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Integrative medicine for relief of nausea and vomiting in the treatment of colorectal cancer using oxaliplatin-based chemotherapy: a systematic review and meta-analysis

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Key words

Systematic review, natural products, nausea, vomiting, colorectal cancer, oxaliplatin, integrative medicine, traditional medicine

Abstract

The management of chemotherapy-induced nausea and vomiting (CINV) remains an issue in the treatment of colorectal cancer using oxaliplatin based regimens. Certain traditional plant-based medicines (TMs) have histories of use for nausea and vomiting and have integrated with conventional therapies for CINV. To assess the effectiveness of integrative management of CINV, meta-analysis was conducted of 27 randomised controlled studies (1,843 participants) published from 2005 to 2013. The oxaliplatin plus TM groups showed significantly reduced CINV (RR 0.65 [0.59, 0.71], $I^2=28\%$) compared to oxaliplatin controls, with or without the addition of conventional anti-emetics. Further sensitivity analyses based on the ingredients of the TMs identified six plants (*Atractylodes macrocephala*, *Poria cocos*, *Coix lacryma-jobi*, *Astragalus membranaceus*, *Glycyrrhiza uralensis*, *Panax ginseng*) that were associated with significant reductions in CINV without important heterogeneity. Experimental studies of these six plants have reported inhibitory effects on nausea and vomiting (or its animal equivalent), regulation of gastrointestinal motility, gastro-protective effects, and antioxidant actions which may at least partially explain the effects identified in the meta-analyses of the clinical trial results. These plants warrant further clinical research as additions to chemotherapy regimens in patients whose CINV is not sufficiently well-controlled by conventional therapies.

Abbreviations

- 5-FU: 5-Fluorouracil
- AEs: Adverse Events
- CINV: Chemotherapy-induced Nausea and Vomiting
- CNKI: China Academic Journals
- CQVIP: Chinese Science and Technology Journals
- CRC: Colorectal Cancer
- FOLFOX: 5-Fluorouracil (5-FU) plus Leucovorin (LV) combined with Oxaliplatin
- G-CSF: Granulocyte colony-stimulating factor
- KPS: Karnofsky Performance Status
- LV: Leucovorin
- NCI-CTC: National Cancer Institute Common Toxicity Criteria
- RCT: Randomized Controlled Trial
- RD: Risk Difference
- RR: Risk Ratio
- TMs: Traditional Medicines
- WHO: World Health Organisation

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse event in cancer treatment. Risk factors for CINV following chemotherapy include type of chemotherapeutic drug, patient's age less than 50, female, history of low prior chronic alcohol intake, and history of previous chemotherapy-induced emesis. Over seventy percent of patients receiving oxaliplatin regimens experience CINV (Navari, 2009). CINV tends to get worse as the number of treatment cycles increases. This significantly reduces the quality of life of patients, can result in poor compliance with their chemotherapy schedule and can lead to deterioration of physical and mental status (Lohr, 2008).

The mechanisms of CINV are complex. CINV can be initiated by enterochromaffin cells in the gastrointestinal tract releasing serotonin (5-HT) in response to damage of gastrointestinal epithelium and activation of the chemoreceptor trigger zone which detects potential toxins. Activation of vagal afferent fibres stimulates the vomiting center in the medulla, which in turn sends impulses via efferent fibres to activate the vomiting response. Antiemetic drugs act by blocking neuronal pathways involved at various stages in the emetic response, mainly via antagonism of 5-hydroxytryptamine (5-HT₃) receptors, dopamine receptors, neurokinin-1 (NK-1) and/or acetylcholine, corticosteroid, histamine, cannabinoid, and/or opiate receptors (Lohr, 2008; Navari, 2009).

Oxaliplatin regimens used in colorectal cancer (CRC) are considered to have moderate emetic risk and the preventative use of 5-HT₃ antagonists combined with dexamethasone is recommended, with the additional use of NK-1 antagonists in selected patients (NCCN, 2012). Despite the introduction of these effective anti-emetic agents, CINV remains a significant issue for people undergoing chemotherapy (Navari, 2009).

A number of traditional medicines (TMs) have been used to alleviate nausea and vomiting. Ginger (*Zingiber officinale* Roscoe) has been used for nausea in a number of countries and evidence from animal studies suggests anti-CINV effects (Handiadka *et al.*, 2012a). However, a systematic review of seven randomised controlled trials (RCTs) of ginger in CINV management in various cancers found inconsistent results between studies (Marx *et al.*, 2013). Other plants that have been reported to alleviate CINV in animal models include *Panax ginseng* C. A. Mey., *Panax quinquefolius* L., *Panax notoginseng* (Burk.) F. H. Chen, *Scutellaria baicalensis* Georgi, *Ganoderma lucidum* (Fr.) Karst., Mint oil (*Mentha* spp) and grape seed extract (Handiadka *et al.*, 2012b). A number of possible mechanisms for the reported anti-CINV actions of these plants have been proposed. These include inhibition of 5-HT₃ receptor, substance P and NK1 receptors, antioxidant and free radical scavenging activity, anti-inflammatory actions, chemo and radio-protective effects, immunomodulation, neuromodulation, antispasmodic effects, and regulation of gastrointestinal motility. Since these TMs may contain multiple bioactive compounds it appears likely that multiple mechanisms are involved (Handiadka *et al.*, 2012b, Suzuki *et al.*, 2013).

Previous reviews have reported that multi-ingredient TMs combined with chemotherapy could reduce CINV in various cancers (Dong *et al.*, 2010; Li and Ling, 2012; Ohnishi and Takeda, 2015; Liu *et al.*, 2008). In advanced CRC, a meta-analysis of RCT results showed FOLFOX4 combined with TMs produced a 10.3% reduction in grade 3/4 nausea and vomiting compared to FOLFOX4 alone (Chen *et al.*, 2014). However, numerous TMs were used in these studies so it remains unclear whether any particular plant ingredients were responsible for the reported effects.

The aims of this review and meta-analysis are to assess whether integrative management of CRC, in which TMs are added to oxaliplatin regimens, reduced the incidence of CINV and whether any particular TMs showed promise for further research into their anti-emetic and/or nausea alleviating effects.

Method

PubMed, EMBASE, Cochrane CENTRAL, CINAHL, Science Direct, PsycINFO, China Academic Journals (CNKI) and Chinese Science and Technology Journals (CQVIP) were searched from their respective inception for RCTs that combined an oxaliplatin regimen with TM for the treatment of participants who had been diagnosed with CRC based on pathology tests and measured CINV as an outcome. There was no restriction on participant age or gender, inpatient or outpatient, or route of administration of the TM, or concurrent use of anti-emetic drugs. The terms used for PubMed and a list of journals that were hand-searched are provided in Supp 1.

Review methods were based on Cochrane Handbook 5.1.0 (Higgins and Green, 2011). Data were extracted independently by MC & IZ who also assessed Risk of Bias, with mediation by AZ or BM. Meta-analysis was conducted using Review Manager (RevMan) 5.1 as Risk Ratio (RR) with 95% confidence interval (95% CI) fixed effect model. Heterogeneity was measured using I^2 . Risk difference (RD) was used as a measure of absolute difference. Publication bias was assessed using a funnel plot (Higgins and Green, 2011). Studies with zero events were included to avoid overestimation of effect (Fiedrich *et al.*, 2007). The following subgroup and sensitivity analyses were planned: 1. route of TM administration; and 2. composition of the multi-ingredient orally administered TMs.

The approach to analyzing the subgroups of TM interventions that contained the same ingredients (mainly plants) was based on the method described in (Chen *et al.*, 2015). The rationale for this approach was that many of the multi-ingredient TM interventions used different combinations of the same plants. Therefore, by investigating the pooled effects of multiple studies that employed the same plant, it may be possible to identify which plants contributed to the observed effects on CINV. In addition, it may also be possible to identify specific combinations of plants that showed the greatest contributions to CINV alleviation. Briefly, the approach involved a multi-level procedure. At level 1, all studies that employed the same plant were treated as a sub-group and the pooled RR(95%CI) and I^2 for CINV were calculated. This was done for all plants that appeared in two or more studies. The results were listed in ascending order and significant results were noted. When the sub-group showed no significant effect on CINV and/or there was important heterogeneity in the pooled result (I^2 greater than 30%), the plant was eliminated from further consideration. At level two, subgroups of studies that employed the same two plants in the TM interventions were identified and the RRs were calculated for each pool. At level three, combinations of three plants were considered and so on until there were no possible combinations that showed significant effects. This approach produced a matrix of pooled RRs for multiple sub-groups of studies.

The following five criteria were applied to the matrix of results to identify plants and combinations of plants that showed promise for further research into their effects on CINV. 1. the RR of the sub-group of studies that employed the plant was significantly lower than the control; 2. the RR was equal or lower than the RR for all the orally administered multi-ingredient TM interventions; 3. no important heterogeneity (I^2 below 30%); and 4: the RR results for the plant were significant at multiple levels of combination; 5. the plant was not always combined with another particular plant, therefore it was possible to assess the independent contribution of that plant.

Results

Following screening of the 2,648 citations derived from database searches and the 54 studies from print journal searches, 88 full-text studies were evaluated. Finally, 30 studies were included in the review. Three studies did not provide data suitable for pooling (Chen *et al.* 2005; Deng and Shen, 2010; Liang *et al.*, 2009), so 27 studies, published from 2005 to 2013, that enrolled 1,843

(T:960/C:883) assessable participants were included in the meta-analyses (Figure 1). Six studies employed commercially available injections and 21 studies used orally administered TMs. All studies used the WHO system or the National Cancer Institute Common Toxicity Criteria (NCI-CTC). These systems are comparable and divide nausea and vomiting into 4 grades (Miller *et al.*, 1981; National Cancer Institute, 1999). Study characteristics are presented in Table 1.

Methodological assessment

Thirteen studies (48.1%) were judged as 'low' risk of bias for sequence generation (Table 1). One study was blinded, used a placebo control for the TM and described allocation concealment (Kono *et al.*, 2013). The other studies were judged as 'high risk' for blinding of outcome assessment since nausea is a subjective outcome which is usually recorded by participants and personnel so results could have been influenced by lack of blinding. Two studies were judged as 'high risk' for incomplete outcome data since reasons for dropouts were not given and 'intent to treat' was not used (Li *et al.*, 2007; Zhang *et al.*, 2010). Studies with no dropouts were judged as 'low risk'. Studies were judged as 'low risk' of selective outcome reporting when there was a published protocol and results for all outcome measures were reported. Studies with no protocol were judged as 'unclear'. The Funnel Plots suggest risk of publication bias was low for the oral administration group (Figure Supp 1).

Meta-analysis of reduction of nausea and vomiting

Meta-analysis was conducted for all grades of nausea and vomiting combined. When RR is less than +1 and RD is less than zero (IV model, fixed, 95% CI), it favors the test group. A lower RR indicates a lower risk of nausea and vomiting.

Total group

For all 27 studies, the test groups showed significantly reduced nausea and vomiting (RR 0.65 [0.59, 0.71], $I^2=28\%$)(Figure 2). The absolute risk reduction was 24% compared to controls (RD= -0.24 [-0.28, -0.19], $I^2=48\%$). In the 17 studies that stated anti-emetic drugs, such as ondansetron or granisetron, were used in both groups the RR was 0.68 [0.60, 0.77], $I^2=32\%$ whereas in the studies that did not mention use of anti-emetic drugs (n=10) the RR was 0.60 [0.51, 0.70], $I^2=19\%$.

Injection group

Four different injection products were tested in 6 studies (Table 1). There was a significant reduction in nausea and vomiting (RR 0.73 [0.61, 0.86], $I^2=60\%$, RD= -0.20 [-0.29, -0.12], $I^2=50\%$) in the TM plus oxaliplatin groups. The heterogeneity was moderate to substantial (Figure 2). Co-kushen Injection (n=2) (Ding *et al.*, 2010; Tao and Xu, 2013) showed significantly reduced nausea and vomiting (RR 0.66 [0.50, 0.86], $I^2=64\%$) but there was substantial heterogeneity. Kang'ai Injection (n=2) (Qiu 2011; Yang, 2008) showed a significant reduction with no important heterogeneity (RR 0.47 [0.29, 0.77], $I^2=28\%$).

Oral administration group

The TMs were administered orally as decoctions, capsules or tablets in 21 studies. The combination of TMs plus oxaliplatin showed a significant reduction in nausea and vomiting incidence compared to the same oxaliplatin regimens (RR 0.62 [0.55, 0.69], $I^2=5\%$). The absolute risk reduction was 25% (RD -0.25 [-0.30, -0.20], $I^2=49\%$)(Figure 2).

Effects of individual plant-based ingredients in orally administered TMs

The orally administered TMs contained 98 different plant-based ingredients with an average of 12 ingredients per TM intervention. The 48 plants that were used in two or more studies were included in the following sub-group analyses. Thirty of these plants showed significant RRs for reduction of incidence of CINV with low heterogeneity ($I^2 < 30\%$). The effects of these plants were also assessed when they appeared as pairs, triplets and higher level combinations in the TM interventions. Significant RR results with low heterogeneity that were equal or lower than the total pool for the oral interventions RR 0.62 [0.55, 0.69] are reported in Table 2 and Table Supp 1. The full botanical name and Chinese name in pin yin of each plant is given when it is first mentioned in the text. Subsequently, the name is shortened to genus only.

The following plants were the most frequently used in the TM interventions: *Poria cocos* (Schw) Wolf (fu ling)(n=16); *Atractylodes macrocephala* Koidz. (bai zhu) (n=16); *Coix lacryma-jobi* L. (yi ren) (n=14); *Astragalus membranaceus* (Fisch.) Bge. (huang qi) (n=13), and *Codonopsis pilosula* (Franch.). Nannf. (dang shen) (n=12).

Level 1: Single plants

Of the 30 plants included at the level 1 analysis (Table 2), most were always associated with another particular plant in the TM interventions so it was not possible to determine if they made an independent contribution to the RR result. However, the following seven plants did not always appear in association with another particular plant. Of these, *Panax ginseng* C. A. Mey. (ren shen) (n=4) had the lowest RR (0.51 [0.39, 0.66], $I^2=0\%$), followed by *Poria* (n=16) (RR 0.61 [0.54, 0.69], $I^2=15\%$), *Coix* (n=14) (RR 0.61 [0.53, 0.70], $I^2=29\%$), *Codonopsis* (n=12) (RR 0.61 [0.52, 0.72], $I^2=28\%$), *Panax notoginseng* (Burk.) F.H. Chen (tian qi) (n=4) (RR 0.61 [0.43, 0.87], $I^2=0\%$), *Atractylodes* (n=16) (RR 0.62 [0.54, 0.71], $I^2=13\%$), and *Astragalus* (n=13) (RR 0.65 [0.55, 0.76], $I^2=0\%$).

Level 2: Pairs of plants

Seven pairs of plants showed RRs that were lower than the total pool (Table Supp1). The lowest RRs were for *Panax G.+Astragalus* (n=4) (RR 0.49 [0.35, 0.67], $I^2=0\%$) followed by *Poria+ Dioscorea opposita* Thunb.(shan yao)(n=5)(RR 0.56 [0.47, 0.67], $I^2=0\%$).

Level 3: Combinations of three plants

Six different triplets showed significant RRs that were lower than the total pool. The combination of *Dioscorea+Coix+Poria* (n=3) had the lowest RR (0.49 [0.37, 0.65], $I^2=0\%$), followed by *Panax G +Atractylodes+Coix* (n=3) (RR 0.52 [0.39, 0.69], $I^2=0\%$).

Level 4: Combinations of four plants

Atractylodes+Poria+Coix+ Glycyrrhiza uralensis Fisch (gan cao) was the only combination that was significant and lower or equal to the pool (RR 0.51 [0.38, 0.70], $I^2=0\%$, n=3).

Level 5: Combinations of five plants

Three combinations of five plants showed RRs lower than the total pool. *Astragalus+Atractylodes+ Coix+ Lycium barbarum* L. (gou qi zi) + *Scutellaria barbata* D. Don. (ban zhi lian)(n=3) had the lowest RR (0.58 [0.41, 0.83], $I^2=0\%$).

Level 6: Combinations of six plants

Six combinations of six plants showed significant RRs lower than the total pool. The lowest RR (0.50 [0.36, 0.69], $I^2=0\%$) was for Panax G+ Dioscorea + Coix+ Glycyrrhiza+ Atractylodes+ Poria (n=2).

Level 7: Combinations of seven plants

One combination of seven plants was lower than the total pool: Codonopsis+ Atractylodes+ Astragalus+ Coix+ Poria+ *Crataegus pinnatifida* Bge (shan zha)+ *Hordeum vulgare* L. (mai ya) (n=2) (RR 0.47 [0.33, 0.68], $I^2=0\%$).

TMs with consistent results at multiple levels

Six plants showed significantly reduced RRs that were lower than or equal to the pool with low heterogeneity at multiple levels. Atractylodes, Poria and Coix appeared at all seven levels when used as components of various TM interventions. Glycyrrhiza appeared at five levels while Astragalus and Panax G appeared at four levels.

Discussion

The meta-analysis showed reduction in CINV in both the injection and oral groups but there was substantial heterogeneity in the injection group ($I^2=60\%$) compared to the oral group ($I^2=5\%$). In the oral intervention studies the absolute risk reduction was 25% which was higher than for the injection group (20%). In a previous meta-analysis of tumour response rate, the injection groups appeared more effective than the oral groups (Chen *et al.*, 2015). One likely reason for these differences is the injection products are mainly aimed at aiding tumour response rather than reducing CINV. Nevertheless, the result for the two studies of Kang'ai injection, which is composed of Panax G, Astragalus and *Sophora flavescens* Ait., showed significant reduction in CINV incidence without important heterogeneity ($I^2=28\%$).

It has been suggested that combining certain TMs with anti-emetics results in greater benefit (Dong, 2012). In the total group, there was a slightly reduced benefit in the 17 studies that used anti-emetic drugs compared to the ten that did not. However, it is possible that some studies did not report the use of anti-emesis medications since these are in routine use. Therefore this result is difficult to interpret. This issue warrants further investigation.

The following six plants appeared at multiple levels of combination in the oral interventions: Atractylodes (n=16), Poria (n=16), Coix (n=14), Astragalus (n=13), Glycyrrhiza (n=5), and Panax G (n=4). This list contains the plants with the highest overall frequencies, such as Atractylodes and Poria, and also some lower frequency plants such as Glycyrrhiza and Panax G. Conversely, some relatively frequent plants such as Curcuma (n=7) did not show an elevated RR. Therefore, the selection process did not simply reflect overall frequency within the data set.

Ginger was not included in the final analyses, although it appeared to significantly reduce CINV (RR 0.43 [0.31, 0.61]), since it was used in only two studies and the heterogeneity was substantial ($I^2=69\%$). A number of other plants used traditionally for nausea were also excluded for the same reasons. It is important to note that the plants selected above are not the only plants that showed improved RR for CINV when they were included in a TM intervention, what they showed was consistent effects in multiple studies and in multiple combinations. Another caveat on the interpretation of these results is that the short-listed herbs cannot be ranked in order of effectiveness since each RR was based on a different sub-group of studies.

Based on the information in the clinical trial reports it was not possible to determine whether the short-listed plants were included in order to reduce CINV or for other reasons. This issue is made more complex since plants are considered to have multiple effects in traditional medicine. However, all are traditionally used for treating gastrointestinal disorders including nausea, bloating, fatigue, poor appetite, and diarrhoea (Bensky *et al.*, 2004).

The effects of extracts and compounds derived from the six plants identified as potentially reducing CINV have received research attention in experimental models in animals and cell-lines to assess their effects on emesis, pica, gastrointestinal motility and gastro-protection. The volume of published research is variable with Ginseng, Atractylodes, and Poria having received the most attention. This research is reviewed for each of the six plants below.

Panax ginseng

The anti-emetic effect of Korean red ginseng total extract (KRG) on nausea and vomiting was investigated in ferrets administered intraperitoneal cisplatin (7.5mg/kg) which induced both nausea and vomiting with one-hour latency. The animals were monitored every 30 mins and the total number of episodes of nausea and vomiting were marked. Pre-treatment with orally administered KRG one hour and two hours before cisplatin significantly attenuated the cisplatin-induced nausea and vomiting in a dose-dependent manner. No significant effect was evident when KRG was administered 4 hours prior to cisplatin (Kim *et al.*, 2005).

In rodents, emetics do not produce vomiting but instead induce pica - the eating of kaolin. In rats, the effects of an extract of Korean ginseng (KG) administered before and after cisplatin, on pica, food intake, body weight, haematological parameters and histopathology was investigated by Raghavendran *et al* (2011). Pre-treatment with KG one hour before cisplatin significantly reduced kaolin intake at 24, 48, and 72 hours post-cisplatin. Normal food intake significantly improved compared to the group that received cisplatin alone and there was less reduction in body weight. Post-treatment KG showed similar effects. The increases in the levels of white blood cells, neutrophils, lymphocytes induced by cisplatin were significantly lower in the rats pre-treated with KG, suggesting that KG reduced cisplatin-induced inflammation. Cisplatin-induced damage to the gastric mucosa and small intestine was reduced by pre-treatment, but not by post-treatment, with KG (Raghavendran *et al.*, 2011). A similar result was obtained using American ginseng berry extract (AGBE) and ginsenoside Re which is one of its constituents. Pre-treatment reduced cisplatin-induced pica and improved food intake. When tested for antioxidant actions, both AGBE and ginsenoside Re were found to scavenge superoxide and hydroxyl radicals (Mehendale *et al.*, 2005).

Pre-treatment with ginsenoside Rg2 has been reported to have an inhibitory effect on human 5-HT_{3A} receptors expressed in *Xenopus* oocytes that was dose dependent and reversible (Choi *et al.*, 2003). Using the same model, similar effects have been reported for two ginsenoside metabolites (Lee *et al.*, 2004). These studies suggest that the reported effects of ginseng on nausea and vomiting may be via antagonism of the 5-HT_{3A} receptor.

Poria cocos

Tai *et al* investigated the effects of a range of triterpenes extracted from Poria in frogs orally administered copper sulphate as an emetic. The latency to first emesis was significantly prolonged compared to controls by some, but not all, triterpenes. Those showing a significant anti-emetic effect had an exo-methylene group at C24 in their side chain (Tai *et al.*, 1995).

The effects of three Poria-derived triterpenoids [PA: Pachymic acid; DA: dehydroeburicoic acid; HA: 3 β -hydroxylanosta-7,9(11), 24-trien-21-oic acid] on human 5-HT_{3A} receptors was investigated in *Xenopus* oocytes using a two electrode voltage-clamp technique. Each triterpenoid showed concentration dependent, reversible inhibition on 5HT-induced inward current with HA showing the highest potency (Lee *et al.*, 2009).

Atractylodes macrocephala

The effects of an extract of *Atractylodes* on restitution of the intestinal mucosa after damage, was investigated in a cell migration model using intestinal epithelial (IEC-6) cells treated with *Atractylodes* extract, spermidine (SPD, 5 μ mol/L) as the positive control, the polyamine inhibitor alpha-difluoromethylornithine (DFMO, 2.5mmol/L) as the negative control, and a no treatment control. At doses of 100mg/L and 200mg/L, *Atractylodes* significantly increased IEC-6 cell migration after wounding compared to no treatment and the effect was comparable to that of SPD. The effect of *Atractylodes* was retained when combined with DFMO. *Atractylodes* exposure increased cellular polyamine content and other markers indicating a polyamine dependent mechanism (Song *et al.*, 2015). In human gastric mucosa epithelium, *Atractylodes* extract promoted the growth of human gastric mucosa cells, DNA synthesis and pepsin secretion, but had no effect on acid secretion (Zhu *et al.*, 2003).

Atractylodes has been reported to enhance gastric emptying and small intestinal motility in mice fed *Atractylodes* extract plus the marker Blue dextran 2000, compared to a saline control (Li *et al.*, 1996). This prokinetic effect could be blocked by atropine in a study of isolated mouse ileum which indicated the effect may be mediated via muscarinic receptors (Ma *et al.*, 1996). In guinea pig colon sections, *Atractylodes* extract was reported to increase smooth muscle contraction (Ding *et al.*, 2005).

Astragalus membranaceus

A number of studies have investigated the effect of *Astragalus* on gastrointestinal motility. In healthy dogs, the investigators measured the myoelectric activity in the duodenum and jejunum after 25% concentrated solution (1 ml/kg) *Astragalus* extract was injected into the dog's empty stomach. The duration of each myoelectric cycle, each phase of the cycle and the electrical potential were measured. The results showed *Astragalus* could significantly extend the duration of myoelectric cycles in the duodenum and jejunum but the motility enhancing effect was most pronounced in the jejunum (Yang *et al.*, 1993). In normal mice, *Astragalus* significantly enhanced small intestine motility and antagonized the inhibitive effects of atropine and the non-selective beta-adrenergic agonist isoproterenol. In the stomach, *Astragalus* also antagonized inhibition of gastric emptying induced by atropine (3mg/kg), but did not antagonize the dopamine-serotonin receptor antagonist metoclopramide (0.8mg/kg) (Zheng *et al.*, 2003).

In healthy humans, small intestine transmission time was measured by using a hydrogen breath test to determine the peak value of lactose absorption after taking 18 g lactose orally. After taking *Astragalus* for one week, the time to the peak value of lactose absorption was significantly shortened, compared to before administration of *Astragalus*, suggesting increased motility (Qiao *et al.*, 2001).

Glycyrrhiza (Licorice)

The effects of aqueous extracts of several TMs, including *Glycyrrhiza*, *Astragalus* and *Atractylodes*, were tested in isolated smooth muscle strips taken from different gastric regions of the rat. *Glycyrrhiza*, *Astragalus*, and *Atractylodes* increased longitudinal and circular fundic muscle tension;

Glycyrrhiza and Atractylodes enhanced longitudinal muscle tension in strips from the gastric body; while Glycyrrhiza increased the motility index of pyloric circular muscle (Zheng *et al.*, 1998).

A study that investigated the effects of isoliquiritigenin (a flavonoid in Glycyrrhiza spp.) on gastrointestinal motility in mice fed a charcoal meal, found an inhibitory effect at low doses (0.003, 0.03 mg/kg) and a prokinetic effect at high doses (3 and 30 mg/kg). Subsequent *in-vitro* studies indicated that the spasmogenic effect involved activation of muscarinic receptors, while the spasmolytic effect was associated with blockade of calcium channels (Chen *et al.*, 2009).

Sato *et al* investigated the effect of glycycomarin, a compound from Glycyrrhiza, on carbamylcholine (CCh)-induced contraction of mouse jejunum and reported an antispasmodic effect related to the inhibition of the phosphodiesterase 3 pathway (Sato *et al.*, 2006).

Coix

The effect of de-hulled Coix seed was examined in an indomethacin-induced gastric lesion model in rats. Erosion of the gastric mucosa was examined by imaging and by histopathological observation. Coix extract was found to produce dose-dependent gastroprotection against indomethacin. This effect was at least partially due antioxidant actions of the phenolic acids in Coix (Chung *et al* 2011). A methanol extract of Coix seeds was found to reduce nitric oxide and superoxide production in RAW 264.7 macrophages (Seo *et al* 2000).

Safety of the TM interventions

The included studies did not report any serious adverse events associated with TMs and the meta-analyses results did not show increased CINV in any of the studies. Also, when combined with anti-emetic drugs the TMs did not appear to reduce their effectiveness, rather, the results were suggestive of enhanced effect. In an analysis of the effects of TMs on tumour response in CRC, the use of TMs was not associated with any reduction in the efficacy of the oxaliplatin-based chemotherapy (Chen *et al.*, 2015). The six plants identified by the sensitivity analyses are all in common use in traditional medicine (Bensky *et al.*, 2004).

Conclusions

In nausea and vomiting associated with oxaliplatin based chemotherapy for CRC, the addition of TMs appears to significantly reduce incidence based on a meta-analysis of 27 studies. This effect was most pronounced in the group of 21 studies that administered the TMs orally. There was low statistical heterogeneity in this group, the oxaliplatin regimens and CINV measurements were consistent across studies and there was considerable similarity in the TMs used but the lack of blinding in most studies may have led to overestimation of the effects on CINV. Further sensitivity analysis of the TMs based on their ingredients, identified six plants that were associated with significant reductions in CINV without important heterogeneity in the meta-analysis results. Experimental studies of these six plants have reported inhibitory effects on nausea and vomiting (or its animal equivalent), regulation of gastrointestinal motility, gastro-protective effects, and/or antioxidant actions which may at least partially explain the effects identified in the meta-analyses of the clinical trial results. These plants warrant further clinical research as additions to chemotherapy regimens in patients whose CINV is not sufficiently well-controlled by conventional therapies.

Figure legends

Figure 1. Flow diagram of the search and selection process of RCTs of Oxaliplatin regimens combined with traditional medicine (TM) for colorectal cancer (CRC) with incidence of nausea and vomiting as an outcome

CT: clinical trial of TM without randomisation; DU: duplicate publication; MT: multi-cancer CT; RE: review; Other: not a controlled trial, not a CT of TM.

Figure 2: Forest plot of the effects of traditional medicine (TM) interventions on CINV incidence in colorectal cancer (CRC) treated with oxaliplatin regimens

Figure Supp. 1: Funnel plot of CINV outcomes of 27 studies of TMs for CRC: oral and non-oral groups

RR: risk ratio of CINV

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Figure 1. Flow diagram of the search and selection process of RCTs of Oxaliplatin regimens combined with traditional medicine (TM) for colorectal cancer (CRC) with incidence of nausea and vomiting as an outcome

CT: clinical trial of TM without randomisation; DU: duplicate publication; MT: multi-cancer CT; RE: review; Other: not a controlled trial, not a CT of TM.

Figure 2: Forest plot of the effects of traditional medicine (TM) interventions on CIN V incidence in colorectal cancer (CRC) treated with oxaliplatin regimens

Table 1: Characteristics of randomised controlled trials of traditional medicines (TM) combined with oxaliplatin-based regimens for colorectal cancer (CRC) with nausea and vomiting incidence as an outcome

First author (year).	Sample size T/C; Gender (M) T/C; Age T/C	TM Intervention; dosage & duration	Oxaliplatin regimen; dose, cycles (T/C); anti-emetic drug.	Risk of bias (SG, AC, BPt, BOA, IOD, SOR)
Ding X (2010).	30/30; 18/20; 64.5/63 (med.)	Co-Kushen injection; 20 ml, ID, day 1-7, 14 day/cycle, for 8 cycles.	FOLFOX4: Ox.85 mg/m ² , 2 hours ID, day 1, LV 200mg /m ² , ID, day 1-2, 5-FU 400mg /m ² , bolus, 600mg /m ² , ID, 22 hours, day1-2, 8/8 cycles.	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L SOR: U.
Fang M (2008)	48/45; 30/28; 59.5 ± 11.3/56.4 ± 10.3	Javanica oil emulsion injection; 30 ml, ID, day 1-14 / cycles, for two cycles	FOLFOX 4: 2 cycles (all); anti-emetic drug used (unknown)	SG: L, AC: U, BPt: H, BOA (subj): H, IOD: L, SOR: U.
Hu A (2006).	28/22; 18/14; 49.3±4.5/48.5±4.3	Treatment with 4 different TM decoctions according to symptom differentiation; one decoction per day, for more than 30 days.	FOLFOX: Ox.130 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-2, 5-FU 2400mg /m ² , ID, 46 hours, cycle/21 days, 2/2 cycles; Granisetron, Metoclopramide.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Kono T (2013).	27/23; NS; 67/61 (mean)	TJ-107 Goshajinkigan aqueous extract; or placebo was administered orally, tid, before each meal (7.5 g/day) for 26 wks	FOLFOX4, or mFOLFOX6: Ox.85 mg/m ² , ID, day 1, LV 200mg /m ² , ID, 5-FU 400 mg bolus, follow 2400 mg /m ² , ID for 46 hours, 14 days/cycle, 8/8 cycles or more.	SG: L, AC: L, BPt: L, BOA (obj): L, IOD: L, SOR: L.
Lao G (2012).	30/30; 21/23; 35.1±20.2/36.7±20.1.	Jianpijiedu decoction; one decoction per day, 21 days /cycle, for two cycles.	FOLFOX: Ox.130 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1, 5-FU 500 mg bolus day 1, 2400mg /m ² , ID, 48 hours, day 1-2, 21 days /cycle, 2/2 cycles; 5-HT3 receptor antagonist and dexamethasone.	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Li H (2007).	65/52; 43/36; 58/59 (med.)	Aidi injection; 60ml, ID, day 1-10, 14 days/cycle, for 11wks.	FOLFOX 4: 5.5/5.5 cycles (mean); Granisetron.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Li Y (2007).	20/18; 22 (all); 72.2 (med. all)	Wenshenjianpi decoction; one decoction per day, for med. 10-12 wks.	FOLFOX 4: 6/5.5 cycles (med.).	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: H, SOR: U.

Lim M (2012).	24/23; 17/14; 56.89±14.77/55.37±16.01	Pianzaihuang capsule; two capsules, bid; 14 days/cycle, 8-10 cycles.	FOLFOX4; 8-10/8-10 cycles.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Liu H (2009).	36/34; 16/18; 50.2 (mean)	Kang'ai fangyi pian; one decoction per day, 21 days / cycle, for 3 cycles.	FOLFOX: Ox.130 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-5, 5-FU 300 mg /m ² , ID, day 1-5, 21 days / cycle, 3/3 cycles.	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Liu J (2005).	43/21; 23/10; 61.52 ±10.12 /60.11 ±9.78	Jianpihuoxue formulae; one decoction per day, 30 days/ cycle, 3 cycles.	FOLFOX; Ox.150 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-5, 5-FU 500 mg /m ² , ID, day 1-5, 30 days/ cycle, 3/3 cycles; Ondansetron hydrochloride.	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Liu W (2011).	16/16; 11/10; 51/52(mean)	Yi er kang capsule; 4-6 capsules, bid, for 5-25 months.	FOLFOX: Ox.130 mg/m ² , ID, day 1, LV 100mg /m ² , ID, day 1-5, 5-FU 400 mg /m ² , ID, day 1-5, 21 days / cycle, 6 /6 cycles; Ondansetron.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Ma J (2005).	28/25; 15/13; 58.1/57.5(mean)	Jianpixiaoliu decoction; one decoction per day, 90 days/ cycle, 2 cycles.	FOLFOX: Ox.130 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-5, 5-FU 375 mg /m ² , ID, day 1-5, 21 days / cycle, 6/6 cycles.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Qiu Z (2011).	22/21; 14/13; 56.9/52.7(med.)	Kang'ai injection; 40 ml, ID, day 1–10, 14 days/ cycle, for 4 cycles.	FOLFOX4, 4/4 cycles.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Song W (2012).	20/20; 12/13; 56.4±9.1 /48.3±8.2	Xiaoliuhuaajichangfang II; one decoction per day, 21 days/ cycle, 2 cycles.	FOLFOX: Ox.135 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-2, 5-FU 2400 mg /m ² , ID, for 48 hours, 21 days/ cycle, 2 /2 cycles; Ramosetron, Metoclopramide.	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Tao C (2013).	74/74; 51/50; 60.1+7.9 /60.4+8.9.	Co-kushen injection; 15 ml per day, ID, started 14 days before chemotherapy, 5wks/cycle, for 1 cycle.	FOLFOX: Ox.135 mg/m ² , ID, day 1, LV 200mg/m ² , ID, 2 hours, day 1-5, 5-FU 500mg/m ² , ID, 8-10 hours, day1-5, 3wks/cycle, 1/1 cycle.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Wang H (2008).	34/34; 20/22; 52.58±8.12/51.1 1±7.72	Yiqiguoxiebuchang decoction; one decoction per day, for 3 mths.	FOLFOX: Ox.85 mg/m ² , ID, day 1, LV 200mg/m ² , ID, day 1-2, 5-FU 500 mg bolus day 1, 5-FU 2500 mg/m ² , ID, for 48 hours, 21 days/ cycle, 4/4 cycles; Ondansetron hydrochloride.	SG: U, AC: U, BPt: H BOA (obj): L, IOD: L, SOR: U.
Wang J	30/30; 18/21;	Yichangning decoction; one	FOLFOX4, 21 days /cycle, 2/2 cycles;	SG: L, AC: U, BPt: H, BOA

(2011).	52.3±6.2/ 56.7±7.8.	decoction per day, for 2 mths.	Ondansetron.	(obj): L, IOD: L, SOR: U.
Wu G (2010).	33/25; 23/17; 55.4 ±13.6 /52.8 ±15.2.	Fupiyiwei decoction; one decoction per day, for 24 wks.	FOLFOX 4: 12/12 cycles; Ondansetron hydrochloride	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Xu Y (2010)	61/60; 38/37; 53/52(mean)	Jiangniling formulae; one decoction per day, 14 days/cycle, for 8-10 cycles	FOLFOX 4: 11.1/7.8 (mean) cycles; Granisetron.	SG: U, AC: U, BPt: H, BOA (subj): H, IOD: L, SOR: U.
Yang Y (2008).	30/30; 16/19; 51.07+10.44 /51.33+10.95.	Kang'ai injection; 50 ml, ID, day1- 20, 30days/cycle, for 2 cycles.	FOLFOX4, 4/4 cycles; Granisetron.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Yang Z (2005)	30/30; 18/20; 29- 70 /28- 69	Xuesaitong injection, 500 mg,ID; Huangqi injection,60 ml,ID; Shenmai injection, 50 ml, ID &TM decoction, one decoction per day, day1-5, 21 days/ cycle, for 2 cycles.	FOLFOX: Ox.200 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-5, 5-FU 500 mg /m ² , ID day 1-5, 2/2 cycles.	SG: U, AC: U, BPt: H, BOA (subj): H, IOD: L, SOR: U.
Zhang H (2008)	31/29; 28/23; 52.35/53.4(me an)	3 TM decoctions based on symptom differentiation; one decoction per day. Started one week before chemotherapy till one week after chemotherapy completed.	FOLFOX 4: 4/4 cycles; Ondansetron hydrochloride.	SG: U, AC: U, BPt: H, BOA (subj): H, IOD: L, SOR: U.
Zhang Q (2006).	38/30; 35(all); 54.8(mean all).	Yiqihuoxue formulae; one decoction per day, 21 days/ cycle, for 3 cycles.	FOLFOX: Ox.125 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-2, 5-FU 500 mg /m ² bolus, day 1-2, 2000 mg /m ² ID for 72 hours, 21 days/cycle, 3/3 cycles; Ondansetron hydrochloride	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Zhang Q (2010).	60/60; 35/33; 56.2 (mean all);	Gubenxiaoliu capsule; 4 capsules, bid, for 8 wks.	FOLFOX4, 4/4 cycles; Ondansetron hydrochloride.	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Zhang W (2013).	32/32; 15/16; 56.8±10.1/46.4± 9.2.	Xiaoliuhuaaji Decoction I; one decoction per day, for 5 mths.	FOLFOX: Ox.135 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-2, 5-FU 2400 mg /m ² , ID for 48 hours, 21 days/cycle, 6/6 cycles; Ramosetron.	SG: L, AC: U, BPt: H, BOA (obj): L, IOD: L, SOR: U.
Zhang Y (2010).	21/20; NS; NS;	Jianpijiedu decoction; one decoction per day, for 4 wks.	FOLFOX 4: 2/2 cycles.	SG: U, AC: U, BPt: H, BOA (obj): L, IOD: H, SOR: U.

Zou B (2007)	32/27; 29/22; 53/54.3(mean)	Gubenkang'ai decoction; one decoction per day, for 6 wks.	FOLFOX: Ox.135 mg/m ² , ID, day 1, LV 200mg /m ² , ID, day 1-2, 5-FU 2400 mg /m ² , ID, for 48 hours, day 1, 21 days/ cycle, for 2 cycles(all); Granisetron, Metoclopramide.	SG: U, AC: U, BPT: H, BOA (subj): H, IOD: L, SOR: U.
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T: treatment group, C: control group, M: male, N: number, NS: not stated, ID: intravenous drip, TM: Traditional medicine. 5-FU: 5-Fluorouracil; LV: Leucovorin; Ox.: Oxaliplatin; FOLFOX: Ox. + 5-FU + LV; bid: twice per day; tid: three times per day; qd: once per day; Wk: week; Mth: month; med.: median.

Risk of Bias Categories: SG: Sequence Generation, AC: Allocation Concealment, BPT: Blinding of Participants/Personnel, BOA (obj): Blinding of Outcome Assessment (subjective outcome measure i.e. nausea), IOD: Incomplete Outcome Data, SOR: Selective Outcome Reporting. Risk of Bias Judgements: L: low risk, U: Unclear risk, H: High risk

Table 2: Effects of specific TMs on CINV: Level 1 single TMs

Traditional Medicine (species)	N studies	N participants	RR [95% CI]	I ²
<i>Hordeum vulgare</i> L. (mai ya)	2	98	0.47 [0.33, 0.68]	0
<i>Crataegus pinnatifida</i> Bge (shan zha)	2	98	0.47 [0.33, 0.68]	0
<i>Massa medica fermentata</i> (shen qu)	2	120	0.47 [0.30, 0.73]	0
<i>Panax ginseng</i> C. A. Mey. (ren shen)*	4	222	0.51 [0.39, 0.66]	0
<i>Glycyrrhiza uralensis</i> Fisch (gan cao)*	3	170	0.51 [0.38, 0.70]	0
<i>Magnolia officinalis</i> Rehd. et Wils (hou po)	3	179	0.54 [0.38, 0.77]	0
<i>Amomum kravanh</i> Pierre ex. Gagnep. (bai dou kou)	2	117	0.54 [0.36, 0.81]	0
<i>Dioscorea opposita</i> Thunb. (shan yao)	5	321	0.56 [0.47, 0.67]	0
<i>Sophora flavescens</i> Ait. (ku shen)	2	92	0.56 [0.35, 0.92]	0
<i>Lycium barbarum</i> L. (gou qi zi)	3	168	0.58 [0.41, 0.83]	0
<i>Cornus officinalis</i> Sieb. et Zucc. (shan zhu yu)	2	139	0.59 [0.46, 0.75]	0
<i>Paeonia suffruticosa</i> Andr. (mu dan pi)	2	139	0.59 [0.46, 0.75]	0
<i>Alisma orientalis</i> (Sam.) Juzep. (ze xie)	2	139	0.59 [0.46, 0.75]	0
<i>Rehmannia glutinosa</i> Libosch. (shu di huang)	3	199	0.60 [0.47, 0.75]	0
<i>Nelumbo nucifera</i> Gaertn. (lian zi)	2	110	0.60 [0.41, 0.88]	0
<i>Poria cocos</i> (Schw) Wolf (fu ling)*	16	1012	0.61 [0.54, 0.69]	15
<i>Coix lacryma-jobi</i> L. (yi ren)*	14	945	0.61 [0.53, 0.70]	29
<i>Codonopsis pilosula</i> (Franch.). Nannf. (dang shen)	12	747	0.61 [0.52, 0.72]	28
<i>Paeonia lactiflora</i> Pall. (bai shao)	5	272	0.61 [0.48, 0.76]	0
<i>Panax notoginseng</i> (Burk.) F.H. Chen (tian qi)	4	245	0.61 [0.43, 0.87]	0
<i>Atractylodes macrocephala</i> Koidz. (bai zhu)*	16	976	0.62 [0.54, 0.71]	13
<i>Eclipta prostrata</i> L. (mo han lian)	2	129	0.63 [0.41, 0.97]	0
<i>Sophora japonica</i> L. (huai hua)	3	150	0.63 [0.46, 0.86]	0
<i>Scutellaria barbata</i> D. Don. (ban zhi lian)	6	356	0.64 [0.50, 0.81]	0

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<i>Astragalus membranaceus</i> (Fisch.) Bge. (huang qi)*	13	733	0.65 [0.55, 0.76]	0
<i>Ligusticum chuanxiong</i> Hort. (chuan xiong)	2	114	0.65 [0.46, 0.92]	0
<i>Angelica sinensis</i> (Oliv.) Diels. (dang gui)	2	118	0.68 [0.50, 0.92]	11
<i>Hedyotis diffusa</i> Willd. (she she cao)	4	228	0.69 [0.51, 0.93]	0
<i>Akebia quinata</i> (Thunb.) Decne. (ba yue zha)	5	264	0.70 [0.51, 0.95]	0
<i>Curcuma zedoaria</i> (Berg.) Rosc. or <i>C. phaeocaulis</i> Val. (e zhu)	7	439	0.71 [0.57, 0.88]	0
<i>Spatholobus suberectus</i> Dunn (ji xue teng)	3	192	0.73 [0.55, 0.98]	0

*Included in the final six TMs.