

An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics

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Summary

Numerous studies have indicated that in cancer treatment Chinese herbal medicines in combination with chemo-, radio-, or targeted-therapy can be used to enhance the efficacy of and diminish the side effects and complications caused by these therapies. Therefore, an understanding of Chinese herbal medicines is needed by physicians and other health care providers. This review provides an update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics. First, some Chinese herbal medicines (e.g. Astragalus, Ginseng, *Scutellaria barbata*, TJ-41, TJ-48, PHY906, Huachansu injection, and Kanglaite injection) that are commonly used for treating the cancer and/or reducing the toxicity induced by chemo-, radio-, or targeted-therapy are discussed. These Chinese herbal medicines have been shown to possess great advantages in terms of suppressing tumor progression, increasing the sensitivity of chemo-, radio-, or targeted-therapeutics, improving an organism's immune system function, and lessening the damage caused by these therapeutics. Second, some clinical trials using Chinese herbal medicines as adjuvant improving cancer treatment related side effects and complications are reviewed. Some Chinese herbal medicines have a significant effect on reducing cancer-related fatigue and pain, improving peripheral neuropathy and gastrointestinal side effects including diarrhea, nausea, and vomiting, decrease the incidence of bone marrow suppression, protecting anthracycline-induced cardiotoxicity and radiation-induced pneumonitis, and relieving EGFR-TKIs related acneiform eruptions and other side effects. 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, rigorously designed trials on potential Chinese herbal medicine must be further examined involving cancer treatment especially molecular targeted-therapy in the future.

Keywords: Chinese herbal medicine, adjuvant treatment, chemotherapy, radiotherapy, targeted therapy

1. Introduction

Cancer constitutes one of the leading causes of morbidity and mortality worldwide. Based on GLOBOCAN (a project of the International Agency for Research on

Cancer) estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide (1). Because of the growth and aging of the population, as well as an increasing prevalence of established risk factors such as smoking, overweight, physical inactivity, and changing reproductive patterns associated with urbanization and economic development, the morbidity and mortality of cancer is predicted to be increased quickly in the next few decades worldwide, especially in low- and middle-income countries (2). It is projected that by 2030 an estimated 21.4 million new cases of cancer

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and 13.2 million cancer deaths will occur annually around the world, which brings an enormous burden on society (3).

Chemotherapy, radiotherapy, targeted therapy and immunotherapy are examples of anticancer therapies currently being utilized in patients with malignant tumors in middle and advanced stages for controlling tumor growth, prolonging survival time, and improving quality of life (QOL) to some extent. However, these therapies either alone or in combination have been shown to have numerous limitations and drawbacks including myelosuppression, gastrointestinal tract reaction, cardiac damage, liver and renal dysfunction, rash, hand-foot syndrome, or local radiation damage, and so on (4,5). In particular, with molecular-targeted drugs widely used, adverse effects of such treatments including acneiform eruptions, paronychia, xerosis, mucositis, and alopecia are thought to be less severe, but can still be significant (6). Not only can these toxicities severely affect patients' QOL, but in some specific instances, they can be associated with increased response to therapy (7). Therefore, it is of paramount importance that clinicians familiarize themselves with the basic management of the adverse effects caused by these drugs. More effective or adjunctive therapies must be soon developed for relieving adverse effects and complications of anticancer therapeutics.

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, are better than striving to reduce the lump and completely kill all cancer cells (5). In the process of "survival with cancer", complementary and alternative medicine (CAM) might play an important role.

Traditional Chinese medicine (TCM) especially Chinese herbal medicines, as an important component of CAM, has evolved over thousands of years in China, Japan, and other Asian countries with its own unique system of theories, diagnostics and therapies. TCM has been increasingly used in the last decades and become well known for its significant role in preventing and treating cancer. It is widely used by TCM physicians and other health care providers to control the side effects and toxicities of cancer therapies, which improves the patient's QOL, prevents recurrence, and prolongs survival (8).

In our previous reviews of recent years, we have indicated that some Chinese herbal medicines as adjuvant treatment in combination with chemo- or radio-therapy were capable of enhancing the sensitivity of chemo- and radio-therapeutics, improving an organism's immune system function, and diminishing the side effects and complications caused by chemo- and radiotherapy (3), and we have also indicated that some Chinese herbal

medicines as adjuvant treatment played important roles in different stages of cancer lesions including post-operation, radiotherapy or chemotherapy stages (5). Here an update of the new laboratory and clinical studies especially from 2015 to March 2018 on Chinese herbal medicines as adjuvant treatment especially on relieving adverse effects and complications of anticancer therapeutics will be focused. First, some Chinese herbal medicines that are commonly used on cancer patients to treat the cancer and/or reduce the toxicity induced by chemo-, radio-, or targeted-therapy are discussed. Second, clinical trials of Chinese herbal medicines as adjuvant cancer treatment to reduce side effects and complications during chemo-, radio-, or targeted-therapy are reviewed. This review should contribute to an understanding of Chinese herbal medicines as adjuvant treatment for cancer and provide useful information for development of more effective anti-cancer drugs.

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

Chinese herbal medicines in current use are usually classified as single herbs, compound formulations (a combination of several herbs), and Chinese medicine preparations. The biological ingredients of herbal medicines are mainly extracted from plants, animal parts, shells, insects, and even stones and minerals. In recent decades, a large number of herbal medicines including single herbs, traditional herbal formulations, and Chinese medicine preparations have been widely used on cancer patients around the world especially in China for managing common cancer symptoms of fatigue, chronic pain, anorexia, insomnia, limbs edema, and constipation (9). Numerous basic and clinical studies have been conducted to identify effective anticancer agents in Chinese herbal medicines and ascertain their properties as related to the treatment of cancer. Several herbal medicines have been found to have potentially beneficial effects on cancer progression and may ameliorate chemo-, radio-, or targeted-therapy induced complications and side effects (10,11). Therefore, the anticancer pharmacology of the Chinese herbal medicines most commonly used as adjuvant treatment in cancer therapy must be understood.

2.1. Single herbss

Based on TCM classic theory, the formation of tumors are usually due to deficiency of vital energy (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 lumps as time goes by (5,12). According to the above theory, TCMS which are used for cancer treatment usually fall

into three categories: the first one with properties of spiriting vital energy (Qi and blood), the second one with the properties of promoting blood stasis, and the third with properties of clearing heat and detoxifying. Thus, according to references and our clinical experience, we will choose some single herbs commonly prescribed by traditional Chinese physicians for cancer treatment and give them a brief introduction especially regarding clinical studies (Table 1).

2.1.1.1. Some single Chinese herbal medicines with properties of spiriting vital energy

Panax ginseng *Panax ginseng* (Ren-Shen in Chinese or Ginseng in Korea) is a well-known and popular Chinese herbal medicine, 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 (13). Much of the pharmacological research has shown that *Panax ginseng* has potent immune modulation, vasorelaxation, anti-oxidation, anti-inflammation, and anticancer properties (14). *Panax ginseng* contains many active components such as ginsenosides, peptides, essential oil and polysaccharides, among which, ginsenosides (e.g., Rg3 and Rb1) are considered an excellent option for their anticancer property (15). Ginseng and its active components have been reported as an adjuvant treatment to synergistically enhance efficacy of conventional therapy (e.g., chemo- and radio-therapeutics), reduce the risk of development and recurrence of some types of cancer (e.g., stomach, liver, pancreas, and colon cancer), and improve host intrinsic response to cancer and quality of patients' life (16). An epidemiological study indicated that patients taking ginseng had a 50% lower risk of cancer recurrence compared to patients not taking ginseng (17). In the following, we emphasize some basic and clinical research in recent years about Ginseng and its active components.

A pilot study indicates that Ginseng has potential as an effective treatment for advanced cancer patients in improving response and survival rate (18). A phase III trial was developed by Mayo Clinic Rochester (Rochester, USA) to evaluate the efficacy of Ginseng on cancer-related fatigue and indicated that Ginseng showed great benefit for ameliorating cancer-related fatigue without any discernible toxicity (19). Moreover, Ginseng appears to be a promising radio-protector and is capable of attenuating the deleterious effects of radiation on human normal tissue, especially for cancer patients undergoing radiotherapy (20). It could improve radiation-induced liver injury, which might be associated with the modulation of oxidative stress, inflammatory reactions, and apoptosis (21).

Ginsenoside Rg3 is recognized to boost immune response and has anti-cancer activity against a majority

of carcinomas including non-small cell lung cancer (NSCLC). An *in vitro* study indicated Rg3 might be a new agent targeting programmed death ligand 1 (PD-L1) in chemotherapy refractory NSCLC (22). Moreover, a multicenter, large-sample, randomized clinical trial on improving the median survival time of advanced NSCLC by a combination of Ginsenoside Rg3 and chemotherapy was conducted by Zhang *et al.* They indicated that a combination of Ginsenoside Rg3 with chemotherapy could prolong the survival of patients with advanced NSCLC, improve patients' symptoms and reduce chemotherapy induced myelosuppression (23).

Although evidence of efficacy in relation to Ginseng and its active components use is obvious, well-designed clinical trials are required to provide more information for scientists and healthcare consumers. Furthermore, using cautions and adverse reactions of Ginseng are crucial for people. Ginseng should be avoided by children and used with some prudence by patients medicated with blood pressure medicines, blood-thinning medications, hormones, or insulin due to possible drug-herb interactions (recommendation performed by American Cancer Society) (24). Ginseng is relatively nontoxic but in high doses (*i.e.*, superior to 3 g ginseng root daily) can confer adverse symptoms such as insomnia, nervous excitation, headaches, and nausea. Ginseng may present steroid/hormone like effects, so in women who have breast or endometrial cancer special attention for its use is recommended (25).

Radix Astragali *Radix Astragali* (Huang-Qi in Chinese), the root of *Astragalus membranaceus* Bunge, is one of the most famous and frequently used herbal medicines and healthy food supplements used as a tonic. It has been widely used to treat cancer and other immune disorders in China and Southeast Asia for thousands of years (26). The chemical composition of *Radix Astragali* mainly includes triterpenoid saponins, polysaccharides, flavonoids, amino acids, and trace elements, of which triterpenoid saponins (e.g., Astragaloside IV and Astragaloside II) represent the major beneficial constituents responsible for the bioactivities and efficacies of *Radix Astragali* on human health (27). *Radix Astragali* and its active constituents have been proposed as an adjuvant treatment to synergistically enhance efficacy and reduce toxicity of chemo-, radio-, or targeted-therapeutics on breast, gastric, liver, colon, and lung cancers and so on.

Multiple randomized clinical trials have suggested that *Radix Astragali*-based intervention can reduce symptoms, improve QOL and immunologic function, increase plasma nerve growth factor (NGF) levels, and delay the progression of chemotherapy-induced peripheral neuropathy (CIPN) (28). In addition, Huangqi injection combined with chemotherapy has an enhanced anti-tumor effect and can improve the short-term prognosis and clinical outcome in children with acute lymphoblastic leukemia (ALL) (29). It could reduce

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>Panax ginseng</i>	Ren-Shen in Chinese, Ginseng in Korea	As a tonic, prophyllactic 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, antimicrobial, antiviral, hepatoprotective, hypoglycemic	<i>Clinical:</i> (i) Ren-Shen: Ameliorating cancer-related fatigue without any discernible toxicity; (ii) Ren-Shen: Improving radiation-induced liver injury; (iii) Ginsenoside Rg3: prolong the survival of patients with advanced NSCLC and reduce chemotherapy induced myelosuppression. <i>Preclinical:</i> Ginsenoside Rg3 a new agent targeting PD-L1 in chemotherapy refractory NSCLC.	16-21,23
<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; (ii) Delay the progression of CIPN; (iii) Decrease infectious rate in ALL children with chemotherapy. <i>Preclinical:</i> Astragaloside IV inhibit cancer cell invasion <i>via</i> Rac1/ MAPK and PKC- α -ERK1/2-NF- κ B pathway	28-30
<i>Radix Codonopsis</i>	Dang-Shen in Chinese	As a tonic with the efficacy strengthening spleen and nourishing lung	Polysaccharides, alkaloids, phenylpropanoids, triterpenes, and polyacetylenes	Antioxidant, antimicrobial, antitumor, immunomodulation	<i>Clinical:</i> (i) Reducing the immunosuppressive effect of radiotherapy; (ii) Improving chemotherapy induced CIN, reduce myelosuppression and/or enhance immune response of patients	37-39
<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> Improve tumor response rate and alleviate chemotherapy-related adverse events. <i>Preclinical:</i> Combined with oxaliplatin: Inhibit the migration and invasion of gastric cancer cells <i>via</i> regulating the EMT process.	46 45
<i>Angelicae Sinensis Radix</i>	Dang-Gui in Chinese, Dong Quai in English, Toki in Japanese, or Tanggwi in Korea	With nourishing Yin, promoting blood circulation, and moisturizing dryness functions	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	54
<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> Curcumin: (i) Modulates chemo-resistance and radio-resistance; (ii) Protects normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy and radiotherapy induced toxicity.	58,59
<i>Hechois 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>Clinical:</i> Enhance the overall survival of patients with GC. <i>Preclinical:</i> Suppress colorectal cancer growth through multiple cellular pathways including MAPK, STAT3, AKT and ERK signaling.	62 61-64
<i>Scutellaria barbata</i>	Ban-Zhi-Lian in Chinese, Banjiryun in Korea	With the efficacy of clearing heat and detoxifying	Phenolic acids, flavonoids, triterpene acids and sterol glucosides	Antitumor, anti-inflammatory	<i>Preclinical:</i> (i) Inhibit migration and invasion of colorectal cancer cells <i>via</i> suppression of PI3K/AKT and TGF- β /Smad signaling pathways; (ii) Inhibit 5-FU resistance in colorectal cancer by regulating PI3K/AKT pathway <i>Clinical:</i> Improve atatinib-induced paronychia in cancer patient.	66,67 69

Abbreviations: programmed death ligand 1 (PD-L1); chemotherapy-induced peripheral neuropathy (CIPN); epithelial-mesenchymal transition (EMT); gastric cancer (GC).

bone marrow suppression caused by chemotherapy drugs and increase neutrophil count during remission induction chemotherapy to reduce the incidence and duration of infection in children with ALL (30).

Astragaloside IV could inhibit breast cancer cell invasion by suppressing Vav3 mediated Rac1/MAPK signaling and inhibit lung cancer invasion via the PKC- α -ERK1/2-NF- κ B pathway (31,32). Astragaloside IV also could inhibit progression of glioma via blocking MAPK/ERK signaling pathway (33). In addition, Astragaloside II could inhibit autophagic flux and enhance chemosensitivity of cisplatin in human cancer cells (34).

Radix Codonopsis *Radix Codonopsis* (Dang-Shen in Chinese) is a famous traditional Chinese medicine and has long been used for replenishing energy deficiency, strengthening the immune system, lowering blood pressure and improving appetite in China, Japan and Korea (35). In many cases, it is utilized primarily as a substitute for the much more costly *Panax ginseng* and is therefore called the poor man's ginseng. Phytochemical studies indicate that polysaccharides, alkaloids, phenylpropanoids, triterpenes, and polyacetylenes are the main components of *Radix Codonopsis* (36). Recently, *Radix Codonopsis* and its active constituents have been proposed to have functions of antioxidant, antimicrobial, antitumor and improving immunity. They are reported as adjunctive cancer therapeutics with activities of immunomodulation, anti-proliferation and attenuation of adverse effects induced by cytotoxic therapy.

Radix Codonopsis was used as an adjuvant in cancer patients during radiotherapy. It could reduce the immunosuppressive effect of radiotherapy on delayed hypersensitive reaction, and the lymphocyte response to PHA and IL-2 (37). Some TCM decoctions of which *Radix Codonopsis* was a main ingredient could effectively improve clinical symptoms, signs and QOL of cancer patients. A modern agent Shenqi Fuzheng Injection, prepared from *Codonopsis Radix* and *Astragali Radix*, commonly used as a supplementary therapy for cancers, could reprogram the immunosuppressive microenvironment *in vivo* to enhance the cytotoxicity of tumor-infiltrating immune cells in melanoma (38). Combining oxaliplatin regimens with some TCM decoctions containing *Radix Codonopsis* in the management of colorectal cancer (CRC) could effectively improve chemotherapy induced CIN, reduce myelosuppression and/or enhance immune response of patients (39). In addition, polysaccharides from *Radix Codonopsis* exhibited significant inhibitory effects on tumor cell growth, invasion, and migration of human epithelial ovarian cancer cells (40). Polysaccharides from *Radix Codonopsis* also could inhibit melanoma metastasis via regulating integrin signaling (41).

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. Thus, more rigorous trials are needed to confirm the efficacy of *Radix Codonopsis* and its active constituents on cancer therapy in the future.

Poria cocos *Poria cocos* (Fu-Ling in Chinese or Hoelen in Japanese), is an important medicinal and edible fungus that grows in association with pine trees, and its dried sclerotium has been used as a traditional medicine in China for centuries (42). It is a well known Chinese herbal medicine used to treat diabetes, dysentery, chronic fatigue syndrome, diarrhea, dizziness, edema, insomnia, kidney problems, nervousness, urination problems, and weakness (5). The chemical composition of *Poria cocos* mainly includes triterpenes, polysaccharides, steroids, amino acids, choline, histidine, etc. (43). Recently, *Poria cocos* and its active constituents have been reported to have functions of anticancer, anti-inflammatory, antioxidant, antiviral and improved immunity (44). They have been proposed as an adjuvant treatment to synergistically enhance efficacy and reduce toxicity of chemo-, radio-, or targeted-therapeutics on leukemia, lung, and colorectal cancers and so on.

Poria cocos combined with oxaliplatin could significantly inhibit the migration and invasion of gastric cancer cells via regulating the epithelial-mesenchymal transition (EMT) process of gastric cancer (45). Moreover, *Poria cocos* as one of the most frequently used herbs combined with the FOLFOX4 chemotherapy regimen could effectively improve tumor response rate, one year survival and QOL of patients. It also could alleviate chemotherapy-related adverse events including neutropenia, nausea and vomiting, and neurotoxicity, compared to the FOLFOX4 chemotherapy regimen alone (46). In addition, Pachymic acid, a lanostane-type triterpenoid from *Poria cocos*, could induce apoptosis of human lung cancer cells through activation of the JNK and ER stress pathways (47), and induce apoptosis of bladder cancer cells via the mitochondrial apoptosis pathway (48). Triterpenes from *Poria cocos* also could suppress growth and invasiveness of pancreatic cancer cells through downregulation of MMP-7 (49).

Taken together, although *Poria cocos* and its active constituents have been reported as an adjuvant treatment for cancer therapy, more rigorous trials are needed to confirm the efficacy of *Poria cocos* and its active constituents for cancer therapy in the future.

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

Angelicae Sinensis Radix *Angelicae Sinensis Radix*, (Dang-Gui in Chinese, Dong Quai in English, Toki in Japanese, or Tanggwi in Korea), is a well-known Pharmacopoeia-recorded medical material in China with nourishing Yin, promoting blood circulation, and moisturizing dryness functions. It is usually used to strengthen heart, lung, and liver meridians, as well as lubricate the bowel (5). Furthermore, it has been called

"female ginseng" due to its superior efficacy in treating gynecological conditions including dysmenorrhea, pelvic pain, recovery from childbirth and menopausal symptoms (50). 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 (51). *Angelicae Sinensis Radix* and some of its active constituents have been reported to possess hematopoietic, antioxidant, immunoregulatory, anti-cancer, memory, radioprotective, and neuroprotective effects. Moreover, some reports indicated that *Angelicae Sinensis Radix* and some of its active constituents exhibited great anticancer effects in liver, oral, and lung cancers *via* inducing apoptosis, revising multidrug resistance or modulating lymphocyte activity and improving immunity (52,53). In addition, the decoction containing *Radix Angelicae Sinensis* could enhance radiosensitivity of radiation in human liver cancer cells by modulating caspase-dependent apoptosis protein (54).

Although *Angelicae Sinensis Radix* 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 *Angelicae Sinensis Radix* and its active constituents for cancer therapy in the future.

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 (5). The major bioactive compounds of *Curcuma longa* contain curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with curcumin being the most abundant ingredient (55). It has been shown that curcumin has a variety of pharmacological effects such as antioxidant, anti-cancer, anti-inflammatory, and anti-microbial activities. Anti-cancer effects of curcumin are involved in cell cycle arrest, apoptosis, angiogenesis and metastasis *via* a wide range of cellular and molecular pathways involved in cancer pathogenesis including NF- κ B, MAPK, PTEN, P53, and microRNAs (miRNA) network (56). Curcumin has been widely used to fight against cisplatin-resistant cancer cells and decrease its unwanted side effects (*e.g.* ototoxicity, nephrotoxicity and neurotoxicity) (57). Curcumin might be a safe and effective inhibitor of P-glycoprotein (P-gp) to overcome multidrug resistance (MDR) in human cancer (58). In addition, some research 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) (59).

Moreover, curcumin has also been shown to protect normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy and radiotherapy induced toxicity (5).

However, since most of such findings have yet to be confirmed in clinical studies, its effect on humans is not clearly known. Thus, the future prospect of research on *Curcuma longa* and curcumin will be a very exciting field of research for the coming decades and will provide us with better mechanisms of utilizing them as adjuvant drugs against cancer in the near future.

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

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. It was recorded in Chinese pharmacopoeia (2015 ed) with the functions of inducing diuresis to reduce edema, clearing away the heat evil and detoxification, and promoting blood circulation to arrest pain. Up to now, 171 compounds have been reported from *Hedyotis diffusa willd*, including iridoids, flavonoids, anthraquinones, phenolics and their derivatives, volatile oils and miscellaneous compounds. *In vitro* and *in vivo* studies show these phytochemicals and plant extracts to exhibit a range of pharmacological activities of anti-cancer, antioxidant, anti-inflammatory, anti-fibroblast, immunomodulatory and neuroprotective effects (60). Recently, *Hedyotis diffusa willd* and some of its active constituents have gained increasing attention as an antitumor herb. Clinically, this herb has often been applied as a critical element in many TCM formulae for the treatment of various cancers, including gastric cancer (GC) and colorectal cancer (61-64). A latest retrospective matched-cohort study presented that *Hedyotis diffusa willd* was the most commonly prescribed single herb for treating GC patients and complementary TCM therapy enhanced the overall survival of patients with GC in Taiwan (62). It probably produced the therapeutic effects against GC by synergistically regulating many biological pathways, such as nucleotide excision repair, apoptosis, cell cycle, PI3K/AKT/mTOR signaling pathway, VEGF signaling pathway, and Ras signaling pathway (61). *Hedyotis diffusa willd* could suppress colorectal cancer growth through multiple cellular pathways including MAPK, STAT3, AKT and ERK signaling (63). It also could suppress metastasis in 5-FU-resistant colorectal cancer cells by regulating the TGF- β signaling pathway (64). Although *Hedyotis diffusa willd* is widely studied in laboratory and clinical studies, more rigorous trials are needed to confirm the efficacy of *Hedyotis diffusa willd* and its active constituents on cancer therapy in the future.

Scutellaria barbata *Scutellaria barbata* (Ban-Zhi-Lian in Chinese or Banjiryun in Korea), a herbal plant in *Astragalus* genus, is a well-known anti-inflammatory

and anti-cancer herb with the properties of clearing heat, activating blood and dissolving stasis according to TCM theory. It has been widely used for treatment of various kinds of cancer, such as colorectal, liver, breast and lung cancer in China and other Asian countries for many years (65). Chromatographic analysis has demonstrated that scutellarein, apigenin, baicalein and luteolin are main components of *Scutellaria barbata*. *Scutellaria barbata* was reported to process the effects of promoting apoptosis, and inhibiting cell proliferation and angiogenesis in human colon cancer cells. It could inhibit migration and invasion of colorectal cancer cells via suppression of PI3K/AKT and TGF- β /Smad signaling pathways (66). It also could inhibit 5-FU resistance in colorectal cancer by regulating PI3K/AKT pathway (67). Moreover, *Scutellaria barbata* could regulate immune function of Lewis-bearing C57BL/6 mice with a decrease of IL-17, IL-10, FOXP3, TGF- β 1, ROR γ t, and IL-6 levels and increase of IL-2 and IFN- γ levels (68). In addition, a decoction of Ban-Zhi-Lian (*Scutellaria barbata*) with Bai-Hua-She-She-Cao (*Hedyotis diffusa Willd*) could effectively improve afatinib-induced paronychia in patients (69). However, there are few reports on the anticancer effects of the active constituents of *Scutellaria barbata*. A water-soluble polysaccharide SPS2p, isolated from the whole grass of *Scutellaria barbata*, could inhibit proliferation and EMT, and promote apoptosis of human colon cancer HT29 cells via PI3K/AKT pathway (70). In the future, more rigorous trials are needed to confirm the efficacy of *Scutellaria barbata* and its active constituents for cancer therapy.

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" (5). Currently, several traditional Chinese herbal formulations, such as Bu-Zhong-Yi-Qi-Tang (TJ-41), 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 recorded as a tonic for the treatment of weakness including fatigue, visceroptosis, gastrointestinal motility disorder, and rectal prolapse due

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 Korean	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) Reversing cisplatin resistance through induction of apoptosis and autophagy in lung cancer cells; (ii) Inhibiting 5-FU-induced intestinal mucositis via the suppression of inflammatory cytokine up-regulation. <i>Clinical:</i> (i) Have protective effect of intestine and hematopoietic organs against radiation damage. (ii) Improving localized radiotherapy-induced immune deterioration; (iii) Improving cancer-related fatigue and QOL; (iv) Reducing radiation or chemotherapy induced side effects.	72,73 73-75
Shi-Quan-Da-Bu-Tang	Juzentaiho-to or TJ-48 in Japanese, Sijieondaebotang in Korean	Includes 10 herbs: <i>Ginseng radix</i> , <i>Astragal radix</i> , <i>Angelicae radix</i> , <i>Rehmanniae radix</i> , <i>Atractylodis lanceae rhizoma</i> , <i>Cinnamomi cortex</i> , <i>Portia</i> , <i>Paeoniae radix</i> , <i>Ligustici rhizoma</i> <i>Glycyrrhizae radix</i>	Antitumor, immunomodulation	<i>Clinical:</i> (i) Regulating T cells through decreasing Foxp3+ Treg populations in advanced pancreatic cancer patients; (ii) Inhibiting B16 cell metastasis by inducing NK cell activity. (iii) Combined with anti-PD-1 antibody: increasing treatment response rates for B16 melanoma. <i>Preclinical:</i> Alleviating bone marrow suppression caused by TS-1 in mice.	77-79 5
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>Zizyphus 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> Inhibiting cell proliferation and promoting apoptosis of HCC cells via regulating the expression of Bax, Bcl-2, CDK4 and cyclin-D1. <i>Clinical:</i> (i) Preventing the development of HCC from hepatitis C virus-associated liver cirrhosis (HCV-LC) in the HCV-LC patients; (ii) considered to be a useful method against stomatitis prevention and sharp pain mitigation from chemotherapy.	80 82,83
Huang-qin-tang	PHY906	Includes 4 herbs: <i>Scutellaria baicalensis</i> <i>Georgi</i> , <i>Paeonia lactiflora</i> <i>Pall</i> , <i>Glycyrrhiza uralensis</i> <i>Fisch</i> , <i>Ziziphus jujuba</i> <i>Mill</i>	Antitumor, anti-inflammatory	<i>Preclinical:</i> Enhancing the anti-tumor activity of Sorafenib in nude mice bearing HepG2 xenografts by targeting on the inflammatory state of microenvironment of tumor tissue. <i>Clinical:</i> Enhancing the antitumor efficacy of some anticancer drugs but also alleviating chemo- or targeted-therapy (e.g., CTP-11) induced side effects.	85 86,87

to chronic diarrhea. Furthermore, it has been identified as an effective drug for the treatment of TCM spleen-qi deficiency in clinical practice in recent years. It contains 7 herbs including *Pinellia tuber*, *Scutellaria baicalensis*, *Zingiberis rhizoma*, *Zizyphi fructus*, *Coptidis rhizoma*, *Glycyrrhiza radix*, and *Panax ginseng* (3). Recently, much of the pharmacological research has shown that Bu-zhong-yi-qi-tang has potent immunomodulatory and anticancer properties.

A study was conducted by Li *et al.* to investigate the frequencies and patterns of Chinese herbal medicine treatment for lung cancer patients and the effect of Chinese herbal medicine on their survival probability in Taiwan (71). They indicated that the use of Chinese herbal medicine as an adjunctive therapy might reduce the mortality hazard ratio of lung cancer patients and Bu-zhong-yi-qi-tang was found to be the top formula prescribed by traditional Chinese physicians for lung cancer patients. Yu *et al.* found that co-treatment with Bu-zhong-yi-qi-tang and cisplatin might reverse cisplatin resistance through induction of apoptosis and autophagy in lung cancer cells (72). Moreover, Bu-zhong-yi-qi-tang could inhibit 5-FU-induced intestinal mucositis, and this effect might be due to the reduction in apoptosis and necrosis in intestinal mucosal epithelia *via* the suppression of inflammatory cytokine up-regulation (73). Bu-zhong-yi-qi-tang was reported to have a protective effect for intestine and hematopoietic organs against radiation damage. It also could effectively improve localized radiotherapy-induced immune deterioration *via* increasing the number of CD19+ B cells in patients with end stage cancer (74). In addition, Bu-zhong-yi-qi-tang might have beneficial effects on cancer-related fatigue and QOL 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 used to treat malignant tumors (75).

3.2. Shi-Quan-Da-Bu-Tang

Shi-quan-da-bu-tang (Juzentaiho-to or TJ-48 in Japanese, or Sipjeondaebo-tang in Korean) 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 *Glycyrrhizae radix* (5). It has been used for many years for the treatment of various kinds of diseases such as anemia, rheumatoid arthritis, atopic dermatitis, chronic fatigue syndrome, and ulcerative colitis. Recently, Shi-quan-da-bu-tang has been reported to have antitumor effects and to modulate immune responses. It could reduce the side effects of 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.

A Pilot, randomized, double-blind, placebo-controlled trial ($n = 32$) was conducted to evaluate the efficacy and safety of Shi-quan-da-bu-tang for anorexia in patients with cancer (76). The results showed that 4 weeks of Shi-quan-da-bu-tang treatment effectively improved the QOL and anorexia in patients. As Shi-quan-da-bu-tang is commonly used by patients with lung cancer undergoing outpatient chemotherapy, a QOL questionnaire for cancer patients treated with anticancer drugs was conducted in patients ($n = 16$) with non-small cell lung cancer (77). Significant improvement was observed in the total QOL score, mainly owing to improvement in patients "physical condition." 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 (78). Moreover, the effect of Shi-quan-da-bu-tang on natural killer (NK) cell activity and metastasis in combined treatments with anti-PD-1 antibody in a mouse model of melanoma metastasis was investigated (79). The data suggested that Shi-quan-da-bu-tang could inhibit B16 cell metastasis by inducing NK cell activity. Additionally, combination therapy with Shi-quan-da-bu-tang and anti-PD-1 antibody increased treatment response rates for B16 melanoma. In addition, TJ-48 was effective in alleviating bone marrow suppression caused by TS-1 (an oral anticancer drug containing a 5-FU derivative Tegafur) in mice (5).

3.3. 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*) (5). Much pharmacological research has shown that Xiao-chai-hu-tang 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 Xiao-chai-hu-tang for cancer treatment. These studies have demonstrated that Xiao-chai-hu-tang treats cancer by enhancing immune regulation, anti-angiogenesis and apoptosis of tumor cells.

Xiao-chai-hu-tang could halt cell proliferation and promote apoptosis of human hepatocellular carcinoma (HCC) cells *via* regulating the expression of Bax, Bcl-2, CDK4 and cyclin-D1 (80). A cross-sectional analysis of the National Health Insurance Research Database in Taiwan was conducted to investigate the prescription frequency and patterns of Chinese herbal medicines for

HCC patients. They found that the herbal preparation of Xiao-chai-hu-tang was the most obviously increased and important Chinese herbal medicine being used for HCC patients (81). A cohort study that also used the Taiwanese National Health Insurance Research Database was conducted to investigate the effects of Chinese herbal medicine on HCC risk among patients with chronic hepatitis B. They suggested that the use of some Chinese herbal medicines including Xiao-chai-hu-tang was associated with a significantly reduced HCC risk in patients with chronic hepatitis B, which supports the integration of TCM into clinical practice to influence a favorable prognosis (82). In addition, Xiao-chai-hu-tang 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, Xiao-chai-hu-tang gargle was considered to be a useful method against stomatitis prevention and sharp pain mitigation from chemotherapy (83).

3.4. 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), which was first recorded in "Shang Han Lun". It has been used for over 1800 years to treat a variety of gastrointestinal symptoms including diarrhea, nausea and vomiting, and abdominal cramps (5). PHY906 (KD018) 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 (3). A series of preclinical and clinical studies to investigate the anticancer activities of PHY906 has been conducted in recent years. PHY906 not only enhances the antitumor efficacy of some anticancer drugs but also alleviates chemotherapy-induced side effects, such as diarrhea (84). PHY906 can serve as an adjuvant to Sorafenib, CTP-11, 5-FU, leucovorin (LV), and capecitabine in the treatment of advanced colorectal, pancreatic, and liver cancer (85,86).

According to a preclinical study, PHY906 was reported to enhance the anti-tumor activity of Sorafenib in nude mice bearing HepG2 xenografts by targeting the inflammatory state of the microenvironment of tumor tissue (85). PHY906 was also demonstrated to decrease toxicity from fractionated abdominal irradiation by promoting faster recovery of the intestine (87). Additional preclinical studies have shown that PHY906 could reduce the toxicity associated with CTP-11 treatment while increasing CTP-11's antitumor effects in metastatic colorectal cancer (86). Clinical studies indicated that PHY906 treatment could result in a significant decrease in patient's gastrointestinal toxicity, and no PHY906-associated toxicity has been observed (84).

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 (3). 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 (5). 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 properties of spiriting 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, immune-regulation, and so on (e.g., Huachansu injection and Brucea javanica 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" (88). 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 (3). It is used extensively throughout China to modify the immunological function of patients with chronic diseases including cancer and cerebrovascular diseases such as, angina, coronary heart disease, heart failure, and so on. Currently, many trials have studied the Shenqi fuzheng injection in combination with chemo- or radio-therapy 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 (89-91).

Table 3. Chinese medicine preparations commonly used clinically 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 Astragalii</i> <i>Codonopsis pilosula</i>	Antitumor, immunomodulation	Improve the chemotherapy efficacy and the quality of survival (KPS), strengthen cellular immune function, and decrease the chemotherapy and/or radiotherapy toxicities. <i>Preclinical:</i> attenuate cranial radiation therapy-induced brain injury in mice <i>via</i> inhibition of the NF-κB signaling pathway and microglial activation.	89-91 92
Kanglaite injection	Extracted from <i>Semen Coicis</i> <i>Yokunin</i>	Antitumor	<i>Preclinical:</i> (i) Combined with Gefitinib: promoting apoptosis and increasing sensitivity to Gefitinib in human lung adenocarcinoma cells; (ii) Inhibiting TNF-α-mediated EMT in colorectal cancer cell lines <i>via</i> inhibition of NF-κB pathway. <i>Clinical:</i> (i) Combined with gemcitabine: demonstrated encouraging clinical evidence of anti-neoplastic activity and a well-tolerated safety profile; (ii) Combined with FOLFOX regimen: strengthen the overall response rate, improve the QOL, reduce nausea and vomiting, and reduce the incidence of leucopenia.	93,94 96,97
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> (i) Combined with doxorubicin: increase apoptosis of HCC cells through the Fas- and mitochondria-mediated pathways; (ii) Regulating cancer cell migration by matrix metalloproteinases of human breast carcinoma cells; (iii) Inhibiting proliferation and inducing apoptosis in human bladder cancer cells by Fas/FasL and TNF-α/TNFR1 pathway. <i>Clinical:</i> (i) Improving objective tumor response and reducing chemotherapy-related side effects; (ii) Combined with TACE could significantly increase the objective response rate and 2-year survival rate; (iii) Reducing the quantity of pericardial effusion and improving the patient's QOL.	98-101 102-104
Brucea javanica oil emulsion injection	Extracted from <i>Brucea javanica</i> Merr.	Antitumor	<i>Clinical:</i> (i) Enhancing chemotherapeutic effect, improving QOL, and reducing adverse effects of platinum-contained chemotherapeutics; (ii) Intrapleural injection of chemotherapy drugs plus BJOEI has a better benefit of ORR for treating malignant pleural effusions and improves the QOL of malignant pleural effusions patients.	107-110

Abbreviations: epithelial mesenchymal transition (EMT); tumor necrosis factor-alpha (TNF-α); transcatheter arterial chemoembolization (TACE); Brucea javanica oil emulsion injection (BJOEI); overall response rate (ORR).

A meta-analysis indicated that Shenqi fuzheng injection combined with chemotherapy (e.g., FOLFOX regimen and XELOX regimen) in treatment of colorectal cancer could improve chemotherapy efficacy and quality of survival (KPS), strengthen cellular immune function (CD3+, CD4+, CD4+/CD8+ and NK+), and reduce adverse events such as leukocytopenia, thrombocytopenia and gastrointestinal toxicity (89). Additional meta-analysis demonstrated that the Shenqi fuzheng injection intervention with conventional chemotherapy exhibited better therapeutic efficacy than the conventional chemotherapy group with a statistically significant higher objective tumor response in the treatment of lung, breast, and digestive cancers. Cotreatment with Shenqi fuzheng injection could enhance NK, CD3 +, CD4 + level, and CD4 +/CD8 + ratio compared with the conventional chemotherapy group (90). Moreover, Shenqi Fuzheng injection can improve the clinical efficacy and decrease the radiation toxicities in the NSCLC patients treated with radiation (91). In addition, Shenqi fuzheng injection could attenuate cranial radiation therapy-induced brain injury in mice *via* inhibition of the NF-κB signaling pathway and microglial activation (92).

4.2. Kanglaite injection

Kanglaite injection is an acetone extract of herbal medicine coix seed (*Semen Coicis Yokuinin*) prepared as an herbal medicine 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 (5). Since that time, over 1 million cancer patients have received Kanglaite injection. Kanglaite injection is mainly used for the treatment of NSCLC, liver cancer, gastric cancer, etc. It has been found to significantly decrease cancer load, improve QOL of cancer patients, and may ameliorate multiple drug resistance of cancers when combined with chemo-, radio-, or targeted-therapy in clinical use.

According to a preclinical study, Kanglaite injection combined with Gefitinib had an outstanding apoptosis promotion effect on A549 cell lines of lung adenocarcinoma, and Kanglaite injection could increase sensitivity of A549 cells of human lung adenocarcinoma to Gefitinib (93). Additionally, a recent study reported that Kanglaite injection could inhibit tumor necrosis factor-alpha-mediated epithelial mesenchymal transition (EMT) in colorectal cancer cell lines *via* inhibition of NF-κB pathway (94).

In clinical practice, Kanglaite injection was reported to provide objective evidence for lung cancer and significantly reduce the expression of miRNA-21 in patients with advanced lung cancer (95). Moreover, a randomized, open-label, safety and exploratory efficacy study of Kanglaite injection plus Gemcitabine versus Gemcitabine in patients with advanced pancreatic cancer

was published in 2017 by Schwartzberg *et al.* This multi-centered, randomized phase 2 trial indicated that Kanglaite injection (30 g/day) plus a standard regimen of gemcitabine demonstrated encouraging clinical evidence of anti-neoplastic activity and a well-tolerated safety profile (96). In addition, 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 QOL, reduce nausea and vomiting, and reduce the incidence of leukopenia (III-IV) (97).

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 (3). 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 (5). It also could effectively enhance physical immunity and improve the QOL with little toxicity in cancer patients.

Pre-clinical studies have shown that Huachansu effectively inhibits growth and induces apoptosis in human HCC. Combination of Cinobufacini and doxorubicin could increase apoptosis of HCC cells through the Fas- and mitochondria-mediated pathways (98). Additionally, recent studies reported that cinobufacini might be able to regulate cancer cell migration accelerated by matrix metalloproteinases of human breast carcinoma cell line MDA-MB-231 (99,100). Moreover, Huachansu could efficiently inhibit proliferation and induce apoptosis in human bladder cancer cells *in vitro* and *in vivo*, which was largely mediated by Fas/FasL and TNF- α /TNFR1 pathway (101).

A meta-analysis suggested that Huachansu could be a promising supplement to routine chemotherapy in treating advanced NSCLC. It could effectively improve objective tumor response of NSCLC patients and reduce chemotherapy-related side effects including leukocytopenia, thrombocytopenia, and nausea and vomiting and so on (102). Another meta-analysis demonstrated that cinobufacini combined

with transcatheter arterial chemoembolization (TACE) could significantly increase the objective response rate and 2-year survival rate compared with TACE only in patients with advanced HCC (103). In addition, Huachansu injection has been reported to be effective for treating malignant pericardial effusion, pleural effusions, and ascites by intracavitary injection. Huachansu injection could effectively relieve the patient's cardiac tamponade symptoms and improve the patient's QOL with the levels of CA-125 in pericardial effusion decreased and the quantity of pericardial effusion significantly reduced (104). Recently, a randomized phase II study demonstrated that Cinobufacin injection, when combined with gemcitabine, failed to improve the outcome of patients with locally advanced and/or metastatic pancreatic cancer (105). This is partly due to the insufficient efficacy of Cinobufacin injection in current formulation. Therefore, development of a more potent drug formulation demands a clear knowledge of the active components in Cinobufacin, and identification of their putative biomarkers.

4.4. Brucea javanica oil emulsion injection

Brucea javanica oil emulsion injection (BJOEI) is one of TCMs products, which takes Brucea Jen petroleum ether extracts as raw material and purified soybean lecithin as emulsifier (106). It is employed as adjunctive therapy in the treatment of lung carcinoma, brain metastasis of lung carcinoma, and gastrointestinal tumorigenesis.

The anticancer activity of BJOEI might be attributed to the following properties: inducing apoptosis, disturbing the cell cycle, disrupting cellular energy metabolism, and depressing expression of vascular endothelial growth factor (107). A great number of published studies have proved that BJOEI can perform a synergistic antitumor effect by improving tumor response, boosting KPS, reducing the incidence of adverse events and stimulating immunity during chemotherapy or radiotherapy (108).

A meta-analysis involving twenty-one studies and 2234 cases indicated that BJOEI could enhance the chemotherapeutic effect in NSCLC patients, improve the QOL, and reduce adverse effects of platinum-contained chemotherapeutics including nausea and vomiting and leucopenia, and thus it is worth referring to the clinic (107). Moreover, BJOE combined with chemotherapy could be considered as a safe and effective regimen in treating patients with advanced gastric cancer. A meta-analysis demonstrated that BJOEI combined with chemotherapy (*e.g.*, Potassium capsule, Cisplatin, 5-FU, and Oxaliplatin) for treating gastric cancer possessed the property of prominently relieving nausea and vomiting, diarrhea, neutropenia, neurotoxicity, and so on (109). In addition, intrapleural injection of traditional chemotherapy drugs plus BJOEI has a better benefit of overall response rate (ORR) for treating malignant pleural effusions and improves the QOL of malignant

pleural effusions patient, compared with traditional chemotherapy drugs alone (110). The participation of BJOEI could reduce the toxicity caused by chemotherapy drugs. However, more prospectively designed, large-sample, and multicenter rigorously randomized controlled trials (RCTs) should be needed for BJOEI in future studies.

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

In conventional Western medicine, chemotherapy, radiotherapy and targeted-therapy are major conventional cancer therapies and bring great benefit to the survival of patients; however, these treatments typically affect multiple organ systems including gastrointestinal tract, heart, liver, kidney, marrow, skins, peripheral nerves, blood vessels, and so on. Fatigue, pain, diarrhea, nausea, vomiting, hair loss, cardiac injury (e.g., myocardial ischemia, hypertension, cardiomyopathy, and arrhythmia), bone marrow suppression, liver and kidney dysfunction, and peripheral neuropathy symptoms are common side effects and complications during chemo-, radio- or targeted-therapy (5,9). These complications and side effects inconvenience and cause discomfort to patients and they may also limit or prevent delivery of therapy at its optimal dose and time, potentially causing fatalities. Among them, febrile neutropenia is a life-threatening condition that requires immediate attention, especially in patients with chemotherapy-related neutropenia, and cardiovascular disease represents the most common potentially life-threatening late effects (111,112). Thus, more effective therapies to help prevent and control complications and side effects of conventional cancer therapies must soon be developed. Some TCMs have been found to be adjunctive in cancer therapies. Here we will give a brief outline on the use of TCMs to reduce some complications and side effects associated with conventional cancer therapies in clinical studies (Table 4).

5.1. 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 (5,113). Regardless of cancer type and treatment modality, nearly all patients experience fatigue during cancer treatment and nearly a third report chronic fatigue that persists for years after treatment completion. It significantly interferes with patients' daily activities and decreases their QOL. Additionally, these symptoms can be accompanied by depression and impairment in cognition and sleep. However, it remains under-recognized and under-treated, partly because of limited understanding of its pathophysiology and lack of effective treatments. Traditional Chinese medical

comprehensive therapy might have its advantages in dealing with this condition.

A systematic review of randomized clinical trials involving 10 trials and 751 participants was conducted to analyze the effect of Chinese herbal medicine for cancer-related fatigue (114). The findings showed that Chinese herbal medicine plus chemotherapy or supportive care was superior to chemotherapy or supportive care in improving quality of life including relieving cancer-related fatigue and anxiety. 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 (115). Shenmai-san was found to be effective for treating cancer-related fatigue and had anti-fatigue activity as shown on a QOL questionnaire and laboratory data (e.g., WBC, Hb, platelet, CEA, heart rate variability, and liver and renal functions). Furthermore, Bu-Zhong-Yi-Qi-Tang was reported to have beneficial effects on cancer-related fatigue and quality of life in cancer patients (75). Taken together, the findings from a limited number of trials suggest that Chinese herbal medicine seems to be effective and safe in the treatment of cancer-related fatigue. However, the current evidence is insufficient to draw a confirmative conclusion due to the poor methodological quality of included trials. Thus, conducting rigorously designed trials on potential Chinese herbal medicine is warranted.

5.2. Chronic 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% of cancer patients especially who have bone metastasis experienced pain during their illness (5). 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 increase the peripheral release of endogenous analgesic agents, reduce pain mediator secretion and induce central nervous system (CNS) analgesia. These studies demonstrated that the use of TCM to treat pain triggered by cancer is effective and economical and furthermore produces fewer side effects (116).

Wen Jing Zhi Tong Fang, is a Chinese herbal medicine first recorded in the Qing Dynasty and composed of *evodia rutaecarpa* (Wuzhuyu), *semen sinapis* (Baijiezi), *ephedra sinica* (Mahuang), and *asarum sieboldii* (Xixin). It is designed for cancer pain relief through dredging healthy *Qi* to warm and activate blood

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

Chinese herbal medicines	Complications and side effects	Clinical trials of TCMs as adjuvant treatment in cancer therapy				Ref.
		Patients (n)	Experimental group	Control group	Outcomes	
TJ-41	Fatigue	n = 40	TJ-41	Nothing	Fatigue levels increased (experimental group vs. control group, p < 0.05)	75
Shen-mai-san	Fatigue	n = 60	Shen-mai-san	Placebo	QOL and laboratory data (e.g., CEA, heart rate variability, and liver and renal functions) improved	115
Wen Jing Zhi Tong Fang	Chronic pain	n = 62	Wen Jing Zhi Tong Fang + appropriate analgesic drug	Appropriate analgesic drug	Relieving cancer-related pain with reduced doses of analgesic drugs, less adverse reactions, and improved QOL.	117
Fufang E-Jiao Jiang	Bone marrow suppression	n = 64	Fufang E-Jiao Jiang + chemotherapy + rhIL-11 + rhG-CSF	Chemotherapy + rhIL-11 + rhG-CSF	Relieving the myelosuppression caused by GP regimen and increasing white cell and blood platelets counts	119
Elemene injection	Bone marrow suppression	n = 765	Elemene injection + radiation	Radiation	Reducing the incidence of bone marrow suppression and improving QOL	120*
TJ-43	Gastrointestinal function	n = 60	TJ-43	Placebo	Reducing anorexia and maintaining food intake caused by cisplatin-including chemotherapy	122
PHY906	Gastrointestinal function	n = 24	PHY906 + chemotherapy	Chemotherapy	Some gastrointestinal side effects such as diarrhea, abdominal cramps, and vomiting were reduced	5
AC591	CIPN	n = 72	AC591 + chemotherapy	Chemotherapy	Preventing oxaliplatin-induced neuropathy without reducing its antitumor activity	123
Aidi injection	Radiation pneumonitis	n = 1,192	Aidi injection + radiotherapy	Radiotherapy	Alleviating the radiation pneumonitis, radiation esophagitis, and myelosuppression of radiotherapy	128*
Zhi-Gan-Cao-Tang	Cardiotoxicity	A case report	Zhi-Gan-Cao-Tang + Anthracycline compounds	Anthracycline compounds	Chest X-ray: great improvements in pulmonary edema and cardiomegaly.	131
Xiao-chai-hu-tang (TJ-9)	Acneiform eruptions	A case report	TJ-9 + Gefitinib	Gefitinib	Exhibiting significant effects on acneiform eruptions induced by Gefitinib	132

*A systematic review and meta-analysis; Abbreviations: Bu-Zhong-Yi-Qi-Tang (TJ-41); Liu-jun-zi-tang (TJ-43); Huangqi Guizhi Wuwu decoction (AC591); Chemotherapy induced peripheral neuropathy (CIPN).

and by promoting circulation through the back meridians, which is considered to be the source of yang *Qi* (healthy *Qi*) and have broad connections with the viscera. The application of CMWC on back meridians combined with WHO 3-step analgesic ladder treatment was effective in relieving cancer-related pain with reduced doses, less adverse reactions, and improved QOL (117). Shuangbai San is a Chinese herb preparation used externally to treat pain. It contains 6 Chinese herbal medicines: Oriental Arborvitae, Rhubarb, Phellodendron amurense, Mint, Eupatorium japonicum, and Corydalis). A multicenter, randomized, double-blind, placebo-controlled trial indicated that the use of Shuangbai San could effectively relieve mild pain in liver cancer patients and improve their QOL (118). In all, TCM interventions appear to have beneficial effects on cancer-related pain. 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.

5.3. 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 cancer therapy 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 (5). 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. 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) chemotherapy regimen and increasing white cell and blood platelet counts compared to using rhIL-11 and rhG-CSF groups alone (119). In addition, the elemene injection combined radiotherapy in the treatment of lung cancer with brain metastases appears to improve the treatment response rate and alleviated symptoms. The combined treatment has showed positive impact to reduce the incidence of bone marrow suppression and improve QOL (120). Kushen injection combined with radiotherapy significantly improved the clinical effect and reduced the incidence of adverse events including bone marrow suppression, radiation pneumonia, and radiation esophagitis (121). In all, TCM interventions appear to have beneficial effects for alleviating myelosuppression caused by chemotherapy in cancer patients. However, there are several limitations associated with the current published studies of 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.

5.4. 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-, radio-, or targeted-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 for treating gastrointestinal side effects.

Liu-jun-zi-tang (TJ-43 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*) (5). TJ-43 enhances digestive tract motility,

improves the gastric accommodation reflex, protects against gastric mucosal injury, and enhances appetite. Based on these mechanisms, TJ-43 has been used to treat various gastrointestinal tract diseases, such as functional dyspepsia, gastroesophageal reflux disease, and chemotherapy-induced nausea. A placebo-controlled, double-blind, randomized trial was conducted to evaluate the efficacy of TJ-43 for chemotherapy-induced anorexia (122). TJ-43 was shown to have the effect of reducing anorexia and maintaining food intake caused by cisplatin-including chemotherapy in patients with lung cancer. 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 (5,86).

5.5. Peripheral neuropathy

Chemotherapy induced peripheral neuropathy (CIPN) is a common significant and debilitating side-effect resulting from the administration of neurotoxic chemotherapeutic agents. These pharmaco-chemotherapeutics can include taxanes, vinca alkaloids, platinum analogues, and others. Moderate to severe CIPN significantly decreases the quality of life and physical abilities of cancer patients. However, there are currently no effective drugs to prevent CIPN. Recently, many clinical trials have suggested that some TCMs may be effective at treating CIPN.

AC591 is a standardized extract of Huangqi Guizhi Wuwu decoction, an herbal formula recorded in "Synopsis of the Golden Chamber" for improving limb numbness and pain. AC591 could prevent oxaliplatin-induced neuropathy without reducing its antitumor activity, and might be a promising adjuvant to alleviate sensory symptoms in clinical practice (123). Goshajinkigan, a Japanese traditional herbal medicine (Kampo), is a promising drug which is widely used to treat diabetic neuropathy and CIPN in Japan. It could relieve the oxaliplatin-induced cold hyperalgesia and mechanical allodynia without affecting anti-tumor activity of oxaliplatin, and, therefore, might be useful for the oxaliplatin-induced neuropathy in clinical practice (124).

5.6. Radiation pneumonitis

Radiotherapy pneumonitis (RP) caused by radiation-induced lung toxicity is the most serious complication (125). It typically presents 1-6 months after radiation therapy. The clinical features usually include mild dry cough, mild fever, and mild dyspnea, but in some cases, severe respiratory failure appears and leads to death. The incidence of moderate to severe radiotherapy pneumonitis with radiotherapy is 10-20%. When RP

is left untreated for a long time, it may develop into pulmonary fibrosis, which has a high rate of mortality. 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.

A systematic review involving twenty-two RCTs and 1819 participants was conducted to evaluate the efficacy and safety of herbal medicines as adjunctive therapy for the prevention of radiation pneumonitis in patients with lung cancer who undergo radiotherapy (126). The findings showed that the herbal formulas used in combination with radiation therapy consisted mainly of those that tonify yin, tonify qi, and nourish blood. Among them, *Ophiopogonis Radix* is the most commonly used herb that nourishes yin, *Astragali Radix* is a typical herb with qi-tonifying effects, and *Angelicae Sinensis Radix* is a classic herb that nourishes blood for lung cancer as adjunctive therapy with radiotherapy. A recent systematic review reported that *Astragalus*-containing Chinese herbal medicines are effective at protecting against radiotherapy pneumonitis as adjunctive therapy during conservative radiotherapy (127). Aidi injection (Z52020236, China Food and Drug Administration (CFDA)) is an adjuvant chemotherapy drug commonly used in China, which is composed of the extracts from *Astragalus*, *Eleutherococcus senticosus*, *Ginseng*, and *Cantharidin*. *Astragalus*, *Eleutherococcus senticosus*, *Cantharidin* and *Ginseng*, and others are important traditional Chinese medicine, which appear to have antitumor activity, immunoregulation, and attenuation to the acute or subacute toxicity induced by chemotherapy (128). Aidi injection plus radiotherapy could significantly improve the clinical efficacy and QOL of patients with lung cancer. Aidi injection could alleviate the myelosuppression, radiation pneumonitis, and radiation esophagitis of radiotherapy. It had the attenuation and synergistic efficacy to radiotherapy. In all, there is some encouraging evidence that oral administration of herbal medicines combined with radiotherapy may benefit patients with thoracic cancer by preventing or minimizing radiation pneumonitis. However, due to the poor methodological quality of the identified studies, a definitive conclusion could not be drawn. To confirm the merits of this approach, further rigorously designed large scale trials are warranted.

5.7. Cardiotoxicity

Anthracycline compounds (*e.g.*, doxorubicin, epirubicin, and daunorubicin) are some of the most effective antineoplastic drugs in the treatment of both hematological malignancies and solid tumors (129). Moreover, anthracycline-based treatments are first-line chemotherapy agents used to treat breast cancer both in the adjuvant and neoadjuvant setting. Unfortunately, anthracycline-associated dose-dependent cardiotoxicity

is a limiting factor in clinical use. Extensive efforts have been devoted to identifying strategies to prevent anthracycline-induced cardiotoxicity. However, most cardioprotective agents have shown little effect in clinical trials. In recent years, some Chinese herbal medicines have been reported to have beneficial effects on anthracycline-induced cardiotoxicity.

Platycodon grandiflorum (Jie-Geng) is an herb that has been used in TCM for thousands of years to treat cardiovascular disease. In TCM theory, *P. grandiflorum* can nourish *Qi* and relieve symptoms, such as palpitations, shortness of breath, and chest pain. A randomized controlled trial indicated the cardioprotective effects and safety of *P. grandiflorum* in patients with early breast cancer receiving anthracycline-based chemotherapy (130). *Zhi-Gan-Cao-Tang*, an herbal formula recorded in "Shang-Han-Lun" to supplement *Yang-Qi*, nourish the *Ying*-blood, and strengthen the heart spirit as complementary medicines to relieve heart failure-related symptoms. It was reported that *Zhi-Gan-Cao-Tang* was the most frequent formula Chinese herbal formula prescribed by TCM practitioners for treating heart failure. A case was presented that anthracycline-induced cardiotoxicity resolved slowly following the administration of modified *Zhi-Gan-Cao-Tang* in an 18-year-old adolescent male with refractory acute lymphoblastic leukemia (ALL) (131). After 2 months of *Zhi-Gan-Cao-Tang* treatment, the follow-up chest X-ray showed great improvements in pulmonary edema and cardiomegaly.

5.8. Molecular-targeted drugs-related adverse effects

With molecular-targeted drugs especially epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (*e.g.*, Gefitinib and Afatinib) widely used, adverse effects of such treatments including acneiform eruptions, paronychia, xerosis, mucositis, and alopecia are thought to be less severe, but can still be significant (6). Not only can these toxicities severely affect patients' QOL, but in some specific instances, they can be associated with increased response to therapy. The incidence of acneiform eruptions is about 60-80% in patients using EGFR-TKIs. It usually appears within 1 to 3 weeks after EGFR-TKIs treatment and reaches a peak within 3 to 5 weeks. Li *et al.* reported that *Xiao-chai-hu-tang* exhibited significant effects on acneiform eruptions induced by Gefitinib (132). In addition, some Chinese herbal medicines with the properties of "clearing heat", "detoxifying" and "cooling blood" exhibited significant effects on acneiform eruptions induced EGFR-TKIs such as *Cortex moutan*, *Radix paeoniae rubra*, *Fructus Kochiae*, and so on (133). However, there are few reports on the effects of Chinese herbal medicines on molecular-targeted drugs-related adverse effects in English. Moreover, due to the poor methodological quality of the identified studies, a definitive conclusion could not be

drawn. To confirm the merits of this approach, further rigorously designed large scale trials are warranted.

6. Conclusion

In conclusion, Chinese herbal medicines substantially influence cancer therapy as adjuvant treatment. In cancer treatment, Chinese herbal medicines in combination with chemo-, radio-, and targeted-therapy are capable of enhancing the efficacy of and diminishing the side effects and complications caused by these therapies. Chinese herbal medicines have great advantages in terms of suppressing tumor progression, increasing the sensitivity of chemo-, radio-, and targeted-therapy, improving an organism's immune system function, and lessening the damage caused by these therapies. They have a significant effect on reducing cancer-related fatigue and pain, improving peripheral neuropathy and gastrointestinal side effects including diarrhea, nausea, and vomiting, decrease the incidence of bone marrow suppression, protecting anthracycline-induced cardiotoxicity and radiation-induced pneumonitis, and relieving EGFR-TKIs related acneiform eruptions and other side effects. 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, more rigorously designed trials on potential Chinese herbal medicine must be further examined involving cancer treatment especially molecular targeted-therapy in the future.

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