

Chinese Herbal Medicine for Symptom Management in Cancer Palliative Care

Systematic Review And Meta-analysis

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Abstract: Use of Chinese herbal medicines (CHM) in symptom management for cancer palliative care is very common in Chinese populations but clinical evidence on their effectiveness is yet to be synthesized.

To conduct a systematic review with meta-analysis to summarize results from CHM randomized controlled trials (RCTs) focusing on symptoms that are undertreated in conventional cancer palliative care.

Five international and 3 Chinese databases were searched. RCTs evaluating CHM, either in combination with conventional treatments or used alone, in managing cancer-related symptoms were considered eligible. Effectiveness was quantified by using weighted mean difference (WMD) using random effect model meta-analysis.

Fourteen RCTs were included. Compared with conventional intervention alone, meta-analysis showed that combined CHM and conventional treatment significantly reduced pain (3 studies, pooled WMD: -0.90 , 95% CI: -1.69 to -0.11). Six trials comparing CHM with conventional medications demonstrated similar effect in reducing constipation. One RCT showed significant positive effect of CHM plus

chemotherapy for managing fatigue, but not in the remaining 3 RCTs. The additional use of CHM to chemotherapy does not improve anorexia when compared to chemotherapy alone, but the result was concluded from 2 small trials only. Adverse events were infrequent and mild.

CHM may be considered as an add-on to conventional care in the management of pain in cancer patients. CHM could also be considered as an alternative to conventional care for reducing constipation. Evidence on the use of CHM for treating anorexia and fatigue in cancer patients is uncertain, warranting further research.

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Abbreviations: AMED = Allied and Complementary Medicine Database, CBM = Chinese Biomedical Databases, CENTRAL = Cochrane Central Register of Controlled Trials, CHM = Chinese herbal medicines, CI = confidence interval, NRS = Numeric Rating Scale, RCTs = randomized controlled trials, RR = relative risk, SR = systematic review, WMD = weighted mean difference, XELOX = capecitabine + oxaliplatin.

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INTRODUCTION

Cancer has been considered as a global public health issue.¹ With continuing improvement in cancer treatment, more individuals diagnosed with cancer are surviving with the disease, indicating that a large number of patients will live with cancer and cancer treatment-related symptoms.^{2,3} Symptoms that are frequently experienced by cancer patients include fatigue, paresthesias and dysesthesias, chronic pain, anorexia, insomnia, limbs edema, and constipation.⁴ Studies have found that among cancer patients, the prevalence was 60% to 90% for fatigue,⁵ around 66% for paresthesias and dysesthesias,⁶ 50% to 70% for chronic pain,⁷ around 85% for anorexia,⁸ 30% to 50% for insomnia,⁴ 31% for limbs edema,⁶ and 30% to 80% for constipation.⁹ Quality of life among cancer patients are affected when they experience 1 or more of these symptoms.³

Despite the high prevalence of these symptoms reported in cancer patients, treatments from conventional medicine are far from satisfactory. Currently, treatment options for managing fatigue are very limited. Within these few choices, adverse effects have further restricted their clinical use,¹⁰ leaving this symptom widely under-treated.¹⁰ For paresthesias and dysesthesias, although co-analgesics and antidepressants are available for controlling these symptoms, their effectiveness is not satisfactory. A substantial number of patients are not sufficiently relieved, with 10% to 15% of patients being refractory to pharmacotherapy.^{11,12} For the management of cancer-related pain, the World Health Organization analgesics ladder (non-opioids, adjuvants, and opioids analgesics) provides a stepwise relief approach.¹³ However, about 40% would continue to have

poorly controlled pain despite the treatment.¹⁴ Progestational agents and corticosteroids may be effective for anorexia, but both of them cause considerable adverse effects without improving survival.^{15,16,17} For insomnia, although benzodiazepines and nonbenzodiazepine hypnotics are often prescribed, evidence on their effectiveness among cancer patients is lacking.¹⁸ Other study has suggested that the use of sleeping pills may worsen symptoms severity and quality of life among cancer patients.¹⁸ Finally, evidence on the effect of antidepressants on improving sleep quality is mixed for cancer patients.⁴

In view of these evidence gaps in conventional medicine, the role of Chinese herbal medicine (CHM) in symptom management can be explored. There are systematic reviews (SRs) demonstrating the effectiveness of CHM as an adjuvant treatment for improving quality of life,¹⁹ increasing survival rate,²⁰ and reducing chemotherapy-induced toxicity²¹ among cancer patients. Another SR indicated mixed results for reducing pain.²² However, there are several shortcomings with regard to existing SRs. For instance, 1 SR did not reporting details on treatment prescription used in control groups as well as baseline treatment, limiting the usefulness of evidence reported.²² Another SR²¹ did not report the herbal compositions prescribed in the included trials. Although results from this SR indicated that the adjuvant use of CHM significantly reduced chemotherapy-induced toxicity,²¹ clinical usefulness of such evidence is restricted by poor reporting.

More importantly, there are no existing SRs synthesizing evidence on the effectiveness of CHM for managing common cancer symptoms of fatigue, paresthesias and dysesthesias, chronic pain, anorexia, insomnia, limbs edema, and constipation. In view of this research gap, this SR aims to summarize results from CHM randomized controlled trials (RCTs) focusing on these outcomes.

METHODS

This systematic review and meta-analysis was strictly reported according to the PRISMA checklist. Ethical approval was not necessary for this study because all the analyses were conducted based on the data retrieved from published trials.

Inclusion Criteria

We included studies according to the following criteria:

1. RCTs comparing effect of CHM, either in combination with other treatments or used alone, in managing cancer or cancer treatment-related symptoms. There is no restriction of the type of cancer diagnosis.
2. The RCT has to report the effectiveness of CHM on at least 1 of the following outcomes measured with validated instruments: fatigue, paresthesias and dysesthesias, chronic pain, anorexia, insomnia, limbs edema, and constipation. For measurement of pain, 3 validated scales (Visual Analogue Scales, Numerical Rating Scales, and Verbal Rating Scales) recommended by the Research Network of the European Association of Palliative Care²³ should be used.
3. The RCT included at least 1 CHM indexed in the 2010 China Pharmacopeia Chinese herbal medicine index.²⁴ We did not impose any restriction on the forms of CHM, with single herbs, herbal formulations, and Chinese proprietary medicines included.
4. Control group included conventional treatment, chemotherapy, radiotherapy, placebo, or no treatment.

5. RCT reported detailed information on the regimens prescribed in both treatment and control groups. Follow-up duration should also be clearly reported where applicable.

Literature Search

Five international databases and 3 Chinese databases were searched without any language restriction. International databases included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL Plus, the Allied and Complementary Medicine Database (AMED). When searching MEDLINE²⁵ and EMBASE,²⁶ specialized search filter for clinical trials were used. Chinese databases include Chinese Biomedical Databases, Wan Fang Digital Journals, and Taiwan Periodical Literature Databases. Detailed search strategies and related results were shown in Appendix 1, <http://links.lww.com/MD/A692>.

Literature Selection, Data Extraction, and Risk of Bias Assessment

Eligibility of the retrieved studies were screened and assessed according to inclusion criteria. The following data were extracted from included RCTs: 1) Basic characteristics of the RCT, name of first author, year of publication, country where the trial was conducted, eligibility criteria for participants, diagnostic criteria of 2) Information related to patients' characteristics, CHM, control interventions, and outcomes. 3) Effect size for each interested outcome and adverse effects related to CHM treatment.

The Cochrane risk of bias tool²⁷ was used to assess risk of bias of included RCTs. Risk of bias in 6 domains were assessed for each included RCT, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, and selective reporting. Based on the information provided by the trial authors, each domain was judged to have low, high, or unclear risk of bias.

Two reviewers independently selected the literature (JZ, MF), extracted the data, and assessed the risk of bias of included studies (XW, PL), with disagreement resolved by discussion and consensus. A third reviewer (VC) was consulted if disagreement cannot be resolved between the two reviewers.

Data Analysis

Relative risk (RR) and 95% confidence interval (CI) was used to express effectiveness of CHM when the outcome was dichotomous. Weighted mean difference and 95% CI was used when the outcome was continuous. Level of heterogeneity across trials was measured with I^2 statistic, with $I^2 < 25%$ considered as low level of heterogeneity, 25% to 50% as moderate level, and higher than 50% as high level.²⁸ Random effects model was used to account for variations across trials²⁹ during data synthesis.

Publication bias would be assessed using funnel plot if more than 10 trials were available for a single outcome.³⁰ The symmetry of the funnel plot would be assessed with Egger test, with a $P < 0.1$ indicating presence of publication bias. Data analyses were conducted with STATA Version 13.0 (STATA Corporation, College Station, TX), with a 2-tailed significance level of 0.05 except for test for publication bias ($P = 0.10$). The protocol of this SR has been registered in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/DisplayPDF.php?ID=CRD42015023931>).

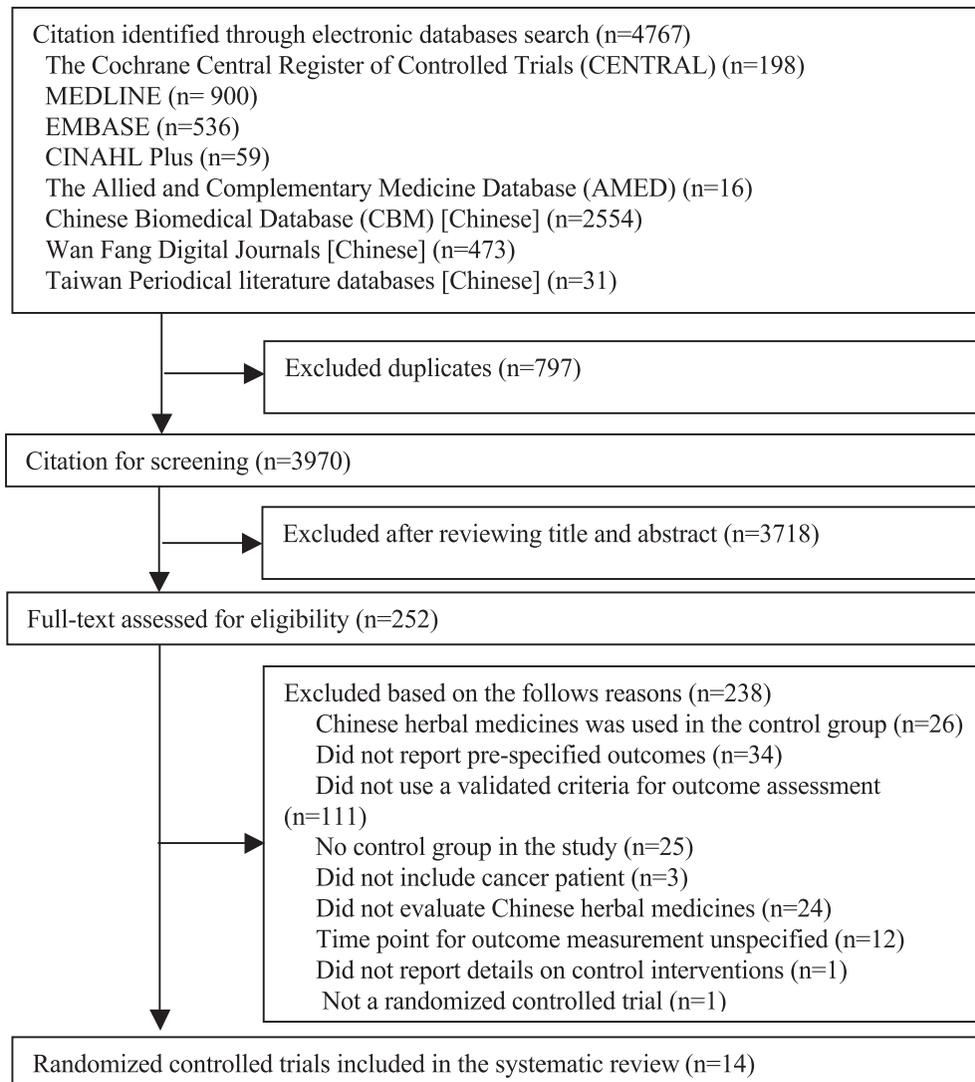


FIGURE 1. Flow chart for literature selection of randomized controlled trial on Chinese herbal medicine for symptoms management in cancer palliative care.

RESULTS

Study Selection

Electronic databases search yielded 4767 records, of which 797 duplications were excluded, and 3970 records remained for citation screening. Three thousand seven hundred eighteen citations were excluded after the screening of titles and abstracts, and 252 full texts were retrieved for eligibility assessment. Among them, 238 publications were excluded because of the following reasons: CHM was used in the control group (n = 26); did not report prespecified outcomes (n = 34); did not use a validated instrument for outcome assessment (n = 111); no control group in the study (n = 25); did not include cancer patients (n = 3); did not evaluate CHM (n = 24); time points for outcome measurement were unspecified (n = 12); did not report details on the control interventions (n = 1), not an RCT (n = 1), and did not report number of patients in each group (n = 1). As a result, 14 RCTs were included in this SR.

Detailed flow chart for literature selection can be found in Figure 1.

Characteristics of Included Studies

The 14 RCTs were published between 2006 and 2013, and all were conducted in mainland China. Majority of the included RCTs did not have any restrictions on the site of tumors (n = 8). Three only included colorectal cancer patients, the remaining 3 focused on patients with hematological malignancies, lung cancer, and breast cancer respectively. Forms of CHM included oral medications, external applications, and clyster. Details of each CHM prescription were shown in Appendix 2, <http://links.lww.com/MD/A692>.

Six RCTs^{31–36} assessed the effectiveness of CHM for constipation by directly comparing it with conventional medicine; 7 RCTs investigated the add-on effects of CHM on top of conventional medicine or chemotherapy for managing fatigue,^{37–40} pain,^{41,42} anorexia,^{40,43} and constipation⁴⁰ in cancer

TABLE 1. Basic Characteristics of Included Randomized Controlled Trials on Chinese Herbal Medicine for Symptoms Management in Cancer Palliative Care

First author, year of publication; country	Study design, sample size	Cancer site (tumor stage)	Characteristics of patients: male/female mean age (y)	Intervention in the treatment group regimen for CHM	Intervention in the treatment group	Outcome	Time of outcome assessment
Ju, 2006 ⁴¹ ; China	2-arm RCT, 124	Various types of cancer (NR)	T: 38/23, 62 (Median); C: 40/23, 62 (median)	Jia-wei-xiang-sha-lu-jun-zi decoction + fentanyl transdermal patch; once/day for 15 days	Fentanyl transdermal patch alone 25 µg/h, 15 days	Pain	Immediately after the treatment
Zhao, 2006 ³¹ ; China	2-arm RCT, 42	Hematological malignancies (NR)	T: 12/10, 43 ± 10; C: 10/10, 41 ± 9	Qing-shu particles; 8 g/time, twice/day for 10 days	Mosapride 5 mg/time, twice/day for 10 days	Constipation	Immediately after the treatment
Fu, 2006 ⁴³ ; China	2-arm RCT, 64	Lung cancer (advanced stage)	T: NR, NR; C: NR, NR	Qi-ge-kai-wei decoction + megestrol acetate tablet; twice/day for 30 days	Megestrol acetate tablet only, 160 mg/day for 30 days	Anorexia	Immediately after the treatment
Zhang, 2009 ³⁷ ; China	2-arm RCT, 64	Breast cancer (recurrent or metastatic)	T: NR, 52; C: NR, 40	Fu-zheng decoction + AT chemotherapy 30 mL, twice/day for 63 days	AT chemotherapy alone; once/day, 3 weeks as a cycle for 3 cycle	Fatigue	Immediately after the treatment
Gao, 2010 ³² ; China	2-arm RCT, 62	Various types of cancer (NR)	T: 19/23, 67.6; C: 9/11, 66.9	Yi-qi-run-chang decoction 300 mL/day for 14 days	Lactulose 15 mL/time, 3 times/day for 14 days	Constipation	Immediately after the treatment
Sun, 2010 ³⁸ ; China	2-arm RCT, 35	NSCLC, CRC (advanced stage)	T: NR, NR; C: NR, NR	Ren-shen-yang-rong decoction + chemotherapy 100 mL/time, twice/day for 2 cycles, each cycles lasted for 14–21 days	Chemotherapy only; NSCLC: combination of 2 platinum-related medicine, 21 days as 1 cycle for 2 cycles CRC: FOLFOX or FOLFIRI, 14 days as 1 cycles for 2 cycles	Fatigue	Immediately after the treatment
Gui, 2010 ³³ ; China	2-arm RCT, 70	CRC (TNM II-III)	T: 19/17, 56.2 ± 3.6; C: 16/18, 53.0 ± 4.1	Modified Bu-zhong-yi-qi decoction 300 mL/day for 14 days	Polyethylene glycol 4000 particles 10 g/time, twice/day for 14 days	Constipation	Immediately after the treatment
Lin, 2011 ³⁵ ; China	2-arm RCT, 70	Various types of cancer (TNM III-IV)	T: 19/16, 68 ± 5.14; C: 17/18, 66 ± 5.05	Chinese herbal medicine as clyster; once/day for 7 days	0.9% Normal saline 500–1000 mL as clyster; once/day for 7 days	Constipation	Immediately after the treatment
Li, 2011 ³⁴ ; China	2-arm RCT, 70	Various types of cancer (NR)	T: 19/16, 69.23 ± 0.90; C: 21/14, 70.12 ± 0.70	Jia-wei-ji-chuan-jian as clyster; once/day for 10 days	Glycerin 10 mL as clyster; once/day for 10 days	Constipation	During 14 days follow up after the treatment
Wu, 2011 ⁴⁴ ; China	2-arm RCT, 62	Various types of cancer (NR)	T: 20/11, 55; C: 18/13, 57	Radiotherapy + hyperthermia + Gui-dan-san-zi-san; treated according to the condition of the patients for 14 days	Radiotherapy alone, 30 gray/time, 10 times in 14 days	Pain	During 28 days follow up after the treatment
Wang, 2012 ⁴⁰ ; China	2-arm RCT, 40	CRC (NR)	T: 11/9, 56.1 ± 8.48; C: 11/9, 57.5 ± 9.66	Tong-tai decoction + XELOX regimen chemotherapy; 100 mL/time, twice/day for 42 days	XELOX regimen alone, capecitabine 1000 mg/m ² , oral, twice/day, from day 1 to day 14; oxaliplatin 130 mg/m ² , intravenous infusion on day 1. 21 days as a cycle for 2 cycles	Constipation, anorexia, fatigue	Immediately after the treatment

First author, year of publication; country	Study design, sample size	Cancer cite (tumor stage)	Characteristics of patients: male/female mean age (y)	Intervention in the treatment group regimen for CHM	Intervention in the treatment group	Outcome	Time of outcome assessment
Huang, 2012 ³⁹ ; China	2-arm RCT, 62	Various types of cancer (TNMIII-IV)	T: 23/9, 42.5 ± 10.6; C: 22/8, 41.6 ± 10.3	Jian-pi-xiao-ji decoction + chemotherapy 200 mL/day for 42 days	Chemotherapy alone; Esophageal: DFO; CRC: FOLFOX4, Nasopharyngeal: DF; NSCLC.		
Zhao, 2013 ³⁶ ; China	2-arm RCT, 50	Gemcitabine + Cisplatin; breast cancer: CAF or PA. 21 days as 1 cycle for 2 cycles.	Fatigue	Immediately after the treatment			
Jiang, 2013 ⁴² ; China	2-arm RCT, 63	Various types of cancer (moderate to advanced stage) CRC (advanced stage)	T: NR, NR; C: NR, NR T: NR, NR; C: NR, NR	Improved Zeng-ye-tang-jia-jian clyster; once/day for 10 days Self-developed Chinese herbal medicine formula + FOLFOX6 chemotherapy 200 mL/day for 60 days	1% to 2% soapy water clyster; once/day for 10 days FOLFOX6 chemotherapy alone; once/2 weeks, 2 weeks as 1 cycle for 4 cycles	Constipation Pain	Immediately after the treatment Immediately after the treatment

AT = chemotherapy = Epirubicin + Taxol, C = control, CAF = Cyclophosphamide + Pirarubicin + 5-Fluorouracil, CRC = colorectal cancer, DF = Cisplatin + 5-Fluorouracil, DFO = Cisplatin + 5-Fluorouracil + Leucovorin, XELOX = Capecitabine + Oxaliplatin, FOLFIRI = 5-Fluorouracil + Leucovorin + Irinotecan, FOLFOX = 5-Fluorouracil + Leucovorin + Oxaliplatin, FSI = Fatigue Symptom Inventory, PA = Cisplatin + Pirarubicin, RCT = randomized controlled trial, NR = not reported, NSCLC = non-small cell lung cancer, T = treatment, TNM = tumour-node-metastasis stage.

patients; the remaining RCT⁴⁴ compared the combination of Gui-dan-san-zi-san, hyperthermia and radiotherapy with radiotherapy alone in reducing pain among cancer patients. Treatment durations range from 7 to 60 days, with the majority of them assessed outcome immediately after completion of CHM treatment, with only 2 RCTs^{35,44} followed up the patients after the treatment ended. Details were seen in Table 1.

Risk of Bias of Included RCTs

All the included RCTs were published in Chinese and provided limited information regarding risk of bias. Although all RCTs stated that patients were randomly allocated to treatment and control groups, only 4 of them described how the random sequences were generated and were judged to have low risk of bias for sequence generation. One of the 14 RCTs mentioned the use of sequentially numbered, opaque, and sealed envelope for allocation concealment and hence judged to have low risk of bias. The remaining 13 were judged to have unclear risk of bias as no information about allocation concealment were provided. Thirteen and 8 RCTs were judged to have high risk of bias for blinding of participants and personnel, and blinding of outcome assessments, respectively. The remaining 1 and 4 RCTs were judged to have unclear risk of bias for blinding of participants and personnel, and blinding of outcome assessments, respectively. On the other hand, all the included RCTs had low risk of bias for incomplete outcome data and selective reporting for our interested outcomes. Details are presented in Table 2.

Effectiveness of CHM for Symptom Management for Cancer Palliative Care

Pain

Three RCTs reported results on pain relief (Figure 2). Changes in pain severity were measured with Numeric Rating Scale in these 3 studies. One RCT⁴² only included advance colorectal cancer patients while the remaining 2 RCTs^{41,44} included patients with various types of advanced cancer. Meta-analysis of these trials showed that, combined CHM and conventional treatment significantly reduced pain score as compared with conventional medicine alone (pooled WMD: -0.90, 95% CI: -1.69 to -0.11, I² = 87.7%). Significant heterogeneity was observed, which may account for by the differences in CHM formulae, treatment duration, cancer types, and baseline treatment. Subgroup analysis was not conducted because of the limited number of studies. Sensitivity analysis based on rigor was not conducted as all the 3 RCTs were judged to have unclear risk of bias for sequence generation.

One⁴¹ of the 3 RCTs reported adverse events. As compared to fentanyl transdermal patch alone, patients who used additional Jia-wei-xiang-sha-liu-jun-zi decoction had similar occurrence in vomiting, dizziness, drowsiness, abdominal discomfort, and skin allergy.

Constipation

Seven RCTs investigated the effect of CHM in managing constipation (Table 3). One RCT⁴⁰ compared Tong-Tai decoction plus chemotherapy to chemotherapy alone. No difference was found in terms of the proportion of patient achieving satisfactory relief between the 2 groups. The remaining 6 RCTs³¹⁻³⁶ compared CHM to conventional medications in managing constipation. Results showed that CHM and conventional medications had similar effect in reducing constipation.

TABLE 2. Risk of Bias of Included Randomized Controlled Trials on Chinese Herbal Medicine for Symptoms Management in Cancer Palliative Care

First author, year of publication	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Ju, 2006 ⁴¹	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB. Lost to follow-up was 1/61 = 1.64% in treatment group and 3/63 = 4.76% in control group	Low RoB [#]
Zhao, 2006 ³¹	Unclear RoB*	Unclear RoB [†]	Unclear RoB. No mention about this domain. Based on the information provided by the article, we cannot decide whether blinding of participants and personnel is possible	Unclear RoB	Low RoB [†]	Low RoB [#]
Fu, 2006 ⁴³	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]
Zhang, 2009 ³⁷	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]
Gao, 2010 ³²	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]
Sun, 2010 ³⁸	Low RoB. Random sequence was generated with computer-generated random number	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB. Lost to follow-up were 3/18 = 16.67% in treatment group, 2/17 = 11.76% in control group. The difference is less than 10%.	Low RoB [#]
Gui, 2010 ³³	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]
Lin, 2011 ³⁵	Low RoB. Patients were randomized according to random number table	Unclear RoB [†]	High RoB [‡]	Unclear RoB	Low RoB [†]	Low RoB [#]
Li, 2011 ³⁴	Low RoB. Random sequence was generated with computer-generated random number	Low RoB. Random sequences were stored in sequentially numbered, opaque and sealed envelope	High RoB [‡]	Unclear RoB	Low RoB [†]	Low RoB [#]
Wu, 2011 ⁴⁴	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]
Wang, 2012 ⁴⁰	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]
Huang, 2012 ³⁹	Low RoB. Patients were randomized according to random number table	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]
Zhao, 2013 ³⁶	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	Unclear RoB	Low RoB [†]	Low RoB [#]
Jiang, 2013 ⁴²	Unclear RoB*	Unclear RoB [†]	High RoB [‡]	High RoB [§]	Low RoB [†]	Low RoB [#]

CHM = Chinese herbal medicine, RoB = risk of bias.

* The article stated that patients were randomly assigned to treatment and control groups.

† The article did not mention any information about allocation concealment.

‡ The CHM was used as an additional treatment, it is impossible to blind participants and personnel unless a placebo was used.

§ Outcome assessors were the patients.

|| No information on who are the outcome assessors.

No lost to follow-up.

All Interested outcome was reported.

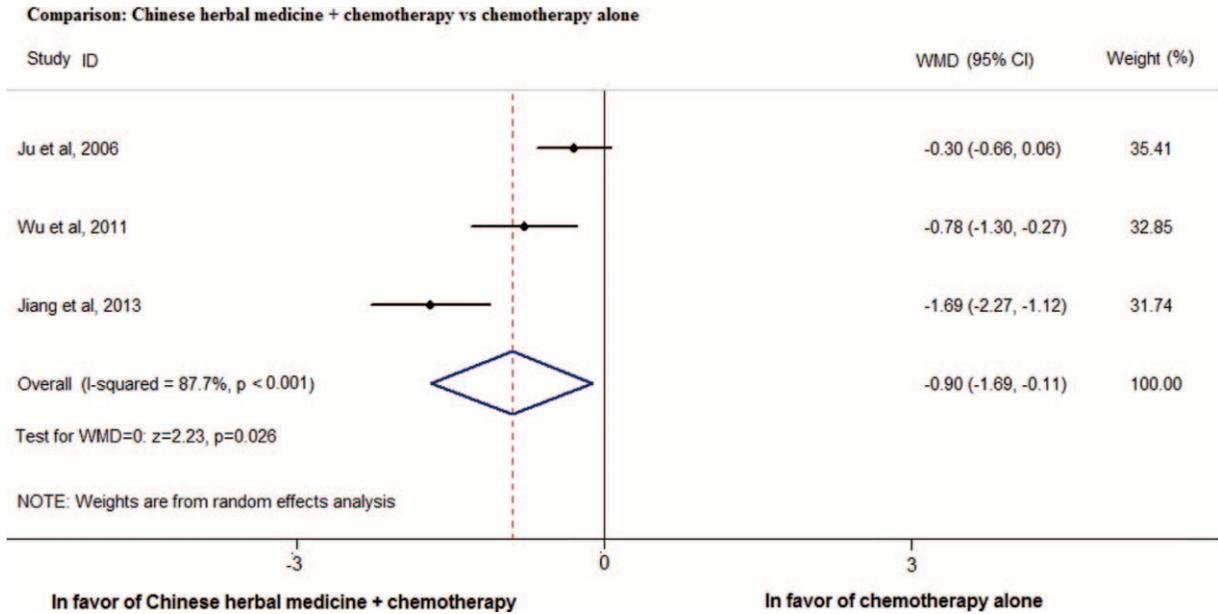


FIGURE 2. Meta-analysis on the additional use of Chinese herbal medicine for reducing pain score in cancer patients (Comparison: Chinese herbal medicine + chemotherapy vs chemotherapy alone).

Data were not pooled because of the differences in the definition of satisfactory relief among included studies.

Three of the 7 RCTs mentioned adverse events. Two^{31,33} of them reported no adverse events in both treatment and control groups except for mild abdominal discomfort. No additional treatment was required to manage this event. The remaining one⁴⁰ reported that no significant difference between Tong-tai decoction plus XELOX (capecitabine + oxaliplatin) and XELOX alone group with respect to the incidence of chemotherapy-induced toxicity among colorectal cancer patients.

Fatigue

Four RCTs reported reduction of fatigue (Table 3). Three RCTs^{38–40} reported no significant difference between combined use of CHM and chemotherapy versus chemotherapy alone for reducing fatigue. The remaining RCT³⁷ compared the combination of chemotherapy (Epirubicin plus Taxol) and Fu-zheng decoction to chemotherapy alone in breast cancer patients. After 9 weeks of treatment, the combined treatment group showed significantly lower Fatigue Symptom Inventory score than the chemotherapy alone group (MD: -18.62, 95% CI: -24.08 to -13.16). Because of the heterogeneity in outcome measurement approach, data were not pooled among included RCTs.

Three of the 4 RCTs provided information on adverse effect. Two studies^{37,39} reported that the CHM and chemotherapy-combined treatment group had significantly lower incidence in chemotherapy-induced toxicity including leucopenia, neurotoxicity, and nausea and vomiting. One³⁸ reported that there was no adverse event observed.

Anorexia

Two RCTs reported evidence on CHM for treating anorexia in cancer patients (Table 3). One⁴³ compared Qi-ge-kai-wei decoction plus megestrol acetate versus megestrol acetate alone in advanced lung cancer patients. Although a higher

proportion of patients in the combined treatment group reported improvement (93.8% versus 87.5%), the difference was not of statistical significance. The other RCT⁴⁰ found that the combined use of Tong-tai decoction and chemotherapy showed more improvement than chemotherapy alone in advanced colorectal cancer patients (55.0% versus 45.0%), but again no significant difference was found. Considering the clinical heterogeneity of these 2 studies, and different criteria used for defining satisfactory relief, meta-analysis was not conducted.

One study⁴³ reported adverse effects. Although the CHM and conventional medicine combined treatment group showed fewer incidence in alanine aminotransferase increment, for thrombotic vasculitis, edema, high blood pressure or blood glucose, constipation, heart failure, and difficulty in breathing, the difference was not significant.

DISCUSSION

This SR summarized evidence on the effectiveness of CHM for the management of pain, constipation, fatigue, and anorexia among cancer patients. Fourteen RCTs with a total of 878 cancer patients were included in this SR. Our results showed that the combined use of CHM and conventional medicine slightly relieved pain when compared with conventional treatment alone. CHM alone showed similar effectiveness with conventional medicine in managing constipation. The additional use of Fu-zheng decoction can reduce fatigue in breast cancer patients who are receiving chemotherapy. Current evidence did not show any superior effect on combined use of CHM and conventional medicine for anorexia when compared to conventional medicine alone. On safety, patients in the combined group generally showed lower or similar occurrence of adverse events when compared with patients in conventional medicine only group. We did not identify any eligible RCT providing evidence on CHM for managing paresthesias and dysesthesias, insomnia and limbs edema in cancer patients.

TABLE 3. Effectiveness of Chinese Herbal Medicine Symptoms Management in Cancer Palliative Care

First author and year of publication	Comparison	Outcome assessment	Treatment (No. of patients)		Control (No. of patients)		Effective size (95% CI)
			Effective	Total	Effective	Total	
Constipation Zhao, 2006 ³¹ Gui, 2010 ³³	Qing-shu particles vs mosapride Modified bu-zhong-yi-qi decoction vs PEG4000	Effective rate	17	22	17	20	RR: 0.95 (0.58, 1.56)
			33	36	26	34	RR: 1.10 (0.75, 1.61)
Gao, 2010 ³² Li, 2011 ³⁴	Yi-qi-run-chang vs lactulose Jia-wei-ji-chuan-jian as clyster vs glycerin as clyster	Effective rate	35	42	16	20	RR: 1.02 (0.66, 1.59)
			31	35	22	35	RR: 1.22 (0.80, 1.84)
Lin, 2011 ³⁵	Chinese herbal medicine as clyster vs normal saline as clyster	Effective rate	33	35	21	35	RR: 1.29 (0.85, 1.96)
Wang, 2012 ⁴⁰	Tong-tai decoction + XELOX vs XELOX alone	Effective rate	11	20	11	20	RR: 1.00 (0.51, 1.96)
Zhao, 2013 ³⁶	Improved Zeng-ye-tang-jia-jian clyster vs soapy water clyster	Effective rate	23	25	17	25	RR: 1.18 (0.74, 1.90)
Fatigue Zhang, 2009 ³⁷	Fu-zheng decoction + AT chemotherapy vs AT chemotherapy alone	FSI score (130 score in total)	54.20 (11.50)*	30	72.82 (10.67)*	34	MD: -18.62 (-24.08, -13.16)
			11	15	3	15	RR: 2.54 (0.82, 7.83)
Sun, 2010 ³⁸	Ren-shen-yang-rong decoction + chemotherapy vs chemotherapy alone	Effective rate	16	20	6	20	RR: 1.93 (0.87, 4.25)
Wang, 2012 ⁴⁰	Tong-tai decoction + XELOX vs XELOX alone	Effective rate	19	32	11	30	RR: 1.39 (0.75, 2.58)
Huang, 2012 ³⁹	Jian-pi-xiao-ji decoction + chemotherapy vs chemotherapy alone	Symptom free rate	30	32	28	32	RR: 1.04 (0.71, 1.51)
Anorexia Fu, 2006 ⁴³	Qi-ge-kai-wei decoction + megestrol acetate tablet vs megestrol acetate tablet alone	Effective rate	11	20	9	20	RR: 1.14 (0.56, 2.35)
Wang, 2012 ⁴⁰	Tong-tai decoction + XELOX vs XELOX alone	Effective rate					

AT chemotherapy=Epirubicin+Taxol, CI=confidence interval, FSI=Fatigue Symptom Inventory, PEG4000=Polyethylene glycol 4000 particles, RR=relative risk, XELOX=Capecitabine + Oxaliplatin.

* Mean and standard deviation of fatigue symptom inventory score.

The role of CHM in symptom management of cancer patients has gained increasing attention. Based on previous SRs, no firm conclusion has been reached on using CHM for the managing pain^{45,46} and fatigue,⁴⁵ because of the lack of “rigorous clinical trials.” In current SR, we only included RCTs which reported detailed methodological details. Results from our study suggested that clinicians may consider additional use of CHM on top of conventional care for better management of pain and fatigue, of which both are undertreated in clinical practice.^{47,48} CHM could be considered as an alternative choice for treating constipation in cancer patients as it has similar effectiveness as conventional medicine.

All included RCTs generally had short treatment duration, with 2 of them shortly followed up the patients (14–28 days) after treatment. That raises the question of whether treatment and follow-up durations were long enough for CHM to demonstrate its beneficial effects.²² Future RCTs on this area should consider appropriate treatment and follow-up duration based on expert consensus.

All the included RCTs were published in Chinese and we have observed a lack of compliance to the Chinese version CONSORT statement.⁴⁹ Poor reporting is the major contributor to uncertainties in our risk of bias assessment. For example, although all the studies stated themselves as RCTs, more than half of them (10/14) did not provide information on how random sequences were generated. Also, only 1 RCT mentioned about allocation concealment. Blinding is another key limitation to the evidence base as all the included outcomes were measured in a subjective manner.⁵⁰ As a result, we cannot exclude the possibility of overestimating or underestimating the effectiveness of CHM.⁵¹ That said, all included studies had good performance in preventing bias related to incomplete outcome data and selective outcome reporting.

Among RCTs that reported adverse event outcomes, results were consistent with other reviews,^{22,45} which indicated that CHM is generally safe with low risk of incurring serious adverse effect. However, safety issue did not receive attention in 6 of the 14 RCTs, which indicates the need of paying more attention on safety surveillance in future trials.²²

During literature selection, more than 100 RCTs were excluded due to not using validated instrument in outcome assessment. This phenomenon is consistent with findings from other researchers.²² Self-developed outcome assessment criteria were often used in these studies without prior validation, and some of them did not even provide information on the criteria they used. That could be considered as a huge waste of research resources as results from these studies cannot generate any useable or meaningful clinical evidence. Future RCTs are strongly suggested to use internationally recognized and validated scales to measure outcomes, so as to facilitate the comparison with similar studies, and enhance usefulness of the research findings.

Readers should be noted that all the included RCTs were conducted in Chinese population under Chinese health care settings, which may limit the generalizability of results. Because of the limited number of included studies, we did not assess the publication bias in this SR, so we cannot determine whether such bias exist or not.

In conclusion, CHM may be considered as an add-on to conventional medicine in the management of pain in cancer patients. CHM could also be considered as an alternative to conventional medicine for reducing constipation. Evidence on the use of CHM for treating anorexia and fatigue in cancer patients is uncertain, warranting further research. Future RCTs

should improve in the following areas: 1) choosing an internationally recognized and validated instruments for outcome measurement; 2) reporting detailed safety outcomes; and 3) implementing strict adherence to the CONSORT reporting statements.^{49,52}

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