitizing and radio-protective effect on cancer cells. Curcumin in combination with radiation has been found to significantly enhance radiation-induced inhibition and apoptosis of the prostate cancer cell line PC3 (21).

Ginseng (*Panax ginseng*) is one of the most widely used herbal medicines and has been used as a restorative tonic in China, Japan, and South Korea for thousands of years. It can improve circulation, increase blood supply, and aid recovery from weakness after illness (22). Currently, much of the pharmacological research has shown that Ginseng has potent immune modulation, vasorelaxation, anti-oxidation, anti-inflammation, and anticancer properties. Ginseng has potential as a chemo-preventive agent or adjuvant treatment in stomach, liver, pancreas, and colon cancer

by inhibiting the inflammation-to-cancer sequence (23). Ginseng appears to be a promising radio-protector and is capable of attenuating the deleterious effects of radiation on normal human tissue, and especially for cancer patients undergoing radiotherapy. This activity may be associated with its anti-oxidation and immune modulation properties (24). In addition, an epidemiological study indicated that patients taking ginseng had a 50% lower risk of cancer recurrence compared to patients not taking ginseng (25).

Garlic (*Allium sativum*) has been used for medicinal purposes for thousands of years. Historically, garlic has been used to treat infections, diarrhea, rheumatism, and snakebites. Currently, much of the pharmacological research has shown that garlic has anti-bacterial, anti-hypertensive, anti-thrombotic, anticancer, immuno-stimulant, and hyperglycemic activity (26). Garlic contains a high concentration of sulfur-containing compounds (*e.g.* allicin and alliin) that appear to be the active substances in garlic. Numerous preclinical studies have shown that garlic and its active constituents have an anticancer effect on various tumors and especially on colon tumors by

controlling DNA repair, inhibiting cell proliferation and angiogenesis, inducing differentiation and apoptosis, inhibiting metabolism, and scavenging carcinogen-induced free radicals (27,28). In addition, epidemiological studies have shown a decreased risk of stomach, esophageal, and colorectal cancer with increased consumption of garlic (27).

Mylabris (*Mylabris phalerata*) is the dried body of the Chinese blister beetle and has been used as a Chinese herbal remedy for more than 2,000 years. The active constituent of mylabris is cantharidin (29). Recent preclinical studies have shown that mylabris and cantharidin have anticancer activity on various cancers and especially on liver and esophageal cancer by inducing cell apoptosis and regulating the immune system (29,30). However, their toxicity on the renal system and suppression of bone marrow limits their clinical usage. Therefore, several modified cantharidin analogues (e.g. norcantharidin) have been synthesized chemically in order to achieve anticancer properties comparable to the original compound but with less of a toxic effect on non-cancer cells. Such analogues may be more suitable for medical investigation than cantharidin itself (30).

Toad venom, known as Chansu in China, is obtained from the postauricular and skin glands of the toad (*Bufo bufo gargarizans* Cantor). Chansu has been widely used as an anodyne, cardiotoxic, antimicrobial, local anesthetic, and antineoplastic agent in China and other Asian countries for thousands of years (12). It is the major component of several popular traditional Chinese medications such as Liushenwan, Shexiangbaixinwan, and Niuhuangxiaoyanwan. These Chinese medications have long been used in China, Japan, Korea, and other Asian countries and are currently used as alternative medicines. Bufadienolides, such as bufalin, cinobufagin, resibufogenin, and telocinobufagin, are the major active constituents derived from Chansu (31). Preclinical studies of Chansu and its constituents have shown they have a potent anticancer effect on leukemia and liver, lung, and prostate cancers by inhibiting cell proliferation and inducing cell apoptosis (32). In addition, some Chinese medicine preparations (e.g. Huachansu) containing Chansu have been prepared and are widely used in clinical cancer treatment in China (33).

## 2.2. Traditional herbal formulations

Traditional herbal formulations (or Kampo in Japanese) are compound formulations that mostly come from Shang Han Lun and Jin Gui Yao Lue, two classics of traditional medicine edited by Zhang Zhongjing, a well-known Chinese physician during the Han Dynasty (34). A brief outline on the oncologic pharmacology of the most commonly used traditional herbal formulations is presented below (Table 2).

TJ-41 (Bu-Zhong-Yi-Qi-Tang in Chinese, Hochu-ekki-to in Japanese or Bojungikki-Tang in Korean) is a traditional herbal formulation widely used in China, Japan, and South Korea. It contains 7 herbs including *Pinellia tuber*, *Scutellaria baicalensis*, *Zingiberis rhizoma*, *Zizyphi fructus*, *Coptidis rhizoma*, *Glycyrrhiza radix*, and *Panax ginseng* (35). Currently, much of the pharmacological research has shown that TJ-41 has potent immunomodulatory and anticancer properties. TJ-41 has a significant chemo-preventative effect on ovarian and liver cancer lines by inducing apoptosis and arresting the cell cycle (36,37). The oral administration of TJ-41 is able to enhance concomitant immunity against tumor development and restore the antitumor T cell response in tumor-bearing mice (38). In addition, TJ-41 has been shown to reduce the extent of side effects such as leucopenia and intestinal damage and fatigue occurring as a result of radiation or chemotherapy to treat malignant tumors (39,40).

TJ-48 (Shi-Quan-Da-Bu-Tang in Chinese and Juzen-taiho-to in Japanese) is a famous traditional herbal formulation that has long been used to treat anemia, anorexia, extreme exhaustion, and fatigue. It contains 10 herbs including *Angelica sinensis*, *Paeonia lactiflora*, *Atractylodes macrocephala*, *Poria cocos*, *Cinnamomum cassia*, *Astragalus membranaceus*, *Liquisticum wallichii*, *Glycyrrhiza inflata*, and *Rehmannia glutinosa* (41). Currently, TJ-48 has been shown to have an antitumor effect on various cancers (e.g. endometrial carcinoma and malignant glioma) by regulating estrogen receptors or enhancing systemic immunological function (42,43). Furthermore, TJ-48 has the advantage of minimal toxicity in combination with chemotherapy or radiation therapy. The combination of TJ-48 and mitomycin C (MMC) resulted in significantly longer survival in p-388 tumor-bearing mice than MMC alone, and TJ-48 decreased the diverse effects of MMC such as leukopenia, thrombopenia, and weight loss (41).

PHY906 is a modified pharmaceutical preparation derived from the traditional herbal formulation Huang-Qin-Tang, which has been used for over 1,800 years in the Orient to treat a wide range of gastrointestinal symptoms, including nausea, vomiting, cramping, and diarrhea. PHY906 consists of four commonly used herbs, *Scutellaria baicalensis* Georgi, *Paeonia lactiflora* Pall, *Glycyrrhiza uralensis* Fisch, and *Ziziphus jujube* Mill, at a ratio of 3:2:2:2 (44). Numerous studies have shown that PHY906 not only reduces gastrointestinal toxicity and enhances the antitumor efficacy of some anticancer drugs but also alleviates chemotherapy-induced side effects, such as diarrhea. Clinical trials indicate that PHY906 can serve as an adjuvant to CTP-11, 5-fluorouracil (5-FU), leucovorin (LV), and capecitabine in the treatment of advanced colorectal, pancreatic, and liver cancer (45-47). PHY906 treatment results in a significant decrease in patient nausea and diarrhea, and no PHY906-associated toxicity has been observed.

**Table 2. Traditional herbal formulations commonly used in cancer treatment**

Common name	Other names	Composition	Biological activity	Evidence of anticancer activity	Ref.
TJ-41	Bu-Zhong-Yi-Qi-Tang; Hochu-ekki-to; Bojungikki-Tang	Includes 7 herbs: <i>Pinellia tuber</i> , <i>Scutellaria baicalensis</i> , <i>Zingiberis rhizoma</i> , <i>Zizyphi fructus</i> , <i>Coptidis rhizoma</i> , <i>Glycyrrhiza radix</i> , <i>Panax ginseng</i>	Immunomodulatory, anticancer	<i>Precinical:</i> Inhibits cancer growth by inducing apoptosis, arresting the cell cycle, and enhancing immunity  <i>Clinical:</i> Attenuates the adverse toxicity of chemo- or radio-therapy	35-40
TJ-48	Shi-Quan-Da-Bu-Tang; Juzen-taiho-to	Includes 10 herbs: <i>Angelica sinensis</i> , <i>Paeonia lactiflora</i> , <i>Atractylodes macrocephala</i> , <i>Poria cocos</i> , <i>Cinnamomum cassia</i> , <i>Astragalus membranaceus</i> , <i>Liquisticum wallichii</i> , <i>Glycyrrhiza inflata</i> , <i>Rehmannia glutinosa</i>	Immunomodulatory, anticancer	<i>Precinical:</i> Inhibits cancer growth by regulation of estrogen receptors or enhancement of systemic immunological function  <i>Clinical:</i> Improves quality of life and survival	41-43
PHY906	Huang-Qin-Tang	Includes 4 herbs: <i>Scutellaria baicalensis</i> Georgi, <i>Paeonia lactiflora</i> Pall, <i>Glycyrrhiza uralensis</i> Fisch, <i>Zizyphus jujube</i> Mill	Anti-inflammatory, anticancer	<i>Precinical:</i> Enhances the antitumor efficacy of some anticancer drugs and alleviates chemotherapy-induced side effects, such as diarrhea  <i>Clinical:</i> Potentiates the anti-tumor effect of chemotherapeutic agents and attenuates chemotherapy-induced side effects	44-47

### 2.3. Chinese medicine preparations

Chinese medicine preparations are a form of Chinese herbal medicine that are isolated from single herbs or traditional herbal formulations and that are prepared using modern advanced pharmaceutical technology. There are various dosage forms including injections, tablets, pills, capsules, and liquids. Compared to traditional decoctions, Chinese medicine preparations are safer, more effective, and easier to use (12). Thus, Chinese medicine preparations are becoming increasingly popular in China and are attracting worldwide attention. A brief outline on the oncologic pharmacology of the most commonly used Chinese medicine preparations that have been approved by the State Food and Drug Administration (FDA) of China is briefly presented below (Table 3).

Huachansu (Cinobufacini) injection, an aqueous extract from the skin and parotid venom glands of the toad (*Bufo bufo gargarizans* Cantor) that contains Chansu, is a Chinese medicine preparation widely used in clinical cancer therapy in China (33). Cardiac glycosides including bufalin, resibufogenin, and cinobufagin are the three major active constituents to which the antitumor activity of huachansu may be attributed (48,49). Pre-clinical studies have shown that huachansu effectively inhibits growth and has anti-hepatitis B virus (HBV) activity on human hepatocellular carcinoma (HCC) cells (50-52). Huachansu induces apoptosis of HCC cell lines HepG2 and Bel-7402 *via* a mitochondria-mediated apoptotic pathway (51). Clinical data showed that

Cinobufacini used alone or in combination with other chemotherapeutic agents (*e.g.* gemcitabine and oxaliplatin) had significant anticancer activity against human cancers, such as HCC, non-small-cell lung cancer, pancreatic cancer, and gallbladder carcinoma (33,53). A pilot study of huachansu in patients with HCC, non-small-cell lung cancer, and pancreatic cancer showed that huachansu improved the quality of life of patients and even reduced tumor shrinkage with little toxicity (33). Another clinical study using huachansu in combination with gemcitabine and oxaliplatin in treating gallbladder carcinomas showed that huachansu substantially enhanced the antitumor efficacy of gemcitabine and oxaliplatin and improved the quality of life of patients (53).

Kanglaite injection is an acetone extract of herbal medicine coix seed (*Semen Coicis Yokuinin*) prepared as an herbal medicine using modern advanced pharmaceutical technology. The injection has been approved for the treatment of lung and hepatic cancer in China (35). Preclinical experiments have shown that kanglaite may inhibit tumor cell mitosis at the boundary of the G2/M phase of the cell cycle and induce apoptosis through activation of the Fas/FasL pathway (54). A phase I study of Kanglaite in 16 patients with refractory solid tumors (*e.g.* lung, colon, prostate, and esophageal cancer) was conducted at the Huntsman Cancer Institute (Salt Lake City, UT, USA) and no dose-limiting hematologic or symptomatic toxicity was observed in the first cycle at a maximum dose of up to 50,000 mg/day (55). A recent randomized phase II study at the Shanghai Cancer Hospital of Fudan University

**Table 3. Chinese medicine preparations commonly used in cancer treatment**

Common name	Composition	Biological activity	Evidence of anticancer activity	Ref.
Huachansu injection	<i>Bufo bufo gargarizans</i> Cantor	Anticancer, anti-HBV	<i>Precinical:</i> Induces cancer cell apoptosis through a mitochondria-mediated apoptotic pathway  <i>Clinical:</i> Potentiates the anti-tumor effect of chemotherapeutic agents, attenuates chemotherapy-induced side effects, improves quality of life and survival	33,48-52
Kanglaite injection	<i>Semen Coicis</i>	Anticancer	<i>Precinical:</i> Inhibits the cell cycle in the G2/M phase and induces apoptosis through activation of the Fas/FasL pathway  <i>Clinical:</i> Potentiates the anti-tumor effect of chemotherapeutic agents	35,53-55
Shenqi fuzheng injection	<i>Astragalus propinquus</i> , <i>Codonopsis pilosula</i>	Immunomodulatory, anticancer	<i>Precinical:</i> Potentiates the anti-tumor effect of chemotherapeutic agent and attenuates chemotherapy-induced side effects  <i>Clinical:</i> Potentiates the anti-tumor effect of chemotherapeutic agents, attenuates chemotherapy-induced side effects, improves quality of life and survival	56,57

(Shanghai, China) used an MMC/cisplatin (DDP) regimen in combination with kanglaite as a salvage treatment for patients with advanced breast cancer ( $n = 60$ ) (56). Results indicated that there was no additional benefit when kanglaite was added to the MMC/DDP combination in the management of breast cancer, so the effect of kanglaite on cancer will be evaluated further in a phase II study.

The Shenqi fuzheng injection is isolated from two kinds of herbal medicines, *Astragalus propinquus* (huangqi) and *Codonopsis pilosula* (dangshen), using modern advanced pharmaceutical technology. The injection has been approved by China's FDA primarily as an antitumor injection since the 1990s (57). Currently, many trials have studied the shenqi fuzheng injection in combination with chemotherapy (e.g. 5-FU and cisplatin) in patients with lung, breast, and colorectal cancer; some have shown that the shenqi fuzheng injection may play an important role in the treatment of advanced cancers by improving tumor response and reducing the toxicity of chemotherapy (57,58). However, most of these trials were conducted in China and little is known about use of the shenqi fuzheng injection outside of China. Thus, the mechanisms of the injection's action must be investigated and the injection must be clinically evaluated further.

### 3. Clinical trials of Chinese herbal medicines as adjuvant treatment in cancer therapy

In conventional Western medicine, chemotherapy and radiotherapy are major conventional cancer therapies. These therapies are directed at killing or eradicating cancer cells. Unfortunately, distinguishing between cancer cells and normal healthy cells is difficult for most cancer treatments, leading to the damage of normal cells (59,60). The results of this damage are called complications and side effects of cancer

treatment and mainly include fatigue, pain, infection/fever, anemia, diarrhea, nausea and vomiting, hair loss, and bone marrow suppression (61). These complications and side effects inconvenience and cause discomfort to patients and they may also limit or prevent the delivery of therapy at its optimal dose and time, potentially causing fatalities (62). Thus, more effective therapies to help prevent and control the complications and side effects of conventional cancer therapy must soon be developed. Several Chinese herbal medicines have been found to be adjunctive in chemo- and radiotherapy. However, numerous clinical trials have been published only in China or other Asian countries and cannot be found on PubMed. Thus, reports of clinical trials published on PubMed were searched to provide a brief outline on the use of Chinese herbal medicines to reduce complications and side effects associated with conventional cancer therapy (Table 4).

#### 3.1. Fatigue

Fatigue is regarded as a highly prevalent and unavoidable side effect experienced during the course of cancer and chemo- or radio-treatment. Many studies have found that the prevalence rates of fatigue in cancer patients exceed 60% (63). Cancer-related fatigue significantly interferes with patients' daily activities and decreases their quality of life. However, it remains under-recognized and under-treated, partly because of limited understanding of its pathophysiology and lack of effective treatments (64). Several Chinese herbal medicines may have beneficial effects on cancer-related fatigue and quality of life for cancer patients. In a pilot randomized clinical trial, 40 patients with cancer-related fatigue were randomized into an experimental group treated with Bojungikki-tang for 2 weeks and a control group without any intervention (40). The participants in the trial included breast cancer patients ( $n = 11$ , 27.5%), colon cancer patients ( $n = 5$ , 12.5%),

**Table 4. Clinical trials of Chinese herbal medicines as adjuvant treatment to reduce complications and side effects**

Complications and side effects	Patients	Experimental group	Control group	Outcomes	Ref.
Fatigue	<i>n</i> = 40 (breast, stomach, and colon cancer)	TJ-41 + chemotherapy or radiotherapy	Chemotherapy or radiotherapy	Fatigue level increased (experimental group <i>versus</i> control group, <i>p</i> < 0.05).	40
Pain	<i>n</i> = 250	Kang-Fu-Zhi-Tong adhesive plaster	Morphine	The analgesic effect was equivalent in the 2 groups ( <i>p</i> > 0.05). The analgesia time was prolonged significantly (experimental group <i>versus</i> control group, <i>p</i> < 0.001).	66
Radiation pneumonitis	<i>n</i> = 100 (lung cancer)	Liangxue Jiedu Huoxue Decoction + radiotherapy	Radiotherapy	The incidence rate of radiation pneumonitis was lower in the treatment group than in the control group (13.04% <i>versus</i> 33.33%, <i>p</i> < 0.05).	66
Gastrointestinal side effects (diarrhea, nausea, and vomiting)	<i>n</i> = 24	PHY906	Chemotherapy (capecitabine)	Some gastrointestinal side effects such as diarrhea were reduced.	70
Hepatotoxicity	<i>n</i> = 84	Chinese herbal formulations (Xiao-Chai-Hu-Tang, Huang-Lian-Jie-Du-Tang or Yin-Chen-Wu-Ling-San) + chemotherapy	Chemotherapy	The serum levels of ALT and AST in combination treatment group were lower than in the control group.	72
Cachexia	<i>n</i> = 22	Atractylenolide I	Fish-oil	Atractylenolide I ameliorated the symptoms of gastric cancer cachexia	74
Idiopathic sweating	<i>n</i> = 32	Yu-Ping-Feng-San	Nothing	Twenty-six patients (81.3%) had cessation of sweating during or after treatment	75

stomach cancer patients (*n* = 5, 12.5%), lung cancer patients (*n* = 5, 12.5%), and patients with other cancers (*n* = 14, 35.0%). Before the trial started, participants had undergone chemotherapy or radiotherapy for nearly one and a half years. Results showed that the fatigue level in the experimental group improved significantly compared to that in the control group (*p* < 0.05). Furthermore, liver and kidney function (the serum levels of alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), and creatinine) were measured to test the toxicity of Bojungikki-tang and no serious adverse effects occurred during the trial. However, more rigorous trials are needed to confirm the efficacy of Bojungikki-tang and other herbal medicines on cancer-related fatigue.

### 3.2. Pain

Pain is a common symptom of cancer and the causes of pain can be disease or treatment-related (*e.g.* surgery, chemotherapy, or radiotherapy). The prevalence of pain in patients with cancer has been reported to be between 50% and 70% during cancer treatment (65). As indicated in current WHO guidelines, combined treatments are the standard of care for cancer pain (66). Trials have suggested that Chinese herbal medicines may be effective at treating cancer pain and that their effects are similar to those of Western

analgesics. Chinese herbal medicines may reduce the side effects of conventional analgesics, thus enhancing cancer patients' quality of life (67). In a randomized controlled clinical trial, 250 patients with cancer pain were randomized into an experimental group treated with a Chinese medicine preparation in the form of Kang-Fu-Zhi-Tong adhesive plaster (*n* = 182) and a control group treated with morphine (*n* = 68) (67). The results showed the analgesic effect in the 2 groups was equivalent after 3 days of treatment (*p* > 0.05). However, the analgesia time was significantly prolonged in the herbal treatment group compared to that in the morphine group (*p* < 0.001).

### 3.3. Respiratory tract infections

Radiation pneumonitis is one of the most common complications during radiotherapy for thoracic tumors. It impacts the quality of life of patients and is life-threatening. Although corticosteroid therapy is useful in the treatment of acute pneumonitis, it causes numerous side effects (68). Clinical trials have suggested that Chinese herbal medicines may be effective at treating radiation pneumonitis with few side effects. In a prospective randomized clinical study, 100 lung cancer patients scheduled to receive radiotherapy were randomly divided into a treatment group (Liangxue Jiedu Huoxue Decoction

+ radiotherapy) and control group (radiotherapy) with 50 patients in each group (69). Results showed that the incidence rate of radiation pneumonitis was lower in the treatment group than in the control group (13.04% versus 33.33%,  $p < 0.05$ ). Furthermore, the extent of lung injuries and the symptoms of radiation pneumonitis improved in the treatment group.

#### 3.4. Gastrointestinal side effects

Gastrointestinal side effects including diarrhea, nausea, and vomiting are the most common symptoms occurring in patients receiving chemo- or radio-therapy (70). However, there is still no effective treatment to ameliorate diarrhea, nausea, or vomiting in cancer patients. Recently, clinical trials have suggested that Chinese herbal medicines may be effective at treating these side effects. A phase study was conducted using PHY906 in combination with capecitabine in patients with advanced pancreatic and gastrointestinal malignancies (71). Twenty-four cancer patients were randomly divided into 4 groups and treated with different concentrations of capecitabine (1,000, 1,250, 1,500, and 1,750 mg/m<sup>2</sup>, bid) in combination with PHY906 (800 mg, bid) for 14 days. Results showed that there was no dose-limiting toxicity at the maximum dose level of 1,750 mg/m<sup>2</sup> and some gastrointestinal side effects such as diarrhea were reduced. These findings suggest that PHY906 increased the therapeutic index of capecitabine in patients by reducing its side effects.

#### 3.5. Hepatotoxicity

Hepatotoxicity is a common side effect of chemotherapy. Its prevalence ranges from 33 to 65.6% among patients with cancer, and up to 30% of patients have grade III or IV hepatotoxicity (72). If hepatotoxicity is severe (as indicated by AST and ALT levels), chemotherapy may be canceled or delayed for some cancer patients. However, there are no drugs that effectively protect liver function and elevation of liver enzymes is sometimes accompanied by severe thrombocytopenia and other aggravated side effects (73). Chinese herbal medicines may be effective at improving hepatotoxicity. A case-control study was conducted using the medical records of 89 patients with cancer who received a total of 184 courses of chemotherapy. Of the 184 courses, 42 in which Chinese herbal formulations (Xiao-Chai-Hu-Tang, Huang-Lian-Jie-Du-Tang or Yin-Chen-Wu-Ling-San) were used in combination with chemotherapy served as the experimental group while the remaining 142 courses served as the control group (73). Results showed that the combined treatment group had lower serum levels of ALT and AST than did the control group. This suggests that use of Chinese herbal medicines might result in the protection of liver function during

chemotherapy.

#### 3.6. Other complications or side effects

Cachexia is a syndrome characterized by body weight loss and metabolic abnormalities. It is responsible for 22% of all cancer patients' deaths and is associated with a shorter survival period and reduced quality of life (74). However, no effective systemic anticancer therapy is available, and the toxicity of conventional chemotherapy may diminish a patient's nutritional status. Therefore, a novel agent to improve the symptoms of cachexia and quality of life for patients with advanced cancer must be identified. A randomized pilot study of atractylenolide I (the main bioactive chemical compound of the Chinese herb *Rhizoma atractylodis*) was conducted in patients with gastric cancer-related cachexia (75). A total of 22 cancer patients were randomly divided into 2 groups: a group given atractylenolide I and a control group given fish oil for 7 weeks. Results showed that atractylenolide I ameliorated the symptoms of gastric cancer-related cachexia (as gauged by parameters such as appetite, body weight, and mid-arm muscle circumference) presumably by mediating cytokine (IL-1, IL-6, and TNF- $\alpha$ ) production and inhibiting proteolysis-inducing factor.

End-stage cancer patients frequently suffer from idiopathic sweating that may be associated with greater susceptibility to upper airway infections and subsequent sepsis. The traditional Chinese herbal formulation Yu-Ping-Feng-San includes three herbs (*Saposhnikovia divaricata*, *Rhizoma atractylodis*, and *Astragalus propinquus*) and has been used in traditional Chinese medicine for more than 400 years to manage sweating. A prospective clinical study was conducted to evaluate the effect of Yu-Ping-Feng-San on end-stage cancer patients ( $n = 32$ ) with idiopathic sweating and adverse reactions (76). Quantitative measurement of sweating showed that 26 patients (81.3%) had ceased idiopathic sweating during or after treatment. This study indicated that Yu-Ping-Feng-San may be effective at relieving idiopathic sweating in end-stage cancer patients. However, a randomized, double-blinded clinical trial should be conducted to verify this therapeutic effect.

#### 4. Conclusion

In conclusion, Chinese herbal medicines substantially influence cancer therapy as adjuvant treatment. In cancer treatment, Chinese herbal medicines in combination with chemo- or radio-therapy are capable of enhancing the efficacy of and diminishing the side effects and complications caused by chemo- and radio-therapy. Chinese herbal medicines (*e.g.* Astragalus, Turmeric, Ginseng, TJ-41, PHY906, Huachansu injection, and Kanglaite injection) have great

advantages in terms of suppressing tumor progression, increasing the sensitivity of chemo- and radio-therapeutics, improving an organism's immune system function, and lessening the damage caused by chemo- and radio-therapeutics. They have a significant effect on reducing cancer-related fatigue and pain, improving respiratory tract infections and gastrointestinal side effects including diarrhea, nausea, and vomiting, protecting liver function, and even ameliorating the symptoms of cachexia. This review of those medicines should contribute to an understanding of Chinese herbal medicines as adjuvant treatment for cancer and provide useful information for the development of more effective anti-cancer drugs. However, randomized, effective Chinese herbal medicines must be further examined in controlled clinical trials involving cancer patients.

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