

The positive role of traditional Chinese medicine as an adjunctive therapy for cancer

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SUMMARY Traditional Chinese medicine (TCM), especially Chinese herbal medicines and acupuncture, has been traditionally used to treat patients with cancers in China and other East Asian countries. Numerous studies have indicated that TCM not only alleviates the symptoms (e.g., fatigue, chronic pain, anorexia/cachexia, and insomnia) of patients with cancer and improves their quality of life (QOL) but also diminishes adverse reactions and complications caused by chemotherapy, radiotherapy, or targeted-therapy. Therefore, Chinese herbal medicines and acupuncture and other alternative therapies need to be understood by TCM physicians and other health care providers. This review mainly summarizes the experimental results and conclusions from literature published since 2010, and a search of the literature as been performed in the PubMed, MEDLINE, Web of Science, Scopus, Springer, ScienceDirect, and China Hospital Knowledge Database (CHKD) databases. Some Chinese herbal medicines (e.g., *Panax ginseng*, *Panax quinquefolius*, *Astragali radix*, Bu-zhong-yi-qi-tang (TJ-41), Liu-jun-zi-tang (TJ-43), Shi-quan-da-bu-tang (TJ-48), and Ban-xia-xie-xin-tang (TJ-14)) and some acupuncture points (e.g., Zusanli (ST36), Zhongwan (CV12), Neiguan (PC6) and Baihui (GV20)) that are commonly used to treat cancer-related symptoms and/or to reduce the toxicity of chemotherapy, radiotherapy, or targeted-therapy are highlighted and summarized. Through a review of literature, we conclude that TCM can effectively alleviate adverse gastrointestinal reactions (including diarrhea, nausea, and vomiting) to these anti-cancer therapies, decrease the incidence of bone marrow suppression, alleviate cardiotoxicity, and protect against chemotherapy-induced peripheral neuropathy and radiation-induced pneumonitis. Moreover, TCM can alleviate epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI)-related acneiform eruptions, diarrhea, and other adverse reactions. The hope is that this review can contribute to an understanding of TCM as an adjuvant therapy for cancer and that it can provide useful information for the development of more effective anti-cancer therapies. However, more rigorously designed trials involving cancer treatment must be conducted in the future, including complete quality control and standardized models at the cellular, organic, animal and clinical levels, in order to study TCM in multiple forms and at multiple levels.

Keywords Traditional Chinese Medicine (TCM), Chinese herbal medicines, acupuncture, cancer-related symptoms, anti-cancer therapy-related adverse reactions and complications

1. Introduction

Cancer incidence and mortality are rapidly increasing worldwide. Cancer has become the second leading cause of death globally behind only ischemic heart disease, and it imposes serious economic burdens (1). Cancer will rank as a single leading barrier to increasing life expectancy in every country of the world. Based on the WHO Global Cancer Observatory (GLOBOCAN) 2018 registry, over the next four decades cancer deaths are expected to overcome those due to ischemic heart

disease, with a 2.08-fold increase (versus a 1.76-fold increase in ischemic heart disease) by the year 2060 (2). Although a combination of screening, prevention, and successful treatment has resulted in a vast number of cancer survivors, in China alone there were 4,285,033 new cases and 2,865,174 deaths reported in 2018 according to the Global Cancer Observatory (3), and in the United States alone this amounts to nearly 16 million current cancer survivors, which is expected to increase to 20.3 million by 2026 (4). Thus, cancer prevention and treatment remain a major challenge for the world in the

coming years.

Currently, chemotherapy, radiotherapy, targeted-therapy, and immunotherapy are common anticancer therapies being used to treat patients with malignancies in the intermediate and advanced stages by controlling tumor growth, prolonging survival, and improving quality of life (QOL) to some extent (5). However, these therapies either alone or in combination have been found to have numerous limitations and drawbacks including myelosuppression, gastrointestinal reactions, cardiac damage, and liver and renal dysfunction, rashes, hand-foot syndrome, and local radiation damage (6). Not only can these toxicities severely affect patients' QOL, but some patients may discontinue treatment because they cannot tolerate these toxicities. With advances in medicine and updated knowledge, cancer therapy has entered a stage of diversified comprehensive treatment. Therefore, more effective or adjunctive therapies must soon be developed to treat cancer. Traditional Chinese medicine (TCM), especially Chinese herbal medicines and acupuncture, may represent a promising option.

TCM mainly includes herbal medicine, acupuncture, moxibustion, and massage. An important component of complementary and alternative medicine, TCM has evolved over thousands of years with its own unique system of theories, diagnostics, and therapies in Asian countries, and especially China. In recent decades, TCM has been increasingly used and has 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 alleviate the symptoms of patients with cancer and to control the adverse reactions and the toxicities of cancer therapies, thus improving patient QOL, preventing recurrence, and prolonging survival (7).

In reviews published over the past 10 years, the current authors have indicated that some Chinese herbal medicines used as adjuvant therapy in combination with chemotherapy, radiotherapy, or targeted-therapy are capable of enhancing the sensitivity of these anti-cancer therapeutics, improving an organism's immune system, and diminishing the adverse reactions and complications caused by chemotherapy, radiotherapy, or targeted-therapy. The current authors have also indicated that some Chinese herbal medicines as adjuvant therapy played an important role in alleviating the symptoms of patients with different stages of cancer lesions including those after surgery, radiotherapy or chemotherapy (5,6,8).

The current review will focus on the positive role of TCM as an adjunctive therapy for cancer. In this review, some individual Chinese herbal medicines (Table 1), Chinese herbal formulas (Table 2), and acupuncture points (Table 3) that are commonly used to treat cancer-related symptoms are discussed and trials of TCM therapies as adjuvant cancer therapies to reduce adverse reactions and complications during chemotherapy, radiotherapy, or targeted-therapy are also highlighted and summarized. This review mainly

Table 1. Individual Chinese herbal medicines as adjuvant therapy for cancer

Common name	Other names	Efficacy according to TCM theory	Major active ingredients	Biological activity	Clinical evidence of anticancer activity	Ref.
<i>Panax ginseng</i>	Ren-Shen in Chinese or Ginseng in Korea	As a tonic, prophylactic, and restorative agent with action to invigorate	Ginsenosides, essential oil, peptidoglycans, polysaccharides, nitrogen compounds, fatty acids, and phenolic compounds	Antitumor, antioxidant, immunomodulation, anti-ulcer, anti-adhesive, antioxidant, hepatoprotective, and hypoglycemic actions	Alleviates CRF without any discernible toxicity	14-15
<i>Panax quinquefolius</i>	Xi-Yang-Shen in Chinese or Wisconsin Ginseng in American	As a tonic with action to enhance qi, nourish yin, clear heat, and promote flow	Ginsenosides, and polysaccharides	Anti-aging, anti-cancer, anti-stress, anti-fatigue, immunostimulatory, and anxiolytic action	Has a potential clinical benefit in safely treating CRF	17-18
<i>Astragali radix</i>	Huang-Qi in Chinese	As a tonic with action to invigorate	Isoflavonoids, triterpenoid saponins, polysaccharides, amino butyric acids, and various trace elements	Antitumor, antioxidant, hepatoprotective, anti-diabetic, antimicrobial, antiviral, and immunomodulatory action	Alleviates CRF, adverse gastrointestinal reactions, and bone marrow suppression	5, 19-20
<i>Semen Ziziphi Spinosa</i>	Suan Zao Ren in Chinese	Nourishing and calming the mind	Sanjiminine A, Jujuboside A, spinosin, and other flavonoids	Sedative and hypnotic action	As an effective replacement therapy for insomnia	47-48
<i>Colla corii asini</i>	E-Jiao in Chinese	As a tonic to enrich the blood	Peptides and proteins produced by partial hydrolysis of collagen	Anti-anemic and anti-aging action	Promotes the recovery of bone marrow hemopoietic function in cancer patients with myelosuppression	56-57
<i>Rhizoma Corydalis</i>	Yan Hu Suo	Activating the blood, invigorating the body, and relieving pain	Protoberberine alkaloids, aporphine alkaloids, opiate alkaloids, organic acids, steroids, and carbohydrates	Action to inhibit arrhythmia, myocardial infarction, coronary artery dilation, tumors, and thrombosis	Has the potential to mitigate antineoplastic drug-induced cardiotoxicity	61-62

Note: Abbreviations: traditional Chinese medicine (TCM); cancer-related fatigue (CRF).

Table 2. Some Chinese herbal formulas as adjuvant therapy for cancer

Common name	Other names	Composition	Biological activity	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>Pinelliae rhizoma</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 action, immunomodulation, and alleviation of fatigue	Alleviates CRF and improves QOL; reduces adverse reactions to radiotherapy or chemotherapy.	5,21-23
Shi-quan-da-bu-tang	Juzentaiho-to or TJ-48 in Japanese; Sipjeondaebotang in Korean	Includes 10 herbs: <i>Panax ginseng</i> , <i>Astragali radix</i> , <i>Angelicae radix</i> , <i>Rehmanniae radix</i> , <i>Atractylodes lanceae rhizoma</i> , <i>Cinnamomi cortex</i> , <i>Portia</i> , <i>Paeoniae radix</i> , <i>Ligustici rhizoma</i> , <i>Glycyrrhizae radix</i> .	Antitumor, immunomodulation, and alleviation of fatigue	Reduces the incidence of adverse reactions to chemotherapy; alleviates cancer-related anorexia/cachexia; prevents nutritional disorders, and increases physical fitness.	26-28,40
Liu-jun-zi-tang	Yukgunja-tang in Korean, Rikkunshito or TJ-43 in Japanese	Includes 6 herbs: <i>Ginseng radix</i> , <i>Portia cocos</i> , <i>Rhizoma atractylodis macrocephalae</i> , <i>Glycyrrhizae radix et rhizoma</i> , <i>Pinelliae rhizoma</i> , <i>Pericarpium citri</i> , <i>common ginger</i> , and <i>Jujube</i> .	Gastroprotective action	Effective at treating chemotherapy-induced dyspepsia and cancer cachexia-anorexia syndrome; alleviates the symptoms of postgastrostomy syndrome and improves the long-term QOL in patients with gastric cancer who have undergone proximal gastrectomy.	6,41
Sheng-jiang-xie-xin-tang	None	Includes 8 herbs: <i>Fresh Zingiberis rhizoma</i> , <i>Glycyrrhizae radix</i> , <i>Codonopsis radix</i> , <i>Zingiberis rhizoma</i> , <i>Astragali radix</i> , <i>Pinelliae rhizoma</i> , <i>Coptidis rhizome</i> , and <i>Jujubae fructus</i> .	Gastroprotective action	Reduces chemotherapy-induced hematological and gastrointestinal toxicities without affecting the clinical response to chemotherapy.	53
Huang-qi-gui-zhi-wu-wu-tang	AC591	Includes 5 herbs: <i>Hedysarum Multijugum Maxim</i> , <i>Cinnamomi Ramulus</i> , <i>Paeoniae radix alba</i> , <i>Zingiber officinale Roscoe</i> , and <i>Jujubae fructus</i> .	Alleviation of limb numbness and pain	Reduces chemotherapy-induced peripheral neuropathy.	67-69
Ban-xia-xie-xin-tang	Ban-xia-xie-xin-tang in Chinese or Hangeshashinto or TJ-14 in Japanese	Includes 5 herbs: <i>Coptis rhizoma</i> , <i>Panax ginseng</i> , <i>Glycyrrhizae radix</i> , <i>Jujube</i> , <i>Pinelliae rhizoma</i> , <i>ginger</i> , and <i>Scutellariae radix</i> .	Antioxidant action, anti-inflammatory, bactericidal, and analgesic action as well as action to promote healing	Alleviates chemotherapy-induced diarrhea and oral mucositis and radiation-induced enteritis; reduces the incidence of EGFR-TKI-induced skin rashes, paronychia, diarrhea, and oral mucositis.	78-82

Note: Abbreviations: cancer-related fatigue (CRF); quality of life (QOL); epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs);

Table 3. Clinical trials of acupuncture therapy as adjuvant therapy for cancer

Symptoms or adverse reactions	Sample	Acupuncture points	Outcome	Ref.
Chronic pain	n = 42	Acupuncture at Siguanyue (Taichong (LR3), Hegu (LI4), Neiguan (PC6), Zusanli (ST36), and Sanyinjiao (SP6).	Significantly reduced cancer pain.	33
Adverse gastrointestinal reactions	n = 150	Acupuncture at Zusanli (ST36), Zhongwan (CV12), and Neiguan (PC6)	Acupuncture combined with the slow intravenous injection of tropisetron hydrochloride was effective at preventing and treating vomiting induced by chemotherapy to treat lung cancer.	51
Adverse gastrointestinal reactions	n = 58	Moxibustion at Baihui (GV20) and Zhongwan (CV12)	Moxibustion combined with an 5-HT receptor antagonist markedly reduce the incidence and severity of nausea and vomiting caused by chemotherapy with cisplatin in patients with lung cancer.	52
Bone marrow suppression	A systematic review and meta-analysis	Acupuncture at Zusanli (T36), Neiguan (PC6), Geshu (BL17), Feishu (BL13), Guanyuan (RN4), and Shenshu (BL23)	Acupoint stimulation markedly reduced bone marrow suppression caused by conventional therapy, it increased hemoglobin levels and platelet counts in patients with lung cancer, and it decreased chemotherapy-induced nausea and vomiting.	58
CIPN	n = 6	Acupuncture at ST34 (Liang Qiu) as well as at EX-LE12 (Qi Duan) and EX-LES (Ba Feng)	Acupuncture alleviated CIPN.	70

Note: Abbreviations: chemotherapy-induced peripheral neuropathy (CIPN).

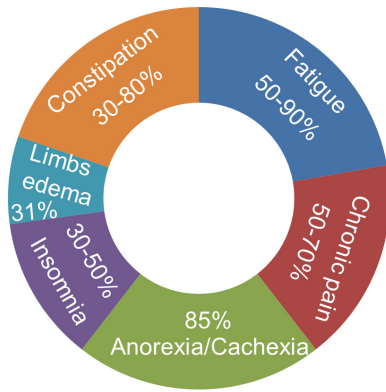


Figure 1. Common cancer-related symptoms and their incidence.

summarizes experimental results and findings from literature published since 2010. A search of the literature was conducted in the PubMed, MEDLINE, Web of Science, Scopus, Springer, ScienceDirect, and China Hospital Knowledge Database (CHKD) databases. The hope is that this contributes to an understanding of TCM as adjuvant therapy for cancer and that it provides useful information for development of more effective anti-cancer therapies.

2. TCM as adjuvant therapy for cancer-related symptoms

Patients with cancer experience multiple symptoms including fatigue, chronic pain, anorexia, insomnia, limbs edema, and constipation that seriously impair patients' daily functioning and their QOL. As shown in Figure 1, some studies of patients with cancer have reported that the prevalence of fatigue was 50% to 90%, that of chronic pain was 50% to 70%, that of anorexia/cachexia was around 85%, that of insomnia was 30% to 50%, that of limb edema was 31%, and that of constipation was 30% to 80% (9,10). Despite the high prevalence of these symptoms in patients with cancer, conventional therapies are far from satisfactory. Some individual Chinese herbal medicines, Chinese herbal formulas, and acupuncture points have been found to be effective in alleviating the symptoms of patients with cancer. The current review provides a brief outline on the use of TCM to reduce some cancer-related symptoms (Table 4).

2.1. Fatigue

According to the National Comprehensive Cancer Network (NCCN), cancer-related fatigue (CRF) has been defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (11). Regardless of the type of cancer and treatment modality, nearly all patients experience

Table 4. Clinical trials of traditional Chinese herbal medicines as adjuvant therapy to alleviate cancer-related symptoms

Symptoms	Chinese herbal medicine	Sample	Dosage	Outcome	Ref.
Fatigue	<i>Panax Ginseng</i>	n = 30	<i>Panax Ginseng</i> 800 mg taken daily for 29 days	High-dose <i>Panax Ginseng</i> was safe, it alleviated CRF, and it improved overall QOL, appetite, and sleep at night.	14
Fatigue	Korean red Ginseng	n = 219	Korean red Ginseng 2,000 mg/day for 16 weeks	Korean red Ginseng was safely combined with mFOLFOX-6 chemotherapy in patients with colorectal cancer and reduced CRF compared to a placebo.	15
Fatigue	American ginseng	n = 364	American Ginseng 2,000 mg/day for 8 weeks	American ginseng alleviated CRF without causing discernible toxicities.	17
Fatigue	American ginseng	n = 28	American Ginseng (2,000 mg/day) combined with methylphenidate (10-40 mg/day) for 30 days	The combination of methylphenidate and American ginseng caused no discernible toxicities and it displayed a potential clinical benefit in CRF.	18
Fatigue	TJ-41	n = 40	TJ-41 for 2 weeks	TJ-41 might have beneficial effects on CRF and QOL in patients with cancer.	22
Fatigue	TJ-48	n = 45	TJ-48 combined with chemotherapy	TJ-48 combined with chemotherapy might improve the progression-free survival of patients with postoperative recurrence of non-small cell lung cancer by preventing nutritional disorders and increasing physical fitness.	28
Chronic pain	Wen Jing Zhi Tong Fang	n = 62	Wen Jing Zhi Tong Fang combined with an appropriate analgesic	Relieved cancer-related pain with reduced doses of analgesics, fewer adverse reactions, and improved QOL.	36
Anorexia/cachexia	TJ-48	n = 32	TJ-48 3 g/day for 4 weeks	Improved QOL and alleviated anorexia in patients with cancer.	40
Anorexia/cachexia	TJ-43	n = 40	TJ-43 twice a day for 4 weeks (dose of 3.0 g taken a total of 56 times)	Increased the anorexia/cachexia subscale scores of patients with cancer.	41

Note: Bu-Zhong-Yi-Qi-Tang (TJ-41); Shi-quan-da-bu-tang (TJ-48); Liu-jun-zi-tang (TJ-43); cancer-related fatigue (CRF); quality of life (QOL).

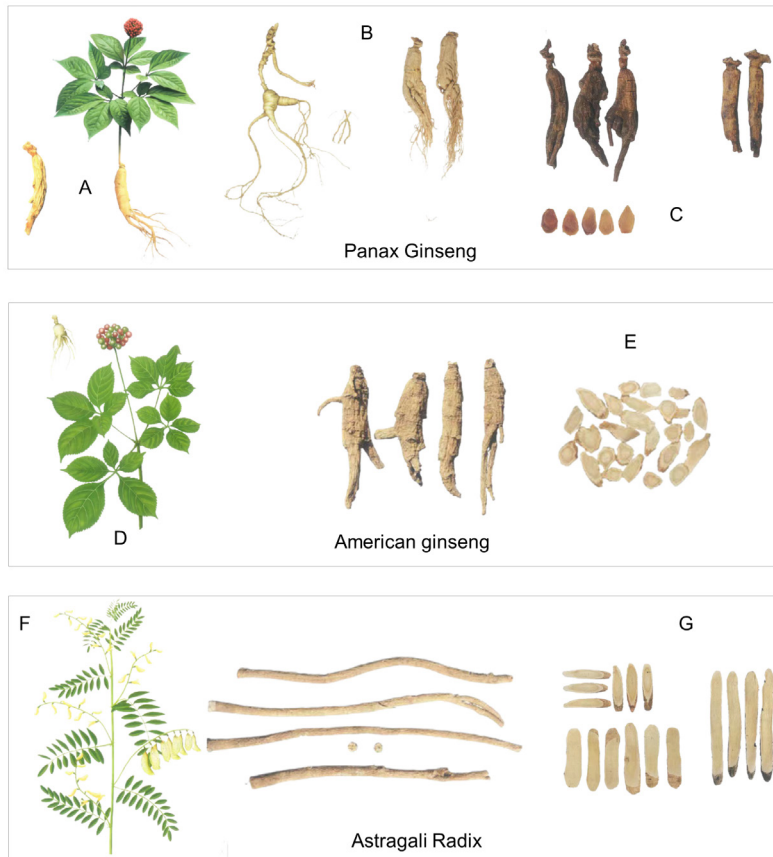


Figure 2. Some individual Chinese herbal medicines that are commonly prescribed by traditional Chinese physicians for the treatment of cancer-related fatigue (CRF). (A) The *Panax Ginseng* plant; (B) White ginseng or raw ginseng for use in TCM; (C) Heat-processed ginseng or red ginseng for use in TCM; (D) The American ginseng plant; (E) American ginseng for use in TCM; (F) The *Astragali radix* plant; (G) *Astragali radix* for use in TCM. (Note: The pictures are from <http://sao.dajiazhongyi.com/> with modifications)

fatigue during cancer treatment and nearly a third report chronic fatigue that persists for years after treatment concludes. It significantly interferes with patients' daily activities and decreases their QOL. However, CRF is frequently under-recognized and under-treated, partly because of limited understanding of its pathophysiology and lack of effective interventions. Therefore, many patients with cancer use integrative therapies during and after cancer treatment, including treatments such as natural products (e.g. Chinese herbal medicines and supplements) and mind-body practices (e.g. yoga, mindfulness, and acupressure) (12). Based on the literature and the current authors' clinical experience, some individual Chinese herbal medicines (Figure 2) or formulas that are commonly prescribed by traditional Chinese physicians for the treatment of CRF are described here, along with clinical studies.

Asian Ginseng or *Panax ginseng* (Ren-Shen in Chinese or ginseng in Korea) is a well-known and popular Chinese herbal medicine that is believed to be the king of herbs in the Orient, and particularly in China, Korea, and Japan. It has been used for several thousand years with purported action as a tonic, prophylactic, and restorative agent for weakness and fatigue. Modern pharmacological studies have indicated that the main active components of *Panax ginseng* are ginsenosides, which have been found to have a variety of beneficial effects, including anti-inflammatory, antioxidant, and anticancer actions (13). An open-label preliminary study

in which 30 patients with CRF took *Panax ginseng* 800 mg daily for 29 days was conducted to assess the safety of high-dose *Panax ginseng* for CRF (14). Results indicated that high-dose *Panax ginseng* was safe, it alleviated CRF, and it improved overall QOL, appetite, and sleep at night. In addition, a randomized, double blinded, placebo-controlled, parallel, multi-center trial in which patients with colorectal cancer who received mFOLFOX-6 were randomly assigned to take either Korean red ginseng 2,000 mg/day ($n = 219$) or a placebo ($n = 219$) for 16 weeks was conducted to evaluate whether Korean red ginseng could improve CRF compared to a placebo (15). Korean red ginseng is a processed form of Asian ginseng consumed as a powder after steaming and drying or concentrated and fermented after extraction with water or alcohol. The aforementioned study found that Korean red ginseng intake was more effective at alleviating fatigue compared to a placebo in patients with colorectal cancer receiving mFOLFOX-6 chemotherapy. Moreover, fatigue-related QOL and stress indices declined less from the baseline in the Korean red ginseng group than in the placebo group.

American ginseng or *Panax quinquefolius* (Xi-Yang-Shen in Chinese or Wisconsin ginseng in English) is also one of the most popular herbal medicines due to its purported actions against aging, cancer, stress, fatigue, and anxiety. It is native to eastern North America and widely inhabits several Canadian and US states. Along with ginsenosides, polysaccharides have been identified

as one of the major bioactive ingredients in American ginseng, and polysaccharides may possess paradoxical immunostimulatory and immunosuppressive properties (16). A multisite, double-blind randomized trial in which cancer survivors with fatigue ($n = 364$) took 2,000 mg of American ginseng vs. a placebo for 8 weeks was conducted to evaluate the efficacy of American ginseng on CRF (17). Results substantiated the benefit of American ginseng, 2,000 mg daily, in alleviating CRF over an 8-week period, and there were no discernible toxicities associated with the treatment. A retrospective review of medical records was conducted to evaluate the safety and effectiveness of combination therapy with methylphenidate (10–40 mg/day) and American ginseng (2,000 mg/day) (18). After about 30 days of follow-up, there was a significant reduction in the fatigue score in 60% of patients with no discernible associated toxicities, indicating that the combination of methylphenidate and American ginseng had a potential clinical benefit in treating CRF.

Astragali radix or *Astragalus* (Huang-Qi in Chinese) is a well-known herbal medicine with purported tonic properties that has been widely used to treat cancer and other immune disorders in China and Southeast Asia for thousands of years. Mounting evidence suggests that *Astragali radix* possesses diverse therapeutic activities including anti-cancer, anti-viral, anti-hyperglycemic, antioxidant, and immunomodulatory actions. It is usually prescribed to treat weakness, wounds, anemia, fever, multiple allergies, chronic fatigue, and loss of appetite, uterine bleeding, and uterine prolapse (19). Thus far, more than 100 compounds have been isolated and identified from *Astragali radix*; saponins, flavonoids, and polysaccharides are deemed to be the main bioactive constituents of *Astragali radix* that contribute to its anti-cancer and immunomodulatory actions (20). *Astragali radix* is one of the most frequently prescribed TCMs and a main component of formulas to treat chronic fatigue (e.g., Bu-zhong-yi-qi-tang and Shi-quan-da-bu-tang). It has been widely used by TCM physicians as an adjuvant therapy to reduce symptoms and improve QOL and immunologic function in patients with various cancers including breast, gastric, liver, colon, and lung cancer (5). However, no randomized clinical trials have compiled evidence of the efficacy of *Astragali radix* as an adjuvant therapy for the treatment of CRF except for those in Chinese databases. Therefore, well-designed clinical trials need to be conducted to provide more information for TCM physicians, researchers, and healthcare consumers.

Bu-zhong-yi-qi-tang (Hochuekki-to or TJ-41 in Japanese, or Bojungikki-Tang in Korean) is a long-standing formulation that has been widely used in China, Japan, and South Korea. It is purported to be a tonic for the treatment of weakness including fatigue, visceroptosis, gastrointestinal motility disorder, and rectal prolapse due to chronic diarrhea. Moreover, it has

been described as an effective drug for the treatment of a spleen-*qi* deficiency in clinical TCM practice over the past few years. It contains 7 herbs including *Pinelliae rhizoma*, *Scutellaria baicalensis*, *Zingiberis rhizoma*, *Zizyphi fructus*, *Coptidis rhizoma*, *Glycyrrhizae radix*, and *Panax ginseng* (6). Recently, several pharmacological studies have indicated that Bu-zhong-yi-qi-tang has potent immunomodulatory, anticancer, and fatigue-reducing actions.

Li *et al.* conducted a study to investigate the frequency and forms of Chinese herbal medicine given to patients with lung cancer and the effect of Chinese herbal medicine on the probability of their survival in Taiwan (21). They indicated that the use of Chinese herbal medicine as an adjunctive therapy might reduce the mortality hazard ratio of patients with lung cancer, and Bu-zhong-yi-qi-tang was found to be the leading formula prescribed by traditional Chinese physicians for patients with lung cancer. A pilot randomized clinical trial suggested that Bu-zhong-yi-qi-tang might have beneficial effects on cancer-related fatigue and QOL in patients with cancer without any significant adverse effects (22). In comparison to the control group, patients administered Bu-zhong-yi-qi-tang for 2 weeks had decreased levels of fatigue improved scales for assessing overall general QOL. Minagawa *et al.* found that Bu-zhong-yi-qi-tang might be useful for management of general fatigue in patients with castration-resistant prostate cancer (CRPC) after the introduction of enzalutamide (23).

According to basic studies, the alleviation of CRF and anti-cancer action of Bu-zhong-yi-qi-tang might be attributed to activation of the immune system. It may modulate peripheral immunity and suppress the immune escape of tumors by increasing the infiltration of tumor lymphocytes, decreasing the expression of PD-1 in peripheral blood and reducing the infiltration of PD-1 and PD-L1 in tumors (24). In addition, Bu-zhong-yi-qi-tang alleviates neuroinflammation and oxidative stress in a mouse model of chronic fatigue syndrome by reducing the expression of IL-1 β , IL-6, and IFN- γ in the hippocampus (25).

Shi-quan-da-bu-tang (Juzentaiho-to or TJ-48 in Japanese, or Sipjeondaebotang in Korean) is a well-known Chinese herbal formula purported to invigorate and to enhance health and immunity. There are 10 herbs in Shi-quan-da-bu-tang including *Ginseng radix*, *Astragaliradix*, *Angelicae radix*, *Rehmanniae radix*, *Atractylodis lanceae rhizoma*, *Cinnamomi cortex*, *Poriacocos*, *Paenoniaeradix*, *Ligustici rhizoma*, and *Glycyrrhizae radix* (6). It has been used for many years to treat 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 found to have antitumor action by alleviating CRF and modulating immune responses in patients with cancer.

Because it purportedly treats the syndrome of a dual deficiency of *qi* and *blood* by balancing *Yin* and

Yang, Shi-quan-da-bu-tang is the third most commonly prescribed herbal medicine in South Korea. A pilot, randomized, double-blind, placebo-controlled, cross-over trial (registration number NCT02858856) has been conducted in South Korea by Cheon *et al.* since 2017 to evaluate the feasibility of Shi-quan-da-bu-tang for cancer-related fatigue, and it should provide meaningful data on the treatment of CRF (26). As Shi-quan-da-bu-tang is commonly used by patients with lung cancer undergoing outpatient chemotherapy, patients being treated for non-small cell lung cancer ($n = 16$) completed a QOL questionnaire (27). Significant improvement in the total QOL score was noted, mainly due to improvement in the patients' "physical condition." In addition, Kawai *et al.* indicated that Shi-quan-da-bu-tang combined with chemotherapy might reduce the incidence of adverse reactions, prevent nutritional disorders, and increase physical fitness, thereby improving the progression-free survival of patients with postoperative recurrence of non-small cell lung cancer (28).

2.2. Chronic Pain

Pain is the most common symptom of cancer at diagnosis and increases in prevalence throughout and beyond cancer treatment. Causes of cancer-related pain include the tumor itself or its metastases inflaming or eroding bone, viscera, or nerves, or pain related to tissue or nerve damage induced by cancer treatments such as surgery, chemotherapy, and radiation (29). Chronic pain can lead to a mood disturbance, dyspepsia, and poor QOL, in addition to the burden of a life-threatening disease. As indicated in current WHO guidelines, three-step analgesic ladder therapies are the standard of care for cancer pain. However, over half of all patients with cancer still suffer intolerable pain. Moreover, the inadequate management of chronic cancer-related pain has a significant harmful impact on the QOL for patients. Many patients suffer adverse effects from analgesic regimens, such as constipation, nausea, drowsiness, confusion, and hallucinations (30). Over the past few years, many clinical trials have suggested that TCM as adjunctive therapy increases the peripheral release of endogenous analgesics, reduces pain mediator secretion, and induces central nervous system (CNS) analgesia. Use of TCM to treat pain triggered by cancer is effective, economical, and causes fewer adverse reactions.

Acupuncture is a branch of TCM that modulates neurological processes to bring about an effect. Insertion of fine needles at acupuncture points can activate nerve fibers and peripheral afferent receptors, produce sensory interactions at various levels of the CNS, and release various transmitters, thus producing anti-inflammatory, neuroendocrine, and neuroimmune signals. Over the past few years, various acupuncture methods have been widely used in treating chronic cancer-related pain and

adverse effects of cancer treatments. A recent survey found that 47.9% of patients with cancer were willing to undergo acupuncture if treatments were covered by insurance (31). A systematic review and meta-analysis including 14 randomized clinical trials with 920 patients indicated that acupuncture and/or acupressure was significantly associated with lower pain intensity in patients with cancer compared to a sham control, suggests a potential role for a combination of acupuncture and acupressure to help reduce opioid doses in patients with cancer (32). A single-blind, randomized controlled pilot trial involving 42 patients with moderate to severe cancer pain indicated that acupuncture at Si Guan Xue (Taichong (LR3) and Hegu (LI4)) and at commonly used acupoints including Neiguan (PC6), Zusanli (ST36), and Sanyinjiao (SP6) tended to be effective in reducing cancer pain (33). A recent meta-analysis has identified three well-designed randomized clinical trials that corroborate the use of acupuncture for aromatase inhibitor-associated arthralgia and musculoskeletal symptoms (34). Moreover, a systematic review indicated that interventions including acupuncture/acupressure, tai chi/qi gong, hypnosis, meditation, music therapy, yoga, massage, reflexology, and Reiki may alleviate cancer-related pain in patients with breast cancer (35).

Some studies have indicated that a warm compress of Chinese medicine on the back meridians relieves cancer pain, reduces doses of and adverse reactions to adjuvant analgesics, and improves QOL. Wen Jing Zhi Tong Fang is a Chinese herbal medicine first documented in the Qing Dynasty and consisting of *Evodia rutaecarpa*, *Semen sinapis*, *Ephedra sinica*, and *As arum sieboldii*. Its use on back meridians combined with a WHO 3-step analgesic ladder treatment was effective at relieving cancer-related pain (36).

In summary, TCM interventions appear to have beneficial effects on cancer-related pain. However, studies on TCM have several limitations such as indeterminate results, small sample sizes, and limited examination of outcomes. Therefore, further studies with a rigorous design and larger sample size need to be conducted to re-evaluate the effectiveness of TCM in treating cancer-related pain.

2.3. Cancer-related anorexia/cachexia

Cancer-related anorexia/cachexia is defined as a metabolic, paraneoplastic syndrome characterized by decreased food intake, involuntary weight loss, and loss of fat and muscle (37). It is one of the most prevalent and troublesome clinical problems experienced by patients with cancer during and after therapy, it can adversely influence the nutritional status of patients, negatively impact patients' QOL and increase the burden on healthcare resources. Metabolic abnormalities, inflammation, insulin resistance, and increased muscle protein breakdown are often associated with cachexia.

The management of cancer-related anorexia/cachexia is a complex challenge that should address the different causes underlying this clinical event. Among effective treatments, progestogens such as megestrol and medroxyprogesterone are currently considered to be the best available treatment option. Some other drugs including thalidomide, cytokine inhibitors, steroids, nonsteroidal anti-inflammatory drugs, branched-chain amino acids, eicosapentaenoic acid, and anti-serotonergic drugs have been proposed and used in clinical trials (38). Recent studies have indicated that integrated, multi-targeted approaches are more effective than single-agent approaches for the treatment of this syndrome. Some Chinese herbal medicines and herbal remedies including *Ginseng*, *Astragali radix*, Shi-quan-da-bu-tang (TJ-41), Bu-zhong-yi-qi-tang (TJ-48), and Huang-qin-tang (PHY906) and acupuncture therapy might be effective in improving QOL by treating anorexia in patients with cancer (39).

A pilot, randomized, double-blind, placebo-controlled trial ($n = 32$) by Cheon *et al.* found that Shi-quan-da-bu-tang had a potential benefit in terms of anorexia management for patients with cancer (40). Compared to the baseline, 4 weeks of Shi-quan-da-bu-tang treatment improved the QOL as assessed with the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) and alleviated anorexia in patients with cancer. A randomized, controlled trial, pilot study ($n = 40$) was conducted by Ko *et al.* to estimate the efficacy and the safety of Yukgunja-tang (also known as Liu-jun-zi-tang in China and Rikkunshito (TJ-43) in Japanese), and to compile evidence for the use of herbal medicines in the management of cancer-related anorexia (6,41). Results indicated that the FAACT scores and the anorexia/cachexia subscale (ACS) scores differed significantly ($P = 0.023$) between the control and the treatment groups, but there were no significant differences in the scores on a visual analog scale (VAS) for appetite or in the levels of leptin, TNF- α , IL-6, and ghrelin, indicating the efficacy and safety of using Liu-jun-zi-tang as a treatment option for patients with cancer-related anorexia.

2.4. Insomnia

Sleep is essential for health while insomnia or poor sleep is consistently linked to the development of systemic disease, including depression, metabolic syndrome, and cognitive impairments. Recently compiled evidence has suggested the role of sleep in cancer initiation and progression, and especially in breast cancer (42). Insomnia is common among patients with cancer, occurring in approximately 30% to 50% of the cancer population, and manifesting as poor sleep, circadian misalignment, hyperarousal, somnolence syndrome, hot flashes, and nightmares. These problems can lead to fatigue, mood disturbances, and contribute to immune-suppression, which can have a profound impact on QOL

and perhaps affect the course of disease (43). Evidence suggests that management of insomnia through a combination of pharmacologic and non-pharmacologic means can have a positive impact not only on insomnia but also on related symptoms and, consequently, on overall health and QOL. Currently, treatment for insomnia includes cognitive behavioral therapy with sleep hygiene, bright-light therapy, exercise, yoga, melatonin, and hypnotic medications (44). However, these non-pharmacologic treatments still need to be further verified specifically in patients with cancer, while long-term use of benzodiazepine and non-benzodiazepine hypnotic agents is associated with some risks such as dizziness, headache, forgetfulness, bitter mouth, fatigue, withdrawal reaction, lethargy, hangover, and falls. Recently, TCM has begun to garner the attention of clinicians as an alternative for insomnia.

According to the theory of TCM, the heart ("Xin" in Chinese Pinyin) is considered to be closely related to the occurrence of insomnia. TCM Yang-xin-an-shen therapy, which purports to be a therapy to tranquilize the mind by nourishing the heart, is one of the crucial therapeutic principles for insomnia in TCM; TCM includes several Chinese herbal prescriptions that purportedly nourish the heart and tranquilize the mind (45). A comprehensive meta-analysis of 12 trials (1,549 participants) was conducted by Li *et al.* to evaluate the efficacy and safety of Yang-xin-an-shen therapy for insomnia (46). They found that Yang-xin-an-shen therapy was superior to a placebo in terms of polysomnography (PSG) parameters, the Pittsburgh Sleep Quality Index (PSQI) scale, TCM curative efficacy, and PSQI curative efficacy. Moreover, 42 Chinese herbal medicines were used to treat insomnia in that meta-analysis. *Semen Ziziphi Spinosae* (Suan Zao Ren) was used most frequently, followed by *Polygalae radix* (Yuan Zhi), *Caulis Polygoni Multiflori* (Ye Jiao Teng), *Glycyrrhizae radix* (Gan Cao), *Portiacocos* (Fu Ling), *Angelica sinensis* (Dang Gui), *Platycladus semen* (Bai Zi Ren), *Rehmannia glutinosa* (Di Huang), *Schisandra chinensis* (Wu Wei Zi), and *Radix Salviae Miltiorrhizae* (Dan Shen).

Suan Zao Ren, Ye Jiao Teng, Yuan Zhi, Fu Ling, Gan Cao, Dang Gui, Bai Zi Ren, Di Huang, and Wu Wei Zi have frequently been used to treat insomnia in TCM. Suan Zao Ren and Ye Jiao Teng are categorized as Anshen herbals in TCM and are designated as sovereign or minister herbals. Suan Zao Ren, a well-known Chinese herbal medicine, has been used to treat insomnia for thousands of years. It contains complex mixtures of phytochemicals including sanjoinine A, Jujuboside A, spinosin, and other flavonoids that have sedative and hypnotic actions primarily mediated by the GABAergic and serotonergic system (47). Zhou *et al.* collected and analyzed high-quality randomized clinical trials on the treatment of insomnia with formulations containing Suan Zao Ren and found that they were an effective replacement therapy for insomnia (48).

3. TCM to treat adverse reactions and complications of chemotherapy or radiotherapy

Chemotherapy and radiotherapy are major conventional cancer therapies and greatly promote the survival of patients; however, these treatments typically affect multiple organ systems including the gastrointestinal tract, heart, liver, kidneys, marrow, skin, peripheral nerves, and blood vessels. Adverse reactions may be acute (occurring within few weeks after therapy), intermediate, or late (occurring months or years after therapy). Nausea, vomiting, constipation, diarrhea, hair loss, cardiac injury, bone marrow suppression, liver and kidney dysfunction, and peripheral neuropathy symptoms are common adverse reactions and complications during chemotherapy, whereas radiotherapy though administered locally can produce systemic adverse reactions and complications such as radiotherapy pneumonitis, pharyngitis, esophagitis, laryngitis, persistent dysphagia, fatigue, hepatotoxicity, infertility, and cognitive deficits (5,49). These complications and adverse reactions 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. Febrile neutropenia is a life-threatening condition that requires immediate attention, and especially in patients with chemotherapy-related neutropenia, while cardiovascular disease is the most common potentially life-threatening later on (5,50). Thus, more effective therapies to help prevent and control complications and adverse reactions to conventional cancer therapies must soon be developed. Some TCMs have been found to be adjuncts of cancer therapies. TCM combined with chemotherapy or radiotherapy can improve clinical efficacy and the Karnofsky Performance Scale (KPS) score, as well as improve patients' QOL and reduce adverse reactions caused by cancer therapies. The current review will now briefly describe clinical studies outlining the use of TCM to reduce some complications and adverse reactions associated with conventional cancer therapies (Table 5).

3.1. Adverse gastrointestinal reactions

Adverse gastrointestinal reactions including loss of appetite, diarrhea, nausea, vomiting, and constipation, are the most common symptoms occurring in patients with cancer receiving chemotherapy or radiotherapy. However, there is still no effective treatment to alleviate these symptoms in patients with cancer. Many clinical trials have recently suggested that some Chinese herbal medicines and acupuncture and other alternative therapies may be effective at treating adverse gastrointestinal reactions.

A study by Wang *et al.* indicated that acupuncture at Zusanli (ST36), Zhongwan (CV12), and Neiguan (PC6) combined with the slow intravenous injection of

Table 5. Clinical trials of Chinese herbal medicines as adjuvant therapy to alleviate adverse reactions to and complications of cancer therapies

Symptoms	Chinese herbal medicines	Sample	Exposure	Outcome	Ref.
Adverse gastrointestinal reactions	Sheng-jiang-xie-xin-tang	n = 115	Sheng-jiang-xie-xin-tang administered from 1 day prior to chemotherapy to 6 days after chemotherapy	Significantly reduced irinotecan-induced hematological and gastrointestinal toxicities in patients with the UGT1A1*28 or *6 polymorphism.	56
Bone marrow suppression	Fufang E-Jiao Jiang	n = 64	Fufang E-Jiao Jiang + chemotherapy + rhIL-11 + rhG-CSF	Relieved myelosuppression caused by chemotherapy and increased white cell and platelet counts.	56
Cardiotoxicity	Zhi-Gan-Cao-Tang	A case report	Zhi-Gan-Cao-Tang combined with anthracycline compounds	Chest X-ray: substantial alleviation of pulmonary edema and cardiomegaly.	64
CIPN	AC591	n = 72	AC591 combined with chemotherapy	Prevented oxaliplatin-induced neuropathy without reducing its antitumor activity.	69
Radiation pneumonitis	Aidi injection	n = 1,192	Aidi injection combined with radiotherapy	Alleviated radiation pneumonitis, radiation esophagitis, and myelosuppression caused by radiotherapy.	75
Adverse reactions to EGFR-TKIs	TJ-14	n = 29	TJ-14 + minocycline + afatinib in patients with non-small cell lung cancer	Effectively reduced the incidence of an afatinib-induced skin rash, paronychia, diarrhea, and oral mucositis.	82

Note: Abbreviations: chemotherapy-induced peripheral neuropathy (CIPN); Huangqi Guizhi Wuwu decoction (AC591); epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs); Ban-xia-xie-xin-tang (TJ-14).

tropisetron hydrochloride prevented and treated vomiting induced by chemotherapy for lung cancer, with a significantly improved digestive reaction score and KPS score (51). A study by Li *et al.* indicated that moxibustion at Baihui (GV20) and Zhongwan (CV12) combined with a 5-HT receptor antagonist was better than a 5-HT receptor antagonist alone at markedly reducing the incidence and severity of nausea and vomiting caused by chemotherapy with cisplatin in patients with lung cancer without causing obvious adverse reactions (52).

Sheng-jiang-xie-xin-tang is a classical traditional Chinese herbal formulation documented in "ShangHan Lun" for treating digestive system diseases. Sheng-jiang-xie-xin-tang includes 8 herbs: Sheng Jiang (fresh *Zingiberis Rhizoma*), Gan Cao (*Glycyrrhizae radix*), Dang Shen (*Codonopsis radix*), Gan Jiang (*Zingiberis Rhizoma*), Huang Qi (*Astragali radix*), Ban Xia (*Pinelliae rhizoma*), Huang Lian (*Coptidis Rhizoma*), and Da Zao (*Jujubae fructus*). Deng *et al.* indicated that Sheng-jiang-xie-xin-tang significantly reduced irinotecan-induced hematological and gastrointestinal toxicities in patients with the UGT1A1*28 or *6 polymorphism (high risk group) without affecting the clinical response to chemotherapy (53).

Xiang-sha-liu-jun-zi-tang was created by Yunbo Ke, a doctor of Chinese medicine in the Qing Dynasty. Xiang-sha-liu-jun-zi-tang is a classic formula of TCM. Modern studies have indicated that Xiang-sha-liu-jun-zi-tang can be used to treat nausea, vomiting, abdominal distension, and diarrhea. Xiao *et al.* devised a protocol for systematic review and meta-analysis to determine the effectiveness of Xiang-sha-liu-jun-zi-tang in the treatment of chemotherapy-induced nausea and vomiting (CINV) (54). To investigate the effects of TCM on CINV, Lv *et al.* conducted a review including 92 clinical trials and 3,778 patients with different types of cancer, chemotherapy regimens, prescriptions, durations of treatment, and combinations with Western medicines (55). They found that the most frequently used herbs were *Pinelliae rhizoma* (Ban Xia), *Glycyrrhizae radix* (Gan Cao), *Poriacocos* (Fu Ling), and *Atractylodis Macrocephalae rhizoma* (Bai Zhu) to purportedly regulate the flow of *qi* and remove phlegm and dampness in the stomach and spleen. Although all of the reported trials are randomized open trials, the curative effects range from 55.81% to 100%.

3.2. 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 or radio therapy to treat cancer. When 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. Over the past few years, some Chinese herbal medicines, herbal remedies and acupuncture and other alternative therapies have been reported to have beneficial effects on chemotherapy or radiotherapy-related bone marrow suppression.

Colla corii asini (or E-Jiao in Chinese), donkey hide gelatin prepared by stewing and concentrating *Equus asinus* L. donkey hide, is a health food and TCM widely used for rejuvenation and to treat anemia for more than 2,000 years in China (5). Many studies have indicated that E-Jiao and its preparations such as Fufang E-Jiao Jiang may 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 patients with cancer significantly alleviated the myelosuppression caused by a GP (Gemcitabine + DDP) chemotherapy regimen and increased the white cell and platelet counts compared to rhIL-11 and rhG-CSF alone (56). Moreover, Fufang E-Jiao Jiang was found to clearly promote the recovery of bone marrow hemopoietic function in a mouse model of myelosuppression (57). This action may be attributed to (i) improvement in the bone marrow hematopoietic microenvironment; (ii) facilitation the proliferation and preventing the apoptosis of blood and bone marrow nucleated cells (BMNC); and (iii) stimulation of the expression of IL-1 β , IL-3, IL-6, SCF, and GM-CSF and inhibition of the expression of TGF- β .

A systematic review and meta-analysis by Chen *et al.* indicated that acupoint stimulation has immunomodulatory action in patients with lung cancer, as evinced by a significant increase in IL-2, CD3+ and CD4+ T cells, and NK cells but not CD8+ T cells (58). Further analysis also revealed that acupoint stimulation markedly reduces the bone marrow suppression induced by conventional therapy, it increases hemoglobin levels and platelet counts in patients with lung cancer, and it decreases chemotherapy-induced nausea and vomiting. Zusanli (T36), Neiguan (PC6), Geshu (BL17), Feishu (BL13), Guanyuan (RN4), and Shenshu (BL23) were most frequently used acupoints.

3.3. Cardiotoxicity

Cardiotoxicity is a significant complication of various cancer treatments that can negatively impact QOL and prognosis in cancer survivors. Several anticancer agents, including anthracyclines, trastuzumab, alkylating agents, and antimetabolites that have been in use for decades as well as recently introduced anticancer therapies such as tyrosine kinase inhibitors, angiogenesis inhibitors, checkpoint inhibitors, and proteasome inhibitors are associated with significant cardiotoxicity (59). These treatments can cause multiple forms of cardiotoxicity

including arrhythmia, pericardial disease, valvular dysfunction, and myocardial ischemia. In order to optimize outcomes for patients with cancer and cardiovascular disease existing prior to cancer treatment or developing as a consequence of that treatment, a new discipline called "cardio-oncology" has evolved over the past few years (60). Close monitoring for cardiotoxicity and enhanced cardiac management are recommended for patients who receive potentially cardiotoxic therapies, and especially for patients with high-risk factors for serious cardiotoxicity. Through the use of certain β -blockers, ACEI inhibitors, angiotensin receptor blockers, and other drugs for symptomatic treatment, adverse reactions to radiotherapy and chemotherapy can be partially alleviated. In addition, over the past few years, some Chinese herbal medicines have been reported to have beneficial effects on cancer treatment-induced cardiotoxicity.

Dan *et al.* conducted a study to explore the material basis and the rationale of TCM to treat antineoplastic drug-induced cardiotoxicity based on network pharmacology and data mining (61). In that study, five core herbs including *Corydalis rhizoma* (Yan Hu Suo), *Uncaria rhynchophylla* (Gou Teng), *Phellodendri cortex* (Huang Bai), *Forsythia fructus* (Lian Qiao), and *Glycyrrhizae radix* (Gan Cao) were identified in the target-compound-herb network, and these herbs might have the potential to mitigate anti-neoplastic drug-induced cardiotoxicity. *Corydalisrhizoma* is the herb with the most therapeutic potential, and a modern pharmacological study has indicated that it acts against arrhythmia, myocardial infarction, coronary artery dilation, tumors, and thrombosis (62).

Cui *et al.* performed a network pharmacology analysis and compiled experimental evidence to investigate potential protection from cisplatin-induced cardiotoxicity provided by Tongmai Yangxin pills (63). They indicated that Tongmai Yangxin pills regulate the cardiomyocyte free radical balance and reduce apoptosis via the Nrf2/HO-1 pathway and the p38-MAPK pathway, meaning that the medicine might be used to treat platinum chemotherapy-induced cardiac injury. Tongmai Yangxin pills, a traditional Chinese formulation, have been widely used to treat coronary heart disease for several decades. Tongmai Yangxin pills, which consist of the classic formula "Zhi-gan-cao-tang", and "Sheng-mai-san," and the active ingredients of the sovereign drugs are mostly flavonoids, saponins, and lignans that have anti-oxidative stress, anti-inflammatory, and anti-tumor actions.

Zhi-gan-cao-tang is an herbal formula documented in "Shang-Han-Lun" to purportedly supplement Yang-Qi, nourish the Ying-blood, and strengthen the heart spirit to relieve heart failure-related symptoms. Zhi-gan-cao-tang is reported to be the Chinese herbal formula most frequently prescribed by TCM practitioners to treat heart failure. In the case of an 18-year-old adolescent male

with refractory acute lymphoblastic leukemia (ALL), anthracycline-induced cardiotoxicity gradually resolved following the administration of modified Zhi-gan-cao-tang (64). After 2 months of treatment with Zhi-gan-cao-tang, a follow-up chest X-ray revealed substantial alleviation of pulmonary edema and cardiomegaly.

Sheng-mai-san is a well-known TCM formula to treat coronary heart disease with a 3,000-year-old history. Sheng-mai-san consists of three herbs: *Ginseng radix* (Ren Shen), *Ophiopogonis radix* (Mai Dong) and *Schisandrae fructus* (Wu Wei Zi). It has been developed into several TCMs to meet the demands of different patients including a Sheng-mai Oral Solution (Sheng-mai-yin), Sheng-mai Capsules, and a Shen-mai injection (65). These TCMs are widely used to treat heart failure, myocardial infarction, cardiogenic shock, and cardiotoxicity in China. A series of animal studies have reported that the Sheng-mai preparation may increase glutathione peroxidase (GSH-Px) activity, superoxide dismutase (SOD) activity, and Ca^{2+} -ATP enzyme activity and enhance the ultra structure of myocardial tissue in rats with doxorubicin-induced cardiac injury (66). However, few clinical trials have assessed the effectiveness and safety of the Sheng-mai preparation at treating anti-neoplastic drug-induced cardiotoxicity. Further rigorously designed large-scale trials are warranted to verify the merits of the Sheng-mai preparation.

3.4. Peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a common significant and debilitating adverse reaction to the administration of neurotoxic chemotherapeutic agents. These pharmacy-chemotherapeutics can include taxanes, vinca alkaloids, and platinum analogues. Approximately 30% to 40% of patients receiving neurotoxic chemotherapy will develop CIPN (67). Moderate to severe CIPN significantly decreases the QOL and physical abilities of patients with cancer. However, the pathogenesis of CIPN is not fully understood, and there are no drugs that are effective at preventing CIPN. Recently, many clinical trials have suggested that some Chinese herbal medicines and acupuncture and other alternative therapies may be effective at treating CIPN.

Huang-qi-gui-zhi-wu-wu-tang is an herbal formula documented in the "Synopsis of the Golden Chamber" for alleviating limb numbness and pain. It consists of five herbs: *Hedysarum Multijugum Maxim* (Huang Qi), *Cinnamomi Ramulus* (Gui Zhi), *Paeoniae radix alba* (Bai Shao), *Zingiber officinale Roscoe* (Sheng Jiang), and *Jujubae fructus* (Da Zao). Currently, Huang-qi-gui-zhi-wu-wu-tang is mainly used to treat hand-foot syndrome, CIPN, diabetic peripheral neuropathy, and rheumatoid arthritis. Gu *et al.* used the network pharmacology approach to investigate the potential pathogenesis of

CIPN and the therapeutic mechanisms by which Huang-qi-gui-zhi-wu-wu-tang treated CIPN (68). They indicated that the main pathologies of CIPN might involve the inflammatory response and nerve injury and that Huang-qi-gui-zhi-wu-wu-tang played a therapeutic role in CIPN by regulating the inflammatory response and repairing nerve injury, thus verifying the reliability and efficacy of this herbal formula.

AC591 is a standardized extract of Huang-qi-gui-zhi-wu-wu-tang. Pretreatment with AC591 may reduce oxaliplatin-induced cold hyperalgesia, mechanical allodynia, and morphological damage to the dorsal root ganglion. Microarray analysis indicated the neuroprotective action of AC591 depended on the modulation of multiple molecular targets and pathways involved in the down-regulation of inflammation and immune response. In summary, AC591 may prevent oxaliplatin-induced neurotoxicity without reducing its antitumor activity, and it might be a promising adjuvant to alleviate sensory symptoms in clinical practice (69).

A pilot study was conducted by Schroeder *et al.* to evaluate the therapeutic effect of acupuncture on CIPN as measured by changes in nerve conduction studies (NCSes) in patients treated with acupuncture (70). Each patient received a standard 10-week treatment at ST34 (Liang Qiu) as well as at EX-LE12 (Qi Duan) and EX-LE8 (Ba Feng). Results suggested that acupuncture had a positive effect on CIPN as measured by objective parameters (NCSes); a therapeutic intervention with acupuncture over a period of 10 weeks alleviated the symptoms of CIPN and also induced a normalization of histological morphology. Acupuncture might increase the blood flow in the limbs. Increased blood flow to the vasa nervorum and dependent capillary beds supplying the neurons may contribute to nerve repair with measurable improvement of axons or myelin sheaths (71).

3.5. Radiation pneumonitis

Radiation pneumonitis is a well-known complication of thoracic radiation for patients with breast, lung, thymic, and esophageal malignancies and mediastinal lymphomas (72). It typically presents 1-6 months after radiation therapy. The clinical features usually include a mild dry cough, a 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 is 10-20%. When radiation pneumonitis left untreated for a long time, it may develop into pulmonary fibrosis, which has a high rate of mortality. Despite great efforts to develop agents to reduce the severity and incidence of pulmonary toxicities caused by radiotherapy, no effective agents currently exist. General supportive management, mobilization of airway secretions, anti-inflammatory therapy, and management of acute exacerbation are the treatment options. Over the past few years, some TCMs have

been reported to have beneficial effects on radiotherapy-related radiation pneumonitis.

To evaluate the efficacy and safety of herbal medicines as adjunctive therapy for the prevention of radiation pneumonitis in patients with lung cancer undergoing radiotherapy, a systematic review involving 22 randomized clinical trials and 1,819 participants was conducted by Kim *et al.* (73). They indicated that administration of herbal medicines during radiotherapy may prevent or minimize the risk of radiotherapy pneumonia. Because radiation therapy is considered to be a heat toxin pathogen according to TCM theory, prescriptions generally focus on removing heat. Thus, the herbal formulas used with radiotherapy mainly consist of herbs that purportedly nourish *Yin* such as *Ophiopogonis radix* (Mai Dong) and *Adenophorae radix* (Sha Shen), coupled with *qi*-tonifying herbs such as *Astragali radix* (Huang Qi). To evaluate the benefits of Chinese herbal prescriptions containing *Astragali radix* in combination with radiotherapy for non-small cell lung cancer, a meta-analysis of 29 studies and 2,547 individuals was conducted by He *et al.* (74). They indicated that Chinese herbal prescriptions containing *Astragali radix* increased the effectiveness and reduced the toxicity of radiotherapy.

An Aidi injection (Z52020236, China Food and Drug Administration (CFDA)) is an adjuvant chemotherapy drug commonly used in China consisting of extracts from *Astragali radix*, *Eleutherococcus senticosus*, *Panax ginseng*, and *Cantharidin*. It appears to have antitumor and immunoregulatory activity and it attenuates acute or subacute toxicity induced by chemotherapy (75). An Aidi injection plus radiotherapy may significantly improve the clinical efficacy of chemotherapy and the QOL of patients with lung cancer. Moreover, it may alleviate myelosuppression, radiation pneumonitis, and radiation esophagitis.

In summary, there is some encouraging evidence that administration of herbal medicines in combination with radiotherapy may benefit patients with thoracic cancer by preventing or minimizing radiation pneumonitis. However, due to the poor methodological quality of the available studies, a definitive conclusion cannot be reached. Rigorously designed large-scale trials are warranted to verify the merits of this approach.

4. TCM for adverse effects of targeted drugs

When targeted drugs and especially EGFR-TKIs (*e.g.* erlotinib gefitinib, icotinib, osimertinib, and dacomitinib) are widely used, the adverse effects of those treatments including acneiform eruptions, paronychia, xerosis, mucositis, and alopecia are thought to be less severe but can still be significant (76). Not only can these toxicities severely affect patients' QOL, but in some specific instances they can be associated with increased sensitivity to therapy. The incidence of acneiform eruptions is about 47-100% (grade 3/4 1-10%) in patients

receiving EGFR-TKIs. They usually appear within 1 to 3 weeks after EGFR-TKI administration and peak within 3 to 5 weeks.

According to TCM theory, EGFR-TKI-associated adverse effects are categorized as "drug toxicities," and their pathogenesis purportedly involves wind, dampness, and heat invading the lungs due to a deficiency. Thus, the basic principle of treatment is dispelling wind and dampness, promoting eruptions and itching, clearing heat-toxins and cooling the blood, nourishing yin and blood, and moistening dryness. Some herb combinations are commonly prescribed by TCM practitioners for skin toxicity (76). *Schizonepetae herba* (Jing Jie) and *Lonicerae flos* (Fang Feng) are combined to dispel wind. *Schizonepetae herba* (Jin Yin Hua) and *Forsythiae fructus* (Lian Qiao) are combined to clear heat toxins. *Moutan cortex radices* (Mu Dan Pi) and *Paeoniae radix rubra* (Chi Shao) are combined to clear heat and cool the blood. *Taraxaci herba* (Pu Gong Ying) is widely used to remove toxins to reduce swelling in the event of a secondary infection. *Dictamni cortex* (Bai Xian Pi), and *Sophorae flavescens radix* (Ku Shen) are used to promote diuresis and itching if pruritus is a cardinal symptom. Deng *et al.* conducted a meta-analysis including 22 studies involving 16 prescriptions and 50 herbal medicines to evaluate the effect of TCM on EGFR-TKI-induced rashes, and results suggested that TCM may significantly relieve EGFR-TKI-induced rashes and symptoms and improve patients' QOL (77). Herbs with purported cold properties and a bitter flavor that clear heat were used most frequently; *Lonicera Japonica flos* was used in 68.42% of studies on rashes and 66.67% of studies on hand-foot skin reactions while *Sophorae flavescens radix* was used in 52.63% of studies on rashes. However, few studies outside of Asia have examined the effects of these Chinese herbal medicines on adverse effects of targeted drugs. Moreover, due to the poor methodological quality of the available studies, a definitive conclusion cannot be reached.

TJ-14 (Hangeshashinto in Japanese or Ban-xia-xie-xin-tang in Chinese), a famous herbal formula documented in "Shang-Han-Lun," has been used empirically to treat various gastrointestinal disorders such as dyspepsia, gastroenteritis, gastrasthenia, and oral mucositis for thousands of years in China, Japan and other East Asia countries. It consists of seven herbal extracts including *Coptis rhizoma* (Huang Lian), *Panax ginseng* (Ren Sen), *Glycyrrhizae radix* (Gan Cao), *Jujubae fructus* (Da Zao), *Pinelliae rhizoma* (Ban Xia), *Zingiber officinale* (Ginger) (Sheng Jiang), and *Scutellariae radix* (Huang Qin). Some studies have indicated that TJ-14 might possess antioxidant, anti-inflammatory, bactericidal, and analgesic actions and promote healing (78). Over the past few years, TJ-14 has been reported to attenuate adverse reactions to cancer treatment. It is effective against chemotherapy-induced diarrhea and oral mucositis and radiation-

induced enteritis because it suppresses PGE2 or COX-2 (79-81). Moreover, Ichiki *et al.* conducted a single-arm phase II study to evaluate the prophylactic effects of TJ-14 plus minocycline on afatinib-induced diarrhea and skin rashes in patients with non-small cell lung cancer (82). They found that TJ-14 plus minocycline effectively reduced the incidence of afatinib-induced skin rashes, paronychia, diarrhea, and oral mucositis. However, a higher level of evidence from trials with a large sample size is required to verify the efficacy of TJ-14 in treating adverse reactions to EGFR-TKIs.

5. Conclusion

In conclusion, TCM, especially Chinese herbal medicines and acupuncture as adjunctive therapies, has played a positive role in the treatment of various types of cancers. TCM not only alleviates the symptoms of patients with cancer and improves their QOL, but it also diminishes the adverse reactions to and complications caused by chemotherapy, radiotherapy, or targeted-therapy. It can effectively alleviate adverse gastrointestinal reactions to these anti-cancer therapies including diarrhea, nausea, and vomiting, decrease the incidence of bone marrow suppression, alleviate cardiotoxicity, and protect against chemotherapy-induced peripheral neuropathy and radiation-induced pneumonitis. Moreover, TCM can alleviate EGFR-TKI-related acneiform eruptions, diarrhea, and other adverse reactions. In summary, this review should contribute to an understanding of TCM as adjuvant therapy for cancer and provide useful information for the development of more effective anti-cancer therapies.

Although TCM is currently receiving increasing attention worldwide as an alternative and complementary treatment for cancer therapy, published studies have several limitations that should be taken seriously by TCM practitioners: (i) The complexity of TCM theory and prescriptions hampers a full and complete study of TCM with a high level of repeatability and definite findings; (ii) Most of the current studies have mainly focused on efficacy instead of the systematic and in-depth pharmacological actions of medicines; (iii) Clinical studies of TCM lack large-samples, involvement of multiple centers, randomized controls, and a comparison of efficacy, resulting in questions about their scientific validity; and (iv) The clinical effects of herbs are influenced by many factors including species, cultivation, time of harvest, and processing, that can markedly increase uncertainty in active ingredient content (83). In addition, many people currently believe that Chinese herbal medicines are safe because they come from natural products (84). Therefore, TCM practitioners have a duty to advise patients on the toxicity and safety of Chinese herbal medicines. In summary, more rigorously designed trials involving cancer treatment must be conducted in the future, including complete quality

control and standardized models at the cellular, organic, animal, and clinical levels, in order to study TCM in multiple forms and at multiple levels.

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