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Review

Chinese Herbal Medicine for Chemotherapy Induced Gastrointestinal Side Effects: A Systematic Review of Randomized Controlled Trials

Chung-Wah Cheng[a,b], Zhao-Xiang Bian[a,b]*, Li-Dan Zhong[a,b], Justin CY Wu[c], Zhi-Xiu Lin[d], Eric TC Ziea[e] and Vivian CW Wong[e]

[a]Hong Kong Chinese Medicine Clinical Study Centre, Hong Kong Baptist University, Hong Kong SAR
[b]School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR
[c]Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR
[d]School of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong SAR
[e]Chinese Medicine Department, Hospital Authority, Hong Kong SAR
*Correspondence: Prof. Zhao-Xiang Bian, 3/F, Clinical Division, Jockey Club School of Chinese Medicine Building, 7 Baptist University Road, Kowloon Tong, Hong Kong, Tel: 852-34112905, Fax: 852-34112929, *E-mail:* bzxiang@hkbu.edu.hk

ABSTRACT

Objective: To determine how safe and effective Chinese Herbal Medicine (CHM) is in alleviating the nausea, vomiting, oral ulceration, diarrhea and constipation for cancer patients with chemotherapy.

Methods: *Data sources*: A systematic review of Chinese and English articles using Ovid SP, CNKI, VIP Database and Traditional Chinese Medicine Database System. *Study selection*: Only randomized controlled trials (RCTs) for the prevention or treatment of any one of gastrointestinal side effects, namely nausea, vomiting, oral ulceration, diarrhea and constipation, of CHM with or without western medicine (WM) vs WM, placebo or no treatment were included. *Data Extraction*: Independent extraction of articles was first performed by four medical students using predefined data fields. Then, all data, including study quality indicators, was checked by two authors.

Results: Eighty-six RCTs involving 7076 cancer patients were found and analyzed in this review. Because of the heterogeneity of study design and low overall methodological quality, only descriptive summaries were performed. Beneficial effects were found in some CHM interventions, regardless of being taken alone or taken with WM. Moreover, none of serious adverse effect was reported. However, same intervention had not been repeatedly investigated by different research teams.

Conclusions: Implications of the analysis support the efficacy and safety of CHM for the management of gastrointestinal side effects. However, definite clinical recommendation for particular CHM intervention still cannot be made due to low methodological quality of included studies and lack of duplicated verification. Further large scale and high quality RCTs on the same CHM interventions are suggested.

Key words: Chinese herbal medicine, Systematic review, Chemotherapy induced side effects, Gastrointestinal diseases
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Introduction

Chemotherapy is an effective treatment for cancer; it effectively reduces the transformation, proliferation and progression of the malignant cells[1]. However, its toxicity makes all rapidly proliferating tissues at risk, especially the epithelium of the gastrointestinal tract. Traditional Chinese medicine (TCM) is a popular complementary and alternative medicine (CAM) among cancer patients. From a systematic review published in 2011 combining the studies from 18 countries, up to 40% cancer patients currently use of CAM and it is reasonable to assume this growth continues[2].

While herbal medicines show benefits in terms of inducing cancer cells' apoptosis, preventing metastasis, direct palliation of symptoms, boosting the immune system, increasing patients' appetite and facilitating general recovery[3,4], using Chinese herbal medicine (CHM) to reduce the side effects of chemotherapy have been discussed in a few systematic reviews. However, these reviews are each specific for a particular type of carcinoma[5], e.g. Zhang MM et al review for breast cancer[6] and Wu TX et al review for colorectal cancer[3], and none of them concentrates on the gastrointestinal symptoms. How CHM acts, when used with chemotherapy, or how CHM can be integrated into routine cancer treatment in order to reduce chemotherapy's side effects have not been well studied. Nevertheless, these questions are understandably of urgent concern to clinical oncologists and patients alike[7].

In this review, we hope to examine whether CHM can prevent or treat chemotherapy induced nausea, vomiting, oral ulceration, diarrhea and constipation among cancer patients. We review randomized controlled trials (RCTs) that assess the efficacy and safety of CHM [CHM alone or CHM plus western conventional medicine (WM)] against with WM, another form of CAM, placebo or no treatment. These results constitute evidence of the value of integrative

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medicine in cancer treatment and argue for undertaking further, more thorough research on this topic in the near future.

Methods

Criteria for considering studies for this review

Inclusion criteria: RCTs, including cross-over trials, for the prevention or treatment of chemotherapy induced nausea, vomiting, oral ulceration, diarrhea or constipation with CHM among cancer patients were considered. Participants of any age, gender and cancer type were considered. The CHM remedies could be a single herb (or extract from a single herb) or compound formulation, irrespective of preparation (e.g. decoction or granule) and mode of administration (e.g. oral, cutaneous or injection). CHM could be given during and/or after chemotherapy in any dosage and regimen. Interventions could be for the following comparisons: 1) CHM (single herb or compound formulation) versus placebo; 2) CHM versus no treatment; 3) CHM versus another form of CAM; 4) CHM versus WM (s); 5) CHM plus WM(s) versus WM(s) alone.

Exclusion criteria: Studies comparing one kind of CHM to another CHM, or CHM plus one form of intervention to another form of intervention were excluded. Studies with primary outcome measure not specified on nausea, vomiting, oral ulceration, diarrhea and constipation were also excluded.

Primary outcome was the overall effective rate for the CHM interventions in alleviating the nausea, vomiting, oral ulceration, diarrhea and constipation for cancer patients with chemotherapy. Secondary outcomes were the occurrence rate or control rate of these gastrointestinal side effects, and reported adverse effects (AEs).

Search methods for identification of studies

All relevant published and unpublished studies in Chinese or English were identified by searching the following databases. The last search was run in February 2012.

1) Ovid SP, which included the databases of Cochrane DSR (Cochrane Database of Systematic Reviews), ACP Journal Club, DARE (Database of Abstracts of Reviews of Effects), CCTR (Cochrane Central Register of Controlled Trials), CMR (Cochrane Methodology Register), HTA (Health Technology Assessment), NHSEED (NHS Economic Evaluation Database), AMED (Allied and Complementary Medicine), Embase, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R). Detailed search strategy is presented in Table 1.

2) The common search strategy for CNKI (China National Knowledge Infrastructure), Chinese Science and Technology Documents Database (VIP Database) and Traditional Chinese Medical Database System (TCM Database System) is presented in Table 2.

Data collection and analysis

The title and abstract of the search results were scanned, and full articles for all potentially relevant trials were retrieved.

Table 1. Search Strategy for Ovid SP (advanced Ovid search).

#1	chemotherapy	#2	nausea
#3	vomiting	#4	mucositis
#5	anorexia	#6	diarrhea
#7	constipation	#8	abdominal pain
#9	bloating	#10	OR/ #2 to #9
#11	#1 AND #10	#12	Chinese herbal medicine
#13	Chinese herb* medic*	#14	Chinese medic* herb*
#15	herbal medicine	#16	herb* medic*
#17	medic* herb*	#18	herbal
#19	herb*	#20	botanical
#21	traditional Chinese medicine	#22	Chinese medicine
#23	TCM	#24	OR/#12 to #23
#25	randomi*ed controlled trial	#26	controlled clinical trial
#27	random allocation	#28	double-blind method
#29	single-blind method	#30	clin* NEAR trial*
#31	(singl* or doubl* or trebl* or tripl*) NEAR (blind* or mask*)	#32	placebo
#33	placebo*	#34	random*
#35	OR/ #25 to #34	#36	#11 AND #24 AND #35

A data extraction form was used to extract data on: (1) study design; (2) characteristics of trial participants (including age, gender, cancer origin, regimen of chemotherapy); (3) type of intervention (including name of basic formula, form, quality control, available modification); (4) type of outcome measure (including effective rate for preventing and treatment of chemotherapy induced nausea, vomiting, oral ulceration, diarrhea and constipation, occurrence rate and control rate of these gastrointestinal side effect, and reported AEs. Meta-analysis was only performed where individual trial compared same CHM intervention with same control intervention using Review Manager 5. Mean difference with 95% confidence interval was used for continuous data while relative risks with 95% confidence interval was used for binary data. The reasons for the exclusion of studies were recorded.

Table 2. Common Search Strategy for CKNI, VIP Database and TCM Database.

Abstract / Text word contains "cancer (Ai)" OR "carcinoma (Zhongliu)"
AND
Abstract / Text word contains "chemotherapy (hualiao)"
AND
Text word contains "nausea (E'xin)" OR "vomiting (Outu)" OR "mucosal ulceration (Nianmo Kuiyang)" OR "oral ulcer (Kouqiang Kuiyang)" OR "loss of appetite (Nacha)" OR "diarrhea (Fuxie)" OR "constipation (Bianmi)" OR "abdominal pain (Futong)" OR "abdominal bloating (Fuzhang)" OR "stomach flatulence (Weizhang)"
AND
Text word contains "Chinese herbal medicine (Zhongcaoyao)" OR "herb (Caoyao)" OR "botanical medicine (Zhiwuyao)" OR "Chinese proprietary medicine (Zhongchengyao)" OR "Chinese medicine (Zhongyiyao / Zhongyao / Zhongyi)"
AND
Text word contains "randomization (Suiji)" OR "RCT" OR "randomized" OR "randomization" OR "random" OR "randomly"

Note: The Chinese pinyin is embedded in brackets. CKNI: China National Knowledge Infrastructure; VIP Database: Chinese Science and Technology Documents Database; TCM: Traditional Chinese Medicine Database System.

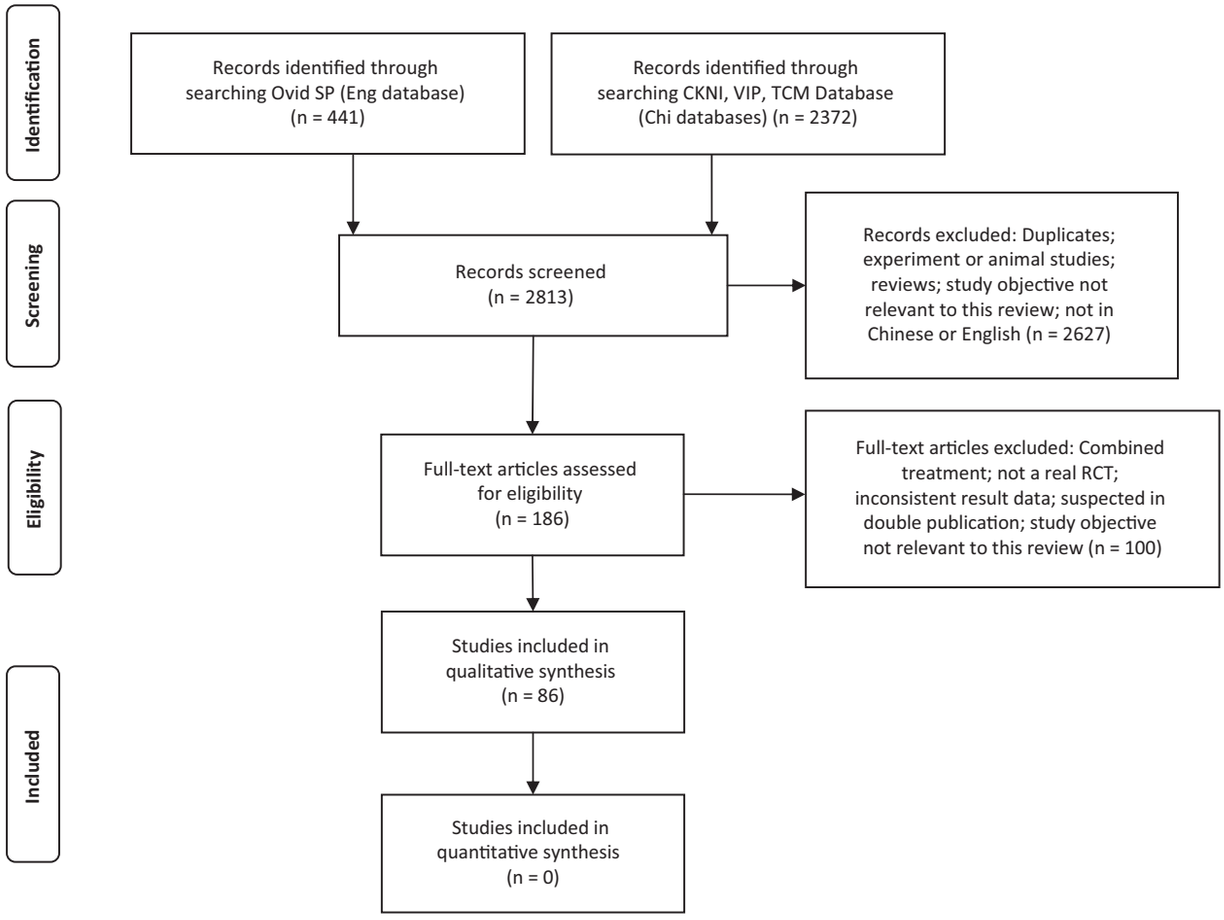

Figure 1. Flow diagram for literature search.

All data were extracted by four medical students and checked by Cheng CW and Bian ZX. Any disagreement was resolved by discussion.

The validity of each eligible study with adequacy of randomization, allocation concealment, blinding and reporting the extent of loss to follow-up was assessed by Cheng CW and Bian ZX independently. The general methodological quality was evaluated with Jadad score (0–5 points), which was a three-point questionnaire targeting on the issues of randomization, blinding and patient flow (withdrawals/dropouts). For which, study scored 3 or more was classified as high quality[8].

Results

Description of studies

The initial search identified 2813 articles. After reviewing the titles and abstracts, 2627 articles were excluded because they were duplicates, experimental or animal studies, reviews, chemotherapy complementary with radiotherapy, in language other than Chinese or English, or they had a study objective not relevant to this review. A total of 186 articles, including three in English, were retrieved for further assessment. Of these, 80 studies were excluded because they were on comprehensive treatments, e.g. CHM with acupuncture comparing with conventional medicine[9], comparing of two CHM interventions[10], or not a true randomized controlled trial[11]. Study objectives not specific on a particular gastrointestinal side effects were also excluded. After further analysis of the results of studies, we found that 12 had inconsistent or incomplete results data[12-23], two were inappropriately analyzed[24,25] and six were suspected of double publication[26-31], so all of these were excluded. The screening process is summarized in Figure 1.

For the 86 included RCTs, except one study conducted in Japan and published in English[32], all were implemented in China and published in Chinese medical journals. They included, in total, 7076 subjects with range of sample size from 30[33,34] to 217[35], and the median sample size was 76. About 80% (69/86) of studies had recruited patients with different organs of cancer origins, while only ten studies investigated the efficacy and safety of CHM interventions for gastrointestinal side effects induced by a single regimen (treatment plan) of chemotherapy[32,36-44]. Seven studies were of cross-over design[34,45-50]. Only one study used placebo control[51], while three compared with no treatment[32,41,52]. Forty-eight studies compared CHM with WM and two studies for constipation compared CHM with honey

water[53] and crude fiber diet[50]. Thirty-four studies compared the combined effects of CHM and WM with WM alone. Three out of 86 studies had three study arms; these were Niu DL et al[54], Zhang KJ et al[55] and Hou FJ et al[52]. Approximately 70% (58/86) of the CHM interventions were in decoction form; of these, 25 were modified during the treatment process according to the patient symptoms and/or Chinese medicine patterns. Other forms of interventions included granules (5/86), gargle (5/86), plaster (4/86), pills (4/86), solution (3/86), capsule (2/86), powder (2/86), tea (2/86), and CHM ice cube (1/86). However, none of studies had reported the quality control of CHM interventions used, in terms of the active ingredients of crude herbs, and any contamination with heavy metals, toxic elements, microbes and pesticide residue. Besides, only five studies declared informed consent were sought from patients before the commencement of studies[32,43,44,56,57]. A table of summary is presented in Additional File 1.

Risk of bias in included studies

The general methodological quality of included studies was poor. Most studies (72/86) only scored 1 point in Jadad scale, while 18 scored 2 points (Table 3). The studies of Liang YJ et al[58] and Mori K et al[32] were the only studies scored 3 points. Although all claimed to be randomized, only 14 used an objective means of allocating participants. Specifically, two[59,60] stated used the SAS software; nine[32,41,57,61-66] used random number or random number table; and three[36,58,67] used manual randomization techniques (e.g. drawing sticks). None of them described how the randomization results were concealed. Therefore, the risk of selection bias is possibly high.

As for blinding, the Long FF study[53] was the only one declaring to be single blind, while Zhou X study[51] was the one with placebo control. However, none of them reported the details about who was blinded or how the allocation of treatment was masked. Therefore, the performance and detection bias were unknown and possibly high. Similarly, the risk of attrition bias is possibly high, as only eight studies[32,43,45,48,50,58,68,69] stated that all patients had completed the treatment courses and/or follow-ups; while none of the others described any withdrawal, failure to follow-up or whether intention-to-treat (ITT) or per-protocol (PP) analysis was adopted.

Furthermore, none of studies had made the registration and uploaded the protocol, while many of them had not clear stated the selection rationale of primary and secondary endpoints. Therefore, the risk of outcome reporting bias was possibly high. Other potential bias included the early termination of Mori et al study[32], after the achievement of statistically significant results in the interim evaluation.

Table 3. Methodological quality assessment with Jadad Scale.

	No. of studies
Checklist Item (1 point each)	
– Described as randomization	86
– With appropriate method for randomization	14
– Described as double-blind	0
– With appropriate method for double-blinding	0
– With description of withdrawals and dropouts	8
Jadad Scale calculation	
1 pt	66
2 pts	18
3 pts	2

Note: Study scored of 3 or more was classified as high-quality.
As all non-randomized studies were excluded and none of included studies were double-blind, items of score deduction for inappropriate methods for randomization and double-blinding were eliminated.

Effects of interventions

The effects of interventions were determined on the basis of primary outcomes of included studied. For those did not clearly define, the first reported outcome measure was selected. Because study design, intervention, and outcome assessment were so heterogeneous, and because the methodological quality of all included studies was so low, only descriptive summaries of nausea and vomiting, oral ulceration, diarrhea and constipation were performed.

1. Nausea and/or vomiting

Sixty-four studies evaluated the effects of CHM for the treatment of chemotherapy induced nausea and/or vomiting. Most studies assessed efficacy by using the 5-grade system of the World Health Organization (WHO), either as it was or with modifications. In this system, the acute (≦24 hours) and sub-acute/delayed toxic effects (>24 hours) were graded as follows: Grade 0 for none, Grade I for nausea, Grade II for transient vomiting, Grade III for vomiting requiring therapy and Grade IV for intractable vomiting[70]. For the definitions of outcome measures, complete response (CR) represented the disappearance of symptom (Grade 0), while partial response (PR) represented a significant improvement (Grades I & II). The overall effective rate was the sum of complete response and partial response (CR+PR). For 4-grade symptom scoring system (none, mild, moderate and severe), the overall effective rate was the sum of patients with no or mild symptoms. A table of summary about the efficacy of included studies on nausea and/or vomiting is presented in Table 4.

Chinese Herbal Medicine vs Placebo / No Treatment. Two studies compared CHM with placebo or no treatment. Zhou X[51] reported brewing Tea of Milkvetch and Wolfberry (Huangqi Gouqi Tea) during chemotherapy had higher effective rate (93.1%) than those taking placebo (21.4%), with $p<0.05$. For the Wu BQ study[41] comparing Antiemetic Decoction (Zhitu Tang), comprising of Ginseng (Renshen), Atractylodes (Baizhu), Poria (Fuling), Liquorice (Gancao), Pinellia (Banxia), Magnolia (Houpo), Immature Bitter Orange (Zhishi), Tangerine Peel (Chenpi), Persimmon Calyx (Shidi), Clove (Dingxiang), Jujube (Dazao) and Ginger (Shengjiang), with no treatment, the occurrence of nausea and vomiting (Grade 1-4) had been deducted with almost 25%, with $p<0.05$. Hence, both studies showed that the CHM interventions were more effective than placebo and no

Table 4. Efficacy of included studies on nausea and/or vomiting.

	CHM (no. of study)			CHM plus WM (no. of study)		
Control	**Superior**	**Comparable**	**Inferior**	**Superior**	**Comparable**	**Inferior**
Placebo / No treatment	2	0	0	0	0	0
Ondansetron	7	9	1	9	4	0
Metoclopramide	8	4	0	4	0	0
Granisetron	2	1	0	10	0	0
Azasetron / Tropisetron	0	0	0	3	1	0
Integrated conventional treatment	0	1	0	5	0	0

Note: CHM: Chinese herbal medicine. WM: Western conventional medicine. *Some studies had more than one primary endpoint. *Only studies compared with the above control were listed out.

treatment for the management of chemotherapy induced nausea and vomiting.

Chinese Herbal Medicine vs Ondansetron. Seventeen studies compared CHM interventions, including one in three arms[55], with ondansetron. Vomiting Tranquilizing Granules (Ouning Fang), comprising of Ginseng (Renshen), Liquorice (Gancao), Hematitum (Daizheshi), Pinellia (Banxia) and Poria (Fuling), from the team of Chen JX and Yao ZP[47,48] and Antiemetic Mixture (Ziou Mixture), comprising of Gingseng (Renshen), Inula (Xuanfuhua), Pinellia (Banxia), Ginger (Shengjiang), Jujube (Dazao), Liquorice (Gancao), Goldthread (Huanglian), Evodia (Wuzhuyu) and Hematitum (Daizheshi), from Wang DS group[71,72] were evaluated twice, while the basic formulation of both Wang YF et al and Xu J et al studies[45,46] were modified of a well-known formula, Decoction of Inula and Hematitum (Xuanfu Daizhe Tang). However, none of them were equivalent in terms of formulation, individualized modification or dosages of each constituent herb. Twelve studies[45-48,55,61,71-76] reported that the overall effective rates of CHM varied from 63.3% to 94.0% while the efficacy of ondansetron varied from 50% to 92.0%. Except for five studies[46,71,72,74,75] showing that CHM interventions were statistically more effective than ondansetron, the others showed that CHM were comparable to ondansetron for the prevention or treatment of nausea and/or vomiting ($p>0.05$). Two studies listed out the severity of symptoms and/or degrees of improvement as outcome measure. One study showed that Warming Gallbladder Decoction (Wendan Tang)[77] was more effective than ondansetron for delayed vomiting, while results for Zhou XJ et al were unclear because statistical analysis had not been done[33]. Three studies reported the efficacy of CHM for both acute and delayed gastrointestinal symptoms. Studies of Guo ZT et al[65] and Zhong Y et al[78] showed significant benefit for delayed nausea and vomiting, but not for the acute stage; while that of Wang ZR[63] showed relatively comparable effects on prevention of nausea and vomiting in a five day follow-up.

Nine studies investigated the effect of taking CHM interventions plus ondansetron with ondansetron alone. Four studies used Decoction of Inula and Hematitum (Xuanfu Daizhe Tang) or its modification as the CHM intervention[34,49,79,80]; however, none of them were equivalent. Seven studies[34,49,80-84] reported the overall effective rates, for which treatment groups varied from 60.0% to 95.8% and ondansetron alone varied from 31.0% to 75.0%. All studies showed that ondansetron plus CHM was statistically more effective than ondansetron alone. Two studies reported the efficacy for acute, subacute or delayed gastrointestinal symptoms. Wu GY's study[79] showed that there were enhancement effects in the prevention of nausea and vomiting from the second day onward in a 5-day follow-up, while Fu DZ's study[85] showed CHM plus ondansetron reduced subacute symptoms [24-48 hours after having chemotherapy], but not for the acute or delayed stages.

Chinese Herbal Medicine vs Metoclopramide. Eleven studies, including two studies in three arms, compared CHM interventions to metoclopramide. One[55] evaluated the efficacy of CHM by comparing it with metoclopramide and ondansetron separately, while the other[54] compared CHM to CHM with metoclopramide, and metoclopramide alone. Decoction of Inula and Hematitum (Xuanfu Daizhe Tang) was the basic CHM formulation for the studies of Zhu X et al[86], Zheng WQ et al[67] and Zhang XH et al[87]; however, none of them used the same formulation, individualized modifications or dosages of each constituent herb. Nine studies[36,54,55,67,86-90] reported the overall effective rates, of which CHM varied from 65.7% to 92.5% and metoclopramide varied from 14.0% to 73.3%. Except three studies[36,54,67] showing that CHM interventions were comparable to metoclopramide, the others showed that CHM were more effective than metoclopramide for the prevention and/or treatment of chemotherapy induced nausea and/or vomiting. Two studies reported the number of patients preventing from nausea and vomiting (control rate), for which the study of Yan WH[91] showed superior effect and that of Liang YJ et al[58] showed a comparable effect when compared with metoclopramide.

Five studies, including one in three arms[54], investigated the combined effect of CHM interventions and metoclopramide to metoclopramide alone. Three studies[54,93,94] reported that the overall effective rates varied from 90.0% to 95.0% for the treatment group (CHM plus metoclopramide) and 40.0% to 79.5% for metoclopramide alone. All showed that metoclopramide with CHM interventions were statistically more effective than metoclopramide alone, with $p<0.05$. Two studies[38,93] reported the occurrence of nausea

and vomiting, and both of them demonstrated an enhancement effect when using CHM plus metoclopramide.

Chinese Herbal Medicine vs Granisetron. Three studies compared CHM interventions to granisetron. Zhang Y et al[95] reported that the occurrence of vomiting for patients taking Pacifying Regurgitation Solution (Pingni Yin), comprising of Persimmon Calyx (Shidi), Clove (Dingxiang), Rhubarb (Dahuang) and Sodium Sulfate (Yuanmingfen), was significantly lower than those taking granisetron. In Bao HY's study[68], the efficacy of plaster Downbearing Counterflow Powder (Jiangni San), comprising of Pinellia (Banxia), Evodia (Wuzhuyu), Clove (Dingxiang), Asarum (Xixin), Inula (Xuanfuhua), Atractylodes (Baizhu) and Codonopsis (Dangshen), was comparable to oral granisetron for the control of vomiting, with $p>0.05$. In another study on Settling Regurgitation Antiemetic Decoction (Zhenchong Jiangni Zhiou Fang)[96], comprising of Inula (Xuanfuhua), Hematitum (Daizheshi), Tangerine Peel (Chenpi), Bamboo Shavings (Zhuru), Pinellia (Banxia), Howthorn (Shanzha), Fermented Mass (Jianqu), Germinated Barley (Maiya), Fragrant Solomonseal Rhizome (Yuzhu), Aucklandia (Muxiang), Goldthread (Huanglian) and Perilla (Zisu), CHM was found to be more effective for controlling delayed vomiting, but less effective for acute vomiting.

Nine studies investigated the combination effect of CHM interventions plus granisetron to granisetron alone. Seven studies[57,62,97-101] reported the overall effective rates, for which combined interventions varied from 68.4% to 95.3% and granisetron varied from 30.2% to 82.1%. All showed that CHM plus granisetron was statistically more effective than granisetron alone, with $p<0.05$. Du XX et al[42] reported that the severity of nausea and vomiting was significantly lower than the experimental group, while significant differences were obtained in the first four days of a 6-day follow-up in Xu W et al's study[102].

Chinese Herbal Medicine vs Azasetron / Tropisetron. Three[44,56,69] studies compared the combination effect of CHM plus tropisetron to tropisetron alone, and one[40] compared the combination effect of CHM plus azasetron to azasetron. Two studies[40,44] reported the overall effective rates, for which treatment groups were 86.9% and 90.0%, and their controls were 66.7% and 69.2%, with all $p<0.05$. Xu S et al's study[56] showed that CHM plus tropisetron was more effective than tropisetron alone in the prevention of both acute and delayed nausea and vomiting. Pinellia Decoction for Draining the Heart (Banxia Xiexin Tang) enhanced the effect of tropisetron on the control of vomiting only on Days 2 to 5 in a 6-day follow-up period[69].

Chinese Herbal Medicine vs Integrated Conventional Treatments. Six studies evaluated CHM or CHM plus integrated conventional treatments with integrated conventional treatments alone. Three studies[103-105] compared to metoclopramide or granisetron with dexamethasone, one[106] compared to ondansetron and metoclopramide, and one[107] compared CHM to ondansetron, metoclopramide and dexamethasone. Six Gentlemen Decoction with Aucklandia and Amomum (Xiangsha Liujunzi Tang) was the basic CHM formulation for the studies of Cai ZB[106] and Li ZJ[105]; however, none of them were equivalent in terms of formulation, individualized modification or dosages of each constituent herb. The overall effective rates of treatment groups varied from 86.7% to 95.0% by comparing with integrated conventional treatments varying from 60.0% to 81.5%. Except Hao WP's study, all showed that CHM or CHM plus conventional interventions were statistically more effective than the groups with conventional interventions alone, with $p<0.05$. Zhang MB[108] demonstrated that the occurrence of nausea and vomiting was statistically lower due to the enhancement effect of Modified Four Gentlemen Decoction (Modified Sijunzi Tang) by comparing patients with ondansetron and omeprazole alone.

2. Oral ulceration

Ten studies evaluated various forms of CHM for the prevention and/or treatment of chemotherapy induced oral ulceration. They were oral CHM pills[37], plaster at acupoint Yongquan (KI 1)[59], CHM powders directly applied on affected areas[66,109] and CHM gargles[35,52,110-113]. Most studies assessed the efficacy by using the 5-grade system of the World Health Organization (WHO), either as it was or with modifications. This system graded acute and sub-acute toxic effects as follows: Grade 0 for no change, Grade I for soreness or erythema, Grade II for erythema, ulcers and solid food available, Grade III for ulcers and liquid diet only, and Grade IV for alimentation not possible[70]. For the definitions of outcome measures, "cure" represented the disappearance of symptoms (Grade 0), "improvement" represented a significant change for the better in terms of soreness, erythema or size of ulcer, and "failure" represented no change or even progression. The overall effective rate was the sum of patients in the categories of "cure" and with "improvement".

Four studies[35,52,110-111] compared CHM with Dobell (compound borax solution), including one three-arm study[52] with "no treatment" control. Gargle with Chinese Cork-tree and Gall (Huangwu Gargle), comprising of Amur Corktree (Huangbai), Gallic (Wubeizi), Verbena (Mabiancao), Catechu (Ercha) and Forsythia (Lianqiao), was the only CHM intervention investigated by Hou FJ et al twice[52,110]. Three studies[35,52,111] reported the occurrence rate of oral ulceration (Grade I to IV), for which the occurrence in patients taking CHM interventions varied from 4.8% to 13.1% while in those taking Dobell varied from 16.7% to 39.1%, and in "no treatment" control patients, occurrence was 24.2%, with all $p<0.05$. One study reported the overall effective rate of Gargle with Chinese Cork-tree and Gall (Huangwu Gargle) as 96.2% and that of Dobell as 79.2% ($p<0.01$)[110].

Three studies used vitamin supplements as comparators. Chen JZ et al[66] compared CHM with vitamin B-complex; Mo L[113] compared CHM with vitamin B2 and vitamin C;

and Wang XJ et al[109] compared CHM with vitamin B2 and methyl violet. All of these CHM interventions were more effective than the comparators (all p<0.05). For Zhao XC et al study[37], patients with Ulcerating Pills (Kuiyang Wan), comprising of Hirudo (Shuizhi), Gadfly (Mengchong), Salvia Chinensis (Zishen), Peach Seed (Taoren), Whitefruit Amomim Fruit (Baidoukou), Angelica (Baizhi), Turmeric (Yujin), Prunella (Xiakucao), Safflower (Honghua) and Red Peony (Chishao) had less patients with severe ulceration (Grade I to IV) when compared to chlorhexidine, but no statistical data provided. Enhancement effect was observed in the studies of Wang KX et al[112] and Zhou XX et al[59], as the overall effective rates increased up to 97.5% and 98.1% for patients with CHM plus conventional treatment comparing with 69.2% and 87.5% for patients with conventional treatment alone.

3. Diarrhea

Six studies evaluated the efficacy of CHM interventions for the prevention and/or treatment of chemotherapy induced diarrhea. Studies accessed the efficacy by using or modifying the TCM references, namely the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine[114], Cure and Improvement Criteria of Clinical Diseases[115], and Spleen and Stomach Application Study in Traditional Chinese Medicine[116]. The term "cure" meant normal bowel movement and the disappearance of related symptom; "improvement" represented a significant improvement in bowel frequency and related symptoms; and "failure" represented no change in bowel frequency and stool type. The overall effective rate was the sum of patients in the categories of "cure" and with "improvement". Pinellia Decoction for Draining the Heart (Banxia Xiexin Tang), equivalence to Hangeshashin-to in Kampo medicine, was the basic CHM formulation for the studies of Mori K et al[32] and Zhang RH et al[117]; however, there were no further information whether they were equivalent in terms of modification or dosages of each constituent herb.

Mori K et al[32] declared that treatment with the CHM Hangeshashin-to caused a significant improvement in diarrhea grades and reduced the frequency of Gradse 3 and 4 diarrhea when compared with no treatment. Three studies[64,117,118] compared CHM with montmorillonite. In these, the overall effective rates for patients taking CHM varied from 86.4% to 97.5% versus 68.4% to 85.0% for those taking montmorillonite, with all p<0.05. Two studies[119,120] compared CHM with bifico. In these studies, the overall effective rates for patients taking CHM were 95.8% and 100% versus 65.0% and 73.2% for those taking bifico, all p<0.01. Hence, the CHM interventions were more effective than montmorillonite, bifico and no treatment for the management of chemotherapy induced diarrhea.

4. Constipation

Six studies evaluated the efficacy of CHM interventions for the prevention and/or treatment of chemotherapy induced constipation. Studies assessed the efficacy by using either the original or a modified version of TCM references, such as the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine[114] and Guidelines for Clinical Research on New Chinese Herbal Medication[121]. By summarizing these references, "cure" was defined as restoring normal bowel movement (e.g. 1 day/time) or original bowel habit and the disappearance of related symptom(s); "significant improvement" was defined as a significant increase in bowel movement frequency (e.g. 2-3 days/time) and disappearance of most related symptoms; "improvement" was defined as advancing the frequency of bowel movement for 1 day or noticeable softening of the stools; and "failure" was defined as no change in bowel frequency and stool type. The overall effective rate was the sum of patients in each of the three categories, "cure", "significant improvement" and "improvement".

The overall effective rates for patients taking CHM interventions were from 77.2% to 94% versus 14.3% to 85.5%[39,43,50,53,60,122]. The study of WH et al[39] was the only one showing a comparable effect between Qingshu Granules, comprising of Polygonum Multiforum (Heshouwu), Cistanches (Roucongrong), Astragalus (Huangqi), Immature Bitter Orange (Zhishi) and Cannabis (Huomaren) and mosapride, with p>0.05. The other showed a superior effect from CHM interventions over PEG4000[43], crude fiber diet[50], honey water[53], bisacodyl[60], or mosapride[122], with p<0.05.

Safety Assessment of Interventions

The common safety assessments were routine physical examination, routine blood, urine and stool tests, cardiac, renal and liver functional tests and electrocardiogram, while the occurrence of any extrapyramidal reaction, including dizzy, somnolence, fatigue and etc, were identified in some studies. In total, only 30 out of 86 studies (34.8%) reported the issues of safety, including taken account of adverse effects (AEs) and/or assessed with different examinations. Of these, three studies[47,57,90] claimed that blood test and some other examinations had been done, but no information about any AEs was reported. Another three studies[32,34,39] did not report with details, while 12 studies[45,48,55,58,61,65,76-78,86,87,96] claimed no AE among the groups of CHM interventions. The AEs of treatment groups were reported in 12 studies. AEs included headache, dizziness, fatigue, somnolence, loss of appetite, loss of taste, thirst, stomach discomfort, abdominal bloating, constipation, diarrhea and changes in blood tests. However, most studies reported fewer AEs in the treatment groups than in their comparators[40,43,69,71,72,80,81,85,105,107]. Only the studies of Zhu TE et al[50] and Xu S et al[56] had higher occurrences of AEs for the CHM intervention or CHM intervention plus conventional medicine. For the former study, about 50% of subjects who had senna leaf tea experienced mild diarrhea compared with 5.7% for those who had the crude fiber diet. For the latter study, there was actually no significant difference among the tropisetron hydrochloride plus CHM intervention group and tropisetron hydrochloride control group. However, whether these

Table 5. Safety issue of included studies.

	No. of studies
Description of adverse effects	27
– CHM group < control group (WM / no treatment)	16
– CHM plus WM group < WM group	6
– CHM group > control group (WM / crude fiber diet)	2
– No reported with details	3
Description of any safety assessment (e.g. physical examination or laboratory tests)	16

Key: CHM: Chinese herbal medicine; WM: Western conventional medicine; "<": Less than; ">": More than.

reported AEs were caused by interventions or induced by chemotherapy regimen itself were not well elucidated. A table of summary about the safety issue of included studies is presented in Table 5.

Discussion

This review identified 86 prospective RCTs testing CHM for the prevention and/or treatment of chemotherapy induced gastrointestinal side effects, namely nausea, vomiting, oral ulceration, diarrhea and constipation. CHM interventions, in general, showed superior or at least comparable when compared with conventional interventions. Even for the only study[78] showed inferior effect on the management of acute vomiting, superior effect was identified for delayed vomiting. Enhancement effects on increasing efficacy and safety could also be noted when being used with conventional interventions. CHM interventions seem to be a perfect complementary and alternative treatment for chemotherapy induced gastrointestinal side effects. However, the results from this review should be interpreted with appropriate cautions.

First, the quality of the included trials was poor, and sample sizes were generally small. Over 80% of studies only got one point in the Jadad scale. Some very important information, such as how patients were recruited, study setting, quality of intervention, sample size calculation, randomization details and statistical analysis, was not well reported. Thus, both false positive and false negative findings could result due to the high risk of bias in selection, performance and detection and attrition. Secondly, there was great heterogeneity among included trials in terms of study design, interventions, patients and outcome measures. Hence, the precision and accuracy of estimates could not be improved as no further statistical analysis could be performed. Thirdly, this review only considered studies for the gastrointestinal side effects of nausea, vomiting, oral ulceration, diarrhea or constipation. The results might not be generalized to gastrointestinal symptoms arising from other causes. Fourth, safety issues were only discussed in some of included studies. Therefore, the safety of these CHM interventions had not been fully addressed. Furthermore, reporting bias, especially for publication bias and selective outcome reporting, was also a major problem in the assessment of health care interventions. All CHM interventions of the included studies showed beneficial effects, no matter with superior or comparable effect of active control, or with acute or delayed effect. Therefore, there was a possible high publication bias and outcome reporting bias. Both of them favoured studies with positive results, and may overestimate the overall benefit of CHM interventions.

Individualization and holism are highly emphasized in TCM theory and practice. Instead of targeting on particular cancer origin and hemotherapy regimen, treatment is formulated according to the TCM syndrome and clinical manifestations of each patient. Therefore, TCM practitioners tend to make their prescriptions by modifying ancient CHM formulas or inventing a new formula for individual patients Furthermore, the prescription is likely to be modified after every visit, as the condition of patent changes. That is the reason why the same intervention is seldom investigated by different researchers. Even though their inventions originate from the same ancient formula—for example, Decoction of Inula and Hematitum (Xuanfu Daizhe Tang) and Six Gentlemen Decoction with Aucklandia and Amomum (Xiangsha Liujunzi Tang) were the basic formulas for several studies, we still cannot categorize these interventions with different modifications, forms and dosages of each constituent herb as equivalent interventions, just like we cannot not mix apples with orange[123]. For the same reason, TCM practitioners also cannot prescribe all included CHM interventions as one prescription to patients directly.

In the era of evidence-based medicine, gold standard evidences can only be produced when studies are designed, implemented and reported with attention to possible biases in every aspect of the study design and implementation[124]. Furthermore, TCM syndrome, as the essence of TCM theory, should also be introduced in the RCTs of CHM interventions. The development of CONSORT [Consolidated Standards of Reporting Trials] for TCM from 2007[125] and SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] 2013[126] are attempts to improve the general methodological quality of RCT on TCM from drafting protocol to prepare final report. For making definite clinical recommendations, further large scale and high quality RCTs strictly followed the CONSORT for TCM and SPIRIT 2013 are highly recommended. Moreover, syndrome differentiation (i.e., classifying patients on the basis of phenotype-like clinical symptoms) is playing a key role in modern research. It may be the bridge for refining the definitions of Western medical terms, more precise treatment can be given—increasing efficacy and reducing AE[127]. In this case, patients having chemotherapy shared the same or similar TCM syndromes as well as the same gastrointestinal symptoms as recognized by Western medicine. For these people, Decoction of Inula and Hematitum (Xuanfu Daizhe Tang) and Six Gentlemen Decoction with Aucklandia and Amomum (Xiangsha Liujunzi Tang) were the basic formula for several included studies on nausea and vomiting, and hence appear to be the right choice for future drug development as well as current prescriptions. For future RCT on TCM for other conditions, the distribution of symptoms should first be

determined. Then, the therapeutic principle and a basic formula can be established according to the specific syndrome differentiated. A standard treatment with repeated and robust verification should be the strongest and practicable evidence for making clinical recommendation.

This review had some potential limitation. First of all, literature search was restricted to Chinese and English. Therefore, there was a possible language bias by excluding those potential literatures in other languages. Secondly, apart from electronic search, none of secondary search had been done. Hence, those grey, unpublished literatures could not be sorted thoroughly. Thirdly, the literature search was made in 2012 and authors of included studies had not been contacted. As a result, some of raw data were not included in this review. Besides, the potential mechanisms of CHM in alleviating gastrointestinal side effects had not been discussed. Further investigation should be made in future.

Conclusions

Definite clinical recommendations for particular CHM interventions for gastrointestinal symptoms of chemotherapy cannot be made from this review. On a broader scale, it provides further evidence that CHM can play a role in harmonizing and complementing Western conventional treatment regimes by enhancing the efficacy and reducing the adverse effect of conventional medicine for chemotherapy-induced nausea, vomiting, oral ulceration, diarrhea or constipation. This type of integrative medicine deserves attention and further research, as the next great step in the advancement of medicine and improvement of human health.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CC and BZ were responsible for the design of review protocol, searching literature, extracting data and drafting the manuscript. ZE and WV participated in the design and approval of review protocol. ZL, WJ and LZ provided constructive comments and helped to draft manuscript. All authors read and approved the final manuscript.

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Additional file 1. Summary of included studies. Description: It is a table summarizing the background information of all included studies.

Ref No	Author	Year	Partici-pants	Cancer Origin	Regimen of Chemotherapy	Design	Treatment	Control	Outcomes	Primary endpoint (Treatment vs Control)	Beneficial effect	Secondary endpoints	Ethics	Name of Basic Formula	Form	Origin	Indivi-dualized modifi-cation	Jadad scale
32	Mori K	2003	41	Lung	Cisplatin plus Irinotecan	parallel	CHM	No treatment	Diarrhea	Severity grading	Superior	1. Occurrence of 3/4 degree diarrhea; 2. stool profile (frequency, duration); 3. AEs	Yes	Hangeshashin-to	Granules	A	N	3
33	Zhou XJ	2004	30	Digestive system, respiratory system & other	Combinated regimens with cisplatin	parallel	CHM	Ondan-setron	Vomiting	Effectiveness grading (Delay)	N/A	1. Effectiveness grading (appetite & defecation)	No report	Antiemetic Magic Plaster (Zhiou Shentie)	Plaster	S	N	1
34	Yuan TC	2007	30	Leukemia, lymphoma & liver	Multiple	cross-over	CHM + Ondansetron	Ondan-setron	Nausea & vomiting	ER of nausea / vomiting: 73.3% vs 50% / 90% vs 70%	Superior	1. Severity grading; 2. AEs	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	Y	1
35	Wu XE	2009	217	Ovary, endometrium, choriocarcinoma, fallopian tube & malignant mole	No report	parallel	CHM	Dobell	Oral ulcer	OR: 13.1% vs 39.1%	Superior	1. Severity grading	No report	N/A	Ice cude	S	N	1
36	Guo YB	2001	60	Colon & rectum	FLP (Cisplatin plus 5-FU plus Leucovorin)	parallel	CHM	Metoclo-pramide	Nausea & vomiting	ER: 65.7% vs 56.0%	Comparable	1. Severity and effectiveness grading; 2. Indivdual symptom assessment (abdominal pain & diarrhea)	No report	Warming Gallbladder Decoction (Wendan Tang)	Decoction	M	N	2
37	Zhao XC	2003	134	Acute leukemia	Cytarabine plus Daunorubicin	parallel	CHM	Chlor-hexidine	Oral ulcer	Severity grading	N/A	1. Propoprtion of mild and severe case; 2. Time to heal	No report	Ulcerating Pills (Kuiyang Wan)	Pills	S	N	1
38	Zhang ML	2005	42	Lung	PE (Cisplatin plus Etoposide)	parallel	CHM + Metoclopramide	Metoclo-pramide	1. Nausea; 2. Vomiting	Patients without: 1. nausea (acute); 2. vomiting (acute)	Superior	1. Patients without nausea/vomiting (for 7 consecutive days)	No report	Minor Pinellia Decoction plus Poria (Xiaobanxia Jia Fuling Tang)	Decoction	A	N	1
39	Zhao WH	2006	42	Lymphoma, multiple myeloma & acute lymphoblastic leukemia	CHOP (cyclophos-phamide plus doxorubicin plus Vincristine plus Prednisone)	parallel	CHM	Mosapride	Constipation	ER: 77.2% vs 85.5%	Comparable	1. Effectiveness grading; 2. Bowel profile (interval, defecation time); 3. AEs	No report	Qingshu Granules	Granules	w/o	N	1
40	Zhang XL	2009	60	Colon	FOLFOX4 (Oxaliplatin plus Leucovorin plus 5-FU)	parallel	CHM + Azasetron	Azasetron	Nausea & vomiting	ER: 90% vs 66.7%	Superior	1. Effectiveness grading; 2. AEs	No report	Minor Pinellia Decoction (Xiaobanxia Tang)	Decoction	M	Y	1
41	Wu BQ	2010	84	Lung	GP (gemcitabine plus cisplatin)	parallel	CHM	No treatment	Nausea & vomiting	OR: 55.0% vs 72.7%	Superior	1. Severity grading	No report	Antiemetic Decoction (Zhitu Tang)	Decoction	S	N	2
42	Du XX	2010	60	Lung	NP (vinorelbine plus cisplatin)	parallel	CHM + Granisetron	Granisetron	Nausea & vomiting	Severity grading	Superior	1. QoL	No report	Spleen and Kidney Mixture (Pishen Mixture)	Solution	S	N	1
43	Gui L	2010	70	Colon & rectum	FOLFOX4 (Oxaliplatin plus Leucovorin plus 5-FU)	parallel	CHM	PEG4000	Constipation	ER: 91.7% vs 76.5%	Superior	1. Effectiveness grading; 2. Bowel profile (interval, abnormality, consistency); 3. AEs	Yes	Tonifying the Middle and Augmenting the Qi Decoction (Buzhong Yiqi Tang)	Decoction	M	N	2
44	Wang XZ	2011	85	Breast	FAG (Cyclophos-phamide plus doxorubicin plus 5-FU)	parallel	CHM + Tropisetron	Tropisetron	Nausea & vomiting	ER: 86.9% vs 69.2%	Superior	1. Grading	Yes	Six Gentlemen Decoction with Aucklandia and Amomum (Xiangsha Liujunzi Tang)	Decoction	S	N	1
45	Wang YF	1998	72	Lymphoma, colon, stomach, lung, esophagus, nasal pharynx, breast, sarcoma & paranasal sinus	Multiple	cross-over	CHM	Ondan-setron	Nausea & vomiting	ER*: 92.7%/93.5% vs 87.8%/87.1% (Acute)	Comparable	1. Effectiveness grading; 2. AEs	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	Y	2

Additional file 1. (Continued)

Ref No	Author	Year	Partici-pants	Cancer Origin	Regimen of Chemotherapy	Design	Treatment	Control	Outcomes	Primary endpoint (Treatment vs Control)	Beneficial effect	Secondary endpoints	Ethics	Name of Basic Formula	Form	Origin	Indivi-dualized modifi-cation	Jadad scale
46	Xu J	1999	60	Lung, esophagus & stomach	Combinated regimens with cisplatin	cross-over	CHM	Ondan-setron	1. Nausea; 2. Vomiting	ER of nausea / vomiting: 63.6% vs 50% / 78.3% vs 81.7%	1. Superior; 2. Comparable	1. Severity and effectiveness grading	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	A	N	1
47	Chen JX	2000	40	Lung, esophagus, stomach, colon, breast, lymphoma & nasal pharynx	Multiple	cross-over	CHM	Ondan-setron	Vomiting	ER*: 85.7/89.5% vs 90.4/84.2%	Comparable	1. Grading; 2. Suppress blood formation of bone marrow	No report	Vomiting Tranquilizing Granules (Ouning Fang)	Granules	S	N	1
48	Yao ZP	2000	204	Lymphoma, lung, esophagus, stomach, colon, rectum, breast, NPC, paranasal sinus & sarcoma	Combinated regimens with and without cisplatin	cross-over	CHM	Ondan-setron	Vomiting	ER (Acute)*: 93.1% vs 89.2%	Comparable	1. Effectiveness grading; 2. ER (Delay); 3. AEs	No report	Vomiting Tranquilizing Granules (Ouning Fang)	Granules	S	Y	2
49	Wang JP	2007	45	Lung, breast, stomach, esophagus & colon	Combinated regimens with cisplatin	cross-over	CHM + Ondansetron	Ondan-setron	1. Nausea; 2. Vomiting	ER of nausea / vomiting (Delay): 62.2% vs 31% / 62.2% vs 35.5%	1. Superior; 2. Superior	1. Severity and effectiveness grading	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	A	Y	1
50	Zhu TE	2011	35	Lung, stomach, colon, breast, overy & cervix	No report	cross-over	CHM	Crude fiber diet	Constipation	ER: 91.4% vs 14.3%	Superior	1. Severity grading; 2. AEs (Diarrhea)	No report	Senna leaf (Fanxieye)	Tea	N/A	N	2
51	Zhou X	2009	57	Urine bladder, prostate, kidney & other	Multiple	parallel	CHM	Placebo	Nausea & vomiting	ER: 93.1% vs 21.4%	Superior	1. Effectiveness grading	No report	Tea of Milkvetch and Wolfberry (Huangqi Gouqi Tea)	Tea	S	N	1
52	Hou FJ	2002	189	Lymphoma, breast & lung	Multiple	parallel	CHM	1. Dobell; 2. no treatment	Oral ulcer	OR: 4.8% vs 16.7% vs 24.2	Superior	1. Severity and effectiveness grading	No report	Gargle with Chinese Cork-tree and Gall (Huangwu Gargle)	Gargle	S	N	1
53	Long FF	2010	62	Stomach, colon, pancreas, lung & breast	No report	parallel	CHM	Honey water	Constipation	ER: 78.1% vs 16.6%	Superior	1. Effectiveness grading	No report	Hemp Seed Pills (Maren Wan)	Pills	A	N	1
54	Niu DL	1995	60	Stomach, esophagus, lymphoma, lung, colon, breast & liver	Multiple	parallel	CHM	1. Metoclo-pramide; 2. CHM + Metoclo-pramide	Nausea & vomiting	ER: 45% vs 40% vs 90%	CHM+WM superior, CHM comparable to WM	1. Severity and effectiveness grading	No report	Antiemetic Mixture (Zhiou Mixture)	Solution	S	N	1
55	Zhang KJ	1999	120	Lung, esophagus, colon & liver	Multiple	parallel	CHM	1. Ondan-setron; 2. Metoclo-pramide	Nausea & vomiting	ER: 75% vs 82.5% vs 42.5%	CHM comparable to WMa, and superior to WMb	1. AEs	No report	N/A	Decoction	S	N	1
56	Xu S	2009	84	Breast, lymphoma & lung	Multiple	parallel	CHM + Tropisetron	Tropisetron	Nausea & vomiting	CR of nausea / vomiting (acute): 66.7% vs 42.9% / 85.7% vs 61.9%	Superior	1. Severity and effectiveness grading; 2. CR (delay); 3. AEs	Yes	3 ancient formulas for 3 different syndromes	Decoction	A	N	1
57	Shi ZY	2011	60	Esophagus, colon, rectum, nasal pharynx, lung & breast	Multiple	parallel	CHM + Granisetron	Granisetron	Nausea & vomiting	ER: 90% vs 66.7%	Superior	1. Effectiveness grading; 2. Time to relief; 3. QoL	Yes	Warming Gallbladder Decoction (Wendan Tang)	Decoction	A	Y	2
58	Liang YJ	1999	50	Nasal pharynx, esophagus, breast, lung & colon	Multiple	parallel	CHM	Metoclo-pramide	1. Nausea; 2. Vomiting	CR: 61.5% vs 58.3%	Comparable	1. Severity and effectivenss grading; 2. Nausea & Vomiting profile (frequecny, duration); 3. AEs	No report	Decoction of Pinellia and Magnolia (Banxia Houpo Tang)	Decoction	A	N	3
59	Zhou XX	2008	79	Lung, stomach, colon, breast, pancreas & other	No report	parallel	CHM + WM	Furacilin + Sodium hydrogen carbonate	Oral ulcer	ER: 97.5% vs 69.2%	Superior	1. Grading; 2. Time (restore normal diet / normal temperature / ulcer healing)	No report	Medicinal Euodia Fruit (Wuzhuyu)	Plaster	S	N	2
60	Su ZT	2011	60	Lung, breast, ovary & stomach	No report	parallel	CHM	Bisacodyl	Constipation	ER: 86.7% vs 60.0%	Superior	1. Effectiveness grading	No report	Four Grinding Decoction (Simo Tang)	Decoction	M	Y	2

Additional file 1. (Continued)

Ref No	Author	Year	Partici-pants	Cancer Origin	Regimen of Chemotherapy	Design	Treatment	Control	Outcomes	Primary endpoint (Treatment vs Control)	Beneficial effect	Secondary endpoints	Ethics	Name of Basic Formula	Form	Origin	Indivi-dualized modifi-cation	Jadad scale
61	Liu QH	2002	80	Gynecological related carcinoma	No report	parallel	CHM	Ondan-setron	Nausea & vomiting	ER: 90% vs 85%	Comparable	1. Effectiveness grading; 2. AEs	No report	Decoction of Patchouli, Magnolia, Pinellia and Poria (Huopo Xialing Tang)	Decoction	M	N	2
62	Huang ZF	2004	62	Lung, nasal pharynx, breast & lymphoma	Combinated regimens with cisplatin	parallel	CHM + Granisetron	Granisetron	Vomiting	ER: 93.8% vs 70%	Superior	1. Effectiveness grading; 2. Time to relief; 3. Symptom improvement	No report	Six Gentlemen Decoction (Liujunzi Tang)	Decoction	M	N	2
63	Huang ZR	2008	102	Lung, esophagus, stomach, colon & ovary	Combinated regimens with cisplatin	parallel	CHM	Ondan-setron	1. Nausea; 2. Vomiting	ER of nausea / vomiting (Acute): 93.8% vs 81.5% / 87.5% vs 74.1%	Comparable	1. ER (for 5 consecutive days)	No report	Six Gentlemen Decoction with Aucklandia and Amomum (Xiangsha Liujunzi Tang)	Decoction	M	N	2
64	Cheng SH	2011	42	No report	No report	parallel	CHM	Montmo-rillonite	Diarrhea	ER: 87.2% vs 72.2%	Superior	1. Effectiveness grading	No report	Peony Decoction (Shaoyao Tang)	Decoction	M	N	2
65	Guo ZT	2011	100	Breast	Multiple	parallel	CHM	Ondan-setron	Nausea & vomiting	ER (Delay): 90% vs 72%	Superior	1. Severity (acute) and effectinenss (delay) grading; 2. QoL; 3. Body weight; 4. AEs	No report	Aconite Decoction for Regulating the Middle (Fuzi Lizhong Tang)	Decoction	M	N	2
66	Chen JZ	2011	60	Colon, stomach, esophagus & nasal pharynx	Multiple	parallel	CHM	Vitamin supplements	Oral ulcer	ER: 100% vs 93.3%	Superior	1. Time to heal; 2. Scoring of symptom severity	No report	Saiweian	Powder	P	N	2
67	Zheng WQ	2003	54	Lung	Multiple	parallel	CHM	Metoclo-pramide	Nausea & vomiting	ER: 77.8% vs 66.7%	Comparable	1. Effectiveness grading; 2. Effective for cough with sputum / SOB	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	N	2
68	Bao HY	2008	80	Lung, breast, esophagus, stomach, colon & lymphoma	Multiple	parallel	CHM	Granisetron	Nausea & vomiting	ER: 80.0% vs 82.5%	Comparable	1. Effectiveness grading	No report	Downbearing Counterflow Powder (Jiangni San)	Plaster	S	N	2
69	Liu KQ	2010	120	Colon, stomach, lung, esophagus, head & neck, breast, cervix, ovary, lymphoma	Combinated regimens with cisplatin	parallel	CHM + Tropisetron	Tropisetron	Nausea & vomiting	ER(acute): 85% vs 78.3%	Comparable	1. ER (for 6 consecutive days); 2. AEs	No report	Pinellia Decoction for Draining the Heart (Banxia Xiexin Tang)	Decoction	M	Y	2
71	Wang DS	2000	88	Colon, esophagus, stomach, lymphoma, breast, cervix, nasal pharynx, lung & urinary bladder	Multiple	parallel	CHM	Ondan-setron	Nausea & vomiting	Compete response rate: 84.7% vs 66.6%	Superior	1. Effectiveness grading; 2. ER; 3. AEs	No report	Antiemetic Mixture (Ziou Mixture)	Decoction	S	Y	1
72	Wang DS	2001	112	Colon, esophagus, stomach, lymphoma, breast, cervix, nasal pharynx, lung & urinary bladder	Multiple	parallel	CHM	Ondan-setron	Nausea & vomiting	Complete response rate: 86.2% vs 64.8%	Superior	1. Effectiveness grading; 2. ER; 2. AEs	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	Y	1
73	Pang XR	2000	164	Esophagus, stomach, lung, breast, lymphoma & testicule	No report	parallel	CHM	Ondan-setron	Nausea & vomiting	ER: 73.2% vs 80.5%	Comparable	1. Effectiveness grading	No report	Nourishing Stomach Pills with Aucklandia and Amomum (Xiangsha Yangwei Wan)	Pills	S	N	1
74	Rong SF	2009	98	Esophagus, stomach, breast, lung, liver, colon, lymphoma & ovary	Multiple	parallel	CHM	Ondan-setron	Nausea & vomiting	ER: 89.8% vs 63.3%	Superior	1. Effectiveness grading	No report	Powder of Ginseng, Poria and Atractylodes (Shenling Baizhu San)	Decoction	A	N	1
75	Zhang DY	2009	132	Lung, esophagus, stomach & colon	Combinated regimens with cisplatin	parallel	CHM	Ondan-setron	Nausea & vomiting	ER: 90.3% vs 75%	Superior	1. Severity grading	No report	Powder of Pinellia and Perilla (Bansu San)	Plaster	S	N	1
76	Yang JD	2011	100	Lung, breast & stomach	No report	parallel	CHM	Ondan-setron	Nausea & vomiting	ER: 90% vs 92%	Comparable	1. Effectiveness grading; 2. AEs	No report	5 ancient formulas for 4 different syndromes	Decoction	M	Y	1

Additional file 1. (Continued)

Ref No	Author	Year	Partici-pants	Cancer Origin	Regimen of Chemotherapy	Design	Treatment	Control	Outcomes	Primary endpoint (Treatment vs Control)	Beneficial effect	Secondary endpoints	Ethics	Name of Basic Formula	Form	Origin	Indivi-dualized modifi-cation	Jadad scale
77	Xu YF	2009	80	Stomach, colon, breast & lung	Multiple	parallel	CHM	Ondan-setron	1. Nausea; 2. Vomiting	1. Effectiveness grading; 2. Severity grading	Superior	1. Severity grading; 2. AEs	No report	Warming Gallbladder Decoction (Wendan Tang)	Decoction	A	N	1
78	Zhong Y	2003	60	Lung, breast, stomach & colon	Multiple	parallel	CHM	Ondan-setron	Vomiting	ER (Acute): 67% vs 80%	Inferior	1. Effectiveness grading; 2. ER (Delay); 3. QoL; 4. Weight; 5. AEs	No report	Six Ingredients Antiemetic Powder (Liuwei Ziou San)	Pills	S	N	1
79	Wu GY	2004	82	Lung, esophagus, stomach, nasal pharynx, liver & unknown	Multiple	parallel	CHM + Ondansetron	Ondan-setron	1. Nausea; 2. Vomiting	ER of nausea / vomiting (Acute): 95.1 vs 92.7 / 92.7% vs 90.2%	1. Comparable; 2. Comparable	1. ER (for consective 5 days)	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	Y	1
80	Zhou B	2008	60	Breast	Multiple	parallel	CHM + Ondansetron	Ondan-setron	Nausea & vomiting	ER (Acute): 93.3% vs 70%	Superior	1. Effectiveness grading; 2. Occurrence of other chemotherapy induced side effect; 3. AEs	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	A	Y	1
81	Ouyang XN	2001	145	Esophagus, stomach, colon, nasal pharynx & lymphoma	Multiple	parallel	CHM + Ondansetron	Ondan-setron	Nausea & vomiting	ER: 95.8% vs 71.2%	Superior	1. Effectiveness grading; 2. AEs	No report	Minor Pinellia Decoction (Xiaobanxia Tang)	Decoction	A	N	1
82	Huang WX	2003	40	Lung, stomach, liver, colon, lymphoma, breast & nasal pharynx	Multiple	parallel	CHM + Ondansetron	Ondan-setron	Vomiting	ER: 92.9% vs 75%	Superior	1. Effectiveness grading	No report	Antiemetic Decoction (Zhiou Tang)	Decoction	S	Y	1
83	Lou YM	2004	78	Lung, breast, stomach & colon	Combinated regimens with cisplatin	parallel	CHM + Ondansetron	Ondan-setron	Nausea & vomiting	ER (Acute): 89.7% vs 66.7%	Superior	1. Effectiveness grading; 2. ER (delay)	No report	Settling Regurgitation Antiemetic Decoction (Jiangni Zhiou Tang)	Decoction	S	N	1
84	Zhang XQ	2005	60	Lung, breast, nasal pharynx, stomach & esophagus	Combinated regimens with cisplatin	parallel	CHM + Ondansetron	Ondan-setron	1. Nausea; 2. vomiting	ER of nausea / vomiting (Delay): 60.0% vs 33.3% / 63.3% vs 33.3%	1. Superior; 2. Superior	1. Severity and effectiveness grading	No report	Four Reversal Powder (Sini San)	Decoction	S	N	1
85	Fu DZ	2006	64	Lung	Multiple	parallel	CHM + Ondansetron	Ondan-setron	1. Nausea; 2. Vomiting	ER of nausea / vomiting (Acute): 78.1% vs 59.4% / 93.8% vs 75%	1. Comparable; 2. Comparable	1. Effectiveness grading; 2. ER (Sub-acute(+) & Delay(-)); 3. AEs / Induced AEs	No report	Detoxifying Decoction with Ginseng and Two Poria (Renshen Erling Jiedu Tang)	Decoction	S	N	1
86	Zhu X	1999	80	Esophagus, stomach, liver, colon, lung, breast, lymphoma, nasal pharynx, thyroid & sarcoma	No report	parallel	CHM	Metoclo-pramide	Nausea & vomiting	ER: 92.5% vs 45%	Superior	1. Effectiveness grading; 2. AEs	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	Y	1
87	Zhang XH	2011	60	Respiratory system, digestive system, uriniary system & other	Multiple	parallel	CHM	Metoclo-pramide	Vomiting	ER: 83.3% vs 73.3%	Superior	1. Effectiveness grading; 2. Time to complete response; 3. AEs	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Granules	A	Y	1
88	Gao J	1995	74	Esophagus, stomach, liver, lung & colon	Multiple	parallel	CHM	Metoclo-pramide	Vomiting	ER: 85.4% vs 51.5%	Superior	1. Effectiveness grading	No report	Tonifying the Spleen and Antiemetic Decoction (Bupi Zhitu Tang)	Decoction	M	Y	1
89	Sun WQ	1999	60	No report	No report	parallel	CHM	Metoclo-pramide	Nausea & vomiting	ER: 90% vs 53.3%	Superior	1. Effectiveness grading	No report	Decoction of Patchouli, Magnolia, Pinellia and Poria (Huopo Xialing Tang)	Decoction	M	N	1

Additional file 1. (Continued)

Ref No	Author	Year	Partici-pants	Cancer Origin	Regimen of Chemotherapy	Design	Treatment	Control	Outcomes	Primary endpoint (Treatment vs Control)	Beneficial effect	Secondary endpoints	Ethics	Name of Basic Formula	Form	Origin	Indivi-dualized modifi-cation	Jadad scale
90	Xiong MN	2001	114	Lung, nasal pharynx, lymphoma, sarcoma, breast, stomach, larynx, esophagus, colon, liver, thoracic tumor, tongue, pancreas, thyroid, urinary bladder, sarcoma, melanoma, parotid, teratoma & unknown	Multiple	parallel	CHM	Metoclo-pramide	Nausea & vomiting	ER: 89.5% vs 14.0%	Superior	1. Effectiveness grading; 2. WBC count	No report	Harmonizing the Middle Mixture (Tiaozhong Mixture)	Solution	S	N	1
91	Yan WH	2001	50	Lung & stomach	Combinated regimens with cisplatin	parallel	CHM	Metoclo-pramide	1. Nausea; 2. Vomiting	CR of nausea / vomiting: 60% vs 32% / 72% vs 36%	1. Superior; 2. Superior	1. CR of nausea & vomiting (for consective 5 days); 2. Appetite	No report	Powder of Ginseng, Poria and Atractylodes plus Decoction of Clove and Persimmon Calyx (Shenling Baizhu San & Dingxiang Shidi Tang)	Decoction	M	N	1
92	Luo SB	2007	76	Breast	Multiple	parallel	CHM + Metoclopramide	Metoclo-pramide	Nausea & vomiting	OR: 39.5% vs 76.3%	Superior	1. Severity grading; 2. Use of rescue drug	No report	Downbearing Counterflow and Tonifying Qi Decoction (Jiangni Buqi Tang)	Decoction	S	Y	1
93	Chen W	2007	98	Breast, lung, liver, stomach, colon, cervix & ovary	No report	parallel	CHM + Metoclopramide	Metoclo-pramide	Nausea & vomiting	ER: 89.8% vs 63.3%	Superior	1. Effectiveness grading	No report	Powder of Ginseng, Poria and Atractylodes (Shenling Baizhu San)	Decoction	M	Y	1
94	Zhang KM	2009	79	Lung, esophagus, stomach & colon	Combinated regimens with cisplatin	parallel	CHM + Metoclopramide	Metoclo-pramide	Nausea & vomiting	ER: 95% vs 79.5%	Superior	1. Severity grading	No report	Six Gentlemen Decoction with Aucklandia and Amomum (Xiangsha Liujunzi Tang)	Decoction	A	N	1
95	Zhang Y	2004	100	Lung, colon, breast & lymphoma	Multiple	parallel	CHM	Granisetron	Nausea & vomiting	OR: 32% vs 58%	Superior	1. Severity grading	No report	Pacifying Regurgitation Solution (Pingni Yin)	Decoction	S	N	1
96	Wang DJ	2010	136	Lung, colon, rectum, ovary, breast, esophagus, stomach & other	Multiple	parallel	CHM	Granisetron	Vomiting	ER (Delay): 88.2% vs 55.9%	Superior	1. Effectiveness grading; 2. ER (acute) (wm>>tcm); 3. AEs	No report	Settling Regurgitation Antiemetic Decoction (Zhenchong Jiangni Zhiou Fang)	Decoction	S	N	1
97	Yang Y	2007	76	Lung, breast, stomach, colon, cervix, lymphoma & esophagus	No report	parallel	CHM + Granisetron	Granisetron	Nausea & vomiting	ER: 91.9% vs 82.1%	Superior	1. Effectiveness grading; 2. Severity scoring	No report	Downbearing Counterflow Solution (Jiangni Yin)	Decoction	S	N	1
98	Zhou XY	2009	38	Lung, stomach, esophagus, colon & breast	Combinated regimens with cisplatin	parallel	CHM + Granisetron	Granisetron	Vomiting	ER (Delay): 68.4% vs 31.5%	Superior	1. Effectiveness grading	No report	Euodia Decoction (Wuzhuyu Tang)	Decoction	M	N	1
99	Cao W	2011	86	Head & neck, chest, abdominal pelvic & limbs	No report	parallel	CHM + Granisetron	Granisetron	1. Nausea; 2. Vomiting	ER of nausea / vomiting: 93% vs 32.5% / 95.3% vs 30.2%	1. Superior; 2. Superior	1. Severity and effectiveness grading	No report	Puyuan Harmonizing the Stomach Capsule (Puyuan Hewei Capsule)	Capsule	P	N	1
100	Yi H	2011	60	Lung, liver, colon, ovary, breast, stomach & esophagus	No report	parallel	CHM + Granisetron	Granisetron	Nausea & vomiting	ER: 93% vs 66.6%	Superior	1. Effectiveness grading	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	Y	1
101	Wang CY	2011	42	Breast, lung, stomach, colon, ovary & cervix	No report	parallel	CHM + Granisetron	Granisetron	Nausea & vomiting	ER: 90.5% vs 71.4%	Superior	1. Effectiveness grading	No report	Powder of Ginseng, Poria and Atractylodes (Shenling Baizhu San)	Decoction	M	Y	1
102	Xu W	2007	80	Lung, stomach, esophagus, nasal pharynx, certix & urinary bladder	No report	parallel	CHM + Granisetron	Granisetron	Nausea & vomiting	ER: 90% vs 72.5%	Superior	1. ER (for 6 consecutive days)	No report	Upward and Downward Capsule (Shengjiang Capsule)	Capsule	S	N	1
103	Cun XN	2004	104	Esophagus, stomach, colon & rectum	Multiple	parallel	CHM + Integrated WM	Integrated WM	Nausea & vomiting	ER: 94.4% vs 68%	Superior	1. Effectiveness grading	No report	Warming Gallbladder Decoction (Wendan Tang)	Decoction	M	N	1

Additional file 1. (Continued)

Ref No	Author	Year	Partici-pants	Cancer Origin	Regimen of Chemotherapy	Design	Treatment	Control	Outcomes	Primary endpoint (Treatment vs Control)	Beneficial effect	Secondary endpoints	Ethics	Name of Basic Formula	Form	Origin	Indivi-dualized modifi-cation	Jadad scale
104	Yang P	2009	120	Lung, colon, ovary, breast, esophagus, lymphoma, stomach & other	No report	parallel	CHM + Integrated WM	Integrated WM	Nausea & vomiting	ER: 95% vs 66.7%	Superior	1. Effectiveness grading	No report	N/A	Decoction	S	N	1
105	Li ZJ	2009	60	Esophagus, lung, breast, nasal pharynx, lymphoma, stomach, colon & rectum	Multiple	parallel	CHM + Integrated WM	Integrated WM	Nausea & vomiting	ER: 86.7% vs 60.0%	Superior	1. Effectiveness grading; 2. Time to stop vomiting; 3. AEs	No report	Six Gentlemen Decoction with Aucklandia and Amomum (Xiangsha Liujunzi Tang)	Decoction	A	Y	1
106	Cai ZB	2008	110	lung, esophagus, nasal pharynx & ovary	Combinated regimens with cisplatin	parallel	CHM + Integrated WM	Integrated WM	Vomiting	ER: 91.7% vs 70%	Superior	1. Effectiveness grading; 2. No. of response (for 5 consective days)	No report	4 ancient formulas for 4 different syndromes)	Decoction	M	Y	1
107	Hao WP	2008	108	Lung, esophagus, stomach, breast, lymphoma, colorectal, cervix, ovary, nasal pharynx & urinary bladder	Multiple	parallel	CHM	Integrated WM	Nausea & vomiting	ER: 92.6% vs 81.5%	Comparable	1. Effectiveness grading; 2. Complete response rate; 3. AEs	No report	Decoction of Inula and Hematitum (Xuanfu Daizhe Tang)	Decoction	M	Y	1
108	Zhang MB	2011	68	Breast, lung, stomach, colon & rectum	No report	parallel	CHM + Integrated WM	Integrated WM	Nausea & vomiting	Severity grading	Superior	Nil	No report	Four Gentlemen Decoction (Sijunzi Tang)	Decoction	M	N	1
109	Wang XJ	2001	60	No report	No report	parallel	CHM	Vitamin supplements + methyl violet	Oral ulcer	Complete response rate (Day 3): 53.3% vs 20%	Superior	1. Effectiveness grading; 2. complete response rate (on Day 7)	No report	Cutch Powder (Ercha Powder)	Powder	N/A	N	1
110	Hou FJ	2001	101	Lymphoma, breast & lung	Multiple	parallel	CHM	Dobell	Oral ulcer	ER: 96.3% vs 79.2%	Superior	1. Severity and effectiveness grading	No report	Gargle with Chinese Cork-tree and Gall (Huangwu Gargle)	Gargle	S	N	1
111	Wang JY	2002	147	Lymphoma, breast & lung	Multiple	parallel	CHM	Dobell	Oral ulcer	OR: 10.5% vs 23.9%	Superior	1. Severity grading; 2. Time to heal	No report	N/A	Gargle	S	N	1
112	Wang KX	2002	100	Malignant mole, choriocarcinoma, breast, lymphoma & lung	Multiple	parallel	CHM + Integrated WM	Integrated WM	Oral ulcer	ER: 98.1% vs 87.5%	Superior	1. Effectiveness grading	No report	N/A	Gargle	S	N	1
113	Mo L	2011	60	Nasal pharynx, head & neck, breast, stomach & colon	Multiple	parallel	CHM	Vitamin supplements	Oral ulcer	Effectiveness grading	Superior	Nil	No report	Kangfuxin Gargle	Gargle	P	N	1
117	Zhang RY	2007	41	No report	No report	parallel	CHM	Montmo-rillonite	Diarrhea	ER: 86.4% vs 68.4%	Superior	1. Effectiveness grading	No report	Pinellia Decoction for Draining the Heart (Banxia Xiexin Tang)	Decoction	M	N	1
118	Shao HM	2008	160	No report	No report	parallel	CHM	Montmo-rillonite	Diarrhea	ER: 97.5% vs 85%	Superior	1. Effectiveness grading	No report	Decoction for Reinforcing the Healthy Qi and Checking the Diarrhea (Fuzheng Zhixie Tang)	Decoction	S	N	1
119	Kong YZ	2001	44	Stomach, colon, pancreas, lung & breast	Multiple	parallel	CHM	Bifico	Diarrhea	ER: 100% vs 65%	Superior	1. Effectiveness grading; 2. Related TCM symptoms; 3. Further treatment	No report	Harmonizing the Stomach and Cleaning the Intestine Solution (Hewei Qingchang Yin)	Decoction	S	N	1
120	Zeng XQ	2009	89	Stomach, colon & rectum	No report	parallel	CHM	Bifico	Diarrhea	ER: 95.8% vs 73.2%	Superior	1. Effectiveness grading; 2. Bowel profile (Diarrhea, abdominal pain); 3. Coldness symptom)	No report	N/A	Decoction	S	Y	1
122	Ding JY	2010	100	Colon, rectum, lung, breast, stomach, pancreas & other	No report	parallel	CHM	Mosapride	Constipation	ER: 94% vs 80%	Superior	1. Effectiveness grading	No report	Milkvetch Decoction with Immature Orange and Atracty lodes (Zhizhu Huangqi Tang)	Decoction	M	Y	1

Key: CHM: Chinese herbal medicine; Integrated WM: Integrated western medicine; N/A: Not available; ER: Effective rate; OR: Occurance rate. Regimen of chemotherapy: multiple for those studies with more than one chemotherapy regimen. Origin: Origin of CHM formula (A: ancient formula; M: modify from ancient formula; S: self invented formula; P: CHM proprietary; w/o: without details). Individual modification: Y for yes; N for no.

Additional file 2. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Nil
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1 & 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Nil
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-6 Additional file
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6 (Table 3)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-11 (Table 4,5)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Nil
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Nil
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Nil

Additional file 2. (Continued)

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14