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Author: Chun-Xiang Su Li-Qiong Wang Suzanne J. Grant Jian-Ping Liu

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Chinese herbal medicine for cancer-related fatigue: a systematic review of randomised clinical trials

Chun-Xiang Su, MM [a, b], Li-Qiong Wang, BS [a], Suzanne J Grant, PhD [c], Jian-Ping Liu, MD, PhD [a,*]

[a] Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Chaoyang District, Beijing 100029, China

[b] School of Nursing, Beijing University of Chinese Medicine, Chaoyang District, Beijing 100102, China

[c] Centre for Complementary Medicine Research, School of Science and Health, University of Western Sydney, Locked Bag 1797, Penrith, NSW 2751, Australia

[*]Corresponding author:

Prof Jian-Ping Liu, MD, PhD,

Centre for Evidence-Based Chinese Medicine,

Beijing University of Chinese Medicine,

11 Bei San Huan Dong Lu, Chaoyang District,

Beijing 100029, China

Jianping_l@hotmail.com; LiuJP@bucm.edu.cn

Tel: +86 10 64286760

Fax: +86 10 64286871

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Summary

Objectives: To assess the effectiveness and safety of Chinese herbal medicine for the treatment of cancer-related fatigue.

Methods: We systematically searched seven electronic databases and two trial registries for randomised clinical trials of Chinese herbal medicine for cancer-related fatigue. Two authors independently extracted data and assessed the methodological quality of the included trials using the Cochrane risk of bias tool. Data were synthesised using RevMan 5.2 software.

Results: A total of 10 trials involving 751 participants with cancer-related fatigue were identified and the methodological quality of the included trials was generally poor. Chinese herbal medicine used alone or in combination with chemotherapy or supportive care showed significant relief in cancer-related fatigue compared to placebo, chemotherapy or supportive care based on single trials. Chinese herbal medicine plus chemotherapy or supportive care was superior to chemotherapy or supportive care in improving quality of life. Data from one trial demonstrated Chinese herbal medicine exerted a greater beneficial effect on relieving anxiety but no difference in alleviating depression. Seven trials reported adverse events and no severe adverse effects were found in Chinese herbal medicine groups.

Conclusions: The findings from 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.

Keywords: cancer-related fatigue, Chinese herbal medicine, systematic review, randomised clinical trial

Introduction

Cancer-related fatigue (CRF) is a pervasive, persistent and subjective sense of tiredness related to cancer disease or cancer treatment,[1] which can not be relieved by sleep or rest.[2] CRF is a rarely independent symptom experienced by people with cancer. It most commonly occurs with other symptoms, such as depression, anxiety, pain, sleep disorder and loss of functional status.[1]

The prevalence of CRF is widely varied according to the populations investigated, the subjective nature of the condition and diverse screening methods that have been used.[3] Overall 50%-90% of people with cancer experience fatigue.[4-6] People with advanced cancer experience fatigue more intensely than cancer survivors and general population when fatigue is measured multidimensionally.[7] It may last for months or even years after cancer eradication.[7]

CRF profoundly impacts on a person's physical, emotional and mental well-being.[8] It has a clear negative impact on quality of life (QoL) of people with cancer and ability to maintain the usual personal, professional and social relationships.[9] The median overall survival is low in people with CRF.[10]

The causes of CRF are difficult to clearly identify owing to its complex nature.[1] A number of causes have been suggested, such as the effect of tumor progression and cancer treatment, comorbid medical conditions including anemia, sleep disturbances, hypothyroidism, inflammation and psychological factors.[11-13]

Any potential reversible causes of CRF (e.g. anemia, sleep disorder or depression) are suggested to being initially treated.[1] Physical exercises, psychosocial therapy, nurse-led fatigue specific intervention, mindfulness-based cognitive therapy, acupuncture and education program have been proven to be effective for managing the symptom of CRF.[14-21] Several pharmacologic agents have been explored, such as psychostimulant methylphenidate, corticosteroids, anabolic steroids, antidepressants, donepezil, L-carnitine, modafanil and amantadine.[22-26] Nevertheless, few of these agents have been studied in large placebo controlled trials and none have been proven to be significantly superior to placebo in the treatment of CRF. The main drug treatment recommended by the latest National Comprehensive Cancer Network guidelines is the use of psychostimulant methylphenidate in selected cases of CRF.[1] However, several trials showed there was no significant difference between psychostimulant methylphenidate and placebo.[27,28]

Chinese herbal medicine (CHM) has been widely used in the treatment of people with cancer in China and other eastern countries.[29] Traditional Chinese medicine (TCM) recognizes CRF as deficiency pattern, which is mainly caused by deficiency of both *qi* and blood, disharmony of *yin* and *yang*, hypofunction of *zang-fu* organs, *qi* stagnation and blood stasis.[30] It is found that CHM has potential beneficial effects on assisting in treating cancer, retarding cancer progression, boosting immune system, ameliorating chemotherapy or radiotherapy-induced complications and side effects, such as pain, fatigue, et al.[31-32]

Although clinical studies of CHM for CRF have been conducted and reported with potential positive results, there is no systematic review on effectiveness and safety of CHM for CRF to

justify their clinical use. Therefore, this review aims to assess the effectiveness and safety of CHM for the treatment of CRF.

Methods

Registration number

The protocol of this systematic review has been registered in PROSPERO (available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013003784).

Eligibility criteria

We included randomised clinical trials (RCTs) regardless of language, blinding, or publication type. People with a clinical diagnosis of CRF with a clear description of diagnostic criteria during and after cancer treatment (including palliative care) were included. There was no age, gender, tumour type, tumour stage and types of cancer treatment restriction. CHM was defined as single herb, Chinese patent medicine, practioner-prescribed herbal formula and herbal products extracted from natural herbs. There was no limitation on the number of herb use, dosage, administration, or duration of the treatment. The control included no treatment, placebo, conventional therapy. We also included those trials on combined therapy of CHM with conventional therapy versus the same conventional therapy. The primary outcome was patient-reported fatigue measured by reliable and valid assessment tools. The secondary outcomes included QoL measured by a validated instrument or tool, improvement of depression or anxiety, adverse events related to CHM.

Data sources and search strategy

We searched the following bibliographic, electronic databases to identify relevant studies for this review. English databases included the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and EMBASE. Chinese databases involved Chinese National Knowledge Infrastructure Databases (CNKI), Chinese Science and Technology Periodical Database (VIP), Chinese Biomedical Literature Database (SinoMed), and Wan Fang Database. The search duration was inception of the databases to November 2013. Ongoing registered clinical trials were searched through WHO International Clinical Trial Registry Platform portal, and the website of International Clinical Trial Registry by U.S. National Institutes of Health.

The following search terms were used separately or combined: 'cancer-related fatigue', 'Chinese traditional', 'Chinese herbal', 'oriental traditional', 'herb', 'herbal medicine' and 'controlled trial'. Language, publication year and publication status were not limited. The reference lists of all eligible articles obtained for additional studies were checked.

Study selection and data extraction

Three authors (Su CX, Wang LQ, Suzanne JG) independently selected eligible trials. Data was independently extracted from the included trials using a piloted, standard data extraction form by two authors (Su CX, Wang LQ). For each trial, we extracted publication year, study type, diagnostic criteria, generation of allocation sequence, allocation concealment, blinding, sample size (total number and number in each arm), demographic characteristics, type of cancer, type of treatment and stage of treatment (e.g. during or after treatment), intervention and control, type

of herbal medicine, treatment dosage, regimen, duration of follow-up, attrition rates, outcomes, conclusions, funding.

We sought further information from the authors of relevant studies if study findings were unclear or missing. We resolved any differences in opinion through discussion or consultation with the third party (Liu JP).

Assessment of risk of bias

Each included trial was independently assessed for risk of bias using the criteria described in the Cochrane Handbook version 5.1.0[33] by the authors with any disagreements resolved by discussion or consultation to the third party. We assessed the following for each study: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other sources of bias. Quality of each trial was divided into low/unclear/high risk of bias. If needed, we contacted the authors of assessed trials for clarification.

Data analysis

Data analysis was performed with RevMan 5.2 software to quantify and compare the efficacy outcomes of CHM versus the control group. If homogeneity of the trials on study design, participants, interventions, control, and outcome measures were acceptable, meta-analysis was performed. We adopted fixed-effect model for the meta-analysis for non-significant heterogeneity and used random-effect model for significant heterogeneity ($p<0.1$). Continuous

data were reported as mean difference (MD) whereas dichotomous data reported as risk ratio (RR) with a 95% confidence interval (CI). Subgroup analyses were done for different outcome measures if the necessary data were available. We planned to conduct a sensitivity analysis to explore the influence of trial quality on effect estimates if a sufficient number of randomised trials were found. Publication bias was explored applying a funnel plot analysis if more than 10 trials were identified.

Results

Study selection

The initial systematic search identified 221 articles of interest, of which 26 were potentially relevant after screening titles and abstracts. Applying our eligibility criteria led to the inclusion of 12 articles describing the results of 10 trials in this systematic review (Fig.1).[34-45]

Study characteristics

Of the 10 trials included in this review, one was multicenter, double-blind placebo RCT with four arms,[34] 9 were RCTs with two arms, of which two were single blind RCTs.[35,40] Five trials were journal articles, [34,36,38,39,43] four postgraduate theses,[35,40-42] and one conference proceeding.[37] The majority of studies (n=8) were carried out in China, the others were undertaken in America[34] and Korea.[38] 66.7% (7/10) were published in Chinese[35, 36,39,40-43] and 33.3% (3/10) were published in English.[34,37,38] None of trials were published prior to 2009. Only two trials provided information about the funding source.[34,39]

In total, 751 participants (448 in intervention group and 303 in control group) were evaluable in the 10 trials. The sample size ranged from 40 to 282 with an average of 75.1 per trial. 61.3% participants across the trials were female except one trial where gender was not stated.[40] The mean age of participants varied considerably and ranged from 27 to 71 years, with the majority of trials reporting a mean age that exceeded the fourth decade. Two trials only recruited CRF inpatients with spleen *qi* deficiency pattern[35,40] and one trial exclusively studied on CRF inpatients with *qi*-blood deficiency pattern.[42] The type of cancer differed across trials although the majority of trial focused on breast cancer and lung cancer. Five trials investigated participants with a specific cancer only,[35-37,39,43] whereas five trials [34,38,41,42] recruited participants with different cancer diagnosis and one failed to report cancer type.[40] All of the 10 trials examined the effects of CHM on participants with CRF during cancer treatment. All trials reported the diagnostic criteria, of which six trials used International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[35,36,39-42] Inclusion criteria were mentioned in 8 trials,[34,35,37-42] of which two trials solely enrolled patients who had a life expectancy of at least 3 months,[39,41] one trial exclusively accepted patients with a life expectancy of more than 6 months.[34] Only three trials failed to describe exclusion criteria.[36,40,43]

All of the 10 trials were classified into four comparisons according to the interventions: (1) CHM versus no intervention (n=1); (2) CHM versus placebo (n=2); (3) CHM plus chemotherapy versus chemotherapy (n=3); (4) CHM plus supportive care versus supportive care (n=4). Three different classes of CHM were investigated in the included trials, involving single herb (n=2), Chinese patent medicine (n=5) and practitioner-prescribed herbal formula (n=3). The formulations

included granule (n=1), powder (n=1), capsule (n=1), herbal extract injection (n=1), oral liquid (n=1), pill (n=2) and herbal formula (fixed formula and practitioner-prescribed herbal formula in 3 trials). All of the included trials provided information about name of manufacturer of CHM or manufacture method of herbal formula except two.[38,43] Control regimens included no intervention, placebo, chemotherapy and supportive care. All trials had a minimum of 14 days study duration with some of up to 56 days.

Patient-reported fatigue as the primary outcome was identified in all trials, with half of trials (n=5) reporting number of participants with fatigue relief whereas the remaining trials (n=5) reporting fatigue severity. CRF was assessed using a wide range of outcome measures and most frequently assessed by Brief Fatigue Inventory (seven trials).[34,35,39-43] Three of the 10 trials failed to measure QoL.[35,39, 40] Information about anxiety and depression was mentioned in only one trial.[37] Seven trials mentioned adverse events.[34,35,37,38,40-42] Follow-up assessment of long-term clinical outcomes of interest was poor with only two trials assessing outcomes after follow-up lasting from 15 days to 12 weeks.[42,43] The characteristics of included trials and the components of CHM in the included trials are listed in Table 1, 2, respectively.

Assessment of risk of bias

We made an attempt to contact the authors of the included trials for clarification and details. Regrettably, only three authors subsequently provided the missing information, the remaining authors either did not respond, or failed to be located.

All trials had considerable flaws in terms of methodological reporting and were assessed as high risk of bias (Fig.2, Fig.3). Appropriate random sequence generation was reported in only five trials where either a computer random number generator[34,38,39,42] or a random number table[36] was employed. Concealment of allocation was adequately conducted in three trials as use of centralized telephone randomisation,[36] opaque sealed envelope[42] and dynamic allocation procedure.[34] There was no evidence of appropriate blinding of participants or study personnel performed in any of the included trials except one.[34] Although unsurprisingly blinding of outcome assessor was not well implemented in any trials, we also judged it to be low risk of bias due to clinical outcomes of interest measured by patient-reported questionnaires. Six of 10 trials provided sufficient information regarding study attrition, of which three trials reported no participants dropped out,[35,40,42] whereas the remaining three trials reported the number and reason of withdraw,[34,38,39] one out of the remaining three trials reported that more than 20% patients withdrew from the study due to some reasons.[34] Intension-to-analysis was conducted in two trials.[34,38] Pre-designed outcomes directly related to CRF were not reported in one trial,[38] and all pre-designed outcomes as reported in the protocol were provided in one trial.[34] Only four trials carried out a sample size calculation.[34,35,38,40] All the included trials reported baseline comparability.

Effects of interventions

Four comparisons including one trial comparing CHM to no intervention,[38] two trials comparing CHM to placebo,[34,37] three trials comparing CHM in combination with chemotherapy to chemotherapy,[36,39,41] and four trials comparing CHM in conjunction with supportive care to

supportive care were identified.[35,40,42,43] Pooling of data via meta-analysis was impossible due to the clinical heterogeneity in terms of participants, intervention and control. Table 3 presents the effect estimates of CHM.

Fatigue severity

Five trials contributed results to this outcome after treatment. One trial comparing CHM (Bojungikki-tang) to no intervention demonstrated no significant relief in fatigue severity measured by the Visual Analogue Scale of Global Fatigue (VAS-F) (MD:-0.80, 95%CI -1.81 to 0.21).[38] Two trials compared CHM to placebo, of which one showed spore powder of G. Lucidum generated significantly lower levels of fatigue in comparison to placebo (MD: 20.08, 95%CI 9.75 to 30.41),[37] and data from the other trial did reveal a trend for higher doses of USA ginseng (2g/day) exerting greater effects on relieving fatigue compared with placebo.[34] However, the effect size of this trial was not estimated using RR and 95% CI due to inaccessibility to post-treatment means +/- standard deviation (SD).[34] The remaining two trials comparing CHM in combination with chemotherapy to chemotherapy showed significant reduction in fatigue favoring CHM over the chemotherapy.[36,39]

Number of participants with fatigue relief

Five trials provided data on this outcome. It was evident that CHM integrated with chemotherapy produced a significant increase in number of participants with fatigue relief when compared to chemotherapy after treatment.[41] Among the rest of four trials comparing CHM combined with supportive care to supportive care, only one trial showed significant difference in increasing the

number of participants with fatigue relief between two groups at the end of treatment.[40]

Improvement of QoL

Of six trials reporting mean improvement of QoL, the findings were not always consistent. Three trials compared CHM to no intervention[38] or placebo.[34,37] Of these, two trials[37,38] showed no statistically significant differences; the other trial[34] reporting the mean change of QoL from baseline found the higher dose of USA ginseng (2g/day) generated an increase in QoL measured by the overall QoL, physical, emotional, mental, and spiritual well-being scales, however, the estimated effect failed to note using RR and 95% CI due to inaccessibility to post-treatment means +/- SD. The remaining three trials indicated that CHM was statistically more beneficial to improve QoL than chemotherapy[36] and supportive care.[42,43]

Only one trial comparing CHM in combination with chemotherapy to chemotherapy provided data on number of participants with improvement of QoL and indicated a significant difference favouring Fufang Ejiao jiang at the end of treatment (RR: 1.59, 95%CI 1.13 to 2.23).[41]

Improvement of anxiety and depression

Only one trial involving 48 people with breast cancer measured anxiety and depression by Hospital Anxiety and Depression Scale (HADS) after treatment.[37] When compared to placebo, spore powder of G. Lucidum exerted a greater beneficial effect on relieving anxiety and decreasing total scores of HADS (anxiety MD: -2.00, 95%CI -3.73 to -0.27; total of HADS MD: -2.70, 95%CI -4.55 to -0.85). However, no clear evidence was found that spore powder of G. Lucidum

was more effective to alleviate depression compared to placebo (MD: -1.50, 95%CI -3.12 to 0.12).

Adverse events

Seven of the included 10 trials reported adverse events while three trials lacked descriptions regarding the occurrence of adverse events.[36,39,43] Among seven trials, four trials stated that none had occurred adverse events in both groups at the end of treatment[35,40,41] or follow-up.[42] Details of adverse events related to CHM were described in the remaining three trials.[34,37,38] Only mild adverse events occurred in CHM referring to dizziness, dry mouth, diarrhea, headache, stomach discomfort, nausea, epistaxis, sore throat, insomnia, flatulence and dyspepsia.

Publication bias assessment

We did not assess publication bias due to the insufficient number of included trials (less than 10).

Discussion

Analysis of effectiveness and safety

This systematic review of 10 RCTs with 751 participants evaluating the effectiveness and safety of CHM for CRF provided evidence that CHM used alone or in combination with chemotherapy or supportive care was more effective than placebo, chemotherapy and supportive care in alleviating CRF. CHM plus chemotherapy or supportive care was superior to chemotherapy or supportive care in improving QoL. Furthermore, there were few adverse effects related to CHM. The possible mechanism of CHM maybe due to activate the immune system, anti-inflammation, antioxidant, ameliorate chemotherapy or radiotherapy-induced complications.[46,47] Based on the

theory of TCM, CRF may present deficiency of both *qi* and blood, disharmony of *yin* and *yang*, *qi* stagnation and blood stasis.[30] Consequently, CHM was applied to invigorate qi and blood, nourish yin and yang, and dissolve blood stasis.

Despite the promising results, we could not draw confirmative conclusion on the beneficial effect and safety of CHM for CRF because the majority of trials incorporated into this systematic review were methodologically weak and at high risk of bias.

Limitations

The significance of the findings of this review is subject to some limitations.

First of all, almost all the included trials were of poor methodology quality. 50% (5/10) trials failed to provide information about randomisation procedure and only 33.3% (3/10) trials were judged to have adequate allocation concealment. Except for one trial, none conducted blinding of participants and personnel. Although two trials comparing CHM in combination with supportive care to supportive care were designed as single-blinding RCT, it's impossible to perform blinding to participants since the participants in control group did not receive placebo of CHM. Few trials provided details on sample estimates.

Furthermore, great clinical heterogeneity of intervention and participants existed in this review. A total of nine different CHMs including two single herbs, four Chinese patent medicines and three practioner-prescribed herbal formulae were investigated in the 10 trials. Therefore, it's impossible to synthesise the data into meta-analysis to explore the effect of a specific CHM. Most

of the included trials recruited participants with different types of cancer and unclear disease stages which may lead to difficulties in the interpretation of the effectiveness of CHM on a specific cancer population with CRF.

Moreover, the majority of included trials conducted short-term interventions (approximately four weeks) which may not be long enough to produce any statistically significant effects on CRF. Further, few trials implemented follow-up to assess the long term effect of CHM on CRF.

In addition, trials in this review failed to focus on the health and economic impacts of the intervention tested, and therefore, little is known about the economic value of CHM for CRF.

Implications for further research

More multicenter, larger, placebo, RCTs of high methodological quality are required to define the true extent of benefit from CHM before a recommendation for use in practice can be made. Randomisation sequence generation should be employed rigorously and allocation concealment be sufficiently conducted. Effective and explicit blinding of participants, personnel and outcome assessor, careful elucidation of any adverse effects and the cost-utility of the therapy are requisite.

Further research is desirable to determine the most optimal CHM regimen for treatment of CRF including types of CHM, frequency and duration of administration. Additionally, future work should focus on a specific cancer at various stages.

Furthermore, a follow-up should be implemented to test the long-term effect sizes of CHM for CRF. Researchers should follow the standards of CONSORT for better trial reporting.[48]

Conclusions

This systematic review suggests that CHM may be effective and safe in the treatment of CRF. However, owing to poor and varying methodological quality of these trials and the heterogeneity of CHM intervention, potential promising findings must be interpreted with considerable caution. It's recommended to employ further rigorous RCTs that overcome the limitations of current trials to increase the strength of evidence.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

SCX conceived and designed the review. SCX, WLQ, SJG were responsible for the searching, screening and selecting studies. SCX and WLQ undertook data extraction and assessment of the methodological quality. SCX contributed to performing data analysis and drafting the manuscript. SCX, LJP were involved in critically revising the manuscript. All authors read and approved the final manuscript.

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Legends

Figure 1 Flow-chart of study selection

Figure 2 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Figure 3 Risk of bias summary: review authors' judgments about each risk of bias item for each included study. "+": low risk of bias; "?": unclear risk of bias; or "-" high risk of bias

Table 1 Basic characteristic of included studies

Table 2 The components of Chinese herbal medicine in the included trials

Table 3 Effect estimates of Chinese herbal medicine for cancer-related fatigue in randomised clinical trials

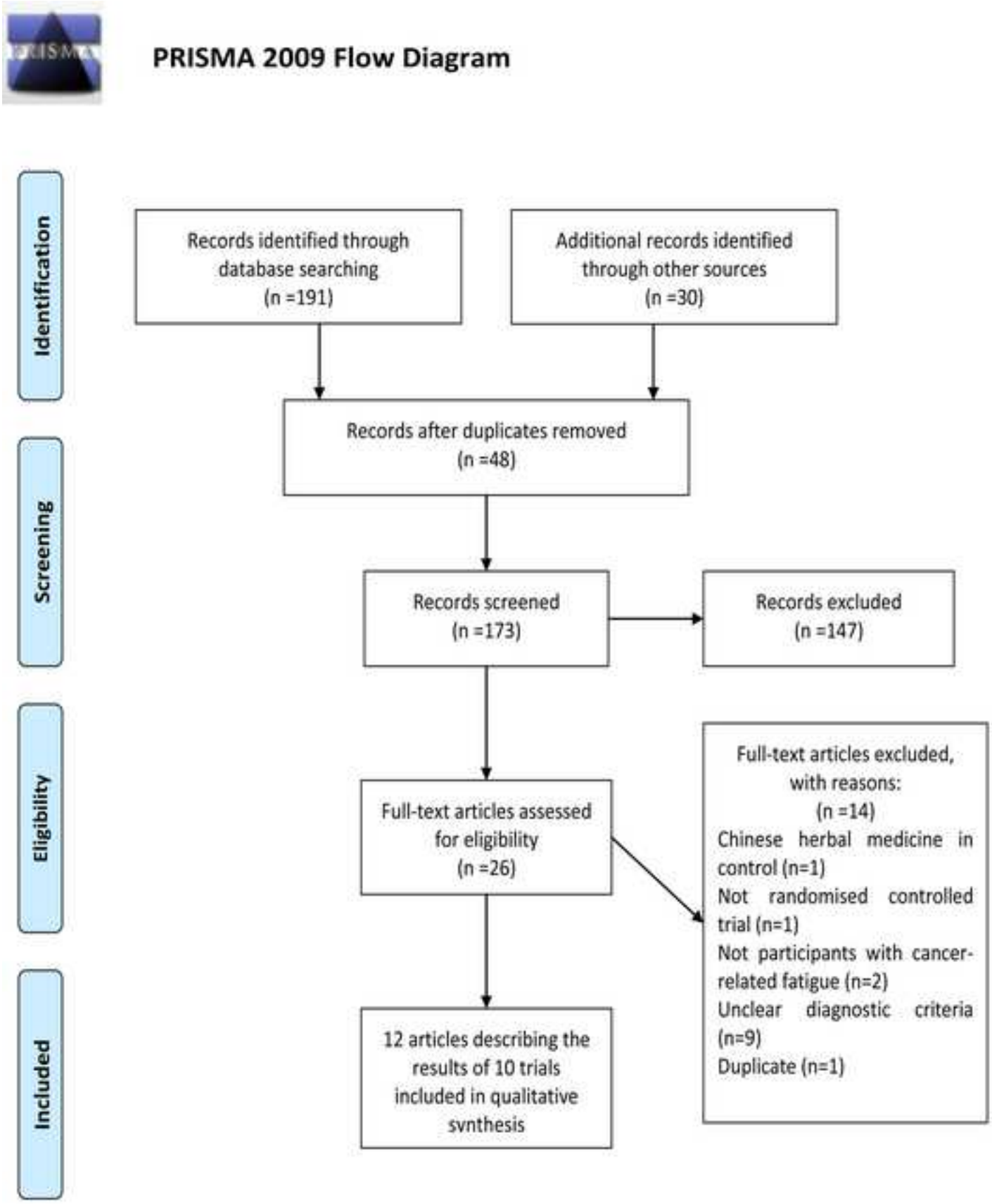
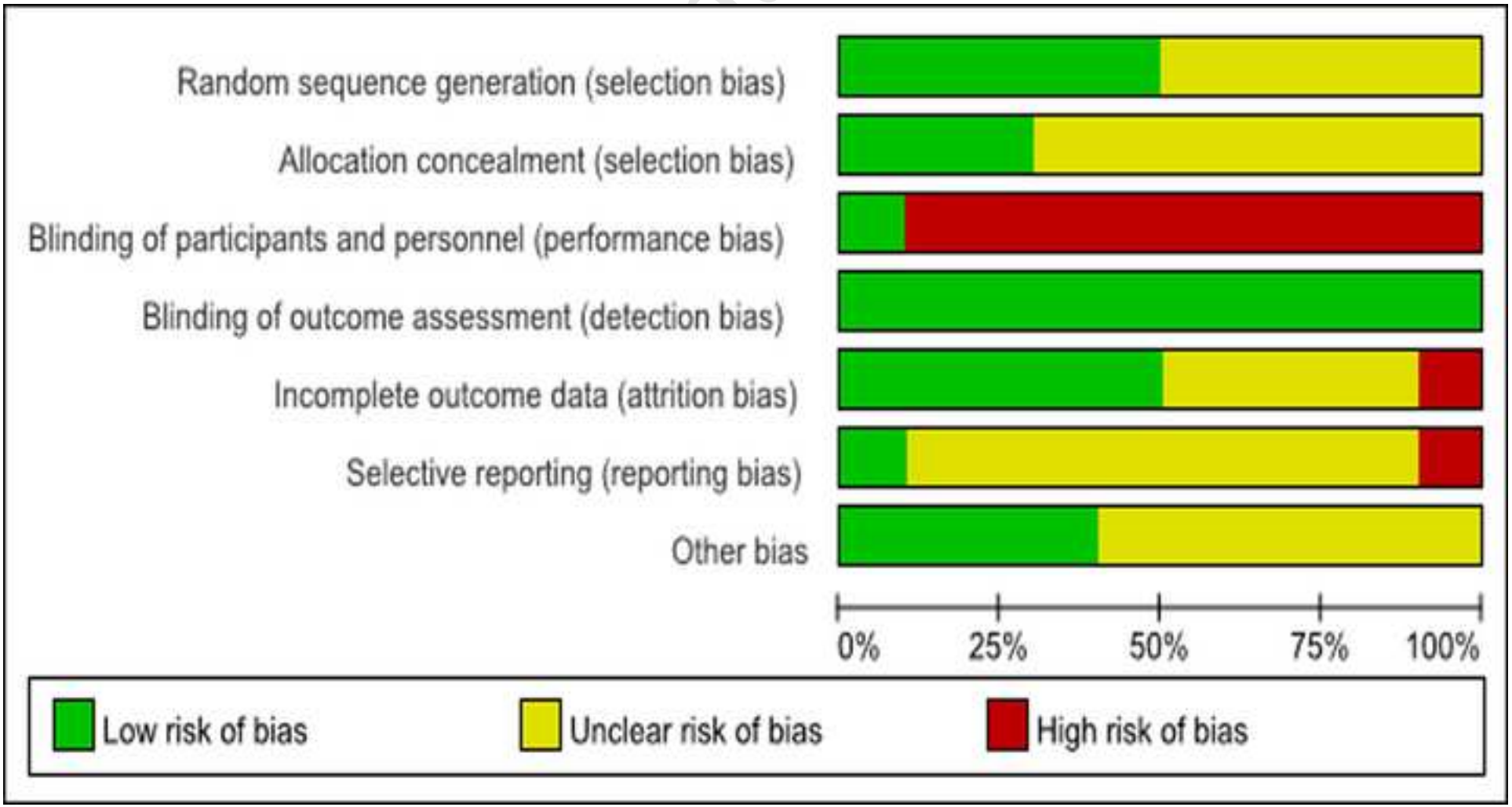


Figure 1. Flow-chart of study selection

Figure


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

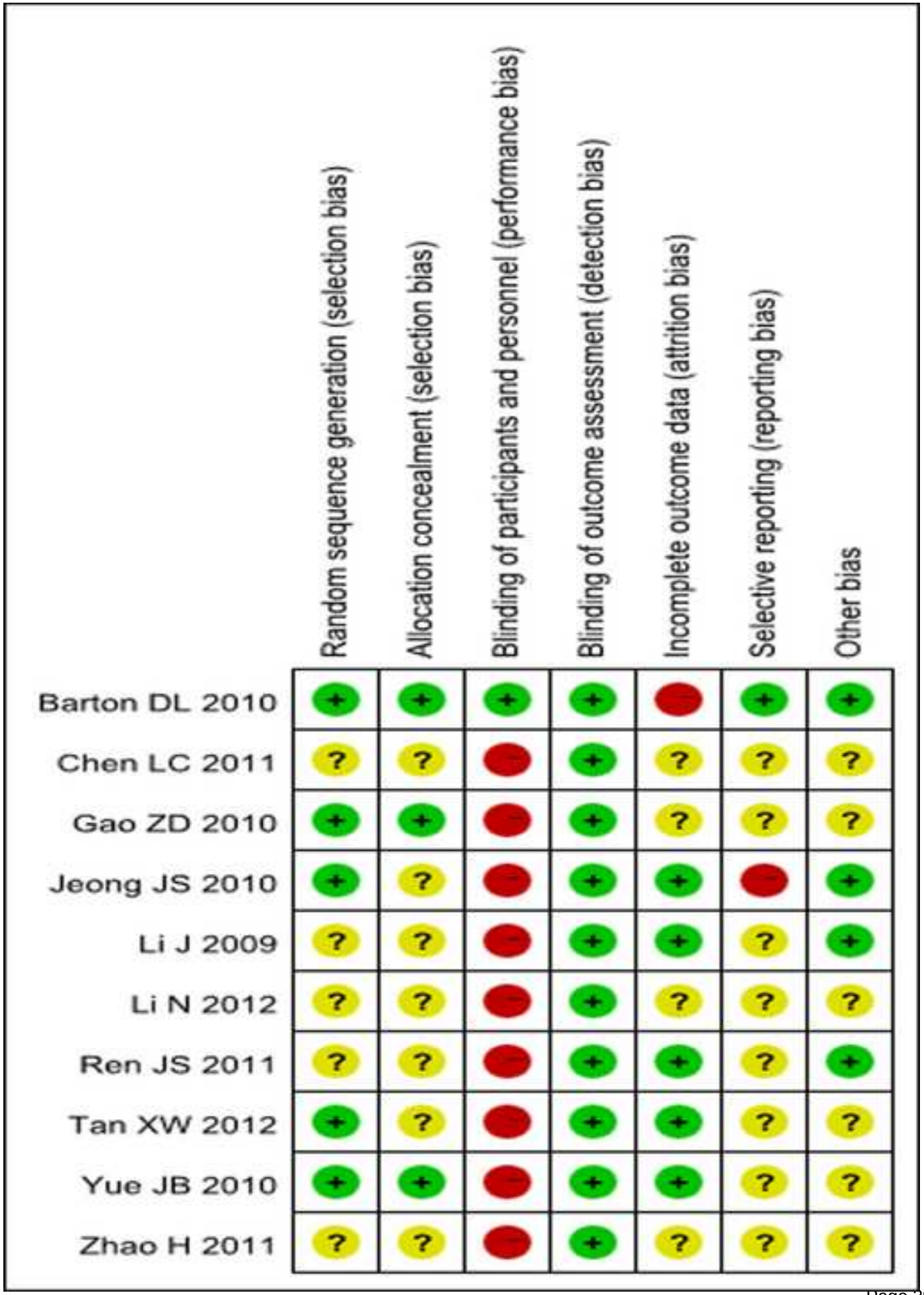


Table 1 Basic characteristic of included studies

Study ID	Participants and diagnostic criteria	Mean age (year) (median/range)	Sample	Women (%)	type of cancer	Intervention	Control	Outcomes measures
Barton DL 2010 [34]	CRF patients Self-designed criteria	I_1: 58±11 I_2: 60±12 I_3: 62±11 C: 62±13	282	58.5	breast cancer, colon cancer, lung cancer, others	USA ginseng 750mg per day, the total milligrams divided into twice daily dosing to be taken in the morning and midafternoon with food for 56 days USA ginseng 1,000mg per day, the total milligrams divided into twice daily dosing to be taken in the morning and midafternoon with food for 56 days USA ginseng 2,000 mg per day, the total milligrams divided into twice daily dosing to be taken in the morning and midafternoon with food for 56 days	Placebo (consisting of long grain white rice flour)	BFI, SF-36,AE
Li J 2009 [35]	CRF inpatients ICD-10	49(30-70)	45	100	breast cancer	Buzhong Yiqi pill, 6g each time, twice a day, taken orally with warm water after a meal for 30 days	supportive care	BFI, AE
Gao ZD 2010 [36]	CRF inpatients ICD-10	48-71	47	36.2	colorectal adenocarcinoma	Kangai injection, 40ml each time, once a day, ivgtt plus chemotherapy for 15 days	chemotherapy	FSI, QoL-C
Zhao H 2011 [37]	CRF patients Self-designed criteria	I: 51.3±9.8 C: 53.2±8.7	48	100	breast cancer	Spore powder of Ganoderma Lucidum,1000mg each time, three times a day for 28 days	placebo	FACT-F, HADS, AE, EORTC-QLQ-C30
Jeong JS 2010 [38]	CRF patients 100-mm VAS-F	I: 49.4 ±10.8 C: 53.4±8.0	40	62.5	breast cancer, gastric cancer, colorectal cancer, lung cancer, others	Bojungikki-tang extract granules 2.5g each time, three times a day, orally for 14 days	waiting list	VAS-F, FACT-G, FACT-F, TOI-F, AE
Tan XW 2012 [39]	CRF inpatients ICD-10	I: 54.3±7.3 C: 59.3±7.4	67	34.3	lung cancer	Practioner-prescribed Jianpi Yiqi Huatan decoction, 150ml each time, taken orally in the morning and evening plus chemotherapy for 14 days	chemotherapy	BFI-C, CFS

Ren JS 2011 [40]	CRF patients ICD-10	53.53(39-65)	45	NR	NR	Buzhong Yiqi pill, 6g each time, twice a day, taken orally with warm water after a meal for 30 days	supportive care	BFI, AE
Li N 2012 [41]	CRF inpatients ICD-10	I: 61±11 C: 60±10	73	42.5	lung cancer, breast cancer, ovarian cancer, intestinal cancer, gastric cancer, kidney cancer, lymphoma, nasopharyngeal carcinoma	Fufang Ejiao Jiang, 20ml each time, three times a day plus chemotherapy for 28 days	chemotherapy	BFI, KPS, AE
Yue JB 2010 [42]	CRF inpatients ICD-10	I:58.0±6.9 (28-70) C:56.80±8.7 (29-69)	44	43.2	non-small cell lung cancer, oesophageal carcinoma	Renshen Yangrong decoction, 100ml each time, three times a day, taken warm orally in the morning, noon and evening half an hour after meal, orally plus rhEPO for 28 days	rhEPO	BFI, AE, EORTC-QLQ-C30
Chen LC 2011 [43]	CRF inpatients BFI	27-70	60	100	breast cancer	Buzhong Yiqi decoction, one dose divided into twice daily to be taken orally in the morning and evening for 20 days	supportive care	BFI, QoL-C

Abbreviation: CRF: cancer-related fatigue; I: intervention group; C: control group; BFI: Brief Fatigue Inventory; SF-36: Medical Outcome Scale Short Form-36; AE: adverse events; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; ivgtt: intravenously guttae; FSI: Fatigue Symptom Inventory; QoL-C: Quality of Life Questionnaires designed by China; FACT-F: Functional Assessment of Cancer Therapy-Fatigue; HADS: Hospital Anxiety and Depression Scale; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; VAS-F: Visual Analogue Scale of Global Fatigue; FACT-G: Functional Assessment of Cancer Therapy-General; TOI-F: Trial Outcome Index-Fatigue; BFI-C: Brief Fatigue Inventory designed by China; CFS: Cancer Fatigue Scale; NR: not reported, that is no information in the articles; KPS: Karnofsky performance score; rhEPO: recombinant human erythropoietin;

Table 2 The components of Chinese herbal medicine in the included trials

Chinese herbal medicine	Formulation	Components	Study ID
USA ginseng	Capsule	USA Ginseng	Barton DL 2010 [34]
Buzhong Yiqi pill	Pill	Astragali Membranacei(fry), Codonopsitis Pilosulae, Radix Glycyrrhizae (fry), Rhizoma Atractylodis Macrocephalae (fry), Radix Angelicae Sinensis, Rhizoma Cimicifugae, Radix Bupleuri, Pericarpium Citri	Li J 2009 [35]; Ren JS 2011 [40]
Aikang injection	Injection	Astragali Membranacei 300g, Radix Ginseng 100g, Oxymatrine 10g	Gao ZD 2010 [36]
Spore powder of G. Lucidum	Powder	Spore powder of Ganoderma Lucidum	Zhao H 2011 [37]
Bojungikki-tang	Granules	Astragali Radix, Atractylodis Lanceae Rhizoma, Ginseng Radix, Angelicae Radix, Bupleuri Radix, Zizyphi Fructus, Aurantii Nobilis Pericarpium, Glycyrrhizae Radix, Cimicifugae Rhizoma, Zingiberis Rhizoma	Jeong JS 2010 [38]
Practioner-prescribed Jianpi Yiqi Huatan decoction	Decoction	Codonopsitis Pilosulae, Rhizoma Atractylodis Macrocephalae, Poriae Cocos, Semen Coicis, Caulis Bambusae in Taeniam, Rhizoma Pinelliae, Pericarpium Citri, Fructus Oryzae Germinates, Fructus Hordei Germinates, Endothelium Corneum Gigeriae Galli,ect.	Tan XW 2012 [39]
Fufang Ejiao Jiang	Oral liquid	Corii Cuon Alpine, Radix Rehmanniae Preparata, Codonopsitis Pilosulae, Radix Ginseng Rubra, Fructus Crataegi	Li N 2012 [41]
Renshen Yangrong decoction	Decoction	Radix Ginseng Rruda 30g, Astragali Membranacei 30g, Rhizoma Atractylodis Macrocephalae 15g, Poriae Cocos15g, Radix Glycyrrhizae6g, Radix Angelicae Sinensis 15g, Radix Polygoni Multiflori 20g, Radix Rehmanniae Preparata 15g, Pericarpium Citri 15g, Shaved Cinnamon Bark 10g, Fructus Schisandrae 10g, Radix Polygalae 15g	Yue JB 2010 [42]
Buzhong Yiqi decoction	Decoction	Astragali Membranacei 40g, Rhizoma Atractylodis Macrocephalae 15g, Pericarpium Citri 10g, Rhizoma Cimicifugae 10g, Radix Bupleuri 10g, Codonopsitis Pilosulae 15g, Radix Glycyrrhizae (fry) 6g, Radix Angelicae Sinensis 20g	Chen LC 2011 [43]

Table 3 Effect estimates of Chinese herbal medicine for cancer-related fatigue in randomised clinical trials

Outcomes or subgroups	No. of studies	No. of participants	Effect estimates	Study ID
1. Fatigue severity (MD scores, 95%CI)				
1.1 Chinese herbal medicine vs no intervention	**1**	**40**		
Bojungikki-tang extract granules *vs* no intervention	1	40	-0.80 [-1.81, 0.21] (0-100mm scale by VASF)	Jeong JS 2010 [38]
1.2 Chinese herbal medicine vs placebo	**2**	**330**		
Spore powder of G. Lucidum *vs* placebo	1	**48**	20.08 [9.75, 30.41] (FACT-F)	Zhao H 2011 [37]
1.3 Chinese herbal medicine plus chemotherapy vs chemotherapy	**2**	**114**		
1.3.1 Kangai injection plus FOLFOX4 *vs* FOLFOX4	1	47	-21.77 [-27.41, -16.13] (FSI)	Gao ZD 2010 [36]
1.3.2 Practioner-prescribed Jianpi Yiqi decoction plus chemotherapy *vs* chemotherapy	1	67	-2.96 [-3.46, -2.46] (0-10 point scale by BFI-C); -11.81 [-14.69, -8.93] (CFS)	Tan XW 2012 [39]
2. Number of participants with fatigue relief (RR, 95%CI)				
2.1 Chinese herbal medicine plus chemotherapy vs chemotherapy	**1**	**73**		
Fufang Eijiao jiang plus chemotherapy *vs* chemotherapy	1	73	2.59 [1.41, 4.78] (0-10 point scale by BFI);	Li N 2012 [41]

2.2 Chinese herbal medicine plus supportive therapy *vs* ***supportive therapy***	**4**	**194**		
2.2.1 Renshen Yangrong decoction plus rhEPO *vs* rhEPO	1	44	1.25 [0.78, 2.01] (0-10 point scale by BFI);	Yue JB 2010 [42]
2.2.2 Buzhong Yiqi decoction plus supportive therapy *vs* supportive therapy	1	60	3.43 [0.82, 14.35] (0-10 point scale by BFI);	Chen LC 2011 [43]
2.2.3 Buzhong Yiqi pill plus supportive therapy *vs* supportive therapy	1	45	1.81 [1.03, 3.16] (0-10 point scale by BFI);	Ren JS 2011 [40]
2.2.4 Buzhong Yiqi pill plus supportive therapy ***vs*** supportive therapy	1	45	1.57 [0.98, 2.50] (0-10 point scale by BFI);	Li J 2009 [35]
3. Quality of life (MD scores, 95%CI)				
3.1 Chinese herbal medicine *vs* ***no intervention***	**1**	**40**		
Bojungikki-tang extract granules *vs* no intervention	1	40	6.60 [-3.02, 16.22] (FACT-G); 8.00 [-6.30, 22.30] (FACT-F); 3.20 [-7.28, 13.68] (TOI-F)	Jeong JS 2010 [38]
3.2 Chinese herbal medicine *vs* ***placebo***	**1**	**48**		
3.2.1 Spore powder of G. Lucidum *vs* placebo	1	48	30:11.20[-1.77, 24.17] (EORTC-QLQ-C30)	Zhao H 2011 [37]
3.3 Chinese herbal medicine plus chemotherapy *vs* ***chemotherapy***	**1**	**47**		
Kangai injection plus FOLFOX4 *vs* FOLFOX4	1	47	24.80 [18.81, 30.79] (QoL-C)	Gao ZD 2010 [36]

3.4 Chinese herbal medicine plus supportive therapy** vs **supportive therapy	**2**	**104**		
3.4.1 Renshen Yangrong decoction plus rhEPO *vs* rhEPO	1	44	12.36 [10.05, 14.67] (EORTC-QLQ-C30)	Yue JB 2010 [42]
3.4.2 Buzhong Yiqi decoction plus supportive therapy *vs* supportive therapy	1	60	Physical:12.60 [7.22, 17.98]; Spirit:13.90 [8.83, 18.97]; Independent ability to survive: 7.70 [3.90, 11.50]; Social relation: 13.70 [8.90, 18.50] (QoL-C)	Chen LC 2011 [43]
4. Number of participants with improved quality of life (RR, 95%CI)				
4.1 Chinese herbal medicine plus chemotherapy** vs **chemotherapy	**1**	**73**		
Fufang Eijiao jiang plus chemotherapy *vs* chemotherapy	1	73	1.59 [1.13, 2.23] (KPS)	Li N 2012 [41]
5. Depression and anxiety (MD scores, 95%CI)				
5.1 Chinese herbal medicine** vs **placebo	**1**	**48**		
Spore powder of G. Lucidum *vs* placebo	1	48	Anxiety:-2.00[-3.73, -0.27] Depression:-1.50 [-3.12, 0.12] Total of HADS:-2.70[-4.55, -0.85]	Zhao H 2011 [37]

Abbreviation: MD: mean difference; CI: confidence interval; vs: versus; VASF: Visual Analogue Scale of Global Fatigue; FACT-F: Functional Assessment of Cancer Therapy-Fatigue; FOLFOX4: fluorouracil, oxaliplatin, calcium folinate; FSI: Fatigue Symptom Inventory; BFI-C: Brief Fatigue Inventory designed by China; CFS: Cancer Fatigue Scale; RR: risk ratio; BFI: Brief Fatigue Inventory; rhEPO: recombinant human erythropoietin; FACT-G: Functional Assessment of Cancer Therapy-General; TOI-F: Trial Outcome Index-Fatigue; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL-c: Quality of Life Questionnaires designed by China; KPS: Karnofsky performance score; HADS: Hospital Anxiety and Depression Scale;.