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FOLFOX 4 combined with herbal medicine for advanced colorectal cancer: a systematic review

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Abstract

This systematic review evaluates the clinical evidence for the addition of herbal medicines (HMs) to FOLFOX 4 for advanced colorectal cancer (ACRC) in terms of tumor response rate (tRR), survival, quality of life and reduction in adverse events (AEs). Seven electronic databases were searched for randomized controlled trials (RCTs) of FOLFOX4 combined with HMs compared to FOLFOX4 alone. Outcome data for 13 randomized controlled trials were analysed using Review Manager 5.1. Risk of bias for objective outcomes including tumor response and survival was judged as low. Publication bias was not evident. Meta-analyses found the addition of HMs improved tRR (RR 1.25, 95%CI 1.06-1.47, $I^2=0\%$), one year survival (RR 1.51, 95%CI 1.19-1.90, $I^2=0\%$), and quality of life in terms of Karnofsky Performance Status (KPS) gained (RR 1.84, 95%CI 1.54-2.19, $I^2=0\%$); alleviated grade 3 and 4 chemotherapy-related AEs for neutropenia (RR 0.33, 95%CI 0.18-0.60, $I^2=0\%$), nausea and vomiting (RR 0.34, 95%CI 0.17-0.67, $I^2=0\%$) and neurotoxicity (RR 0.39, 95%CI 0.15-1.00, $I^2=0\%$), compared to FOLFOX4 alone. The most frequently used herbs were *Astragalus membranaceus*, *Panax ginseng*, *Atractylodes macrocephala*, *Poria cocos*, *Coix lachryma-jobi* and *Sophora flavescens*. In experimental studies, each of these herbs has shown actions that could have contributed to improved tumor response.

Key words (6): colorectal cancer, FOLFOX, herbal medicine, tumor response, quality of life, meta-analysis

Abbreviations

ACRC: Advanced Colorectal Cancer

AEs: Adverse Events

BW: Body Weight

CAM: Complementary and Alternative Medicine

CNKI: China Academic Journals

CQVIP: Chinese Science and Technology Journals

CR: Complete Remission

CRC: Colorectal Cancer

FOLFOX: 5-Fluorouracil (5-FU) plus Leucovorin (LV) combined with Oxaliplatin

HMs: Herbal Medicines

- KPS: Karnofsky Performance Status
- MD: Mean Difference
- NCI-CTC: National Cancer Institute Common Toxicity Criteria
- NK: Natural Killer
- OS: Overall Survival
- PD: Progressive Disease
- PR: Partial Remission
- QoL: Quality of Life
- RCT: Randomized Controlled Trial
- RD: Risk Difference
- RECIST: Response Evaluation Criteria in Solid Tumors
- RR: Risk Ratio
- SD: Stable Disease
- TNM: Tumor Node Metastasis
- tRR: Tumor Response Rate
- TTP: Time to Progression
- WHO: World Health Organisation

Introduction

Complementary and alternative medicine (CAM) use is common in cancer patients and more than 50% of patients use one or more type of CAM after the diagnosis (Vapiwala *et al.*, 2006), mostly with the aim of improving health and well-being, boosting the immune system and controlling symptoms associated with the disease and treatments (Mansky and Wallerstedt, 2006). In a review of studies of CAM usage by colorectal cancer (CRC) patients in Western countries, Sewitch *et al* 2010 reported up to 75% prevalence of CAM use and herbal medicines (HM) were used by 48.7% of CRC patients in a European survey (Sewitch and Rajput, 2010). An estimated 1.5 billion people use Chinese HM worldwide (Dobos *et al.*, 2005). In cancer therapy, Chinese HM has been reported to alleviate adverse events (AEs) induced by conventional cancer therapy and improve patient's quality of life (QoL) (Molassiotis *et al.*, 2009), enhance cellular immunity of cancer patients receiving chemotherapy/radiotherapy (Zhuang *et al.*, 2009), reduce cancer pain (Xu *et al.*, 2007), relieve cancer related fatigue (Jeong *et al.*, 2010), and improve anorexia and cachexia (Lee and Lee, 2010). Meta-analyses of clinical studies have demonstrated the addition of Chinese HMs to conventional therapy appears to improve tumour response and prolong survival in liver cancer (Shu *et al.*, 2005) and in lung cancer (McCulloch *et al.*, 2006)

Experimental studies have demonstrated that bio-active components in a number of single HMs and multi-herb formulae possess anti-cancer potential. In separate reviews, researchers explored the anti-cancer mechanisms of Chinese HMs and summarized these as multi-action and multi-targeted (Han and Li, 2009; Parekh *et al.*, 2009). The actions of HMs include anti-proliferative activity in cancer cells and induction of tumor cell apoptosis (Auyeung and Ko, 2010; Guo *et al.*, 2013; Nguyen *et al.*, 2013; Tin *et al.*, 2007; Wang *et al.*, 2009a); tumour angiogenesis suppression (Jeong *et al.*, 2011; Law *et al.*, 2012; Wang *et al.*, 2009b); telomerase activity inhibition (Yu *et al.*, 2006); immune function regulation (Gong, 2010); reversal of multiple drug resistance (Huang *et al.*, 2011; Wang *et al.*, 2007; Zhang *et al.*, 2011); enhancing the cytotoxicity of the chemotherapy regimen (Cao *et al.*, 2012; Tin *et al.*, 2007); and management of chemotherapy side effects (Chen *et al.* 2009; Zhu *et al* 2007).

The FOLFOX regimen refers to 5-Fluorouracil (5-FU) plus Leucovorin (LV) combined with Oxaliplatin. It is a standard first line combination chemotherapy setting for advanced CRC (ACRC) (Lee and Chu, 2007; Prescrire Editorial Staff, 2010). A number of modalities of FOLFOX regimens, which consist of varying doses and schedules of 5-FU, LV and Oxaliplatin, have been studied in palliative settings. Of these, FOLFOX4 has been the most widely investigated (Waddell and Solimando, 2005). FOLFOX4 comprises a 2-hour infusion of LV (200 mg/ m²/d), followed by a 5-FU bolus (400 mg/ m²/d) and a 22-hour infusion (600 mg/ m²/d) for 2 consecutive days every 2 weeks, together with Oxaliplatin 85 mg/m² as a 2-hour infusion on day 1. It is used in conjunction with anti-

nausea medications. The regimen is repeated every 14 days until disease progression or unacceptable toxicities force cessation (De Gramont *et al.*, 2000).

FOLFOX4 has good evidence of efficacy for ACRC and is widely used but there are still AEs and these remain a major reason for discontinuation (Raftery and Goldberg, 2010). Consequently, clinicians may add HMs to the chemotherapy with the aim of reducing AEs and improving clinical outcomes (Saif *et al.*, 2010). Systematic reviews of Chinese HMs in CRC treatment found that Chinese HM as an adjuvant treatment during chemotherapy for CRC prolonged 1 year and 3 year survival time, improved QoL, and reduced the incidence of chemotherapy-related AEs such as vomiting and nausea, diarrhoea, and leukopenia (Liu and Zhu, 2009; Wu *et al.*, 2005; Zhong *et al.*, 2012). However, these studies included various stages of CRC and various chemotherapy regimens. One systematic review that focussed on randomized or quasi-randomized controlled trials of Chinese HMs for ACRC using a variety of chemotherapy regimens found the addition of the HMs reduced mortality rate, improved 1 year and 3 year survival rate and QoL but the addition of the HMs did not benefit tumor response rate (tRR) (Guo *et al.*, 2012).

This reviews focuses on HMs as adjuvants to FOLFOX4 in the treatment of ACRC. It includes randomized controlled trials (RCTs) published in medical journals and aims to determine which, if any, HMs demonstrate evidence of efficacy and safety in the treatment of ACRC and/or the management of the side effects of FOLFOX4 and to identify which HMs could have beneficial effects in ACRC.

Method

Searches were conducted of PubMed, Cochrane CENTRAL, CINAHL, Science Direct, PsycINFO, China Academic Journals (CNKI) and Chinese Science and Technology Journals (CQVIP) from their inceptions to December 2012. Three groups of search terms were used: 1. Disorder: colorectal cancer and related terms; 2. Intervention: herbal medicine, complementary medicine, Chinese medicine and related terms; and 3. Study type: controlled trial, randomised and related terms, with modifications according to the individual database. Full lists of search terms are available on request. Results were downloaded to Endnote libraries and combined. Reference lists in review articles and clinical studies were also searched.

Included studies were RCTs that employed FOLFOX4 combined with an HM intervention in the test arm and FOLFOX4 in the control arm, regardless of blinding with no restrictions on language or publication year. Participants were aged 18 to 80 years and had been pathologically diagnosed with ACRC that was either metastatic or regionally advanced, with Tumor Node Metastasis (TNM) stage IV, so curative surgical resection was unlikely to be carried out. Test interventions were HMs used

singly or in combination, in any form including extracts and by any administration route. Only studies that provided data on at least one CRC-related primary or secondary outcome measure were included. Outcome measures could include tRR, survival, QoL, immune function and/or AEs.

Data extraction and Risk of Bias assessments were conducted by two reviewers independently (MC & IZ) with mediation by AZ or BM. Data were extracted using pre-designed data collection forms. The validity of the outcomes of the included studies was assessed using the Cochrane Risk of Bias assessment method which includes the following categories of bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias. The approach was according to the Cochrane Handbook version 5.1.0 (Higgins *et al.*, 2011). Each domain was labelled 'low risk' or 'high risk' or 'unclear risk', with the last category indicating that there was insufficient information to judge the potential for bias.

Review Manager (RevMan) 5.1 was used for meta-analysis. Methods were based on Cochrane Handbook 5.1.0. Risk Ratio (RR) or Mean Difference (MD) with 95% confidence intervals (95% CI) using fixed or random-effect models depending upon heterogeneity were used. Risk Difference (RD) was calculated and presented as the percentage difference between the RRs of the test and control groups. The proportion of heterogeneity was measured using I^2 . It was defined as substantial heterogeneity if I^2 was more than 50%. In such cases sensitivity tests were done. When the same outcome was reported by more than 10 studies, publication bias was assessed using a funnel plot (Higgins *et al.*, 2011).

Results

Database searches located 1,927 potentially relevant citations and 37 studies were identified by checking reference lists and print journals. Following screening, 68 studies were considered. These included nine studies that compared HM with placebo, no treatment, or chemotherapy and 58 that compared the combination of HM plus a non-FOLFOX4 chemotherapy regimen with the chemotherapy alone. Thirteen studies (Ding *et al.*, 2010; Fang and Li, 2008; Li *et al.*, 2007b; Li *et al.*, 2007c; Qiu, 2011; Wu G *et al.*, 2010; Xu and Wang, 2010; Yang, 2008; Zeng *et al.*, 2009; Zeng *et al.*, 2008; Zhang *et al.*, 2008; Zhang *et al.*, 2010a; Zhang *et al.*, 2010b) that investigated a combination of HM plus FOLFOX4 versus FOLFOX4 for ACRC were included in this review (Fig 1).

The 13 studies enrolled 940 assessable in-patient participants with 486 participants in the test groups and 454 participants in the control groups. All studies were conducted in China and published in Chinese medical journals from 2007 to 2011. Participant characteristics, interventions and outcome measurements are summarized in Table 1.

Twelve different test interventions were used. Seven studies employed commercially available HM extracts. Kang' ai Injection was used in two studies. Compound Kushen injection, Ginsenoside Rg3 capsules, Aidi injection, Guben Xiaoliu Capsule and Javanica oil injection were each used in one study. Six studies used multi-herbal decoctions. In total, 58 different herbs and/or their extracts were used, with the six most frequent being:

Huang qi *Astragalus membranaceus* (Fisch.) Bge. root (7 studies) (Li *et al.*, 2007b; Li *et al.*, 2007c; Qiu, 2011; Yang, 2008; Zeng *et al.*, 2008; Zhang *et al.*, 2008; Zhang *et al.*, 2010b);

Yi yi ren *Coix lachryma-jobi* L. seed (6 studies) (Li *et al.*, 2007c; Wu *et al.*, 2010; Xu and Wang, 2010; Zeng *et al.*, 2008; Zhang *et al.*, 2008; Zhang *et al.*, 2010a);

Ren shen *Panax ginseng* C.A.Mey. root (5 studies) (Li *et al.*, 2007b; Qiu, 2011; Yang, 2008; Zeng *et al.*, 2009; Zhang *et al.*, 2010a);

Ku shen *Sophora flavescens* Ait. root (5 studies) (Ding *et al.*, 2010; Qiu, 2011; Yang, 2008; Zeng *et al.*, 2008; Zhang *et al.*, 2008);

Bai zhu *Atractylodes macrocephala* Koidz. root (5 studies) (Li *et al.*, 2007c; Xu and Wang, 2010; Zeng *et al.*, 2008; Zhang *et al.*, 2008; Zhang *et al.*, 2010b); and

Fu ling *Poria cocos* (Schw) Wolf sclerotium (4 studies) (Li *et al.*, 2007c; Wu *et al.*, 2010; Xu and Wang, 2010; Zhang *et al.*, 2008).

Methodological assessment

All studies claimed to be randomized. Five studies (38.4%) stated a proper method of generation of randomization sequence, so the risk of bias was judged as 'low' in these studies (Ding *et al.*, 2010; Fang and Li, 2008; Li *et al.*, 2007c; Wu *et al.*, 2010; Zhang *et al.*, 2010a). The other eight studies did not describe the randomization method and were judged as 'unclear'. None of the studies described the procedure of allocation concealment. Therefore, an 'unclear' judgement was made (Table 1).

A placebo group was not used in any of the studies and none reported a method of blinding. There is generally no blinding in oncology trials (Hind D *et al.*, 2008), so we expect that all trials were open to participants and personnel. Thus, there was possible performance bias and detection bias for subjective outcomes such as QoL and AEs. Therefore a 'high' risk of bias was judged for subjective outcomes. Radiologists and laboratory pathologists measured the objective outcomes, such as tumor response and laboratory tests. Outcome data on survival rate and time to progression was obtained from medical records. These kinds of data were unlikely to have been influenced by lack of blinding, so we judged 'low risk' of detection bias for these outcomes. Three studies reported the numbers of participants who dropped out during the trial or were lost to follow-up (Ding *et al.*, 2010; Li *et al.*, 2007c; Zhang *et al.*, 2010b) but no reasons were given and these missing data were not treated as 'intent to treat'. So, these were judged as 'high risk' of attrition bias. Studies that had the same

numbers of participants at the inception as at the outcome reports were judged as 'low risk' of attrition bias. None of the studies had published study protocols. When the study objectives and outcome measures were stated in the study method section and when all outcomes were reported in the results section, the study was judged as 'low risk' of reporting bias (Table 1).

Twelve studies reported on tRR so a Funnel Plot was used to assess publication bias (Fig. 2). The symmetry of the Funnel Plot suggests the risk of publication bias was low for these studies.

Meta-analysis results

Meta-analyses were performed for each of the following outcomes. The numerical data are presented in Table 2.

1. Tumor response rate (tRR)

Twelve studies reported tRR. Ten evaluated tRR using the WHO solid tumor response criteria (Miller *et al.*, 1981) as follows: complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The other two studies (Qiu, 2011; Zhang *et al.*, 2010b) used the RECIST criteria, which use similar categories (Park *et al.*, 2003), so data could be pooled for all studies. CR plus PR was defined as 'clinically effective' so these data were included in meta-analyses. When the Risk Ratio (RR) is more than 1 (IV model, Fixed, 95% CI) it favours the test group. Positive outcomes favour test groups.

The tRR ranged from 30% to 54.1% for the test groups and from 20% to 46.6% for the control groups in the 12 studies (880 participants)(Fang and Li, 2008; Li *et al.*, 2007b; Li *et al.*, 2007c; Qiu, 2011; Wu G *et al.*, 2010; Xu and Wang, 2010; Yang, 2008; Zeng *et al.*, 2009; Zeng *et al.*, 2008; Zhang *et al.*, 2008; Zhang *et al.*, 2010a; Zhang *et al.*, 2010b). There was a significant improvement in tRR for HMs plus FOLFOX4 (test groups) compared to FOLFOX4 alone (Table 2). The pooled tRR in the test groups was elevated to 44.1% (RD 9.2%). For the two studies of Kang'ai Injection, the RD was 3.0% but there was no significant difference between groups. The total numbers of complete remissions (CRs) in the test and control groups were 19 and 8 patients respectively but this difference was not significant (RD 2.8%). The tRR data included 234 (24.9%) participants who were previously treated with chemotherapy for ACRC but separate results were reported for only 126 of these. Previously treated ACRC patients have been found to be less responsive to current first-line settings of chemotherapy (Giantonio *et al.*, 2007). When the subgroups of previously treated (2 studies) and previously untreated (3 studies) patients were analysed, the RD of the pooled tRR was 8.7% in each group but there was no significant difference between test and control groups (Table 2).

2. Overall survival (OS) and time to progression (TTP)

Time to event data for OS was treated as dichotomous data with the number of surviving participants in each treatment group at one year as the event number entry and the total number of participants in each group as the total number entry (Higgins *et al.*, 2011). Three studies reported one year OS. There was a significant difference in favour of the test groups (RD 20.2%) (Table 2). No long-term (two years or more) OS data were reported.

Median OS and median TTP were each reported in three studies. Median OS was 12.5 months for the test group versus 10.8 months for the control group in one study (Li *et al.*, 2007b); 13.6 months (test) versus 10.2 (control) in another study (Zhang *et al.*, 2010b); and 19.8 months (test) versus 18.6 (control) in Ding *et al* (2010). Median TTP was 8.1 months (test) versus 6.9 months (control) in Zhang *et al* (2010b), 9.2 (test) versus 8.7 months (control) in Ding *et al* (2010), and 16.5 months (test) versus 10.2 months (control) in Xu *et al* (2010). Meta-analysis was not feasible.

3. Quality of life (QoL) and body weight (BW)

Ten studies used Karnofsky Performance Status (KPS) to measure QoL changes before and after treatment (Li *et al.*, 2007b; Li *et al.*, 2007c; Qiu, 2011; Wu G *et al.*, 2010; Xu and Wang, 2010; Zeng *et al.*, 2009; Zeng *et al.*, 2008; Zhang *et al.*, 2008; Zhang *et al.*, 2010a; Zhang *et al.*, 2010b). KPS is a single dimension scale that provides a global measurement of patient physical function. Its reliability and validity have been investigated and verified (Granda-Cameron C *et al.*, 2008). Nine studies defined a KPS score gain of ≥ 10 points as ‘improved’; a decline of ≥ 10 points as ‘worse’; and changes of less than 10 points as ‘stable’. Three studies (Yang, 2008; Zeng *et al.*, 2009; Zhang *et al.*, 2010b) included body weight (BW) measurement. BW gain ≥ 1.0 kg was defined as ‘improved’ and weight loss of ≥ 1.0 kg was defined as ‘worse’. Changes in the range between ‘improved’ and ‘worse’ were defined as ‘stable’.

Clinical effectiveness was defined as ‘improved’ for KPS and as ‘improved’ for BW. To minimize bias resulting from small changes in scores, the meta-analyses only included patients who recorded a KPS score that was 10 or more points higher after the intervention compared to prior to the intervention and patients who had gained 1 kg or more. Patients who achieved a stable KPS score and/or stable BW after the intervention were excluded from the analyses.

The KPS improvement was significantly greater in the test groups based on 9 studies (RD 28.8%) (Table 2). In Wu *et al* (2010), KPS was presented as mean plus standard deviation (SD). There was no statistically significant difference before and after the treatment in the test group (MD 0.44, 95% CI - 3.94 to 4.82, $p=0.84$) but there was a significant decline after treatment in the control group (MD

13.40, 95% CI 7.22 to 19.58, $p < 0.0001$), so the mean KPS after treatment was significantly higher in the test group, indicating a relative improvement in the test group (Table 2).

Yang (2008) reported Su Ying's QoL Questionnaire which comprised 12 items which are scored 5-1 according to increase in severity, so the more severe the symptoms the lower the score. In the test group, the total score was not significantly different before and after the treatment (MD -1.57, 95% CI -3.44 to 0.30, $p = 0.10$) but it significantly decreased in the control group after treatment (MD 2.70, 95% CI 1.34 to 4.06, $p < 0.0001$). The between-groups scores after treatment were significantly different in favor of the test group (Table 2). There was a significant difference in body weight improvement in favour of the test group based on three studies (RD 18.9%) (Table 2).

4. Alleviation of adverse events associated with chemotherapy

All 13 studies reported that the HMs alleviated chemotherapy toxicity. The criteria for grading acute and subacute toxicity recommended by WHO (Miller *et al.*, 1981) were used in ten studies and three studies (Qiu, 2011; Yang, 2008; Zhang *et al.*, 2010a) used the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (National Cancer Institute, 1999). These systems use similar grading criteria so we followed Hind (2008) and pooled data where possible (Hind D *et al.*, 2008). Zhang *et al.* reported events as gastrointestinal reactions or myelosuppression (Zhang *et al.*, 2008), and Zeng *et al.* reported toxicity events as totals (all grades) (Zeng *et al.*, 2009). Therefore, these two studies were not included in the meta-analysis.

Most of the AEs were mild (grades 1-2). The three most commonly reported AEs were nausea and vomiting, neutropenia, and neurotoxicity. The meta-analyses included toxic events at grades 3 and 4 only (i.e. severe toxicity) (Table 2). The pooled grade 3 and 4 events for neutropenia ($n=10$, RD 8.7%), nausea and vomiting ($n=9$, RD 9.5%), and neurotoxicity ($n=7$, RD 3.8%) were significantly fewer in the test groups. For the Kang'ai Injection sub-group ($n=2$), significant reductions were found for neutropenia (RD 17.8%) and nausea and vomiting events (RD 15.8%). No significant difference between groups was found for the pooled grade 3 and 4 events for: diarrhoea (5 studies, RD 2.4%), anaemia (3 studies, RD 2.9%), stomatitis (2 studies, RD 2.3%), thrombocytopenia (1 study), or constipation (1 study). Adverse events specific to the HMs were not reported in any of the 13 studies.

5. Effect on immune function

Four studies reported effects on immune function, in terms of the percentage of T-lymphocyte subsets and Natural Killer (NK) cell activity in serum. One study reported benefits for T-cells and NK cells but data were as difference scores, so these could not be included in pooling (Zeng *et al.*, 2009). There

was a significant improvement in the pooled data for CD3+ cells (Wu G *et al.*, 2010), and Ratio CD4+/CD8+ cells (Ding *et al.*, 2010; Zhang *et al.*, 2010a) (Table 2). For CD4+, CD8+ cells and NK cells, there were benefits reported in some studies but the pooled results were too heterogeneous to be meaningful.

Discussion

All thirteen studies included in this review were published after 2007 and all employed FOLFOX4 as a single regimen. Since this is currently the most commonly used first-line chemotherapy regimen for ACRC, the results of this review are of direct clinical relevance.

Internationally recognized measurement systems were used in all included studies, including the TNM staging system, WHO criteria for solid tumor response and grading of acute and subacute toxicity, and the KPS scoring system. Participants' age was in the range 48-60 in nine studies and one study enrolled participants whose mean age was 72.7 years (Li *et al.*, 2007c). From an international perspective, the majority of the cohort was younger than the general population of CRC patients whose median age is over 70. A tendency for trial participants to be younger than the average CRC patient has been found in other ACRC trials but younger patients did not appear to respond better or experience less toxicity than older patients (Hind D *et al.*, 2008), so this difference was judged as not likely to affect the generalizability of results. Overall, the heterogeneity of meta-analyses was low for the clinical outcome measures.

The pooled data indicate the addition of the HMs significantly improved tRR when compared to FOLFOX4 alone (Table 2). In the sub-group analysis of tRR for previously treated and untreated ACRC participants the results showed a similar benefit for the HM in both groups (RD 8.7% in each) but this did not reach significance (Table 2). It is possible that the small number of participants in these sub-groups meant there was insufficient statistical power to detect a difference. The additional HM intervention improved CR (RD 2.8%) but it was not statistically significant. It is notable that FOLFOX4 itself has not yielded high CRs in ACRC (Cassidy *et al.*, 2008; De Gramont *et al.*, 2000; Goldberg *et al.*, 2004; Goldberg *et al.*, 2006). Overall, these results suggested that the HMs conferred an additional benefit to tRR when combined with FOLFOX4 for ACRC. But these results need to be verified by a large scale clinical trial.

The review by Zhong *et al* (2012) included 20 studies that used a number of chemotherapy regimens for a range of CRC stages including two studies that used FOLFOX 4. These two studies were not included in the present meta-analysis since they did not use FOLFOX 4 alone for ACRC, so there is no overlap between these two reviews. Zhong *et al* (2012) reported benefits for tRR, survival, KPS, immune response and chemotherapy AEs. In contrast, the review of 20 RCTs for ACRC by Guo *et al*

(2012) found HM did not benefit tRR. Six of the studies in the present review were also included in Guo *et al* (2012). The likely reason for the different result is Guo *et al* (2012) analyzed tRR separately for each study. Since each study was small, there was insufficient statistical power to detect an effect. In the present review, the focus on a single chemotherapeutic intervention enabled more meaningful meta-analyses, as did the separate analyses of tRR for previously treated and untreated ACRC participants.

One year-OS was greater in the HM plus FOLFOX4 groups compared to FOLFOX4 alone (Table 2). Median OS in the FOLFOX4 plus HM group ranged from 12.5 to 19.8 months (Ding *et al.*, 2010; Li *et al.*, 2007b; Zhang *et al.*, 2010b) and the median TTP ranged from 8.1 to 16.5 months (Ding *et al.*, 2010; Xu and Wang, 2010; Zhang *et al.*, 2010b). So the addition of the HM appeared to modestly improve both median OS and TTP but meta-analyses were not feasible.

Other outcomes

Participants in the test groups were more likely to show a KPS improvement than in the control groups (RD 28.8%). For chemotherapy-related AEs, significant reductions were found in the test groups for grade 3 and 4 neutropenia (T: 3.9% vs C: 12.6%), nausea and vomiting (T: 3.0% vs C: 12.5%) and neurotoxicity (T: 2.2% vs C: 6.0%) (Table 2). These findings were generally consistent with earlier reviews of HM adjuvant to chemotherapy for CRC (Liu and Zhu, 2009; Wu *et al.*, 2005; Zhong *et al.*, 2012).

The results for T-lymphocyte subsets suggest that some HMs may have immune enhancing effects but these data were only available for a few studies and there was substantial heterogeneity in some of the meta-analyses (Table 2). It is notable that the following HMs that were used in these studies, *Astragalus membranaceus*, *Panax ginseng*, *Atractylodes macrocephala*, *Poria cocos* and *Coix lachryma-jobi*, have been reported to have immunomodulatory effects (Gong, 2010; Yang *et al.*, 2002; Yang *et al.*, 2011).

Comparison with other studies of FOLFOX4

The improvement in tRR of 20.0% to 46.6 % (average 34.9%) for the control groups in 12 studies was consistent with the results of a review by Lu *et al* (2010) that pooled 27 clinical studies of FOLFOX4 for ACRC conducted in China (879 participants), none of which involved a comparison with HM (Lu *et al.*, 2010). The review by Lu *et al* found the following tRRs: total 26.10-57.14% (27 studies); previously untreated patients 30.8-65.0% (12 studies); and previously treated patients 16.6-47.6% (12 studies). In this review, the pooled tRRs of 34.9% for all control group participants, 42.4 % for previously untreated participants, and 21.0% for previously treated participants all fell within these ranges, so the results for the control groups in this review are broadly consistent with non-HM studies

conducted in China on FOLFOX4. In the control groups in this review, the median OS was 10.2-18.6 months and the TTP was 6.9-10.2 months, which were similar to the ranges found in the review by Lu *et al* (OS 9.0-17.7 months, TTP 5.47-9.00 months) (Lu *et al.*, 2010).

We noticed the average tRR (34.9%) in the control groups in this review and in the review of Chinese FOLFOX4 studies (Lu *et al.*, 2010) were relatively low compared to large international trials (Cassidy *et al.*, 2008; De Gramont *et al.*, 2000; Goldberg *et al.*, 2004; Goldberg *et al.*, 2006) in which the tRRs were in the range 45.0-58.5%. These international trials only included previously untreated ACRC, whereas in this review the trial participants were both previously treated and untreated ACRC participants and there were no second line treatments in the Chinese trials. Both these factors could adversely affect the outcomes for tRR (De Gramont *et al.*, 2000; Giantonio *et al.*, 2007).

In the included studies, the most common FOLFOX4-related grade 3 and 4 AEs were neutropenia, nausea and vomiting, diarrhoea, and neurotoxicity, which are the same as in the international studies (Cassidy *et al.*, 2008; De Gramont *et al.*, 2000; Goldberg *et al.*, 2004; Goldberg *et al.*, 2006). However, the incidence rates for grade 3-4 neutropenia, neurotoxicity and diarrhoea in the pooled control group data were less than in the international studies. A likely reason for this difference is the relatively short duration of treatment in the studies in this review, since neutropenia and neurotoxicity tend to become more severe the longer the chemotherapy continues (Boisdron-Celle *et al.*, 2002; De Gramont *et al.*, 2000). The grade 3-4 nausea and vomiting rate was comparable to the international studies. This may due to the preventive use of anti-emetic drugs and dose modification in FOLFOX4 protocols which enable control of the severity of nausea and vomiting even with longer treatment.

Limitations to this systematic review

In interpreting the findings of this systematic review a number of factors need to be considered including methodological issues, trial duration, the nature and size of study samples, and variation in the HMs used. All studies claimed to be randomized but only five stated an appropriate method of sequence generation and none provided information on allocation concealment procedures, so there was potential for selection bias. Lack of blinding increases the risk of bias for subjective outcomes such as KPS and AEs such as nausea, so the results for these outcomes should be considered less reliable than for more objective measures such as tRR and OS. Three studies did not report reasons for dropouts or loss to follow-up. Methodological issues of these types have been found in trials of both conventional medicine and HM conducted in China (Wu *et al.*, 2009). Clinical trial reporting needs to be clear, complete and transparent (Moher *et al.*, 2010), so there is a pressing need for improvements in the conduct of clinical trials in China and for proper reporting of methods and results in Chinese journals.

Most the studies were relatively small and small trials appear to overestimate true effects (Higgins *et al.*, 2011). Some trials appear to have included both previously treated and untreated participants without reporting separate results for these two groups who could be expected to show differential responses to interventions. Other issues are quality control of the medicines prepared by the investigators' hospitals and the use of test medicines that comprise multiple ingredients which may vary in quality from batch to batch and may be affected by decoction conditions. These factors limit the comparability of studies. While there was no apparent publication bias based on the Funnel Plot for tRR, there may have been bias in favor of positive trials for other outcomes.

How these HMs might work

Except for Kang'ai injection, which was tested in two studies, different multi-herb decoctions or manufactured products were tested in each study. Therefore, on the basis of the clinical trial results alone, it is difficult to determine which individual herbs could have contributed to the reported effects. The main rationale for combining Chinese HMs with chemotherapy was the alleviation of AEs. Of the six most commonly used herbs in these RCTs, *Astragalus*, *Ginseng*, *Atractylodes*, *Poria* and *Coix* are traditionally used for fatigue, poor appetite, diarrhoea and other gastrointestinal disorders (Bensky *et al.*, 2004) and each of these herbs has been reported to have immunomodulatory effects (Gong, 2010; Shergis *et al.*, 2012; Yang *et al.*, 2011). These actions may at least partially account for the reported improvements in AEs. In addition, recent experimental research into each of the six herbs used most frequently in the 13 studies indicates that each has effects that may contribute to the suppression of tumor growth. The findings of these studies are discussed below.

Astragalus polysaccharides have been shown to have anti-proliferative effects in cell-line studies (Zong *et al.*, 2012). *Astragalus* saponins inhibited proliferation in a human colorectal cancer HT-29 cell line regardless of the p53 status, demonstrated tumor suppressive effects in a nude mice xenograft model, enhanced the cytotoxic effect of 5-FU (Tin *et al.*, 2007) and have demonstrated anti-angiogenic effects (Law *et al.*, 2012). *Astragalus* flavonoids have also been reported to have pro-apoptotic effects in colon cancer HCT-116 cells (Auyeung and Ko, 2010).

A number of studies have found ginsenosides and ginseng polysaccharides to have anti-proliferative and pro-apoptotic effects (Nag *et al.*, 2012; Zong *et al.*, 2012). The ginsenoside Rg3 inhibited growth of tumours *in-vivo* in HCT-116 cells (He *et al.*, 2011) and has shown anti-angiogenic activities (Wang *et al.*, 2009b). Also, the ginseng saponin metabolite, compound K, has been reported to inhibit metastatic growth in hepatocellular carcinoma both *in-vitro* and *in-vivo* (Ming *et al.*, 2011).

Coix seed has a long history as an anti-cancer agent in China and has been developed into an injectable product (Kanglaite Coix oil extract) (Li, 2007; Woo *et al.*, 2007). *Coix* extracts have been

shown to have anti-inflammatory and anti-carcinogenic effects in animal models of CRC (Chung *et al.*, 2010; Li *et al.*, 2011). Polysaccharides from *Poria cocos* appear to potentiate immune response by up-regulating immune stimulators and down-regulating immune suppressors and have shown antitumor activity in various cancer cell lines by suppressing tumor angiogenesis (Rios, 2011).

Compounds derived from *Atractylodes* have shown bio-activity *in-vitro*. Anti-inflammatory effects have been reported for atractylenolide I and atractylenolide III (Li *et al.*, 2007a) and atractylenolide II inhibited proliferation of B16 cells, induced G1 cell-cycle arrest and induced apoptosis (Ye *et al.*, 2011). In mouse splenocytes, *Atractylodes* glycoproteins stimulated both Th1 and Th2 lymphocyte proliferation with a greater effect on Th1 lymphocytes (Lee *et al.*, 2007). In an RCT of cachectic cancer patients (n=64), the administration of a lactone from *Atractylodes* improved mid-arm muscle circumference, reduced the serum levels of interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-alpha) and reduced urine proteolysis-inducing factors (PIF) (Liu *et al.*, 2005).

The alkaloids matrine and oxymatrine found in *Sophora* root have been developed into anti-cancer agents in China and *Sophora* flavonoids appear to have antitumor activity (Sun *et al.*, 2012), for example, sophoflavescenol has shown cytotoxicity in a number of cancer cell lines as well as having antioxidant, anti-inflammatory and apoptotic activities (Jung *et al.*, 2011).

While it appears possible that at least some of the HMs used in these studies may have contributed to tumor response directly, it is also possible that this effect was indirect via alleviating AEs and thereby enabling patients to better tolerate the chemotherapy. Further research is needed to investigate these issues.

Conclusion

The meta-analysis results suggest the addition of these HMs to a FOLFOX4 regimen in ACRC increases tumor response rate (tRR) and one year survival but evidence is lacking for longer term effects. The addition of the HM interventions appear to have improved quality of life and reduced the incidence of severe neutropenia, nausea, vomiting, and neurotoxicity associated with the chemotherapy. Experimental studies on the actions of the most commonly used herbs suggest possible anti-tumor activity which may at least partially explain these results. However, methodological weaknesses were evident in each of the RCTs so any conclusions must be tentative. Further investigation is required using sufficiently powered, rigorously designed RCTs over longer durations.

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Figure Titles and Legends

Fig 1. Flow diagram of the search and selection process of RCTs of FOLFOX4 combined with herbal medicine (HM) for advanced colorectal cancer (ACRC)

Fig 2. Funnel Plot of the 12 studies that reported tumor response rate (tRR)

Label for X axis: Risk Ratio (RR) for tumor response rate (tRR)

Label for Y axis: Sample size of study

Table 1 Characteristics of the thirteen studies included in the analysis

First author (year); Sample size T/C; Duration; Funding.	Gender (M) T/C; Age T/C; KPS all.	Previously untreated T/C; Previously treated T/C; Metastatic sites T/C.	HM: name (manufacturer), ingredients (pinyin, scientific name, part); dosage & administration; FOLFOX4: cycles (T/C).	Outcome measures	HM AEs; Drop outs; Follow-up.	Risk of Bias (SG, AC, BPt, BOA, IOD, SOR)
Ding X (2010); 30/30; 09/2007 to 08/2008; NS.	18/20; 64.5/63; ≥ 70.	NS; NS; NS.	Compound Kushen Injection (Zhendong Jinjing Pharmaceutical Co.): Ku shen, <i>Sophora flavescens</i> Ait. root; Bai tu ling, <i>Heterosmilax yunnanensis</i> Gagnep. root; 20 ml, ID, day 1-7, for 8 cycles; FOLFOX 4: 8/8.	Median OS; Median TTP; AEs (leukopenia, nausea, vomiting, neurotoxicity); T-cell subsets (CD3+, CD4+, CD8+), NK cells.	NS; None; 20 months; T: 4 lost to follow-up C: 5 lost to follow-up	SG: L AC: U BPt: H BOA (sub): H BOA (obj): L IOD: U SOR: L
Fang M (2008); 48/45; 05/2002 to 06/2007; NS.	30/28; 59.5±11.3/56.4±10.3; ≥ 70.	NS; NS; NS.	Javanica oil Emulsion Injection (Shenyang Pharmaceutical University Pharmaceutical Co.): Yan dan zi, <i>Brucea javanica</i> (L.) Merr. seed; 30 ml diluted with saline, 250 mL ID, day 1-14, for 2 cycles; FOLFOX 4: 2/2.	tRR; Chemotherapy AEs (leukopenia, anaemia, thrombocytopenia, nausea, vomiting, diarrhoea, stomatitis, neurotoxicity, alopecia); KPS.	NS; None; NS.	SG: L AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L
Li HJ (2007); 65/52; 10/2002 to 02/2006; NS.	43/36; 58/59 (median); 70(median).	31/20; 34/32; NS.	Aidi Injection (Guizhou Yibai Pharmaceutical Co): Ren shen, <i>Panax ginseng</i> C.A.Mey. root; Huang qi, <i>Astragalus membranaceus</i> (Fisch.) Bge. Root; Ci wu jia, <i>Acanthopanax senticosus</i> (Rupr.et Maxim.) Harms. root; Ban mao, <i>Mylabris phalerata</i> Pallas; 60 ml (0.3g crude drug/ml) diluted with 250 ml 5% glucose	tRR; Chemotherapy AEs (leukopenia, anaemia, thrombocytopenia, nausea, vomiting, diarrhoea, constipation, stomatitis, liver/kidney	NS; None; Until 05/2007.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L

			injection fluid ID, day 1-10, 14 days/cycle, for 11 weeks; FOLFOX 4:5.5/5.5 (mean)	impairment, neurotoxicity, alopecia); Median OS; One year OS; KPS.		
Li YJ (2007); 20/18; 01/2005 to 04/2006; NS.	22 (all); 72.7 (median, all); ≥ 60 .	28(all); 10(all); NS.	Wenshenjianpi decoction (NS): Rou cong rong, <i>Cistanche deserticola</i> Y. C. Ma. herb; Yin yang huo, <i>Epimedium grandiflorum</i> Mot. leaf; Gou ji, <i>Lycium barbarum</i> L. fruit; Dang shen, <i>Codonopsis pilosula</i> (Franch.) Nannf. root; Huang qi, <i>Astragalus membranaceus</i> (Fisch.) Bge. root; Bai zhu, <i>Atractylodes macrocephala</i> Koidz. root; Fu ling, <i>Poria cocos</i> (Schw) Wolf sclerotium; Yi yi ren, <i>Coix lacryma-jobi</i> L. seed; Yu jin, <i>Curcuma wenyujin</i> Y. H. Chen et C. Ling. rhizome; Shan zha, <i>Crataegus pinnatifida</i> Bge. fruit; Mai ya, <i>Hordeum vulgare</i> L. germinating seed; Ban zhi lian, <i>Scutellaria barbata</i> D. Don. herb; modified. One decoction per day orally administered concurrently with chemotherapy for median 10-12 weeks; FOLFOX 4: 6/5.5 cycles (median)	tRR; Chemotherapy AEs (leukopenia, anaemia, thrombocytopenia, liver impairment, nausea, vomiting, diarrhoea neurotoxicity); KPS.	NS; C: 1 no reason given; NS.	SG: L AC: U BPt: H BOA (sub): H BOA (obj): L IOD: H SOR: L
Qiu ZC (2011); 22/21*; 01/2005 to 08/2009; NS.	14/13; 56.9/52.7 (median); ≥ 60 .	22/21; NO; NS.	Kang'ai Injection (Jilin Changbaishan Pharmaceutical Co): Ku shen, <i>Sophora flavescens</i> Ait. root; Ren shen, <i>Panax ginseng</i> C.A.Mey. root; Huang qi, <i>Astragalus membranaceus</i> (Fisch.) Bge. root; 40ml of Kang'ai injection diluted with 250 ml 5% glucose injection fluid ID, day 1-10, 14 days/cycle, for 4 cycles; FOLFOX 4: 4/4 cycles.	tRR; Chemotherapy AEs (leukopenia, nausea & vomiting); KPS.	NS; None; NS.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L
Wu GL (2010);	23/17; 55.4	NS; NS;	Fupiyiwei decoction (NS): Shi hu, <i>Dendrobium loddigesii</i> Rolfe. stem; Cang zhu, <i>Atractylodes</i>	tRR; Chemotherapy AEs	NS; None;	SG: L AC: U

33/25; 10/2004 to 05/2008; Provincial fund.	±13.6/52.8 ±15.2 (mean); ≥ 60.	NS.	<i>lancea</i> (Thumb.) DC. root; Yi yi ren, <i>Coix lacryma-jobi</i> L. seed; Ban xia <i>Pinellia ternata</i> (Thunb.) Breit. tuber; Shan yao, <i>Dioscorea opposita</i> Thunb. rhizome; Fu ling, <i>Poria cocos</i> (Schw) Wolf. sclerotium; Dou kou, <i>Alpinia katsumadai</i> Hayata. seed; Jiao gu lan, <i>Gynostemma pentaphyllum</i> (Thunb.) Mak. herb; Bai shao, <i>Paeonia lactiflora</i> Pall. root; Huo xiang, <i>Pogostemon cablin</i> (Blanco) Benth. herb; One decoction per day oral-administered concurrently with chemotherapy for 24 weeks; FOLFOX 4: 12/12 cycles	(leukopenia, anaemia, thrombocytopenia, nausea, vomiting, diarrhoea neurotoxicity); KPS; T-cell subsets (CD3+, CD4+, CD8+), NK cells.	NS.	BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L
Xu YX (2010); 61/60; 08/2004 to 11/2008; NS.	38/37; 53/52 (mean); ≥ 70.	NS; NS; NS.	Jiangniling decoction (NS): Dang shen, <i>Codonopsis pilosula</i> (Franch.) Nannf. root; Bai zhu, <i>Atractylodes macrocephala</i> Koidz. root; Fu ling, <i>Poria cocos</i> (Schw) Wolf. sclerotium; Bai dou kou, <i>Amomum cardamomum</i> L. seed, Ban xia, <i>Pinellia ternata</i> (Thunb.) Breit. tuber; Sha ren, <i>Amomum villosum</i> Lour. seed; Xiang fu, <i>Cyperus rotundus</i> L. rhizome; Chen pi, <i>Citrus reticulata</i> Blanco. peel; Zhu ru, <i>Phyllostachyl nigra</i> (Lodd.). shaving; Sheng jiang, <i>Zingiber officinale</i> Rosc. rhizome; Yi yi ren, <i>Coix lacryma-jobi</i> L. seed; One decoction per day orally administered concurrently with chemotherapy for 22 weeks; FOLFOX 4: 11.1/7.8 cycles (mean).	tRR; Chemotherapy AEs (nausea, vomiting, diarrhoea, anaemia, leukopenia, thrombocytopenia); TTP; KPS.	NS; None; NS.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L
Yang YF (2008); 30/30; 01/2007 to 11/2007; NS.	16/19; 51.07±10.44/ 51.33 ±10.95 (mean); 40.73±3.49/ 40.90±2.44.	9/7; 21/23; NS.	Kang'ai Injection (Jilin Changbaishan Pharmaceutical Co): Ku shen, <i>Sophora flavescens</i> Ait. root; Ren shen, <i>Panax ginseng</i> C.A.Mey. root; Huang qi, <i>Astragalus membranaceus</i> (Fisch.) Bge. root; 50ml of Kang'ai injection diluted with 250 ml 5% glucose injection fluid ID per day, day 1-20, 30 days/course, for 2 courses;	tRR; Chemotherapy AEs (leukopenia, anaemia, thrombocytopenia, liver impairment, nausea, vomiting, diarrhoea, neurotoxicity); QOL, BW.	NS; None; NS.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L

			FOLFOX 4: 4/4 cycles.			
Zeng DX (2009); 35/32; 02/2007 to 12/2008; Provincial fund.	16/19; 50-70 (range); ≥ 70.	67(all); NO; Liver: 15/19, Lung: 8/7, Others: 9/9.	Ginsenoside Rg3 capsules (Jilin Yatai Pharmaceutical Co): 2 capsules/day, administered concurrently with chemotherapy for 8 weeks. FOLFOX 4: 4X4 cycles	tRR; Chemotherapy AEs (leukopenia, nausea, vomiting, diarrhoea, neurotoxicity); T cell subsets (CD3+, CD4+, CD8+, CD4+/CD8+).	NS; None; NS.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L
Zeng JQ (2008); 30/30; NS; NS.	19/18; 48/60 (median); ≥ 60.	NO; 30/30; Liver: 14/7, Lung: 6/8, Others: 15/12.	Basic HM formula (NS): Huang qi, <i>Astragalus membranaceus</i> (Fisch.) Bge. root; Bai zhu <i>Atractylodes macrocephala</i> Koidz. root; Yi yi ren, <i>Coix lacryma-jobi</i> L. seed; Ban zhi lian, <i>Scutellaria barbata</i> D. Don. herb; Ku shen, <i>Sophora flavescens</i> Ait. root; Mu xiang, <i>Aucklandia lappa</i> Decne. root; Bai hua she she cao, <i>Hedyotis diffusa</i> Willd. herb; modified; One decoction per day orally administered concurrently with chemotherapy for 4 weeks. FOLFOX 4: 2/2 cycles.	tRR; Chemotherapy AEs (leukopenia, gastrointestinal reaction, neurotoxicity); KPS.	NS; None; NS.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L
Zhang HT (2008); 31/29; 03/2003 to 11/2006; NS.	28/23; 52.35/53.4 (mean); ≥ 60.	NS; NS; NS.	3 HM decoctions based on CM 'Zheng' differentiation (NS): 1. Damp heat tenesmus decoction: Ku shen, <i>Sophora flavescens</i> Ait. root; Zhong jie feng, <i>Sarcandra glabra</i> (Thunb.) Nakai. herb; Yi yi ren, <i>Coix lacryma-jobi</i> L. seed; Huai hua, <i>Sophora japonica</i> L. flower-bud; Di yu, <i>Sanguisorba officinalis</i> L. root; Bai jiang cao, <i>Patrinia villosa</i> Juss. herb; Jin yin hua, <i>Lonicera japonica</i> Thunb. flower; Mu mian hua, <i>Bombax malabarica</i> (DC.) Merr. flower; Bai hua she she cao, <i>Hedyotis diffusa</i> Willd. herb; Yin chen, <i>Artemisia capillaris</i> Thunb. herb; Hou po, <i>Magnolia officinalis</i> Rehd. et Wils. bark; Huang lian, <i>Coptis chinensis</i> Franch. root.	tRR; Chemotherapy AEs (gastrointestinal reaction, myelotoxicity); KPS.	NS; None; NS.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: L SOR: L

			<p>2. Toxic stasis in colon decoction: Ku shen, <i>Sophora flavescens</i> Ait. root; Zhong jie feng, <i>Sarcandra glabra</i> (Thunb.) herb; Huai hua, <i>Sophora japonica</i> L. flower-bud; Di yu, <i>Sanguisorba officinalis</i> L. root; Bai jiang cao, <i>Patrina villosa</i> Juss. herb; Jin yin hua, <i>Lonicera japonica</i> Thunb. flower; Bai hua she she cao, <i>Hedyotis diffusa</i> Willd. herb; Yan dan zi, <i>Brucea javanica</i> (L.) Merr. seed; Da ji, <i>Cirsium japonicum</i> DC. herb; Qi ye yi zhi hua, <i>Paris polyphylla</i> Smith. root; Chi shao, <i>Paeonia veitchii</i> Lynch. root; E zhu, <i>Curcuma phaeocaulis</i> Val. rhizome;</p> <p>3. Spleen and kidney deficiency decoction: Dang shen, <i>Codonopsis pilosula</i> (Franch.) Nannf. root; Fu ling, <i>Poria cocos</i> (Schw) Wolf. sclerotium; Huang qi, <i>Astragalus membranaceus</i> (Fisch.) Bge. root; Ku shen, <i>Sophora flavescens</i> Ait. root; Zhong jie feng, <i>Sarcandra glabra</i> (Thunb.) Nakai. herb; Yi yi ren, <i>Coix lacryma-jobi</i> L. seed; Sha ren, <i>Amomum villosum</i> Lour. seed, Lian zi, <i>Nelumbo nucifera</i> Gaertn. Seed; Bai zhu, <i>Atractylodes macrocephala</i> Koidz. root; He zi, <i>Terminalia chebula</i> Retz. seed; He shou wu, <i>Polygonum multiflorum</i> Thunb. root; Bai shao, <i>Paeonia lactiflora</i> Pall. root;</p> <p>One decoction per day orally administered concurrently with chemotherapy. Started one week before chemotherapy till one week after chemotherapy completed.</p> <p>FOLFOX 4: 4/4 cycles.</p>			
Zhang Q (2010); 60/60; 02/2005 to	35/33; 56.2 (mean all); ≥ 60.	32/34; 28/26; Liver: 32/36,	Guben Xiaoliu Capsule (Beijing Chinese Medicine Hospital, affiliated with Beijing Medical University): Dong chong xia cao, <i>Cordyceps sinensis</i> (Berk.) Sacc. ascocarp and	tRR; Chemotherapy AEs (leukopenia, anaemia, thrombocytopenia,	NS; None; Until	SG: L AC: U BPt: H BOA (sub): H

10/2007; Provincial fund.		Lung: 16/19, Others: 51/39.	dead larva; Ling zhi, <i>Ganoderma lucidum</i> (Leyss. ex Fr.) Karst. sporocarp; Yin yang huo, <i>Epimedium grandiflorum</i> Mot. leaf; Zhe bei mu, <i>Fritillaria thunbergii</i> Miq. bulb; Xi yang shen, <i>Panax quinquefolium</i> L. root; Yi yi ren, <i>Coix lacryma-jobi</i> L. seed; Shui zhi, <i>Hirudo nipponica</i> Whitman. whole leech; Quan xie, <i>Buthus martensii</i> Karsch. whole insect; Long kui, <i>Solanum nigrum</i> L. herb; 4 capsules each time, twice a day, orally administered concurrently with chemotherapy for 8 wks. FOLFOX 4: 4/4 cycles.	nausea & vomiting, diarrhoea, neurotoxicity); KPS; T cell subsets CD4+/CD8+, NK cells.	07/2008.	BOA (obj): L IOD: L SOR: L
Zhang Y (2010); 21/20; 01/2005 to 12/2008; State fund.	NS; NS; ≥ 60.	NS; NS; NS.	Jianpi Jiedu decoction (NS): Huang qi, <i>Astragalus membranaceus</i> (Fisch.) Bge. root; Bai zhu, <i>Atractylodes macrocephala</i> Koidz. root; Ba yue zha, <i>Akebia quinata</i> (Thunb.) Decne. fruit; Shi jian chuan, <i>Salvia chinensis</i> Benth. herb; Ye pu tao teng, <i>Vitis quinquangularis</i> Rehder. vine and leaf; One decoction per day orally administered concurrently with chemotherapy, for 4 weeks. FOLFOX 4: 2/2 cycles	tRR; Chemotherapy AEs (leukopenia, anaemia, thrombocytopenia, liver impairment, nausea & vomiting, neurotoxicity); TTP; One year OS; Median OS; KPS; BW.	NS, C: 1 no reason; Until 11/2009.	SG: U AC: U BPt: H BOA (sub): H BOA (obj): L IOD: H SOR: L

T: treatment group, C: control group, M: male, N: number, NS: not stated, ID: intravenous drip, tRR: Tumor Response Rate; BW: Body Weight; QOL: Quality of Life; TTP: Time to Progression; OS: Overall Survival; KPS: Karnofsky Performance Status; CM: Chinese medicine; HM: herbal medicine.

* note error in method section which states 20 in control, whereas elsewhere the number is 21.

Risk of Bias Categories

SG: Sequence Generation, AC: Allocation Concealment, BPt: Blinding of Participants/Personnel, BOA (sub): Blinding of Outcome Assessment (subjective measures), BOA (obj): Blinding of Outcome Assessment (objective measures), IOD: Incomplete Outcome Data, SOR: Selective Outcome Reporting.

Risk of Bias Judgements

L: low risk, U: Unclear risk, H: High risk

Table 2: Results of meta-analyses for each outcome measure

Outcomes	No. studies* (participant No.)	Meta-analysis results (between groups at end of treatment)	Incidence % (n/N) or MD ± SD	RD (%)
Tumor response				
Tumour response rate (tRR)	12 ^{2,13} (880)	RR 1.25, 95% CI 1.06-1.47, <i>p</i> =0.007, I ² =0% FE	T: 44.1% (201/456) C: 34.9% (148/424)	9.2
Complete remission (CR)	9 ^{2,9,12} (718)	RR 1.94, 95% CI 0.89-4.25, <i>p</i> =0.10, I ² =0% FE	T: 5.1% (19/374) C: 2.3% (8/344)	2.8
tRR (previously treated patients)	2 ^{3,10} (126)	RR 1.41, 95% CI 0.77-2.61, <i>p</i> =0.27, I ² =0% FE	T: 29.7% (19/64) C: 21.0% (13/62)	8.7
tRR (previously untreated patients)	3 ^{3,5,9} (161)	RR 1.19, 95% CI 0.85-1.67, <i>p</i> =0.32, I ² =0% FE	T: 51.1% (45/88) C: 42.4% (31/73)	8.7
tRR (Kang'ai Injection subgroup)	2 ^{5,8} (103)	RR 1.07, 95% CI 0.71-1.61, <i>p</i> =0.76, I ² =0% FE	T: 48.1% (25/52) C: 45.1% (23/51)	3.0
Overall survival (OS)				
One year OS	3 ^{3,12,13} (279)	RR 1.51, 95% CI 1.19-1.90, <i>p</i> =0.0006, I ² =0% FE	T: 62.3% (91/146) C: 42.1% (56/133)	20.2
Quality of life (QoL)				
Karnofsky Performance Status (KPS)	9 ^{3-5,7,9-13} (669)	RR 1.84, 95% CI 1.54-2.19, <i>p</i> <0.00001, I ² =0% FE	T: 60.9% (210/345) C: 32.1% (104/324)	28.8
Mean KPS (Wu 2010)	1 ⁶ (58)	MD 12.18, 95% CI 7.96-16.40, <i>p</i> <0.00001	T: before 74.38±11.16, after 73.94±6.35 C: before 75.16±12.78, after 61.76±9.23	NA
Su Ying's QoL Questionnaire (Yang 2008)	1 ⁸ (60)	MD 4.10, 95% CI 2.36 to 5.84, <i>p</i> <0.00001	T: before 40.73±3.49; after 42.30±3.88 C: before 40.90±2.44; after 38.20±2.91	NA
Body weight (BW)	3 ^{8,9,13} (169)	RR 1.88, 95% CI 1.14-3.08, <i>p</i> =0.01, I ² =0% FE	T: 38.4% (33/86) C: 19.5% (16/82)	18.9
Chemotherapy toxicity				
Neutropenia events (grade 3/4)	10 ^{1-6,8,10,12,13}	RR 0.33, 95% CI 0.18-0.60, <i>p</i> =0.0003, I ² =0% FE	T: 3.9% (14/359)	8.7

	(692)		C: 12.6% (42/333)	
Nausea & vomiting (grade 3/4)	9 ^{1,8,13} (633)	RR 0.34, 95% CI 0.18-0.66, $p=0.001$, $I^2=0\%$ FE	T: 3.0% (10/330); C: 12.5% (38/303)	9.5
Neurotoxicity (grade 3/4)	7 ^{1,4,12,13} (529)	RR 0.39, 95% CI 0.15-1.00, $p=0.05$, $I^2=0\%$ FE	T: 2.2% (6/277) C: 6.0% (15/252)	3.8
Diarrhoea (grade 3/4)	5 ^{2,3,6,8,12} (448)	RR 0.39, 95% CI 0.11-1.42, $p=0.15$, $I^2=0\%$ FE	T: 0.9% (2/236) C: 3.3% (7/212)	2.4
Anaemia (grade 3/4)	3 ^{6,12,13} (220)	RR 0.30, 95% CI 0.05-1.89, $p=0.20$, $I^2=0\%$ FE	T: 0% (0/114) C: 2.9% (3/105)	2.9
Thrombocytopenia (grade 3/4)	1 ¹³ (42)	RR 1.00, 95% CI 0.07-14.95, $p=1.00$ FE	T: 4.8% (1/21) C: 5.0% (1/20)	NA
Stomatitis (grade 3/4)	2 ^{2,3} (210)	RR 0.43, 95% CI 0.08-2.31, $p=0.33$, $I^2=0\%$ FE	T: 1.8% (2/113) C: 4.1% (4/97)	2.3
Constipation (grade 3/4)	1 ³ (117)	RR 0.40, 95% CI 0.04-4.29, $p=0.45$ FE	T: 1.5% (1/65) C: 3.8% (2/52)	NA
Myelosuppression (grade 3)	1 ¹¹ (60)	RR 0.47, 95% CI 0.04-4.89, $p=0.53$ FE	T: 3.23% (1/31) C: 6.90% (2/29)	NA
<i>Kang'ai Injection Subgroup</i>				
Neutropenia events (grade 3/4)	2 ^{5,8} (103)	RR 0.19, 95% CI 0.04-0.83, $p=0.03$, $I^2=0\%$ FE	T: 3.8% (2/52) C: 21.6% (11/51)	17.8
Nausea & vomiting (grade 3/4)	2 ^{5,8} (103)	RR 0.27, 95% CI 0.08-0.89, $p=0.03$, $I^2=0\%$ FE	T: 5.8% (3/52) C: 21.6% (11/51)	15.8
Immune function				
CD3+ cells (%)	2 ^{1,6} (118)	MD 4.70, 95% CI 2.27 to 7.13, $p=0.0001$, $I^2=37\%$ FE	NA	NA
CD4+ cells (%)	2 ^{1,6} (118)	MD 9.08, 95% CI 0.10 to 18.05, $p=0.05$, $I^2=95\%$ RE	NA	NA
CD8+ cells (%)	2 ^{1,6} (118)	MD -4.47, 95% CI -9.54 to 0.61, $p=0.08$, $I^2=87\%$ RE	NA	NA
Ratio CD4+/CD8+	2 ^{1,12} (180)	MD 0.28, 95% CI 0.14 to 0.43, $p=0.0002$, $I^2=13\%$ FE	NA	NA
NK cells (%)	3 ^{1,6,12} (238)	MD 4.03, 95% CI 0.51 to 7.55, $p=0.02$, $I^2=88\%$ RE	NA	NA

T: test group; C: control group; RR: risk ratio; N: total number of participants in group(s); n: number of events in group(s); I^2 : test of heterogeneity of meta-analysis, over 50% represents substantial heterogeneity; MD: mean difference; SD standard deviation; RD: Risk difference; NA: not applicable; FE: Fixed Effect model; RE: Random Effect model.

*Included studies: 1. Ding X 2010, 2. Fang M 2008, 3. Li H 2007, 4. Li Y 2007, 5. Qiu Z 2011, 6. Wu G 2010, 7. Xu Y 2010, 8. Yang F 2008, 9. Zeng D 2009, 10. Zeng J 2008, 11. Zhang H 2008, 12. Zhang Q 2010a, 13. Zhang Y 2010b.

Fig 1. Flow diagram of the search and selection process of RCTs of FOLFOX4 combined with herbal medicine (HM) for advanced colorectal cancer (ACRC)

CT: clinical trial of HM without randomisation; DU: duplicate publication; MT: multi-cancer CT; RE: review; Other: not a controlled trial, or not a CT of HM, or outcome is not efficacy.

Fig 2. Funnel Plot of the 12 studies that reported tumor response rate (tRR)
192x171mm (152 x 114 DPI)