

The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer

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Summary

Recent studies indicate that Traditional Chinese medicine (TCM) can play an important role in the whole course of cancer treatment such as recovery stages of post-operative, radiotherapy or chemotherapy stages instead of only terminal stage of cancer. In this review, we have summarized current evidence for using TCM as adjuvant cancer treatment in different stages of cancer lesions. Some TCMs (e.g., TJ-41, Liu-jun-zi-tang, PHY906, Coumarin, and Aescine) are capable of improving the post-operative symptoms such as fatigue, pain, appetite, diarrhea, nausea, vomiting, and lymphedema. Some TCMs (e.g., Ginseng, Huang-Qi, BanZhiLian, TJ-48, Huachansu injection, Shenqi fuzheng injection, and Kanglaite injection) 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 radiotherapy. Taken together, they have great advantages in terms of suppressing tumor progression, relieving surgery complications, increasing the sensitivity of chemo- and radio-therapeutics, improving an organism's immune system function, and lessening the damage caused by surgery, chemo- or radio-therapeutics. They have significant effects on relieving breast cancer-related lymphedema, reducing cancer-related fatigue and pain, improving radiation pneumonitis and gastrointestinal side effects, protecting liver function, and even ameliorating bone marrow suppression. This review of those medicines should contribute to an understanding of Chinese herbal medicines as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer, by providing useful information for development of more effective anti-cancer drugs and making more patients "survival with cancer" for a long time.

Keywords: Traditional Chinese medicine (TCM), adjunctive therapy, the whole course of cancer treatment, post-operation, chemotherapy, radiotherapy

1. Introduction

Cancer is redefined as a chronic health problem like hypertension and diabetes by the World Health Organization (WHO) and is increasing fast in

incidence in all regions of the world. It is predicted to be a worldwide important cause of morbidity and mortality in the next few decades. By 2020 in the world approximately 24.6 million people will live with cancer with about 12.5% of all deaths attributable to cancer, and in China approximately 3.12 million per year or 8,550 new cancer cases per day will emerge with a death toll of 2.5 million; furthermore, the chance of suffering from a malignant tumor is about 22% for a person in his life (1,2). Thus, in the coming years it is still a huge challenge for cancer prevention and therapy in the world especially in low and middle-income countries such as China.

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Surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy are examples of anti-cancer therapies currently being utilized for controlling tumor growth, prolonging survival time, and improving quality of life to some extent. However, these therapies either alone or in combination have been shown to have numerous limitations and drawbacks: (i) Given poor diagnosis and other factors, most cancer patients are diagnosed too late to undergo surgery; even with the surgical indications, a series of complications might occur postoperatively such as bleeding, infection, bile reflux, and lymphedema, and postoperative recurrence and metastasis is quite common in patients who have had a resection. (ii) Chemotherapy and radiotherapy are still major postoperative adjunctive therapies or preferred therapies for patients with malignant tumors in middle and advanced stages, however, there are many side effects and complications such as myelosuppression, gastrointestinal tract reaction, cardiac damage, liver and renal function, or local radiation damage; in addition, cancer cells have ability to develop resistance to these conventional therapeutics over time and some cancers are insensitive to chemotherapy or radiotherapy. (iii) Targeted therapy as a newer type of cancer treatment which can more precisely identify and attack cancer cells, however, some drugs target substances that are more common on cancer cells but are also found on healthy cells and can affect healthy cells, too, causing side effects (e.g., high blood pressure, damage to liver, kidneys, or heart, allergic reactions) (3); in addition, the price of targeted drugs is so high that most patients cannot afford them. (iv) Immunotherapy is another new approach including cytokine infusions, cancer vaccines, and T cell therapy. It can stimulate immune cells to enhance their anticancer activity (4); however, the advantages of immunotherapy on improving the patient's quality of life and prolonging survival time are still unclear currently; furthermore, in addition the price of immunotherapy is so high that most patients cannot afford it. Therefore, more effective or adjunctive therapies must be soon developed for cancer prevention and treatment.

With development of medicine and update of knowledge, cancer therapy has come into a diversified comprehensive treatment stage. Many scholars put forward the concept of "survival with cancer", and they insist controlling cancer and causing cancer cells to "be static" and "hibernate" for a long time, is better than striving to reduce the lump and completely kill all cancer cells (5). In the process of "survival with cancer", traditional Chinese medicine (TCM) might play an important role.

TCM, as an important component of complementary and alternative medicine, evolved over thousands of years with its own unique system of theories, diagnostics and therapies in Asian countries, especially China. In the world including Western countries, TCM has been increasingly used in the last decades and has become well

known for its significant role in preventing and treating cancer. It is estimated that the United States National Cancer Institute (NCI) spends around \$120 million each year on TCM related research projects (6). According to conventional views, we believe that TCM possesses advantages as an adjuvant therapy to alleviate cancer symptoms at terminal stages when Western medicine treatments cannot offer any other treatment options. However, recent studies indicate that TCM can play an important role in the whole course of cancer prevention and treatment such as recovery stages post-operation, and when undergoing radiotherapy or chemotherapy (7). It may be capable of preventing tumorigenesis, shrinking or stabilizing tumors, reducing tumor recurrence and metastasis. It may also be capable of protecting cancer patients from suffering from complications, increasing sensitivity or reducing side-effects of conventional treatment, and improving quality of life and survival (8).

Since cancer is defined as a chronic disease like hypertension and diabetes, the role of TCM in treating chronic diseases especially cancer should not be overlooked. Thus, an understanding of TCM is needed by physicians and other health care providers. In this review, we will summarize the current evidence for using TCM as adjuvant cancer treatment in different stages of cancer lesions. First, some single TCMs and traditional herbal formulations which are commonly prescribed by traditional Chinese physicians for cancer patients will be summarized. Second, some TCM preparations which possess properties such as anti-cancer, improving immunity and protecting bone marrow, and are commonly used in clinical cancer treatment will be summarized. Third, the advantages of TCMs in different stages of cancer treatment such as recovery stages post-operation, and when undergoing radiotherapy or chemotherapy will be summarized. In a word, we hope this review should contribute to an understanding of TCM as adjuvant treatment for different stages of cancer, providing useful information for development of more effective anti-cancer drugs and making more patients "survival with cancer" for a long time.

2. Single TCMs commonly prescribed by traditional Chinese physicians for cancer treatment

Based on traditional Chinese medicine classic theory, the formation of tumors are usually due to deficiency of vital energy or Qi and blood in the body, combined with some pathogenic factors such as external evil invading, emotional abnormality, overeating and so on, leading to Qi stagnation, blood stasis and heat- and dampness-induced toxicity blocking in the body, and then forming a lump or lumps for many days (9,10). According to the above theory, TCMs which are used for cancer treatment usually fall into three categories: the first one with the properties of spiriting vital energy (Qi and blood), the second one with the properties of promoting blood

circulation and removing blood stasis, and the third with properties of clearing heat and detoxifying (11). Numerous studies have shown that many TCMs (e.g., *Ginseng Radix*, *Radix astragali*, *Radix Codonopsis*, and *Poria cocos*) with properties of spiriting vital energy play important roles in cancer treatment with the basis summarized as follows: (i) improving immune system function; (ii) protecting hematopoiesis of bone marrow; (iii) harmonizing gastrointestinal function (12,13). In addition, numerous studies have shown that many TCMs with properties of promoting blood circulation and removing blood stasis (e.g., *Angelica sinensis Radix*, and *Curcuma longa*), or clearing heat and detoxifying (e.g., *Hedyotis diffusa willd*, and *Scutellaria barbata*), also play important roles in cancer treatment involving anti-proliferation, anti-inflammation, anti-oxidation, anti-angiogenesis, anti-thrombotic, immune-modulation and so on (7,11,12,14). Thus, according to references and our clinical experience, we will choose some single TCMs commonly prescribed by traditional Chinese physicians for cancer treatment and give them a brief introduction especially regarding clinical studies (Table 1).

2.1. Some single TCMs with properties of spiriting vital energy

2.1.1. *Ginseng Radix*

Ginseng Radix (Ren-Shen in Chinese or Ginseng in Korea) is a well-known and popular TCM, which is believed to be the king of the herbs in the Orient particularly in China, Korea and Japan. It has been used for several thousand years with mysterious powers as a tonic, prophylactic and restorative agent (15). *Ginseng Radix* is reported to contain many active constituents including ginsenosides, essential oils, peptidoglycans, polysaccharides, nitrogen-containing compounds, fatty acids and phenolic compounds (16). Modern pharmacological studies have shown that *Ginseng Radix* and its active constituents have antitumor, antioxidant, immunomodulation, anti-ulcer, anti-adhesive, antioxidant, hepatoprotective, hypoglycemic activities, and so on (17). They have been proposed to have a chemopreventive effect on lung, gastric, liver, pancreas, and colon cancers and so on in cells, animals or humans (17-19). An epidemiological study indicated that patients taking ginseng had a 50% lower risk of cancer recurrence compared to patients not taking ginseng (12). In the following, we emphasize clinical research in recent years. An observational pilot study of cultivated wild Ginseng phar-maco-puncture (CWGP) was conducted at the East-West Cancer Center of Daejeon University (Daejeon, Korea) and the results indicated that CWGP showed potential as an effective treatment for advanced cancer patients on improving response and survival rate (20). A phase III trial was developed by Mayo Clinic Rochester (Rochester, USA) to evaluate the efficacy

of Ginseng on cancer-related fatigue and the results indicated that 2,000 mg/daily of Ginseng showed great benefit for ameliorating cancer-related fatigue without any discernible toxicity (21). Moreover, Ginseng extract could help in protecting tissue damage from inflammatory cytokines (IL-2, IL-10, IL-12, TNF-alpha, and IFN-gamma) in children after chemotherapy, which might be associated with decreased late complications of childhood (22). In addition, 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, which might be associated with its anti-oxidation and immunomodulation properties (23).

2.1.2. *Radix astragali*

Radix Astragali (Huang-Qi in Chinese), is the dried root of *Astragalus membranaceus Bge. Var. mongholicus*, and one of the most famous and frequently used herbal medicines and healthy food supplements used as a tonic. It has been used for over 2000 years in TCM prescriptions for the treatment of animal bites and poisons, wounds and burns, nephritis, diabetes, albuminuria, hypertension, cirrhosis, and various cancers (24). Chemical constituent investigations on *Radix Astragali* indicated that it contains several bioactive constituents including, isoflavonoids, triterpenoid saponins, polysaccharides, amino butyric acids and various trace elements; of which triterpenoid saponins represent the major beneficial constituents responsible for the bioactivities and efficacies of *Radix Astragali* on human health (25). Modern pharmacological studies have shown that *Radix Astragali* and its active constituents possess antioxidant, antitumor, hepatoprotective, anti-diabetic, antimicrobial, antiviral and immune enhancement activities (25,26). They have been proposed to have an anticancer effect on breast, gastric, liver, colon, lung cancers and so on in cells, animals or humans. *Via* inhibiting cancer cell proliferation, regulating immunity, suppressing angiogenesis, or reducing side effects of chemotherapeutics, they play important roles in cancer therapy (26-28). In the following, we emphasize clinical research in recent years. Some studies indicated that decoctions of Huang-Qi compounds could reduce the proportion of patients who experienced nausea and vomiting and decrease the rate of leucopenia in colorectal cancer patients treated with chemotherapy. Huang-Qi compounds are also associated with increases in the proportions of T-lymphocyte subsets (CD3, CD4 and CD8). That is to say, Huang-Qi compounds may play important roles in stimulating immunocompetent cells and decreasing side effects in patients treated with chemotherapy (29). In addition, to investigate the effect of Huang-Qi injection on short-term prognosis in childhood with acute lymphoblastic leukemia (ALL), a retrospective analysis was performed

Table 1. Single TCMs commonly prescribed by traditional Chinese physicians for cancer treatment

Common name	Other names	Efficacy according to TCM theory	Major active ingredients	Biological activity	Preclinical and/or clinical evidence of anticancer activity	Ref.
<i>Ginseng Radix</i>	Ren-Shen in Chinese, Ginseng in Korea	As a tonic, prophylactic and restorative agent with the efficacy of spiriting vital energy	Ginsenosides, essential oil, peptidoglycans, polysaccharides, nitrogen-containing compounds, fatty acids and phenolic compounds	Antitumor, antioxidant, immunomodulation, anti-ulcer, anti-adhesive, antioxidant, hepatoprotective, hypoglycemic	<i>Clinical: i)</i> Ameliorate cancer-related fatigue without any discernible toxicity; <i>ii)</i> Protect tissue damage from inflammatory cytokines in children after chemotherapy; <i>iii)</i> Attenuating the deleterious effects of radiation	15-23
<i>Radix Astragal</i>	Huang-Qi in Chinese	As a tonic with the efficacy of spiriting vital energy	Isoflavonoids, triterpenoid saponins, polysaccharides, amino butyric acids and various trace elements	Antitumor, antioxidant, hepatoprotective, anti-diabetic, antimicrobial, antiviral, immunomodulation	<i>Clinical: i)</i> Improve gastrointestinal side effects, and ameliorate bone marrow suppression in colorectal cancer patients with chemotherapy; <i>ii)</i> Increase the proportions of T-lymphocyte subsets; <i>iii)</i> Decrease infectious rate in ALL children with chemotherapy	24-31
<i>Radix Codonopsis</i>	Dang-Shen in Chinese	As a tonic with the efficacy strengthening spleen and nourishing lung	Sterol, triterpenes, glycoside, alkaloid, and polysaccharide	Antioxidant, antimicrobial, antitumor, immunomodulation	<i>Clinical:</i> Improve clinical symptoms, signs and quality of life of liver cancer patients	32-34
<i>Poria cocos</i>	Fu-Ling in Chinese, Hoelen in Japanese	As a tonic with the efficacy of strengthening spleen	Triterpenes, polysaccharides, steroids, amino acids, choline, and histidine	Antitumor, anti-inflammatory, antioxidant, antiviral, immunomodulation	<i>Clinical: i)</i> Improve tumor response rate, one year survival and quality of life of patients when combined with FOLFOX4 regimen chemotherapy; <i>ii)</i> Alleviate chemotherapy-related adverse events including neutropenia, nausea and vomiting, and neurotoxicity	32, 35-39
<i>Hehyotis diffusa wild</i>	Bai-Hua-She-She-Cao in Chinese	With the efficacy of clearing heat and detoxifying	Triterpenes, polysaccharide and anthraquinones	Antitumor, chemopreventive, hepatoprotective, antiviral, antibacterial, antidiabetic, antioxidant, gastroprotective	<i>Preclinical: i)</i> Upregulate G0/G1 phase arrest and induce apoptosis in human leukemia cells; <i>ii)</i> Inhibit colorectal cancer growth in mouse through STAT3 pathway; <i>Clinical:</i> Is the most commonly prescribed single Chinese herbs for colon cancer patients post-surgery in Taiwan	11,32, 40-42
<i>Scutellaria barbata</i>	Ban-Zhi-Lian in Chinese, Banjiryum in Korea	With the efficacy of clearing heat and detoxifying	Phenolic acids, flavonoids, triterpene acids and sterol glucosides	Antitumor, anti-inflammatory	<i>Preclinical:</i> Induce colon cancer cell apoptosis, inhibit cell proliferation and tumor angiogenesis via modulation of several pathways, including Akt, p53, STAT3, Erk, and p38 signaling pathways; <i>Clinical:</i> Stable disease and improve the side effects of chemo- or radio-therapy such as dysfunction of liver, diarrhea, fatigue, and pain in breast cancer patients	32, 43-46
<i>Angelicae Sinensis Radix</i>	Dang-Gui in Chinese, Dong Quai in English, Toki in Japanese, Tanggwi in Korea	With the efficacy of promoting blood circulation and removing blood stasis	Ligustilide, butylphthalide, senkyunolide A, phthalide dimers, ferulic acid, comiferyl ferulate, polyacetylenes	Antitumor, neuroprotective, immunomodulation, cardiovascular protective	<i>Preclinical:</i> Enhance radio-sensitivity of radiation in human liver cancer cells by modulating caspase-dependent apoptosis protein	32, 47-49
<i>Curcuma longa</i>	Jiang-Huang in Chinese	With the efficacy of promoting blood circulation and removing blood stasis	Curcumin, demethoxycurcumin, and bisdemethoxycurcumin,	Antitumor, anti-inflammatory, antioxidant	<i>Preclinical:</i> Inhibits carcinogenesis and modulates chemo-resistance and radio-resistance	32, 50-51

on the clinical data of 105 children newly diagnosed with ALL. The results indicated that Huang-Qi injection combined with chemotherapy had an enhanced anti-tumor effect and could improve the short-term prognosis and clinical outcome in children with ALL. Huang-Qi injection could reduce bone marrow suppression induced by chemotherapy or irritation of hematopoiesis of bone marrow and increase granulocyte level, and then decrease infectious rate in ALL children (30). In addition, it was reported that some TCM decoction of which Huang-Qi was a main ingredient could effectively prevent and reduce the occurrence and intensity of acute peripheral neuro-sensory toxicity caused by oxaliplatin (31).

2.1.3. *Radix Codonopsis*

Radix Codonopsis (Dang-Shen in Chinese) is the dried root of *Codonopsis pilosula* (Franch.) Nannf., and belongs to the family Campanulaceae. As one of the most popular TCMs in China, Japan and Korea, *Radix Codonopsis* has been used for thousands of years for treatment of dyspepsia, poor appetite, fatigue and psychoneurosis with properties of making the middle warmer, invigorating the spleen and nourishing the lung according to TCM theory (32). In many cases, it was utilized primarily as a substitute of the much more costly *Panax ginseng* and was therefore called the poor man's ginseng. Some reports indicated that the main bioactive constituents were sterols, triterpenes, glycosides, alkaloids, polysaccharides and so on. Modern pharmacology research indicated that *Radix Codonopsis* and its active constituents had the functions of antioxidant, antimicrobial, antitumor and improving immunity (33). According to basic and clinical studies, they were reported to play important roles in cancer therapy via inhibiting cancer growth, regulating immunity, suppressing invasion and migration, or reducing side effects of chemotherapeutics. *Radix Codonopsis* could induce spleen lymphocyte proliferation, inhibit the decline of IL-2 levels in serum, and improve immune function in mice. Polysaccharides from *Radix Codonopsis* exhibited significant inhibitory effects on tumor cell growth, invasion, and migration of human epithelial ovarian cancer cells (34). Although *Radix Codonopsis* is commonly prescribed by traditional Chinese physicians for cancer treatment in the clinic, there are few clinical studies published currently in English. There was a report that some TCM decoction of which *Radix Codonopsis* was a main ingredient could effectively improve clinical symptoms, signs and quality of life of liver cancer patients. Thus, more rigorous trials are needed to confirm the efficacy of *Radix Codonopsis* and its active constituents on cancer therapy in the future.

2.1.4. *Poria cocos*

Poria cocos (Fu-Ling in Chinese or Hoelen in Japanese),

is a kind of edible and pharmaceutical mushroom, and usually grows around the roots of old, dead pine trees. It is the dried sclerotium of the fungus *Poria cocos* (Schw.) Wolf (Fam. Polyporaceae). It is a well-known TCM used to treat diabetes, dysentery, chronic fatigue syndrome, diarrhea, dizziness, edema, insomnia, kidney problems, nervousness, urination problems, and weakness (32). According to the record of the Chinese Pharmacopoeia (2010 edition), approximately 10% of TCM preparations contain *Poria cocos*. The chemical composition of *Poria cocos* mainly includes triterpenes, polysaccharides, steroids, amino acids, choline, histidine, etc (35). Modern pharmacological studies showed that *Poria cocos* and some of its active constituents had functions of anticancer, anti-inflammatory, antioxidant, antiviral and improved immunity (35,36). According to basic and clinical studies, *Poria cocos* and some of its active constituents were reported to play important roles in cancer therapy via inhibiting cancer growth, regulating immunity, suppressing invasion and migration, or reducing side effects of chemotherapeutics in leukemia, lung, colorectal cancers and so on (37-39). Triterpenes from *Poria cocos* could induce apoptosis of leukemia (HL60) and lung (A549) cells via mitochondrial or death receptor pathways (37). Triterpenes from *Poria cocos* also could suppress growth and invasiveness of pancreatic cancer cells through the downregulation of MMP-7 (38). In addition, a systematic review evaluated clinical evidence for addition of herbal medicines to the FOLFOX 4 regimen chemotherapy for advanced colorectal cancer in the clinic. The results indicated that *Poria cocos* as one of the most frequently used herbs combined with the FOLFOX4 regimen chemotherapy could effectively improve tumor response rate, one year survival and quality of life of patients. It also could alleviate chemotherapy-related adverse events including neutropenia, nausea and vomiting, and neurotoxicity, compared to the FOLFOX4 regimen chemotherapy alone (39).

2.2. Some single TCMs with properties of clearing heat and detoxifying

2.2.1. *Hedyotis diffusa willd*

Hedyotis diffusa willd (Bai-Hua-She-She-Cao in Chinese) has been known as an ingredient of popular herbal teas and a famous TCM for a long time in the Orient and tropical Asia. Three major classes of compounds, including triterpenes, polysaccharides and anthraquinones, have been reported as the main bioactive compounds from this herb (32). *Hedyotis diffusa willd* and some of its active constituents have a wide variety of reported pharmacological activities, including anticancer, chemopreventive, hepatoprotective, antiviral, antibacterial, antidiabetic, antioxidant, and gastroprotective properties (40). It is widely applied in

the treatment of inflammations such as appendicitis, urethritis, and bronchitis, hepatitis, tonsillitis, and sore throat due to its antibacterial activity (32). Recently, *Hedyotis diffusa willd* and some of its active constituents have gained increasing attention as an antitumor herb in liver, lung, prostate, colon, brain, pancreas and other cancers (40). The ethanol extract of *Hedyotis diffusa willd* could upregulate G0/G1 phase arrest and induce apoptosis in human leukemia cells by modulating caspase cascade signaling and altering the gene levels related to cell growth, signal transduction, apoptosis, cell adhesion, cell cycle, DNA damage and repair, transcription and translation by cDNA microarrays (41). The ethanol extract of *Hedyotis diffusa willd* also could inhibit colorectal cancer growth in mice though the STAT3 pathway without apparent adverse effects (42). In addition, a cross-sectional study on the prescription patterns and reasons for the use of TCM for colon cancer patients post-surgery in Taiwan were analyzed and the results indicated that *Hedyotis diffusa willd* was the most commonly prescribed single Chinese herbs for colon cancer (11). However, more rigorous trials are needed to confirm the efficacy of *Hedyotis diffusa willd* and its active constituents on cancer therapy in the future.

2.2.2. *Scutellaria barbata*

Scutellaria barbata (Ban-Zhi-Lian in Chinese or Banjiryun in Korea) is a perennial herb which is natively distributed throughout Korea and southern China and as a well-known herb commonly used in folk medicines. It has been used as an anti-inflammatory and an antitumor agent to treat hepatitis, liver cirrhosis, pulmonary abscess, appendicitis, osteomyelitis, hematemeses, epistaxis, dysentery, jaundice, sore throat, carbuncle, scrofula and malignant tumors for many years. The chemical composition of *Scutellaria barbata* mainly includes phenolic acids, flavonoids, triterpene acids and sterol glucosides (32). Recently, *Scutellaria barbata* and its active constituents have gained increasing attention for its use as an anti-tumor herb in human breast cancer, prostate cancer, leukemia, hepatoma carcinoma, uterine carcinoma, cervical carcinoma, lung carcinoma, skin cancer, colorectal carcinoma, renal adenocarcinoma, nasopharyngeal carcinoma and oral epidermoid carcinoma (43). On the basis of cDNA microarray analysis, the mechanism underlying the anticancer activity of *Scutellaria barbata* appears to involve DNA damage, cell cycle control, nucleic acid binding, protein phosphorylation and dephosphorylation, and dendritic cell functions (44). The ethanol extract of *Scutellaria barbata* was able to induce colon cancer cell apoptosis, inhibit cell proliferation and tumor angiogenesis via modulation of several pathways, including Hedgehog, Akt, p53, STAT3, Erk, and p38 signaling pathways and alteration of the expression of multiple critical target genes such as, Bcl-2, Bax, Cyclin D1, CDK4, and p21

in *in vitro* and *in vivo* studies (45). In addition, a phase 1B dose escalation trial of *Scutellaria barbata* (BZL101) for patients with metastatic breast cancer was conducted by Memorial Cancer Institute (Hollywood, FL, USA). The results indicated that oral administration of BZL101 was safe, well tolerated, and showed promising clinical evidence of anticancer activity in patients. It could effectively stabilize disease and improve the side effects of chemo- or radio-therapy such as dysfunction of liver, diarrhea, fatigue, and pain (46).

2.3. Some single TCMs with properties of promoting blood circulation and removing blood stasis

2.3.1. *Sangelica sinensis Radix*

Angelicae Sinensis Radix (Dang-Gui in Chinese, Dong Quai in English, Toki in Japanese, or Tanggwi in Korea), is the root of *Angelica sinensis* (Oliv.) Diel and has been used for thousands of years worldwide. Since, it has both properties of nourishing blood and promoting blood circulation and removing blood stasis, we will give it a brief introduction in this part. It is usually used to strengthen heart, lung, and liver meridians, as well as lubricate the bowel (32). Furthermore, it is named "female ginseng" because of its use for various health conditions of women including dysmenorrhea, pelvic pain, recovery from childbirth and menopausal symptoms (47). Over 70 compounds have been identified from *Angelicae Sinensis Radix*, including essential oils such as ligustilide, butylphthalide and senkyunolide A, phthalide dimers, organic acids and their esters such as ferulic acid, coniferyl ferulate, polyacetylenes, vitamins and amino acids (48). *Angelicae Sinensis Radix* and some of its active constituents have a wide variety of reported pharmacological activities, including antitumor, neuroprotective, immunomodulatory and cardiovascular protective functions (47). Recently, some reports indicated that *Angelicae Sinensis Radix* and some of its active constituents (e.g., Z-Ligustilide) exhibited great anticancer effects in liver, prostate, and oral cancers via inducing apoptosis, reversing multidrug resistance or modulating lymphocyte activity and improving immunity (47-49). In addition, the decoction containing *Radix Angelicae Sinensis* could enhance radiosensitivity of radiation in human liver cancer cells by modulating caspase-dependent apoptosis protein (49). Although *Radix Angelicae Sinensis* is commonly prescribed by traditional Chinese physicians for cancer treatment in the clinic, there are few clinical studies published currently in English. Thus, more rigorous trials are needed to confirm the efficacy of *Radix Angelicae Sinensis* and its active constituents on cancer therapy in the future.

2.3.2. *Curcuma longa*

Curcuma longa (Jiang-Huang in Chinese), a member

of the ginger family and commonly known as turmeric, is a culinary spice and therapeutic used in Asia for thousands of years to induce color and flavor in food as well as to treat a wide array of diseases such as diabetes, atherosclerosis, acne, jaundice, dysmenorrhea, as well as, cancer (32). Some reports indicated that among all spices, *Curcuma longa* has been proven for its better anticancer potential. Curcuminoids, for example, curcumin, demethoxycurcumin, and bisdemethoxycurcumin, are major components of *Curcuma longa* and they are reported to have numerous pharmacological activities including anti-inflammatory, antioxidant, and anticancer properties. Curcumin, a yellow natural polyphenol, is traditionally used as a spice and coloring in foods and is an important ingredient in curry. Recently, among curcuminoids, the anticancer properties of curcumin have been drawn more attention from researchers. Many studies indicated that its anticancer molecular mechanisms involved cell cycle arrest, angiogenesis and metastasis by regulating molecules such as, Cdk inhibitor, p21/WAF/CIPI, p53, NFκB, STAT-3, c-myc, COX-2, NOS, Cyclin D1, TNFα, MMP-9, bFGF, EGF, GCSF, IL-8, PDGF, TGFα, TNF, VEGF, fibronectin, vitronectin, and collagen. It also has a synergistic effect in combination with chemotherapeutics like cyclophosphamide, doxorubicin, mitomycin, etc. (50). In addition, extensive preclinical research within the last decade in cell culture and in animals has revealed that curcumin can sensitize tumors to different chemotherapeutic agents including doxorubicin, 5-FU, paclitaxel, vincristine, oxaliplatin, etoposide and so on in numerous cancers (e.g., breast, colon, pancreas, gastric, liver, blood, lung, prostate, and ovary) (51). Similar studies have also revealed that curcumin sensitizes a variety of tumors including, glioma, neuroblastoma, cervical carcinoma, epidermal carcinoma, prostate cancer, and colon cancer to radiotherapy. Moreover, curcumin has also been shown to protect normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy and radiotherapy-induced toxicity. However, there are few clinical studies about *Curcuma longa* and its active compound curcumin in cancer therapy published currently in English. Thus, more rigorous trials are needed to confirm the efficacy of *Curcuma longa* and its active constituents on cancer therapy in the future.

3. Traditional Chinese herbal formulations commonly prescribed by traditional Chinese physicians for cancer treatment

Traditional Chinese herbal formulations, or Kampo in Japanese, are a combination of compatible herbs in fixed dosages, most of which come from classical or well known Chinese textbooks of medicine like "Shang Han Lun" and "Jin Gui Yao Lue" (52). Currently, several traditional Chinese herbal formulations, such

as Bu-zhong-yi-qi-tang, have been found to have a potentially beneficial effect for treating various cancers. A brief outline of the anticancer pharmacology of some traditional Chinese herbal formulations commonly prescribed by traditional Chinese physicians for cancer treatment is presented below (Table 2).

3.1. Bu-zhong-yi-qi-tang

Bu-zhong-yi-qi-tang (Hochuekki-to or TJ-41 in Japanese, or Bojungikki-Tang in Korean) is a classical formulation widely used in China, Japan, and South Korea for a long time. It was found by Dongyuan Li (A.D. 1,180-1,251, Jin and Yuan dynasties) as a tonic for the treatment of weakness including fatigue, visceroptosis, gastrointestinal motility disorder, and rectal prolapse due to chronic diarrhea and has been identified as an effective drug for the treatment of TCM spleen-qi deficiency in clinical practice. It contains 7 herbs including *Pinellia tuber*, *Scutellaria baicalensis*, *Zingiberis rhizoma*, *Zizyphi fructus*, *Coptidis rhizoma*, *Glycyrrhiza radix*, and *Panax ginseng* (12). Recently, much of the pharmacological research has shown that Bu-zhong-yi-qi-tang has potent immunomodulatory and anticancer properties. TJ-41 has a significant chemo-preventative effect on ovarian and liver cancer lines by inducing apoptosis or arresting the cell cycle (12). It could restore mitomycin C (MMC)-induced immunosuppression in mice by increasing the activity of bone-marrow cells and natural killer (NK) cells and preventing lethal HSV-1 infection (53). Preoperative administration of TJ-41 in patients with gastrointestinal malignancies showed that it could prevent surgical stress-induced immunosuppression by maintaining NK cell activity and inhibiting the elevation of stress mediators noradrenaline and IL-6 (54). In addition, TJ-41 might have beneficial effects on cancer-related fatigue and quality of life in cancer patients, and it also could 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 (12,55).

3.2. Shi-quan-da-bu-tang

Shi-quan-da-bu-tang (Juzentaiho-to or TJ-48 in Japanese) is a well-known Chinese herbal formulation first recorded in the Chinese Song Dynasty (about A.D. 1,200) and it comprises 10 herbs including *Ginseng radix*, *Astragali radix*, *Angelicae radix*, *Rehmanniae radix*, *Atractylodis lanceae rhizoma*, *Cinnamomi cortex*, *Poria*, *Paeoniae radix*, *Ligustici rhizoma* and *Glycyrrhiza radix* (12). It has been used for many years for the treatment of various kinds of disease such as anemia, rheumatoid arthritis, atopic dermatitis, chronic fatigue syndrome, and ulcerative colitis. Recently, TJ-48 has been reported to have antitumor effects and to modulate immune responses. It could reduce the side effects of

Table 2. Traditional Chinese herbal formulations commonly prescribed by traditional Chinese physicians for cancer treatment

Common name	Other names	Composition	Biological activity	Preclinical and/or clinical evidence of anticancer activity	Ref.
Bu-zhong-yi -qi-tang	Hochuekki-to or TJ-41 in Japanese, Bojungikki-tang in Korea	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>	Antitumor, immunomodulation	<i>Preclinical: i)</i> Have significant chemo-preventative effects on ovarian and liver cancer lines by inducing apoptosis or arresting the cell cycle; <i>ii)</i> Restore mitomycin C-induced immunosuppression in mice; <i>Clinical: i)</i> Prevent surgical, stress-induced immunosuppression; <i>ii)</i> Improve cancer-related fatigue and quality of life in cancer patients; <i>iii)</i> reduce side effects such as leucopenia, intestinal damage and fatigue induced by radiation or chemotherapy	12, 53-55
Shi-quan-da -bu-tang	Juzentaiho-to or TJ-48 in Japanese	Includes 10 herbs: <i>Ginseng radix</i> , <i>Astragal radix</i> , <i>Angelicae radix</i> , <i>Rehmanniae radix</i> , <i>Atractylodis lanceatae rhizoma</i> , <i>Cinnamomi cortex</i> , <i>Poria</i> , <i>Paeoniae radix</i> , <i>Ligustici rhizoma</i> <i>Glycyrrhizae radix</i>	Antitumor, immunomodulation	<i>Preclinical: i)</i> Alleviate bone marrow suppression caused by TS-1 in mice; <i>Clinical: i)</i> Alleviating hematotoxicity among breast cancer patients undergoing chemotherapy; <i>ii)</i> Slow down the process of hepatocarcinogenesis and improve hepatic recurrence-free survival through the inhibition of Kupffer cell-induced oxidative stress in patients with HCC; <i>iii)</i> Regulate T cells through decreasing Foxp3+ Treg populations in advanced pancreatic cancer patients	12, 56-59
Huang-qin-tang	PHY906	Includes 4 herbs: <i>Scutellaria baicalensis</i> Georgi, <i>Paeonia lactiflora</i> Pall, <i>Glycyrrhiza uralensis</i> Fisch, <i>Ziziphus jujuba</i> Mill	Antitumor, anti-inflammatory	<i>Preclinical: i)</i> Enhance the antitumor efficacy of some anticancer drugs such as 5-FU and alleviate radio- or chemo-therapy induced side effects; <i>ii)</i> Regulate intestinal bacteria, alleviate diarrhea and reduce irinotecan-induced mortality in mice; <i>Clinical: i)</i> Provide a safe and feasible salvage therapy combined with capecitabine after gemcitabine failure for advanced pancreatic cancer	12, 60-62
Xiao-chai -hu-tang	Sho-sai-ko-to or TJ-9 in Japanese	Includes 7 herbs: <i>Bupleurum falcatum</i> , <i>Scutellaria baicalensis</i> , <i>Panax ginseng</i> , <i>Zizyphi jujube</i> , <i>Pinellia ternate</i> , <i>Zingiber officinale</i> , <i>Glycyrrhiza glabra</i>	Antitumor, anti-inflammatory, antioxidant, immunomodulation, hepatoprotective, anti-hepatic fibrosis	<i>Preclinical: i)</i> Enhance immune regulation, inhibit angiogenesis and induce apoptosis of cancer cells; <i>Clinical: i)</i> Prevent the development of HCC from hepatitis C virus-associated liver cirrhosis (HCV-LC) in the HCV-LC patients; <i>ii)</i> Decrease the incidence of stomatitis in cancer patients undergoing chemotherapy	12, 63-67

chemotherapy, radiation therapy and surgical treatment, and prevent various types of cancers (e.g., breast, liver, brain and pancreatic cancer) or their metastasis according to numerous preclinical and clinical studies. TJ-48 was effective in alleviating bone marrow suppression caused by TS-1 (an oral anticancer drug containing a 5-fluorouracil derivative Tegafur) in mice (56). TJ-48 was also effective in alleviating hematotoxicity among patients with breast carcinoma receiving chemotherapy, without affecting the presentation of tumor markers (CEA and CA153) in the short term (57). Moreover, TJ-48 could slow down the process of hepatocarcinogenesis and improve hepatic recurrence-free survival through the inhibition of Kupffer cell-induced oxidative stress in patients with hepatocellular carcinoma (HCC) (58). TJ-48 also could increase regulatory activities in T cells through decreasing Foxp3+ Treg populations in advanced pancreatic cancer patients, and this effect might lead to immune-augmentation for various combination therapies (59).

3.3. Huang-qin-tang

Huang-qin-tang is a classical traditional Chinese herbal formulation with four herbs (*Scutellaria baicalensis* Georgi, *Paeonia lactiflora* Pall, *Glycyrrhiza uralensis* Fisch, and *Ziziphus jujuba* Mill), and it was first recorded in "Shang Han Lun" which is one of the famous classics of TCM edited by a well-known Chinese physician during the Han Dynasty Zhongjing Zhang. It has been used for over 1800 years to treat a variety of gastrointestinal symptoms including diarrhea, nausea and vomiting, and abdominal cramps (12,60). PHY906 is a modified pharmaceutical preparation derived from the traditional herbal formulation Huang-qin-tang and it consists of the same four herbs as Huang-qin-tang at a relative weight ratio of 3:2:2:2 (12). To ensure standardization and maintain inter-batch reliability of PHY906, high performance liquid chromatography (HPLC) was used to establish a "chemical fingerprint" of PHY906 by Professor Yung-Chi Cheng and his team (Yale University School of Medicine). Furthermore, they have conducted a series of preclinical and clinical studies to investigate the anticancer activities of PHY906 in recent years. In vivo studies, the combination of PHY906 with irinotecan, capecitabine, 5-FU, and leucovorin (LV) resulted in significant improvement in gastrointestinal toxicities, antitumor activity, and overall survival with no increased host toxicity versus chemotherapeutics alone (60). In the case of irinotecan, for which severe delayed-onset diarrhea is the major dose-limiting toxicity, PHY906 could effectively regulate intestinal bacteria, alleviate diarrhea and reduce drug-induced mortality in mice. Moreover, treatment with PHY906 mitigated the intestinal injuries of fractionated whole abdomen irradiation and improved recovery from radiation injury, which indicated PHY906

as a potential adjunct to radiation therapy (61). In addition, a phase II study was conducted to explore the efficacy of capecitabine combined with PHY906 in patients with advanced pancreatic cancer who were previously treated with gemcitabine-based regimens. The results showed capecitabine plus PHY906 provided a safe and feasible salvage therapy after gemcitabine failure for advanced pancreatic cancer with six-month survival rate at 44% (62).

3.4. *Xiao-chai-hu-tang*

Xiao-chai-hu-tang (Sho-sai-ko-to or TJ-9 in Japanese), a classical traditional Chinese herbal formulation originally recorded in "Shang Han Lun", has been used to treat liver diseases especially chronic hepatitis and liver cancer for thousands of years in China and Japan. It consists of seven medicinal herbs (*Bupleurum falcatum*, *Scutellaria baicalensis*, *Panax ginseng*, *Zizyphus jujube*, *Pinellia ternate*, *Zingiber officinale*, and *Glycyrrhiza glabra*) (63). Much pharmacological research has shown that TJ-9 has potent antiinflammation, antioxidation, immunomodulation, hepatoprotective, anti-hepatic fibrosis, and antitumor properties. Recently, many basic or clinical studies have been conducted to assess the beneficial effects and safety of TJ-9 for cancer treatment. These studies have demonstrated that TJ-9 treats cancer by enhancing immune regulation, anti-angiogenesis and apoptosis of tumor cells (64). TJ-9 exhibited significant growth inhibition of ovarian cancer cell lines, and the mechanisms of the inhibitory effects can be attributed, in part, to apoptosis induced by TJ-9. TJ-9 could effectively inhibit the growth of H22 mouse solid liver cancer and improve the immune function of tumor-bearing mice by increasing NK cells, T lymphocytes and IL-2 levels (65). Furthermore, TJ-9 plays important roles in preventing hepatocarcinogenesis. A study was performed to find a way to prevent the development of HCC from hepatitis C virus-associated liver cirrhosis (HCV-LC) in HCV-LC patients who had received reduction ALT therapy such as TJ-9. The results indicated that chances of surviving for more than ten years without developing HCC for HCV-LC patients (66). In addition, TJ-9 gargle as a gargling agent for patients receiving chemotherapy showed a significantly decreased incidence of stomatitis, and a painkilling effect compared to gargling with providone-iodine and amphotericin B. Thus, TJ-9 gargle was considered to be a useful method against stomatitis prevention and sharp pain mitigation from chemotherapy (67).

4. Chinese medicine preparations commonly used in clinical practice for cancer treatment

Chinese medicine preparations are a form of Chinese herbal medicine that are isolated from single herbs or their active compounds or herbal formulations and

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 (12,32). Thus, Chinese medicine preparations are becoming increasingly popular in China and are attracting worldwide attention.

Currently in China, some Chinese medicine preparations are derived from single TCMs or their active compounds or herbal formulations, which have the properties of spiring vital energy and their anticancer molecular mechanisms mainly by improving immunity (e.g., Shenqi fuzheng injection and Kanglaite injection). Some Chinese medicine preparations are derived from single TCMs or their active compounds or herbal formulations, which have properties of clearing heat and detoxifying, promoting blood circulation and removing blood stasis and their anticancer molecular mechanisms involving apoptosis, cell cycle arrest, angiogenesis and metastasis, immunoregulation and so on (e.g., Huachansu injection and Cantharidin sodium injection). We want to stress that some TCMs and some natural compounds like Mylabris, Chansu, camptothecin derivatives, and vinca alkaloids are toxic. However, the application of these toxicants provides a magic power to deal with severe diseases like cancer, and this process might be described as "fighting fire with fire" (68). Thus, in the following, a brief outline of the oncologic pharmacology of the most commonly used Chinese medicine preparations including some toxicants that have been approved by the State Food and Drug Administration (FDA) of China are briefly presented below (Table 3).

4.1. *Shenqi fuzheng injection*

Shenqi fuzheng injection is an injectable traditional Chinese herbal formula comprised of two herbal medicines, *Radix Astragali* (Huang-Qi) and *Codonopsis pilosula* (Dang-Shen). The injection has been approved by China's FDA since the 1990s. It is commonly used to improve immune function against chronic diseases including cancer and cerebrovascular diseases such as, angina, coronary heart disease, heart failure, and so on (32). Recently, many trials have demonstrated that *Shenqi fuzheng injection* might play an important role in the treatment of various advanced cancers. It could improve immune response *via* raising activity of NK cell, macrophage and T-lymphocyte subgroups without any injuries of heart, liver and kidney function or other adverse reactions in cancers. It also could reduce the toxicity of radiation therapy and chemotherapy. A systematic meta-analysis involving thirteen randomized controlled trials and 860 patients was conducted on *Shenqi fuzheng injection* for advanced gastric cancer (69). It showed that the combination of chemotherapy with *Shenqi fuzheng injection* obtained a series of positive results including improving quality of life,

Table 3. Chinese medicine preparations commonly used in clinical for cancer treatment

Common name	Source or composition	Biological activity	Preclinical and/or clinical evidence of anticancer activity	Ref.
Shenqi fuzheng injection	Comprised of 2 herbs: <i>Radix Astragali</i> <i>Codonopsis pilosula</i>	Antitumor, immunomodulation	<i>Clinical:</i> Improve quality of life, increase complete remission and partial remission efficacy rate, enhance immunity, and decrease adverse events such as nausea, vomiting, oral mucositis, and leucopenia in cancer patients undergoing chemotherapy	32, 69-71
Kanglaite injection	Extracted from <i>Semen Coicis Yokuinin</i>	Antitumor	<i>Clinical:</i> <i>i)</i> Improve the short-term efficacy, improve the quality of life, and decrease the risk of gastrointestinal reaction and myelosuppression in cancer patients undergoing radio- or chemotherapy; <i>ii)</i> combined with hepatic arterial intervention could improve the short-term clinical efficacy, quality of life, and decrease the pain of patients with unresectable HCC	12, 72-74
Huachansu injection	Extracted from the skin and parotid venom glands of the toad <i>Bufo bufo gargarizans</i> Cantor	Antitumor, Anti-HBV immunomodulation	<i>Preclinical:</i> Inhibit cell proliferation, induce cell differentiation and apoptosis, disrupt cell cycle, inhibit cancer angiogenesis, reverse multi-drug resistance, and regulate immune response in cancer cells <i>Clinical:</i> <i>i)</i> Enhance the antitumor efficacy of gemcitabine and oxaliplatin and improve the quality of life of patients; <i>ii)</i> Postpone tumor recurrence and metastasis, prolong the survival time and increase the survival rate of post-surgical patients with HCC; <i>iii)</i> Decrease the quantity of pericardial effusion in cancer patient	12, 75-80
Cantharidin sodium injection	Extracted from <i>blister beetles</i>	Antitumor, immunomodulation	<i>Clinical:</i> <i>i)</i> Improve quality of life; <i>ii)</i> Reduce side effects induced by chemotherapy such as leukopenia and gastrointestinal reactions	81-83

increasing complete remission and partial remission efficacy rate, and decreasing adverse events such as nausea, vomiting, oral mucositis, and leucopenia. Moreover, Shenqi fuzheng injection intervention appeared to be useful to increase efficacy and reduce toxicity when combined with platinum-based chemotherapy for advanced non-small-cell lung cancer (NSCLC) and colorectal cancer (12,70). In addition, the combination of concurrent chemoradiotherapy with Shenqi fuzheng injection in patients with head and neck neoplasms could effectively enhance immunity with the levels of CD3, CD4, and CD4/CD8 increased, improve quality of life, and decrease adverse events such as nausea, vomiting, oral mucositis, skin lesions, and leucopenia (71).

4.2. Kanglaite injection

Kanglaite injection is an anti-tumor drug, which contains extracts from Chinese herbal medicine coix seed (*Semen Coicis Yokuinin*) using modern advanced pharmaceutical technology. In August 1997, Phase III clinical trials were completed and Kanglaite injection was officially launched in China after final approval from the Ministry of Public Health (12). Kanglaite injection is mainly used for the treatment of NSCLC, liver cancer, gastric cancer, etc. It has been found to significantly decrease cancer cachexy, improve quality of life of cancer patients, and may ameliorate multiple drug resistance of cancers when combined with radiotherapy and chemotherapy in clinical use. A systematic meta-analysis involving 34 clinical trials was conducted to assess the effects of Kanglaite injection combined with chemotherapy versus chemotherapy alone in the treatment of advanced non-small cell lung carcinoma (72). It showed that the combination could improve the short-term efficacy,

and performance status and decrease the risk of gastrointestinal reaction compared with systematic chemotherapy alone. Another systematic meta-analysis involving 9 clinical trials indicated that Kanglaite injection combined with hepatic arterial intervention could improve the short-term clinical efficacy, quality of life, and decrease the pain of patients with unresectable HCC (73). Moreover, a network of meta-analysis involving 38 randomized controlled trials and 2,761 participants was conducted to compare which was the best Chinese herb injection based on the FOLFOX regimen for gastric cancer. Kanglaite injection exhibited greater effects than many other Chinese herb injections in clinical efficacy and safety for gastric cancer. It could strengthen the overall response rate, improve the quality of life, reduce nausea and vomiting, and reduce the incidence of leukopenia (III-IV) (74).

4.3. Huachansu injection

Huachansu injection or Cinobufacini injection is a water-soluble preparation extracted from the skin and parotid venom glands of the toad (*Bufo bufo gargarizans* Cantor) which contains Chansu. It has been approved by China's FDA since the 1990s and widely used to treat patients with lung, liver, colon, and pancreatic cancers at oncology clinics in China (12). Cardiac glycosides including bufalin, resibufogenin, and cinobufagin are the three major active constituents to which the antitumor activity of Huachansu injection may be attributed. Huachansu injection exhibited significant effects on inhibition cell proliferation, induction of cell differentiation and apoptosis, disruption of the cell cycle, inhibition of cancer angiogenesis, reversal of multi-drug resistance, and regulation of the immune response in cancer cells (75,76). It also could effectively

enhance physical immunity and improve the quality of life with little toxicity in cancer patients. A pilot study of Huachansu injection in patients with HCC, NSCLC, and pancreatic cancer showed that Huachansu injection could improve the quality of life of patients and even enhanced tumor shrinkage with little toxicity (77). Another clinical study using Huachansu injection in combination with gemcitabine and oxaliplatin in treating gallbladder carcinomas showed that Huachansu injection substantially enhanced the antitumor efficacy of gemcitabine and oxaliplatin and improved the quality of life of patients (78). Moreover, a case-control trial ($n = 120$) was conducted to assess the effects of Huachansu injection plus Jiedu granules (a Chinese medicine compound) *versus* transcatheter arterial chemoembolization (TACE) in post-surgical patients with HCC in Changhai Hospital (Shanghai, China). Huachansu injection plus Jiedu granules could postpone tumor recurrence and metastasis, prolong survival time and increase survival rate of post-surgical patients with HCC (79). In addition, Huachansu injection has been reported to be effective for treating malignant pericardial effusion, pleural effusions, and ascites. Sun *et al.* reported a case of advanced lung cancer with malignant pericardial effusion treated by intrapericardial Huachansu injection instillation (80). Huachansu injection could effectively relieve the patient's cardiac tamponade symptoms and improve the patient's quality of life with the levels of CA-125 in pericardial effusion decreased and the quantity of pericardial effusion significantly reduced. Furthermore, there were little gastrointestinal adverse reactions and myelosuppression in the patient after injection of Huachansu in the pericardial cavity.

4.4. Cantharidin sodium injection

Cantharidin is a sesquiterpene derivative extracted from blister beetles which has long been used as a poisonous TCM to treat life-threatening diseases such as cancer according to the principle "fighting fire with fire". Cantharidin is a potent and selective inhibitor of protein phosphatase 2A (PP2A). Recent pharmacologic studies proved that cantharidin could induce cell cycle arrest and apoptosis, and interfere with the metabolism of nucleic acids and of proteins in cancer cells, significantly inhibit the growth of various cancers including HCC, uterine cervix cancer, nasopharyngeal carcinoma, cutaneous cancer, leukemia, and so on (81). Cantharidin sodium injection is a semi-synthetic derivative of cantharidin. It has been approved by China's FDA since the 1990s and widely used to treat patients with lung, liver, colon, pancreatic, gastric and breast cancers at oncology clinics in China. It could reduce the uptake of amino acids in cancer cells, inhibit protein synthesis, stimulate macrophages, lymphocytes, cause polymorphonuclear cells to produce interleukin, and finally improve immunity and enhance anticancer efficacy (82). Several

clinical studies showed that Cantharidin sodium injection combined with chemotherapy could effectively improve quality of life and reduce side effects induced by chemotherapy such as leukopenia and gastrointestinal reactions without any increase in toxicity in patients with NSCLC, colorectal, breast and gastric cancer (81,83). Although Cantharidin sodium injection is widely used in cancer therapy in China, most of these studies are published in Chinese and little is known about use of the Cantharidin sodium injection outside of China. Thus, the mechanisms of the injection's action must be investigated and the injection must be clinically evaluated further.

5. Clinical trials of TCMs as adjuvant treatment in the whole course of cancer therapy

As is known, surgery, chemotherapy and radiotherapy are major conventional cancer therapies. Although these therapies are directed at killing or eradicating cancer cells, a series of complications and side effects will come along such as upper limb lymphedema, infection/fever, fatigue, pain, anemia, diarrhea, nausea and vomiting, hair loss, and bone marrow suppression. 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. Thus, more effective therapies to help prevent and control complications and side effects of conventional cancer therapy must soon be developed. Some TCMs have been found to be adjunctive in cancer therapy. Here we will give a brief outline on the use of TCMs to reduce some complications and side effects associated with conventional cancer therapy in clinical studies (Table 4).

5.1. Lymphedema

Lymphedema is a serious medical complication commonly associated with breast cancer treatment, such as surgery and/or radiation, and it may occur more than 5 years after surgery. Lymphedema involves the accumulation of protein-rich fluid in the interstitial space, and occurs when the lymphatic system is damaged and no longer properly drains the lymph fluid back to the systemic circulation (84). When the lymphatic system is damaged, fluid accumulates in the affected limb, leading to swelling, fibrosis, reduced range of motion, decreased function, and, in later stages, infection and pain. However, it is difficult to cure once it occurs despite the various treatments which have been developed such as massage, compression garments, bandages, or sleeves, manual lymphatic drainage, individualized exercise, and education regarding skin care and infection prevention (85). In recent years, some reports related to the effectiveness of TCMs use among cancer patients with lymphedema have been reported.

Coumarin, a chemical compound derived from some

Table 4. Clinical trials of TCMs as adjuvant treatment in the whole course of cancer therapy

TCMs		Clinical trials of TCMs as adjuvant treatment in cancer therapy				Ref.
Complications or side effects	Patients	Experimental group	Control group	Outcomes		
Coumarin	n = 31 (post mastectomy)	Coumarin	Placebo	More effective than the placebo in reducing the limb volume and skin temperature and in increasing the softness of the limb tissue	86	
Aescine	n = 20	Sodium aescine + Diosmin	Physiotherapy	Compared to physiotherapy group, the limb volume and the softness of the limb tissue were significantly improved in the combination group	88	
Liu-jun-zi-Tang	n = 19 (post proximal gastrectomy)	Liu-jun-zi-Tang + conventional treatment	Conventional treatment	Significantly improved the symptoms of postgastrectomy syndrome and long-term quality of life in patients with gastric cancer compared to the control group	90	
PHY906	n = 24	PHY906 + chemotherapy	Chemotherapy (Capecitabine)	Some gastrointestinal side effects such as diarrhea, abdominal cramps, and vomiting were reduced	60	
Compound kushen injection	n = 521	Compound kushen injection + radiotherapy or bisphosphonates	Radiotherapy or bisphosphonates	Exhibited significant effects on improving pain relief in patients with bone cancer pain	93	
TJ-41	n = 751	TJ-41 + chemotherapy or supportive care	chemotherapy or supportive care	Significantly relieve cancer-related fatigue and improve quality of life compared to the control group	94	
Shen-mai-san	n = 30	Shen-mai-san + chemotherapy or radiotherapy	Chemotherapy or radiotherapy	Effective for treating cancer-related fatigue and had anti-fatigue activity	95	
Fufang E-Jiao Jiang	n = 64	Fufang E-Jiao Jiang + chemotherapy + rhIL-11 + rhG-CSF	Chemotherapy + rhIL-11 + rhG-CSF	Showed significant effects on relieving the myelosuppression caused by GP regimen chemotherapy and increasing white cell and blood platelets counts compared to the control group	96	
TJ-48	n = 29	TJ-48 + FOLFOX4 regimen chemotherapy	FOLFOX4 regimen chemotherapy	Effectively increase white cell counts and improve the symptoms such as dizziness and fatigue	97	
Shenqi fuzheng injection	n = 48	Shenqi fuzheng injection + antibiotics + high efficient hormone	Antibiotics + high efficient hormone	Significantly improve respiratory symptoms and signs, and regulate subsets of T-lymphocytes, as well as increase patients' quality of life compared to the control group	98	
Xiao-chai-hu-tang, Huang-lian-jiu-du-tang or Yin-chen-wu-ling-san	n = 89	TCMs (e.g., Xiao-chai-hu-tang, Huang-lian-jiu-du-tang or Yin-chen-wu-ling-san) + chemotherapy	Chemotherapy	The serum levels of ALT and AST in combination group were lower than those in the control group	100	

plants such as Tonka beans, might reduce lymphedema and the incidence of secondary infections because it decreases the volume of protein by stimulating proteolysis. A randomized, double-blind, placebo-controlled, cross-over trial to examine the effect of coumarin in 31 women with post-mastectomy lymphedema and 21 men and women with lymphedema of the lower extremity of various causes was conducted with the patients receiving 400 mg of coumarin or placebo for 6 months. The results indicated that coumarin was more effective than the placebo in reducing the limb volume and skin temperature and in increasing the softness of the limb tissue, with mild side effects, such as mild nausea and diarrhea arising in seven patients who took coumarin (86). However, Loprinzi *et al.* reported that coumarin had potential negative and even life-threatening side effects, such as hepatotoxicity (87). Therefore, further research with a rigorous design and larger sample size is needed to re-evaluate the effectiveness of coumarin in treating lymphedema.

Sodium aescine is a Chinese medicine preparation extracted from Horsechestnut seed and is widely used to treat chronic venous insufficiency. It is also widely used to treat soft tissue swelling caused by various reasons such as breast cancer related upper limb lymphedema. To observe the efficacy of sodium aescine combined with Diosmin on upper limb lymphedema in patients after breast cancer surgery, a randomized controlled study was conducted. The results indicated that compared to physiotherapy group ($n = 16$), the limb volume and the softness of the limb tissue were significantly improved in the combination group ($n = 20$) (88). Moreover, a possible mechanism of aescine may be related to inhibiting the activity of enzymes elastase and hyaluronidase (85). However, there are several limitations associated with the current published studies on sodium aescine such as indeterminate results, small sample sizes, and little examination of outcomes. Therefore, further research with rigorous design and larger sample size is needed to re-evaluate the effectiveness of sodium aescine in treating lymphedema.

5.2. Gastrointestinal side effects

Gastrointestinal side effects including loss of appetite, diarrhea, nausea, and vomiting are the most common symptoms occurring in cancer patients after surgery and/or receiving chemo- or radio-therapy. However, there is still no effective treatment to ameliorate these symptoms in cancer patients. Recently, many clinical trials have suggested that some TCMs may be effective at treating gastrointestinal side effects. Liu-jun-zi-Tang (or Rikkunshito in Japanese) is a famous Traditional Chinese herbal formulation including 6 herbs (*Ginseng Radix*, *Poria cocos*, *Rhizoma atractylodis macrocephalae*, *liquorice root*, *pinelliae tuber*, *pericarpium citri*, *common ginger*, and *Jujube*). It is widely used in China

and Japan for the treatment of upper gastrointestinal symptoms of patients with functional dyspepsia, gastroesophageal reflux disease, dyspeptic symptoms of post-gastrointestinal surgery patients, and chemotherapy-induced dyspepsia in cancer patients. Some Japanese researchers found that Liu-jun-zi-tang as a ghrelin enhancer was effective for treating cisplatin-induced dyspepsia and cancer cachexia-anorexia syndrome (89). Liu-jun-zi-tang significantly improved the symptoms of postgastroectomy syndrome and long-term quality of life in patients with gastric cancer who had undergone proximal gastrectomy (90). In addition, some clinical studies have shown that PHY906 enhances the therapeutic indices of a broad spectrum of anticancer agents such as Capecitabine, 5-FU and irinotecan in colorectal, liver, and pancreatic cancers. PHY906 could reduce chemotherapy-induced toxicities especially gastrointestinal side effects (*e.g.*, diarrhea, abdominal cramps, and vomiting) and/or increase chemotherapeutic efficacy without affecting the pharmacokinetics of chemotherapeutic agents (12,60). Furthermore, advanced clinical trials are ongoing to demonstrate the effectiveness of PHY906 as adjuvant therapy for cancer patients undergoing chemotherapy.

5.3. Pain

Pain is a common and burdensome symptom of cancer and the causes of pain can be the cancer itself (the tumor pressed on bones, nerves, or other organs) or its treatment (*e.g.*, surgery, chemotherapy, or radiotherapy). It was reported that 75-90% cancer patients especially who have bone metastasis experienced pain during their illness (91). As indicated in current WHO guidelines, three step analgesic ladder therapies are the standard of care for cancer pain. However, up to 50% of cancer pain is still undertreated. In recent years, many clinical trials have suggested that some TCMs as adjunctive therapy may be effective at treating cancer related pain and that their effects are similar to those of Western analgesics. TCMs may reduce the side effects of conventional analgesics, and then enhance cancer patients' quality of life (12). To assess the effectiveness of oral TCMs in relieving pain secondary to bone metastases in patients, a meta-analysis enrolled a total of 16 randomized controlled trials and 1,008 patients were identified and analyzed (92). The results showed that TCMs plus conventional treatment increased the pain-relief rate compared with the conventional treatment alone. Another meta-analysis enrolled a total of 7 randomized controlled trials and 521 patients were identified and analyzed to assess the efficacy and safety of compound kushen injection (a preparation extracted from *Radix sophorae flavescens*) for bone cancer pain. Compared with radiotherapy or bisphosphonates, compound kushen injection showed significant effects on improving pain relief in patients with bone cancer pain (93). In addition, some clinical

trials indicated that acupuncture might be beneficial for alleviating cancer pain. In all, TCM interventions appear to have beneficial effects on pain secondary to bone metastases in patients. However, there are several limitations associated with the current published studies on TCMs relieving pain such as indeterminate results, small sample sizes, and little examination of outcomes. Therefore, further research with rigorous design and larger sample size is needed to re-evaluate the effectiveness of TCMs in treating cancer related pain.

5.4. Fatigue

Cancer-related fatigue is a highly prevalent, persistent and subjective sense of tiredness related to cancer disease or cancer treatment which cannot be relieved by sleep or rest, and overall 50-90% of people with cancer experience fatigue. It significantly interferes with patients' daily activities and decreases their quality of life (12,94). However, it remains under-recognized and under-treated, partly because of limited understanding of its pathophysiology and lack of effective treatments. Several Chinese herbal medicines may have beneficial effects on cancer-related fatigue and quality of life for cancer patients. To assess the effectiveness and safety of Chinese herbal medicine for the treatment of cancer-related fatigue, a meta-analysis enrolled a total of 10 randomized controlled trials and 751 patients with various cancers such as liver, lung, and breast cancer were identified and analyzed (94). The results showed that some TCMs such as TJ-41 used alone or in combination with chemotherapy or supportive care showed significant relief in cancer-related fatigue and improved quality of life compared to chemotherapy or supportive care based on single trials. In addition, a randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy of Shen-mai-san (a famous Traditional Chinese herbal formulation composed of processed *Ginseng*, *Liriope spicata*, and *Schizandrae fructus*) in patients with cancer who were undergoing chemotherapy or radiotherapy (95). Shen-mai-san was found to be effective for treating cancer-related fatigue and had anti-fatigue activity. According to TCM theory, Shen-mai-san has a synergistic effect for qi and yin deficiency which are similar to chemotherapy- or radiotherapy-induced side effects and has the ability to prevent fatigue. These findings from a limited number of trials suggest that TCM seems to be effective and safe in the treatment of cancer-related fatigue. However, current evidence is insufficient to draw a confirmed conclusion due to the poor methodological quality of included trials. However, there are several limitations associated with the current published studies on TCMs relieving fatigue such as indeterminate results, small sample sizes, and little examination of outcomes. Thus, conducting rigorously designed trials on potential Chinese herbal medicine are warranted.

5.5. Bone marrow suppression

Bone marrow suppression is a reduction in the activity of bone marrow, resulting in decreased numbers of red blood cells, platelets, and white blood cells. One of the most common reasons for a patient to have this condition is chemotherapy treatment for cancer. While the bone marrow is functioning below normal levels, the patient is at risk, and needs to be monitored very closely. In some cases, hospitalization is recommended for people with Bone marrow suppression until their bone marrow is functioning normally. In recent years, some TCMs have been reported to have beneficial effects on chemotherapy-related bone marrow suppression. Colla corii asini (or E-Jiao in Chinese), donkey-hide gelatin prepared by stewing and concentrating from *Equus asinus* L. donkey hide, is a health-care food and traditional Chinese medicine widely used in life-nourishing and clinical hematic antanemic therapy for more than 2,000 years in China (32). Many studies indicated that E-Jiao and its preparations such as Fufang E-Jiao Jiang could effectively promote the recovery of bone marrow hemopoietic function in cancer patients with myelosuppression who were undergoing chemotherapy. Fufang E-Jiao Jiang in combination with conventional interleukin-11 (rhIL-11) and recombinant human granulocyte colony stimulating factor (rhG-CSF) in cancer patients showed significant effects on relieving the myelosuppression caused by GP (Gemcitabine + DDP) regimen chemotherapy and increasing white cell and blood platelet counts compared to using rhIL-11 and rhG-CSF groups alone (96). In addition, TJ-48 was reported to have significant effects on alleviating myelosuppression caused by FOLFOX4 regimen chemotherapy in patients with gastrointestinal malignant tumor. It could effectively increase white cell counts and improve symptoms such as dizziness and fatigue (97). In all, TCM interventions appear to have beneficial effects on alleviating myelosuppression caused by chemotherapy in cancer patients. However, there are several limitations associated with the current published studies on TCMs relieving myelosuppression such as indeterminate results, small sample sizes, and little examination of outcomes. Thus, conducting rigorously designed trials on potential Chinese herbal medicine are warranted.

5.6. Radiation pneumonitis

Radiation pneumonitis is one of the most common complications during radiotherapy of thoracic tumors. It impacts the quality of life of the patients and has a life-threatening danger. However, there is a lack of drugs for prevention and treatment of this disease. In recent years, some TCMs have been reported to have beneficial effects on radiotherapy-related radiation pneumonitis.

Shenqi fuzheng injection combined with antibiotics and short-term pulse therapy with highly efficient hormones had a good effect for radiation pneumonitis compared to the control group treated only by antibiotic and hormone pulse therapy. The combination could effectively improve respiratory symptoms and signs, and regulate subsets of T-lymphocytes (CD3+, CD4+, CD8+ and CD4+/CD8+ ratio), as well as increase patients' quality of life (98). In addition, a prospective randomized clinical study was conducted to assess the effect of a Traditional Chinese herbal formulation composed of Liangxue Jiedu Huoxue Decoction including 7 herbs (*Radix rehmanniae*, *Rhizoma chuanxiong*, *Cortex moutan*, *Peach seed*, *Flos carthami*, *Radix astragali*, and *Fructus forsythiae*). In this 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 (99). 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. In all, TCM interventions appear to have beneficial effects on alleviating radiation pneumonitis caused by radiotherapy in cancer patients. However, there are several limitations associated with the current published studies on TCMs relieving radiation pneumonitis such as indeterminate results, small sample sizes, and little examination of outcomes. Thus, conducting rigorously designed trials on potential Chinese herbal medicine are warranted.

5.7. 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. Although 90% of patients resumed normal liver function after stopping use of hepatotoxic drugs, current chemotherapeutic guidelines require stopping chemotherapy when hepatotoxicity as indicated by AST and ALT levels, reaches four times the upper normal limit. Moreover, there is a lack of drugs that effectively protect liver function and elevation of liver enzymes (12). In recent years, some TCMs have been reported to have beneficial effects on improving hepatotoxicity. To examine the effectiveness of TCM for protecting the liver from the toxic effects of chemotherapy among patients with cancer receiving joint TCM (e.g., Xiao-chai-hu-tang, Huang-lian-jie-du-tang or Yin-chen-wu-ling-san) and chemotherapy, a case-control study involving 89 patients and 184 chemotherapy courses was conducted (100). Use of TCM with chemotherapy resulted in protection of the

liver during chemotherapy, as manifested by lower serum AST and ALT levels. However, this study only examined a limited spectrum of patient outcomes. A future study with more-homogeneous samples and a larger sample size is needed.

6. Conclusion

In conclusion, TCM as adjuvant cancer treatment plays important roles in different stages of cancer lesions including post-operation, radiotherapy or chemotherapy stages. Some TCMs (e.g., TJ-41, Liu-jun-zi-tang, PHY906, Coumarin, and Aescine) are capable of improving the post-operation symptoms such as fatigue, pain, appetite, diarrhea, nausea, vomiting, and lymphedema. Some TCMs (e.g., Ginseng, Huang-Qi, BanZhiLian, TJ-48, Huachansu injection, Shenqi fuzheng injection, and Kanglaite injection) in combination with chemo- or radiotherapy are capable of enhancing the efficacy of and diminishing the side effects and complications caused by chemo- and radiotherapy. Taken together, they have great advantages in terms of suppressing tumor progression, relieving surgery complications, increasing the sensitivity of chemo- and radiotherapeutics, improving an organism's immune system function, and lessening the damage caused by surgery, chemo- or radio-therapeutics. They have significant effects on relieving breast cancer-related lymphedema, reducing cancer-related fatigue and pain, improving radiation pneumonitis and gastrointestinal side effects, protecting liver function, and even ameliorating bone marrow suppression. This review of those medicines should contribute to an understanding of Chinese herbal medicines as an adjunctive therapy in the whole course of cancer treatment instead of only the terminal stage of cancer, with providing useful information for development of more effective anti-cancer drugs and making more patients "survival with cancer" for a long time. However, rigorously designed trials on potential Chinese herbal medicine must be further examined involving cancer patients in the future.

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