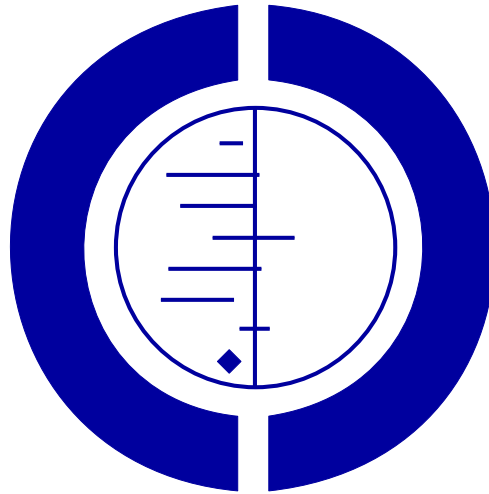


Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients (Review)

Zhang M, Liu X, Li J, He L, Tripathy D



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ABSTRACT

Background

Short term side-effects of chemotherapy include fatigue, nausea, vomiting, mucositis and myelosuppression or neutropenia. These occur during the course of treatment and generally resolve within months of completion of chemotherapy. A variety of Chinese medicinal herbs have been used for managing these side effects.

Objectives

To assess the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy-induced short term side effects in breast cancer patients.

Search strategy

We searched The Cochrane Breast Cancer Specialised Register (15/02/2007), The Cochrane Central Register of Controlled Trials (CENTRAL); (The Cochrane Library 2006, Issue 4); MEDLINE (1966 to December 2006); EMBASE (1990 to December 2006); and Chinese Biomedical Literature (2006, Issue 4). A number of journals were hand searched.

Selection criteria

Randomised controlled trials comparing chemotherapy with or without Chinese herbs in women with breast cancer.

Data collection and analysis

Two authors independently extracted the data, which were analysed using RevMan 4.2. For dichotomous data, we estimated the relative risk. For continuous data, we calculated the weighted mean difference.

Main results

We identified seven randomised controlled trials involving 542 breast cancer patients undergoing or having recently undergone chemotherapy. All studies were conducted and published in China. We did not pool the results because few studies were identified and no more than two used the same intervention. All were of low quality and used CMH plus chemotherapy compared with chemotherapy alone.

CMH combined with chemotherapy showed no statistically significant difference for the outcomes of phlebitis and alopecia. Only one study showed an improvement in nausea and vomiting, and in fatigue. Three indicated an improvement in white blood cells in the group receiving CMH. Two showed an increase in percentage changes in T-lymphocyte subsets CD4 and CD8. One study showed a statistically significant difference for CMH in percentage changes in T-lymphocyte subsets CD3, CD4 and CD8. Two herbal compounds may have improved quality of life. One study reported that CMH may have some effect on reducing toxicity in liver and kidney, but differences were not statistically significant.

Authors' conclusions

This review provides limited evidence about the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy induced short term side effects. Chinese medicinal herbs, when used together with chemotherapy, may offer some benefit to breast cancer patients

in terms of bone marrow improvement and quality of life, but the evidence is too limited to make any confident conclusions. Well designed clinical trials are required before any conclusions can be drawn about the effectiveness and safety of CHM in the management of breast cancer patients.

PLAIN LANGUAGE SUMMARY

Chinese medicinal herbs for the treatment of side-effects from chemotherapy in breast cancer patients

Chinese medicinal herbs (CMH) include any mixture of herbal compounds and decoction (the process by which herbs are boiled and remaining liquid used for health purposes), including the development of herbal formulae and injections, and capsules. Although CMH are used to counteract the side effects of chemotherapy (cancer treatment with chemical agents that are selectively destructive to malignant cells and tissues) in patients being treated for cancer, the evidence for their use for women with breast cancer has not been ascertained. The purpose of this systematic review was to evaluate the effectiveness and safety of CMH in alleviating chemotherapy-induced short term side effects for women either undergoing chemotherapy or having recently undergone chemotherapy. Short term side effects are those that occur during the course of the treatment and generally resolve within months of the completion of the therapy and affect up to 60% of patients. They include nausea and vomiting, mucositis (inflammation of the mucous membranes lining the digestive tract from the mouth down to the anus caused by chemotherapy); neutropenia (a decrease in white blood cells caused by chemotherapy); myelosuppression (a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets), and fatigue (loss of energy and tiredness). This review found seven randomised studies involving 542 breast cancer patients addressing this question. These studies used six different herbal remedies to treat the side effects of chemotherapy, all used CMH plus chemotherapy as the intervention compared with chemotherapy alone. The results suggest that using Chinese herbs in conjunction with chemotherapy or CHM alone may be beneficial in terms of improvement in marrow suppression and Immune system, and may improve overall state of quality of life. However, further trials are needed before the effects of TCM for people with breast cancer can be evaluated with any real confidence. There was no evidence of any harms of CMH.

BACKGROUND

Chemotherapy improves disease-free and overall survival in women with early stage breast cancer and these treatments are generally recommended in those who are at moderate to high risk of recurrence. In advanced breast cancer, these therapies are generally not curative, but may lead to modest improvements in survival; when used in appropriate patients, they can improve quality of life (EBCTCG 2005; Hayes 1995). Chemotherapy is known to have substantial short and long term side effects (Partridge 2001).

Short term side effects are those that occur during the course of treatment and generally resolve within months of completion of therapy. They include fatigue, phlebitis, alopecia, nausea, vomiting, mucositis, anemia, and myelosuppression or neutropenia. The latter can be associated with an increased risk of infection. The most common short term side effect of chemotherapy is fatigue (Berger 1998; Bower 2000; Broeckel 1998; Sitzia 1998). Nausea and vomiting are also common, and up to 60% of patients who receive antineoplastic cancer treatment will experience these side effects (King 1997).

Long term side effects usually have a much later onset and have effects that may last for many years (Ramalingam 2002). Long term side effects include premature ovarian failure, weight gain, cardiac dysfunction, leukemia and possibly cognitive dysfunction.

These side effects affect the quality of life of cancer patients and compromise the ability of physicians to deliver adequate doses of effective chemotherapy (King 1997).

Conventional treatment for chemotherapy in relation to some side effects

Fatigue

The prevalence of cancer-related fatigue increases to 80 to 96% in patients undergoing chemotherapy (Stasi 2003). This fatigue differs from that of everyday life, which is temporary and relieved by rest. Cancer-related fatigue is more severe, more distressing and not relieved by rest. Physiological factors (e.g. anemia, infection, electrolyte imbalance, sleep disorders, pharmacologic treatment) and psychological factors (e.g. mood disorders, stress) contribute to this fatigue. Many studies have shown that a substantial proportion of patients do not discuss feelings of fatigue with their doctors. The limited understanding and appreciation of fatigue has resulted in the lack of a structured approach and treatment for this problem. This tends to be based frequently on dietary and vitamin support, in some cases pharmacologic treatment, and in others complete rest. Specific cancer-related causes of fatigue (anemia, insomnia, depression, metabolic disorders, etc.) should be treated first. Diet, sleep and rest are all strategies that have been used with a certain degree of success (Stasi 2003). The use of erythropoietic

growth factors has also been shown to mitigate chemotherapy-associated anemia and related fatigue (Hudis 2005).

Nausea and vomiting

Chemotherapy-induced nausea and vomiting can be either acute (commencing shortly after administration and most severe during the next 6 to 8 hours) or delayed (occurring after 24 hours). Modern antiemetics are the standard medical treatment for preventing chemotherapy-induced nausea and vomiting, particularly the newly developed serotonin antagonists (Campora 1994). Chemotherapeutic drugs, however, vary in their tendency to cause nausea and vomiting and are classified as high, moderate or low in their emetogenicity. Drugs with high emetogenicity include cisplatin, cyclophosphamide, doxorubicin and methotrexate. For many patients, the nausea and vomiting is refractory to serotonin antagonists and/or may continue for more than 24 hours after administration, when these work best (Cunningham 1997). Nausea and vomiting can be controlled by the newer antiemetics or through the proper use of established agents. One large, randomised study (Gralla 2002; Kris 2006) has shown that, when there is a high or moderate risk of emesis, adding corticosteroids to a serotonin receptor antagonist is safe and effective.

Mucositis and neutropenia or myelosuppression

Chemotherapy-induced mucositis is an important, dose-limiting, and costly side effect of cancer therapy. It occurs in approximately 40% of patients who receive cancer chemotherapy. Concomitant with mucositis is chemotherapy-induced myelosuppression.

The approaches used to prevent chemotherapy-induced mucositis can be divided into three broad categories: alternation of mucosal delivery and excretion of individual chemotherapeutic agents; modification of the epithelial proliferative capabilities of the mucosa; and changing the potential for infective or inflammatory complications. General treatments include effective oral care, dietary modification and topical mucosal protectants. Appropriate use of topical anesthetics and systemic analgesics remain the cornerstone of therapy (Pico 1998).

Cytotoxic chemotherapy suppresses the hematopoietic system, impairing host protective mechanisms and limiting the dose of chemotherapy that can be tolerated. Neutropenic complications associated with myelosuppressive chemotherapy are a significant cause of morbidity and mortality, compromising treatment outcomes and creating excess healthcare costs. All patients who are treated with chemotherapy are at risk of developing neutropenic complications, but it is difficult for clinicians to predict which patients are at greater risk. For certain regimens, it is clear that prophylactic colony stimulating factor reduces the duration of severe neutropenia, but its use in all patients is not considered cost-effective. Researchers have sought to identify risk factors that may predispose patients to neutropenic complications (Crawford 2003). Currently, however, many of the available interventions are costly

and therefore prohibitive for treating the average patient in developing countries such as China.

Chinese medicinal herbs for chemotherapy-induced side effects

Complementary and alternative medicine approaches to health care are widely used around the world. A recent population-based survey of San Francisco women with breast cancer showed that 72% were using at least one type of alternative modality 2 to 4 months after diagnosis, especially those with advanced disease. One of the modalities commonly used among women with breast cancer is traditional Chinese medicine (TCM). Most contemporary studies of TCM for breast cancer emanate from China and reflect the current practice of combining TCM with surgical treatment, hormonal therapy, chemotherapy and radiation. There are no available statistics regarding the proportion of women using this approach in China or elsewhere (Cohen 2002).

Chinese medicinal herbs (CMH) form the mainstay of TCM, which is a 3000-year-old holistic system of medicine combining medicinal herbs, acupuncture, food therapy, massage and therapeutic exercise for both treatment and prevention of disease (Fulder 1996; Kirby 1997). Traditional Chinese herbal practice differs from conventional or allopathic drug practice in three ways: first, Chinese herbal practice advocates the use of whole plants and herbalists generally use unpurified plant extracts containing several constituents; secondly, several herbs may be used at the same time; and thirdly, Chinese herbal practitioners provide herbs to patients according to the specific syndromes they are experiencing, using individualised formulae. In addition, herbal practitioners use different techniques and diagnostic classifications compared with conventional practitioners in order to diagnose particular conditions (Andrew 1999).

Chinese herbs are defined in this review as products derived from plants or parts of plants (e.g. leaves, stems, buds, flowers, roots or tubers (raw or refined) and used for the treatment of disease on prescription from a TCM doctor. The plants included in this review will be restricted to those that are grown in China, since the effects of herbs from other areas may be different because of environmental factors that may affect plant components. For example, the components of the same plant from China or from Japan may be different. Synonyms for herbal medicines include: herbal remedies, herbal medications, herbal products, herbal preparations, medicinal herbs and phytopharmaceuticals. Being relatively convenient and cheap compared with other western medicine interventions, Chinese herbs have been sought and taken by many cancer patients in China and in other countries worldwide.

The treatments employed by TCM physicians are aimed at controlling the side effects and toxicities attributed to cancer therapies, preventing recurrence and prolonging survival (Cohen 2002). It is claimed that CMH may also play an important role in the treatment of breast cancer, especially in accessory treatment, and that injury resulting from surgery, chemotherapy and radiotherapy can

be relieved by TCM, and that recurrence, metastasis and complications can all be prevented. Many CMH have been used in the treatment of breast cancer (Sun 2002).

Two categories of CMH have been described: those that reduce therapeutic toxicity, clear heat (adjust unbalance in internal body such as anti-inflammatory action, reducing temperature etc.) and promote blood circulation (Sun 2002), and those that strengthen the body's resistance and reinforce immunity (humoral and cellular), relieve fatigue, remove toxins, and are antineoplastic and anti-inflammatory (Zhang 2002). CMH may therefore have the potential to improve the overall state of cancer patients' wellbeing and improve their ability to resist the disease. We identified some studies that used CMH to alleviate chemotherapy-induced short term side effects in breast cancer patients. The types of herbs and compound herbal formulae used are outlined in additional Table 01.

Some Chinese trials have tested the effectiveness of CMH in treating chemotherapy-induced short term side effects with interventions of at least one month duration and follow up of at least six months (Sun 2002). Researchers have tended to use different study designs and endpoints because CMH are quite often composed of mixtures of different herbs, and are sometimes customised for each patient by practitioners, based on a patient's syndrome according to traditional Chinese diagnostic patterns (inspection, listening, smelling, inquiry and palpation (Liu 2006)).

This systematic review was therefore necessary to assess the possible effectiveness and safety of CMH in alleviating chemotherapy-induced side effects in breast cancer patients. Furthermore, the review could provide background information to aid the development and conduct of more definitive clinical trials in this area.

OBJECTIVES

The objective of this review was to assess the effectiveness and safety of CMH in alleviating chemotherapy-induced short term side effects in breast cancer patients. Short term side effects were defined as those that occur during the course of treatment and generally resolve within months of the completion of therapy (Partridge 2001).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised clinical trials of CMH for breast cancer patients with chemotherapy-induced side effects were eligible for this review, regardless of blinding, language or publication status.

Types of participants

Inclusion criteria were: Female breast cancer patients receiving chemotherapy either as adjuvant treatment for early or advanced breast cancer or as palliative treatment for metastatic breast cancer and experiencing chemotherapy-induced side effects.

Exclusion criteria were: Female breast cancer patients with other cancers (except for basal cell carcinoma, squamous cell carcinoma or skin cancer).

Types of intervention

When considering Chinese herbs in the intervention group, we included: single herb (or extract from a single herb), Chinese proprietary medicine irrespective of preparation (e.g. oral liquid, tablet, capsule, pill, powder, plaster or injection liquid), mode of delivery (e.g. oral, cutaneous, intramuscular or intravenous injection), dosage and regimen etc. We defined CMH as products derived from plants or parts of plants that have been widely used in China for medicinal purposes. These include both single and compound herbal formulae (Liu 2002).

CMH may be given during and/or after chemotherapy regardless of the course of treatment or the duration of follow up.

We included these types of intervention.

- 1) CMH (single herb or compound herbs) compared with placebo.
- 2) CMH alone compared with conventional medicine alone (as methods of treating the side effects of chemotherapy: e.g. serotonin antagonists).
- 3) CMH combined with conventional medicine compared with conventional medicine alone.

We included Chinese herbal therapies alone or combined with other conventional treatments for the treatment group, provided that control group patients received the same conventional treatment; the only difference between the two groups was whether they received CMH or not.

The types of herbs used are described in additional Table 02.

Types of outcome measures

The primary outcome measures were:

- 1) control of nausea and vomiting, phlebitis and alopecia;
- 2) control of the severity of mucositis, including stomatitis, vaginitis, enteritis, proctitis and conjunctivitis
- 3) relief of fatigue.

We assessed the degree of control of the above symptoms according to the scales used in the original studies (e.g. patient reported and/or clinician evaluated).

The secondary outcome measures were:

- 1) improvement in marrow suppression, including neutropenia (white blood cell (WBC) reduction), anemia and thrombocytopenia as assessed by the World Health Organization Haematological Toxicity Scale (Ramalingam 2002);
- 2) immune system (percentage change in T lymphocytes);

3) adverse events, including infection, hospitalizations and toxicity to the kidney, liver and spleen induced by Chinese herbs (classified and measured according to the tools used in each trial);
 4) long term side effects such as premature ovarian failure, weight gain, cardiac dysfunction, leukemia and cognitive dysfunction if data were available;
 5) health-related quality of life assessed by, but not limited to, the European Organization for Research on Treatment of Cancer QLQ-C30 (Aaronson 1993) or the Rotterdam Symptom Checklist (Watson 1992) if reported.

We assessed primary and secondary outcome measures at the end of the Chinese herbal treatment and/or at the end of follow up as either dichotomous or continuous data.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Breast Cancer Group methods used in reviews.

The specialised register maintained by the Cochrane Breast Cancer Group was searched on 15/02/2007 (details of search strategies used by the group for the identification of studies and the procedure used to code references are outlined in the group's module <http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html>). Studies coded with the key words 'alternative/complementary', and text words 'Shenmai', 'Yiqiyanxue', 'Pishentang', 'Fu Zheng Sheng xue tiao yuan tang', 'Huang Qi' were extracted from the specialised register for consideration.

1. Electronic searching

We searched the following electronic databases regardless of language and publication status: The Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL, 2/2006) (The Cochrane Library 2006, Issue 4), using the search terms for breast cancer and Chinese medicine given in the MEDLINE search strategy below.

Unless stated otherwise, the search terms were free text terms; MeSH is a medical subject heading (MEDLINE medical index term); an asterisk (*) stands for 'any character(s)'

We searched MEDLINE from 1966 to 2006, as follows:

- #1 See search strategy of the Breast Cancer Group
- #2 Chemotherapy
- #3 #1 AND #2

CHINESE MEDICINE

- #4 Medicine, herbal [MeSH, all subheadings and categories included]
- #5 Plants [MeSH, all subheadings and categories included]
- #6 Drugs, Chinese herbal [MeSH, all subheadings and categories included]

- #7 Medicine, Chinese traditional [MeSH, all subheadings and categories included]
- #8 botanical
- #9 Huang qi [MeSH, all subheadings and categories included]
- #10 TCM
- #11 (herb* NEAR (extract* OR single* OR drug* OR compound* OR mixture*))
- #12 herbal medic*
- #13 Shenmai [MeSH, all subheadings and categories included]
- #14 natural
- #15 Chinese herb drugs
- #16 Chinese herb medicine
- #17 drug therapy (TCP)
- #18 Chinese medical formula
- #19 Science of prescription (TCD)
- #20 OR/ #4 to #19

BREAST CANCER AND CHINESE MEDICINE

- #21 #3 AND #20

CLINICAL TRIALS

- #22 See search strategy of the Breast Cancer Group

BREAST CANCER AND CHINESE MEDICINE AND CLINICAL TRIALS

- #23 #21 AND #22

We searched the following additional databases, using the above search strategy for reference: EMBASE (1974 to 2006); Chinese BioMedical disk (CD-ROM) (1979 to 2006); LILACS (www.bireme.br/bvs/l/ibd.htm) (1986 to 2006); Databases of ongoing trials (available from: www.controlled-trials.com); Database for gray literature (SIGLE).

Full electronic search strategies for all databases were available from the editorial base, except the one for the Chinese database

2. Handsearching

We handsearched the reference lists of relevant trials and reviews and the randomised controlled trials in the Chinese Cochrane Centre Database.

In addition, we searched manually the following key journals that were not included in the Chinese Cochrane Centre Database :

- 1) Cancer Research and Clinic (1986 to 2006)
- 2) Tumor (1981 to 2006)
- 3) Journal of Oncology (1995 to 2006)
- 4) Chinese Journal of Surgery of Integrated Traditional and Western Medicine (1994 to 2006)
- 5) Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care (1994 to 2006)
- 6) Chinese Clinical Oncology (1995 to 2006)
- 7) Journal of Practical Oncology (1986 to 2006)
- 8) Foreign Medical Sciences of Traditional Chinese Medicine Section (1978 to 2006)

- 9) Foreign Medical Sciences of Cancer Section (1974 to 2006)
- 10) Chinese Traditional and Herbal Drugs (1981 to 2006)
- 11) Journal of Integrating Chinese Medicine (1991 to 2006)
- 12) Journal of Practical Traditional Chinese Medicine (1993 to 2006)
- 13) Research on Traditional Chinese Medicine (1983 to 2006)

METHODS OF THE REVIEW

Trial selection

The authors screened trials for eligibility for inclusion in the review by retrieving all articles or abstracts that appeared relevant. Two assessors (M Zhang and X Liu) independently reviewed the title, abstract and keywords of every record retrieved. They obtained the full articles for further assessment if the information given suggested that:

1. the study population comprised patients with breast cancer undergoing chemotherapy, regardless of cancer stage;
2. at least one treatment arm used CMH;
3. at least one outcome of interest (nausea and vomiting or mucositis etc.) was reported;
4. the trial compared CMH with placebo or any other active intervention;
5. random allocation to the treatment or comparison group was used.

A third author (J Li) resolved any differences encountered. Where there was still doubt, we acquired the full article for further inspection. When this was not possible, we sought further information. These trials were added to the list of those awaiting assessment pending acquisition of more details.

Quality assessment of the trials

Two authors (M Zhang and X Liu) independently allocated each trial to one of the three quality categories described in the Cochrane Reviewers' Handbook (Alderson 2004). When disputes arose about category allocation, again we attempted resolution by discussion or by consulting a third author (J Li). When this was not possible and we required further information to clarify quality category allocation, we did not enter the data and we allocated the trial to the list of those awaiting assessment.

We assessed trial quality according to the following criteria (Schulz 1995).

1. Minimisation of selection bias.
 - a) Was the randomisation procedure adequate?
 - b) Was allocation concealment adequate?
2. Minimisation of performance bias - were the patients and individuals administering treatment blind to group allocation?
3. Minimisation of attrition bias.

- a) Were withdrawals and dropouts completely described?
- b) Was analysis by intention to treat?

4. Minimisation of detection bias - were outcome assessors blind to the intervention?

On the basis of these criteria, we broadly subdivided studies into one of the following three categories (Clarke 2000).

A All criteria for quality were met: there was a low risk of bias.

B One or more of the criteria for quality were only partly met: there was a moderate risk of bias.

C One or more of the criteria for quality were not met: there was a high risk of bias.

Data extraction

Where possible, we extracted the following data from descriptions of the original studies using a standard extraction form, which included at least the following items.

1. General information: published/unpublished, language, authors, article title, publication details (journal title, year, volume, issue, pagination).
2. Design of the trial: prespecified sample size, generation of randomisation sequence, allocation concealment method, blinding of information, statistical methods, attrition.
3. Participants: diagnostic criteria, total number and numbers in comparison groups, baseline characteristics, age, sex, inclusion criteria, exclusion criteria, study setting.
4. Intervention: types of herb, content of herbal formulae, duration, dosage, dose, co-intervention, control, withdrawals, dropouts, losses to follow up.
5. Outcome: primary outcomes; secondary outcomes and other outcomes at the end of treatment and /or the end of follow up; and number, type and severity of adverse events.
6. Conclusion: positive/negative.
7. Source of funding.

Intention-to-treat analysis

We did not include data from studies where more than 50% of the participants in any group were lost to follow up (this does not include the outcome of 'leaving the study early'). In studies with a less than 50% dropout rate, we considered participants leaving early to have had a negative outcome, except for the event of adverse effects and death.

Data analysis

We analysed the data using MetaView 4.2.2 in Review Manager 4.2 (Cochrane software). We compared each type of Chinese herb with each control intervention. If available and of sufficient quality and similarity (no heterogeneity, e.g. individual trial compared the same herb versus the same control intervention and the same outcome measures), we summarised the data statistically. Where possible, we conducted analyses according to intention to treat.

Dichotomous data

For dichotomous outcomes a standard estimation of the relative risk (RR) and its 95% confidence interval (CI) was calculated (fixed-effect model) to compare the incidence of the side effects of chemotherapy in the treatment group with those in the control group. A RR value of less than 1 indicated a reduction in side effects in the CMH group. Where possible, we also calculated the number needed to treat. If there was heterogeneity, we used a random-effects model.

Continuous data

For continuous outcomes, we estimated the weighted mean difference (WMD) between groups. Again, if we found heterogeneity, we used a random-effects model.

Test for heterogeneity

The fixed effect model was to be used for pooling. The random effects model was to be used if there was heterogeneity between studies ($P < 0.10$, chi-square). We planned to explore possible sources of heterogeneity by subgroup analysis and carry out sensitivity analyses as described below.

Addressing publication bias

We plotted data from all included studies on a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias depending on the number of clinical trials included in the systematic review (Egger 1997).

Sensitivity analysis

We had planned to perform sensitivity analyses to explore the influence of the following factors on estimates of treatment effect.

1. Repeating the analysis excluding unpublished studies (if there were any).
2. Repeating the analysis taking account of study quality.
3. Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry versus other), country.

However, we were unable to perform sensitivity analyses because pooling was not possible owing to the small number of trials.

Subgroup analysis

We had planned to carry out the following subgroup analyses.

1. Age (perimenopausal, postmenopausal).
2. Type of primary treatment.
3. Early compared with advanced breast cancer.
4. Participants receiving different chemotherapy drugs, different durations of treatment and different dosages.
5. Duration of follow up: on the basis of data.

We were unable to perform subgroup analyses owing to the small number of the trials.

DESCRIPTION OF STUDIES

Excluded studies

The initial search identified 88 references (76 from electronic searches and 12 from handsearching) up to December 2006. After reviewing the titles and abstracts, we excluded 71 studies because they were duplicates, experimental or animal studies, or they had a study objective not relevant to this review. A total of 17 references published in Chinese were retrieved for further assessment. Of these, 10 studies (Hou 2000; Huang 2003; Li 2000; Liang 1999; Wang 2003; Wang 1990; Weng 2003; Wu 1997; Yuan 1997; Zhang 1997) were excluded because they did not meet our inclusion criteria (see 'Characteristics of excluded studies').

Awaiting assessment

No studies were awaiting assessment.

Ongoing studies

We were not aware of any studies that were ongoing.

Included studies

We were able to include seven studies (Fang 1995; Hong 2005; Huo 2003; Li 2002; Liu 2000; Situ 2005; Yang 2004). All were said to be randomised, although no detailed descriptions were provided. CMH were used in all included studies. Two studies (Huo 2003; Liu 2000) used Shenmai injections plus conventional chemotherapy as an intervention versus chemotherapy alone. The study by Yang 2004 compared patients treated with Aidi fuzheng injections plus chemotherapy versus chemotherapy alone and the study by Li 2002 compared patients treated with Shenqi fuzheng injections plus chemotherapy versus chemotherapy alone. The study by Situ 2005 investigated Aifukang capsules (a developed formula) plus chemotherapy versus chemotherapy alone on quality of life after operation. The study by Hong 2005 compared Jiawei Guilu Erxian Dan (a mixture of traditional Chinese medicines) plus chemotherapy versus chemotherapy alone on bone marrow inhibition after chemotherapy. The study by Fang 1995 compared an oral decoction of Chinese herbs (the main herbal compound comprising 11 herbs) given 1 month after surgery combined with chemotherapy versus western medicine. All the studies reported two parallel treatment arms. For a full description of these seven studies, see 'Characteristics of included studies'. All included studies were conducted and the reports published in China.

Length of studies

The longest study (Li 2002) took place over a period of 84 days and the shortest ones (Huo 2003; Hong 2005) lasted only for 14 days. The length of one study (Fang 1995) was not reported. Three studies (Liu 2000; Situ 2005; Yang 2004) lasted for between 42 and 56 days.

Participants and setting

All seven trials randomised participants with breast cancer. All participants were Chinese women. Five studies included inpatients (Fang 1995, Huo 2003, Li 2002, Liu 2000, Yang 2004). One (Hong 2005) included outpatients post breast cancer surgery and one (Situ 2005) included both outpatients and inpatients. Five studies (Fang 1995; Hong 2005;Huo 2003; Liu 2000; Situ 2005) included postoperative patients. Two studied (Li 2002; Yang 2004) patients with advanced breast cancer (Stage IV).

Study size

A total of 542 participants were included in the seven studies. Situ 2005 was the largest study, with 120 patients, and Huo 2003 was the smallest, with 48 patients. The remaining studies randomized less than 100 patients: Hong 2005 (n = 92); Fang 1995 (n = 68); Li 2002(n = 75); Liu 2000 (n = 80); Yang 2004 (n = 59).

Diagnosis

The diagnostic criteria for breast cancer were based on World Health Organization (WHO) TNM stage criteria for three studies and a Karnofsky performance status (KPS) greater than 60 (Fang 1995; Hong 2005; Liu 2000); a further three studies (Huo 2003; Li 2002; Situ 2005) used pathological diagnostic criteria and a KPS greater than 60; and in one study (Yang 2004) the criteria were based on the Diagnostic Criteria for Chinese Common Malignant Tumors. All patients in this study had stage IV disease and their KPS scores were greater than 60. Only one study (Situ 2005) documented clear inclusion and exclusion criteria.

Interventions

Variation in formulae, dosages, administration, duration of treatment and control interventions were common in the included studies. In total, 27 different herbal medicines were used. Radix Astragali (Huangqi) was tested in four studies (Fang 1995; Li 2002; Situ 2005; Yang 2004). Radix Codonopsis (Dangshen) was tested in two (Fang 1995; Li 2002). Shenmai injections were used in two studies (Huo 2003; Liu 2000). Four studies used herbal injections (Huo 2003; Li 2002; Liu 2000; Yang 2004); two used herbal decoctions (Fang 1995; Hong 2005) and one (Situ 2005) used herbal capsules. The compositions and dosages of herbal medicines varied (see Additional Table 02).

The treatment groups were given herbal medicines combined with chemotherapy and all the control groups received chemotherapy alone. Huo 2003 used Shenmai injections (40 mL plus 300 mL with 5% amylose, once a day for 14 days) combined with conventional chemotherapy (not specified). Liu 2000 used Shenmai injections (60 mL/day for 42 days) combined with conventional chemotherapy with CMF (cyclophosphamide, methotrexate, fluorouracil), CAF (cyclophosphamide, Adriamycin, fluorouracil), or CAP (cyclophosphamide, Adriamycin, Platino). Yang 2004 used Aidi injections (50 mL/day for 30 days) combined with vinorelbine (25 mg/m²) and Pirarubicin (40 to 50 mg/m²) for 21 days. Fang 1995 used an oral decoction of a mixture of 11 CMH combined with conventional chemotherapy (not specified). Full de-

scriptions of the studies can be found in 'Characteristics of included studies'.

Outcomes

Three studies (Li 2002; Situ 2005; Yang 2004) reported nausea and vomiting, two (Li 2002; Yang 2004) reported phlebitis, one (Situ 2005) reported fatigue, one (Li 2002) reported alopecia, five (Fang 1995; Hong 2005; Li 2002; Liu 2000; Yang 2004) reported bone marrow suppression (proportion of patients with a WBC count < 3.0 10⁹/L) and effect on the immune system (percentage change in T lymphocytes), three (Li 2002; Situ 2005; Yang 2004) reported quality of life, and one study (Li 2002) reported adverse events. All the reported outcomes were measured at the end of treatment, but the timing of measurements varied across trials.

No study reported severity of mucositis or long term side effects.

METHODOLOGICAL QUALITY

Randomisation and allocation concealment

All included studies were described as randomised. Two (Situ 2005; Yang 2004) used a random number table to allocate participants, one (Hong 2005) used a simple randomised method, but the author did not state which one. All other studies claimed to be randomised, but none described how the randomisation process was undertaken. This potentially created some selection bias. Concealment of allocation prior to enrolment was not mentioned in any study. We tried to contact the relevant authors for detailed information by phone or correspondence, but to date we have not received any replies.

Blindness

Descriptions of the blinding process were not reported for the included studies. There were obvious differences in drug types and routes of drug delivery between treatment and control groups in all the studies (see table of 'Characteristics of included studies', particularly 'Methods' and 'Notes').

Loss to follow up, withdrawals and intention-to-treat analysis

None of studies described or reported withdrawals, loss to follow up or intention-to-treat analysis.

Data reporting

The similarities of the comparison groups at baseline were reported in all trials, based on age, sex and disease duration at entry. Only two studies (Liu 2000, Situ 2005) reported inclusion and exclusion criteria. Outcome assessments were made after treatment, but indications for further interventions were stated.

RESULTS

We did not conduct a pooled analysis because there were only two studies that evaluated the same intervention. We did not conduct subgroup analysis because of the small number of included studies in each group. We also did not conduct sensitivity analyses because pooling was not performed.

Control of nausea and vomiting ('Comparisons and data 01.01-01.02')

This was expressed as either dichotomous or continuous data in the original studies.

One study compared patients treated with Shenqi fuzheng injections plus chemotherapy versus chemotherapy alone (Li 2002) and one compared patients treated with Aidi fuzheng injections plus chemotherapy versus chemotherapy alone (Yang 2004). These studies showed no statistically significant difference in nausea and vomiting (RR 0.69, 95% CI 0.47 to 1.03; RR 0.75, 95% CI 0.54 to 1.04, respectively). However, one study (Situ 2005) reported that there was a greater improvement in nausea and vomiting in the treatment group (Aifukang capsules) than in the control group (WMD 0.84, 95% CI 0.57 to 1.11).

Control of alopecia, phlebitis, and fatigue ('Comparisons and data 01.03-01.05')

This was expressed as either dichotomous or continuous data in the original studies.

One study (Li 2002) involving 75 patients receiving Shenqi fuzheng injections plus chemotherapy versus chemotherapy alone reported alopecia. This study showed no statistical difference (RR 0.88, 95% CI 0.41 to 1.85). One study (Situ 2005) comparing Aifukang capsules (a developed formula) plus chemotherapy versus chemotherapy alone reported on fatigue; there was a statistically significant difference (WMD 0.80, 95% CI 0.37 to 1.23). Two studies ; involving a total of 134 patients receiving Aidi fuzheng injections plus chemotherapy versus chemotherapy alone (Yang 2004) or Shenqi fuzheng injections plus chemotherapy versus chemotherapy alone (Li 2002) reported on phlebitis. When comparing the results with patients treated with chemotherapy alone, these two studies showed no statistically significant difference in the occurrence of phlebitis (RR 1.02, 95% CI 0.64 to 1.64; RR 0.50, 95% CI 0.16 to 1.57 respectively).

Reduction in white blood cells ('Comparisons and data 01.06')

This was defined as a WBC count $<3.0 \times 10^9/L$.

Two studies; administering Aidi fuzheng injections plus chemotherapy versus chemotherapy alone (Yang 2004) or Shenqi fuzheng injections plus chemotherapy versus chemotherapy alone (Li 2002) showed no statistical difference in WBC reduction between the two groups (RR 0.98, 95% CI 0.81 to 1.18; RR 0.58, 95% CI 0.33 to 1.03, respectively). One study (Huo 2003) using

Shenmai injections plus conventional chemotherapy as an intervention versus chemotherapy alone showed a lower rate of WBC reduction in the herbal group than in the control group (WBC $>3.0 \times 10^9/L$). This difference was statistically significant (RR 0.25, 95% CI 0.12 to 0.52).

White blood cell change after treatment ('Comparisons and data 01.07')

Three studies involving 132 patients receiving a CMH decoction plus chemotherapy versus chemotherapy alone (Fang 1995), Jiawei Guilu Erxian Dan (mixture of traditional Chinese medicines) plus chemotherapy versus chemotherapy alone (Hong 2005), or Shenmai injections plus conventional chemotherapy versus chemotherapy alone (Liu 2000) demonstrated improvement in WBC change. Compared with chemotherapy alone, the groups who received herbal medicine plus chemotherapy showed a statistically significant difference in WBC improvement (WMD 2.20, 95% CI 1.67 to 2.73; WMD 0.60, 95% CI 0.05 to 1.15; WMD 0.91, 95% CI 0.06 to 1.76, respectively).

T-lymphocyte subsets ('Comparisons and data 01.08-01.10')

Compared with patients treated with chemotherapy alone, one study (Li 2002) administering Shenqi fuzheng injections plus chemotherapy versus chemotherapy alone showed no statistically significant differences in percentage changes of CD3+, CD4+ and CD8+ cells (WMD 1.50, 95% CI -3.18 to 6.18; WMD 3.00, 95% CI -0.46 to 6.46; WMD -2.20, 95% CI -4.83 to 0.43 respectively) four months after treatment. However, the original study reported that the treatment group improved more than the control group. One study (Yang 2004) using Aidi fuzheng injections plus chemotherapy versus chemotherapy alone showed a statistically significant difference in the percentages of CD3+, CD4+ and CD8+ cells (WMD 10.20, 95% CI 6.93 to 13.47; WMD 11.60, 95% CI 8.56 to 14.64; WMD 5.70, 95% CI 4.02 to 7.38, respectively) at least two months after treatment with Aidi injections plus chemotherapy. One other study (Liu 2000) administering Shenmai injections plus chemotherapy versus chemotherapy alone showed no statistically significant difference in the percentage of CD3+ cells (WMD -0.60, 95% CI -4.47 to 3.27), but did show a statistically significant difference in the percentage change of CD4+ and CD8+ cells (WMD 5.66, 95% CI 3.64 to 7.68; WMD 2.08, 95% CI 0.58 to 3.58) for at least two months.

Thrombocytopenia ('Comparisons and data 01.11')

One study (Li 2002) comparing Shenqi fuzheng injections plus chemotherapy with chemotherapy alone showed no statistically significant difference in thrombocytopenia reduction (RR 0.58, 95% CI 0.10 to 3.29). This result was different from that reported in the original study that the treatment group showed more improvement than the control group (30% in the treatment group and 51.1% in the control group (see 'Discussion').

Quality of life ('Comparisons and data 01.12-01.13')

This was expressed as either dichotomous or continuous data.

One study (Situ 2005) comparing Aifukang capsules (a developed formula) plus chemotherapy versus chemotherapy alone showed a statistically significant difference (WMD 14.47, 95% CI 11.24 to 17.70) in favour of the patients treated with Aifukang plus chemotherapy after operation. Quality of life was evaluated in this study using the EuroQLQ-BR23 questionnaire and an additional form developed for the study. Quality of life measured in one study administering Shenqi fuzheng injections plus chemotherapy versus chemotherapy alone (Li 2002) and another administering Aidi fuzheng injections plus chemotherapy versus chemotherapy alone (Yang 2004) was evaluated using the Karnofsky performance status score combined with scores evaluated by the patients (improvement: an increase by 10 points after treatment; reduction: a decrease by 10 points; stable: either an increase or a decrease of less than 10 points). The study by Li 2002 showed an improvement in quality of life (RR 2.19, 95% CI 1.10 to 4.33), but that by Yang 2004 did not demonstrate a statistically significant improvement (RR 1.92, 95% CI 0.98 to 3.74). However, the original study by Yang 2004 reported that there was a statistically significant difference for quality of life between the herbal group and the control group. This may have been because of the small number of participants in this study (see 'Discussion').

Adverse events ('Comparisons and data 01.14-01.15')

The study (Li 2002) that compared Shenqi fuzheng injections plus chemotherapy with chemotherapy alone reported adverse effects of toxicity to kidney and liver and abnormal function. These results were not statistically significant (RR 0.88, 95% CI 0.19 to 4.06; RR 0.88, 95% CI 0.06 to 13.48). Our results differed from those in the original study, which reported that the treatment group had fewer adverse effects than the control group (7.5% in the treatment group and 8.5% in the control group).

DISCUSSION

This review identified seven studies of six different herbal remedies to treat the side effects of chemotherapy in breast cancer patients. All studies compared CMH plus chemotherapy versus chemotherapy alone. Different prescriptions for the elements and dosages of each herbal remedy may cause different outcomes in breast cancer patients. As a result we were unable to pool the data across studies, which may have provided more precise results and greater statistical power to detect differences. To help physicians to understand the effectiveness of each Chinese herbal remedy in treatment of the side effects of chemotherapy, we have described the elements and dosages of all the prescriptions included in this review in additional Table 02.

This review has several limitations. First, all included studies were quite small in size, ranging from 48 to 120 patients, which could

have resulted in both false positive and false negative findings. Secondly, the patients included in individual studies had different stages of breast cancer and were subject to different diagnostic criteria (e.g. three studies (Fang 1995; Hong 2005; Liu 2000) used the WHO TNM staging criteria, three studies (Li 2002; Huo 2003; Situ 2005) used pathologic diagnostic criteria, and one study (Yang 2004) used the Diagnostic Criteria for Common Chinese Malignant Tumors). Thirdly, there were variations in formulae, dosages, modes of administration, duration of treatment and control interventions. Fourthly, the outcome measures were also different (e.g. when reporting WBC count outcome, three studies (Huo 2003; Li 2002; Yang 2004) used a defined reduction in WBC as an outcome measurement, and three other studies (Fang 1995; Hong 2005; Liu 2000) used the WBC count as the outcome measurement). Additionally, different tools were used to assess quality of life (Li 2002; Situ 2005; Yang 2004). Details are given in the table of 'Characteristics of included studies'. The differences noted could have resulted in clinical heterogeneity.

In addition, statistical methods were misused in some of the original studies. One study, by Li 2002, reported that there was a significant improvement in the herbal group for all outcomes measured. After very careful checking by two authors and a statistician using methods including Fisher's exact test and the logrank test, we detected that some statistical methods were used inappropriately in the original study, which led to incorrect conclusions.

It is believed that CMH may reduce therapeutic toxicity, clear heat and promote blood circulation (Sun 2002); they may also strengthen the body's resistance and reinforce immunity (humoral and cellular), relieve fatigue and remove toxins, and are antineoplastic and anti-inflammatory (Zhang 2002). The use of CMH may improve the overall state of these patients' wellbeing and improve their ability to overcome the cancer. There is some evidence in this review that CMH recipes containing Huangqi (Radix Astragali) plus chemotherapy may have beneficial effects that combat marrow suppression (white blood cells) and improve the immune system (T lymphocytes). There is no evidence that Chinese herbal compounds plus chemotherapy improve the control of phlebitis and alopecia.

It was regrettable that the quality of the included trials was poor. We do not think the evidence in this systematic review is strong enough to draw firm conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides limited evidence concerning the effectiveness of CMH in alleviating chemotherapy-induced short term side effects. When used together with chemotherapy, CMH may offer some benefit to breast cancer patients in terms of bone marrow

improvement and quality of life, but the evidence is too limited to make any confident conclusions. Well designed clinical trials are required before any conclusions can be drawn about the value of CMH in the management of breast cancer patients.

Breast cancer patients treated with chemotherapy

Chinese herbal medicine, when used together with chemotherapy, may have the potential to offer benefits in terms of improvements in marrow suppression and the immune system, and in the overall status of quality of life, but the evidence is too limited to make any conclusions with confidence. Furthermore, there has been only limited assessment of the safety of herbal therapy.

Clinicians

How these findings may be incorporated into everyday practice is unclear. Clinicians practising TCM or using Chinese herbs as a medicine supplementary to chemotherapy should be encouraged to review the data from these studies and share them with their patients. They should also support more definitive studies. Western physicians not trained in TCM or the use of CMH should not dismiss these approaches as being without theory or clinical basis, and should likewise support further studies in the field. There are currently no data to make specific recommendations on whether herbal therapy should be used, and which specific regimens would be suited to specific conditions.

Funders and policy makers

TCM and Chinese herbs are widely used and the studies noted here seem to suggest that they may have some effect. This intervention seems to have enough supporting evidence from both ancient practice and modern studies to be worth further investigation in some areas. This review does not provide sufficient evidence to either support or refute the use of TCM or CMH combined with chemotherapy for alleviation of the side effects of chemotherapy in breast cancer patients. Numerous obstacles to the conduction of studies in this area need to be overcome, including the standardization of herbal products, the bridging of gaps between practitioners of herbal therapy and traditional oncologists, and sufficient expertise and funding to conduct the necessary trials.

Implications for research

This review raises many questions. There is some suggestion that the use of CMH, even within the context of western traditions of diagnosis and practice, have some properties that are possibly beneficial, but this remains unclear in the absence of properly randomised trials. Furthermore, we did not find that the identified trials evaluated the holistic and tailored approach of traditional CMH. Any future studies of Chinese herbal medicines plus chemotherapy in breast cancer patients would need to be much larger and take into account clear and consistent clinical criteria in diagnosis, interventions, outcomes and the safety of Chinese herb medicine.

POTENTIAL CONFLICT OF INTEREST

Nil known

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REFERENCES

References to studies included in this review

- Fang 1995** {published data only}
 * * Fang CL. Chinese herbs in the treatment of 30 breast cancer patients caused by postoperative chemotherapy. *Journal of Traditional Chinese Medicine* 1995;**36**(2):115.
- Hong 2005** {published data only}
 * *Hong SZ, Lin Y, Situ HL. A clinical study of Jiawei Guilin Erxian Dan for bone marrow inhibition in mammary cancer after chemotherapy. *New Journal of Traditional Chinese Medicine* 2005;**37**(1):32–3.
- Huo 2003** {published data only}
 Huo J, Chen YP, Zhang DY. Shenmai injections for leukocytopenia reduction caused by chemotherapy for 26 breast cancer patients. *Chinese Journal of Science and Technology of Traditional Chinese Medicine* 2003;**10**(3):178.
- Li 2002** {published data only}
 Li XL, Tian QY, Ma WJ. Clinical study on Shenqi Fuzheng injections combined with chemotherapy for advanced breast cancer patients. *Chinese Practical Medical Journal* 2002;**2**(24):2263–4.
- Liu 2000** {published data only}
 Liu P, Cao YM, Qiao XM, Yang DQ, Zhou B, Shao H. Clinical study on Shenmai injections in promoting postoperative recovery in patients with breast cancer. *Chinese Journal of Integrated Traditional and Western Medicine* 2000;**20**(5):328–9.
- Situ 2005** {published data only}
 Situ HL, Lin Y, Chen QJ, Ou AH, Zhu HY, Liu PX, et.al. Effect of Aifukang on quality of life of breast cancer patients treated with chemotherapy after operation. *Journal of Guangzhou University of Traditional Chinese Medicine* 2005;**22**(1):26–9.
- Yang 2004** {published data only}
 * *Yang L. Clinical study on Aidi injections combined with chemotherapy for advanced cancer patients. *Chinese Journal of Integrated Traditional and Western Medicine* 2004;**24**(8):755–6.
- References to studies excluded from this review**
- Hou 2000**
 Hou W, Zhang ZZ, Yan HF, Lu WP, Dong HT, Huo YH, Yang ZY, et.al. Chinese medicine Arduola Fuzhengling for the treatment of leukocytopenia reduction caused by chemotherapy for 45 breast cancer patients. *Chinese Journal of Folk Therapy* 2000;**7**:42–4.
- Huang 2003**
 * *Huang ZF, Ni HZ, Shi ZY, Zhong K. Xiaoyao Shan formula combined with chemotherapy in the treatment of 32 breast cancer patients. *Chinese Archives of Traditional Chinese Medicine* 2003;**21**(6):1001–17.
- Li 2000**
 Li J, Ni XQ, Li JB, Liang QH, Yuan J, Tang LL. The influence of Fuzheng baozhentang decoction on the quality life of cancer patients with radiotherapy and chemotherapy. *Journal of Zhenjiang College of Traditional Chinese Medicine* 2000;**24**(3):23–5.
- Liang 1999**
 Liang YJ. Clinical study on Shenqi fuzheng injections for advanced malignant tumour. *Journal of Changchuan College of Traditional Chinese Medicine* 1999;**15**(6):22.

Wang 1990

Wang Q, He SJ. Traditional Chinese medicine with western medicine in the treatment of 31 breast cancer patients. *Cancer* 1990;**9**(3):238–9.

Wang 2003

Wang GX, Cui ZM. Observation of Bazhentang decoction in the treatment of leukocytopenia caused by postoperative chemotherapy of breast carcinoma. *Hebei Journal of Traditional Chinese Medicine* 2003;**25**(1):10–2.

Weng 2003

Weng YQ, Tang HJ, Cheng AQ, Tang JX, Cheng YY, Li X. Clinical observation of health-supporting and pathogen-eliminating therapy for toxic and negative effects following chemotherapy in treating breast cancer. *Acta Universitatis Traditionis Medicis Sinensis Pharmacologiae Shanghai* 2003;**17**(3):28–31.

Wu 1997

Wu FX, Xia LM, Wang SY. Yiqibixietang decoction for leucocyte reduction caused by chemotherapy in 38 patients. *Journal of Anhui College of Traditional Chinese Medicine* 1997;**16**(2):24–25.

Yuan 1997

Yuan ZJ, Ouyang SX, Zheng SY. Integrated traditional Chinese with western medicine for leucocyte reduction of malignant tumour by chemotherapy in 58 patients. *Huan Journal of Traditional Chinese Medicine* 1997;**13**(4):32–3.

Zhang 1997

Zhang YZ, Xue DL. Clinical study on Pishentang decoction combined with chemotherapy in the treatment of 30 breast cancer patients. *Chinese Journal of Integrated Traditional and Western Medicine* 1997;**17**(10):632–3.

Additional references

Aaronson 1993

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et, al. The European Organization for Research and on Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993;**85**:365–76. *Journal of National Cancer Institute* 1993;**85**:365–76.

Alderson 2004

Alderson P, Green S, Higgins JPT. Cochrane Reviewers' Handbook 4.2.2 (updated December 2003). In: *Cochrane Database of Systematic Reviews*, Issue 1, 2004. Chichester, UK: John Wiley and Sons. Ltd.

Andrew 1999

Andrew V, Catherine Z. ABC of complementary medicine:Herbal medicine. *BMJ* 1999;**319**(7216):1050–3.

Berger 1998

Berger AM. Patterns of fatigue and activity and rest during adjunctive breast cancer chemotherapy. *Oncology Nursing Forum* 1998;**25**(51):51–2.

Bower 2000

Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: correlates, and impact on quality of life. *Journal of Clinical Oncology* 2000;**18**(4):743–53.

Broeckel 1998

Broeckel JA, Jacobosen PB, Horton J, Balducci L, Lyman CH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology* 1998;**16**(5):1689–96.

Campora 1994

Campora E, Merlini L, Rubagotti A, Rosso R. Ondansetron and dexamethasone versus standard combination antiemetic therapy: A randomised trial for prevention of acute and delayed emesis induced by cyclophosphamide-doxorubicin chemotherapy and maintenance of antiemetic effect. *American Journal of Clinical Oncology* 1994;**17**(6):522–6.

Clarke 2000

Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook included in 4.1 Review Manager (RevMan). Computer program Version 4.1. The Cochrane Collaboration, Updated June 2000.

Cohen 2002

Cohen I, Tagliaferri M, Tripathy D. Traditional Chinese medicine in the treatment of breast cancer. *Seminars in Oncology* 2002;**29**(6):563–74.

Crawford 2003

Crawford J, Dale CD, Lyman GH. Chemotherapy -induced neutropenia. *Cancer* 2004;**100**(2):228–37.

Cunningham 1997

Cunningham RS. 5-HT₃ receptor antagonists: A review of pharmacology and clinical efficacy. *Oncology Nursing Forum* 1997;**24**(Suppl 7):33–4.

EBCTCG 2005

Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**(9472):1687–717.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;**315**(7109):629–34.

Fulder 1996

Fulder S. *The handbook of alternative and complementary medicine*. Oxford: Oxford University Press, 1996.

Gralla 2002

Gralla RJ. New agents, new treatment, and antiemetic therapy. *Seminars in Oncology* Feb. 2002;**29**(Suppl 4):119–24.

Hayes 1995

Hayes DF, Henderson IC, Shapiro CL. Treatment of metastatic breast cancer: Present and future prospects. *Seminars in Oncology* 1995;**22**(Suppl 5):5–21.

Hudis 2005

Hudis CA, Vogel CL, Cralow JR, Williams D, Procrit Study Group. Weekly epoetin alfa during adjuvant chemotherapy for breast cancer: effect on hemoglobin levels and quality of life. *Clinical Breast Cancer* 2005;**6**(2):132–42.

King 1997

King CR. Nonpharmacologic management of chemotherapy-induced nausea and vomiting. *Oncology Nursing Forum* 1997;**24**(Suppl 7):41–8.

Kirby 1997

Kirby AJ, Schmidt RJ. The antioxidant activity of Chinese herbs for eczema and of placebo herbs. *Journal of Ethnopharmacology* 1997;**56**(2):103–8.

Kris 2006

American Society of Clinical Oncology, Kris MG, Hesketh PJ, Somerfield MR, Fever P, Clark-Snow R, Koeller JM, et al. American Society of Clinical Oncology guideline for antiemetics in oncology. *Journal of Clinical Oncology* update 2006;**24**(18):2932–47.

Liu 2002

Liu JP, McIntosh H, Lin H. Chinese medicinal herbs for chronic hepatitis B. In: *Cochrane Database of Systematic Reviews*, 2, 2002. Oxford: Update Software.

Liu 2006

JP Liu, M Yang, YX Liu, ML Wei, Grimsgaard S. Herbal medicines for treatment of irritable bowel syndrome. In: *Cochrane Database of Systematic Reviews*, Issue 1, 2006. Chichester. UK: John Wiley & Sons Ltd.

Partridge 2001

Partridge AH, Burstein Harold HJ, Winer EP. Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. *Journal of the National Cancer Institute Monographs* 2001;**30**:132–42.

Pico 1998

Pico JL, Avila-Garavito A, Naccache P. Mucositis: Its occurrence, consequences, and treatment in oncology the setting. *The Oncologist* 1998;**3**(6):446–51.

Ramalingam 2002

Ramalingam S, Belani CP. Meaning survival in lung cancer patients. *Seminars in Oncology* 2002;**29**(1Suppl):125–31.

Schulz 1995

Schulz KF, Chalmers I, Hayes R, Altman D. Empirical evidence of bias. *Journal of the American Medical Association* 1995;**273**(5):408–12.

Sitzia 1998

Sitzia J, Huggins L. Side effects of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy for breast cancer. *Cancer Practice* 1998;**6**(1):13–21.

Stasi 2003

Stasi R, Abriani L, Beccaglia P, Terzoli E, Amadori S. Cancer-related fatigue. *Cancer* 2003;**98**(9):1786–1800.

Sun 2002

Sun SP. The development of traditional Chinese medicine in treatment of breast cancer. *Chinese Journal of Surgery of Integrated Traditional and Western Medicine* 2002;**8**(6):455–7.

Watson 1992

Watson M, Law M, Maguire GP, Robertson B, Greer S, Bliss JM, et al. Further development of a quality of life measure for cancer patients: The Rotterdam Symptom Checklist (Revised). *Psychooncology* 1992;**1**:35–44.

Zhang 2002

Zhang WB, Wang B, Shi LC. An application of traditional Chinese medicine in the treatment of breast cancer patients. *Chinese Journal of*

(Continued)

Integrated Traditional and Western Medicine in Intensive and Critical Care 2002;9(1):54–5.

*Indicates the major publication for the study

TABLES

Characteristics of included studies

Study	Fang 1995
Methods	Generation of allocation sequence: not stated Blinding: not stated Sample size estimation: no information Withdrawals/drop-outs: no information ITT analysis: no
Participants	Ethnicity: Chinese Setting: inpatients 67 female patients (30 in treatment group, age: 78% of all were at the age of 28 to 68 years, and 40 to 60 years; mean: not stated, disease duration: not given). 37 in control group, age: not given; disease duration: not given) Inclusion: female breast cancer patients with stages I and II diagnosed by TNM criteria Exclusion: not stated
Interventions	Treatment group: oral decoction of Chinese herbs(the main herbal compound comprising 11 herbs) given 1 month after surgery combined with chemotherapy; dosage and duration: not stated. Control group: western medicine alone. No other details
Outcomes	1. Reaction of gastric tract, including loss of appetite, nausea and vomiting 2. Psychiatric symptoms including insomnia, alopecia and debilitation 3. WBC count ($<3 \times 10^9/L$) No follow -up after treatment
Notes	Oral decoction of Chinese herbs: Baishao(Radix Paeoniae) Baihe (Bulbus Lilii) Banxia (Rhizoma Pinelliae) Huangqi (Radix Astragali) Dangshen (Radix Codonopsis) Maidong (Radix Ophiopogonis) Danguai (Radix Angelicae Sinensis) Danshen (Radix Salviae) Xianmao (Rhizoma Curculiginis) Chenpi (Pericarpium).
Allocation concealment	D – Not used
Study	Hong 2005
Methods	Generation of allocation sequence: simple randomisation Blinding: not stated Sample size estimation: no information Withdrawals/drop-outs: no information. ITT analysis: no
Participants	Ethnicity: Chinese. Setting: outpatients 92 women, age 31 to 72 years, mean 48 ; 62 in treatment group (age: 31 to 69 years, disease duration: not given); 30 in control group (age: 33 to 72 years, disease duration: not given)

Characteristics of included studies (Continued)

	Inclusion: Inclusion: post-surgery female patients divided by TNM stages I to III breast cancer: stage I: n = 9 stage II: n = 52 stage III: n = 31 premenopausal: n = 39 postmenopausal: n = 53 Exclusion: not stated
Interventions	All patients in both groups received chemotherapy treatment with CTF one week after surgery: cyclophosphamide 600 mg/m ² pirarubicin 50 mg/m ² 5-fluorouracil 600 mg/m ² Treatment group: Jiawei Guilu Erxian Dan, a mixture of traditional Chinese medicines added to conventional CTF therapy: one dose/day, orally at night, every day for 2 weeks Control group: Batilol added to conventional CTF therapy: 50 mg orally 3 times/day for 2 weeks Both groups after 2 weeks' treatment: if WBC count was below 3 million/dL, granulopoietin was administered subcutaneously, 75 g daily for 2 days until the next chemotherapy treatment WBC count was >5 million/dL
Outcomes	WBC count (based on WHO criteria) Hemoglobin Platelet level in whole blood
Notes	Jiawei Gulu Erxia Dan is composed of: Shenggui Ban (Carapax et Plastrum testudinis) 50 g Lujiao Jiao (Colla Cornus cervi) 12 g Wojiao (Colla Corii asini) 12 g Gouji Zi (Fructus Lycii) 15 g Xiyang Sheng (Radix Panacis quinquefolii) 15 g Sasheng (Radix Glehniae) 30 g
Allocation concealment	D – Not used

Study **Huo 2003**

Methods	Generation of allocation sequence: not stated Blinding: not stated Sample size estimation: no information Withdrawals/dropouts: no information ITT analysis: no
Participants	Ethnicity: Chinese Setting: inpatients 48 female patients aged 36 to 62 years, mean 48.3 Treatment group: n = 26; disease duration: not stated Control group: n = 22; disease duration: not stated Inclusion: no further details Exclusion: not stated
Interventions	Treatment group: Shenmai injections 40 mL + 300 mL with 5% amylaceum by intravenous drip, once daily, commencing on the first day of chemotherapy treatment, for 14 days Control group:

Characteristics of included studies (Continued)

	Based on conventional chemotherapy treatment (no more details given); vitamin C 5.0 g, carnine 300 mg plus 300 mL with 5% amylaceum, by intravenous drip, once daily for 14 days
Outcomes	Control of leukocyte reduction (based on WHO criteria)
Notes	Shenmai injections were developed by Shenzhen Nanfang Pharmaceutical Company Mainly composed of: Renshen (Radix Ginseng) Maidong (Radix Ophiopogoni)
Allocation concealment	D – Not used

Study Li 2002

Methods	Generation of allocation sequence: not stated Blinding: not stated Sample size estimation: no information Withdrawals/dropouts: no information ITT analysis: no
Participants	Ethnicity: Chinese Setting: inpatients 75 female patients 40 in treatment group (mean age: 56.4 years; disease duration: not stated) 35 in control group (mean age: 54.2 years; disease duration: not stated) Inclusion: diagnosed as stage IV relapsed metastatic breast cancer Exclusion: not stated
Interventions	Treatment group: Shenqi Fuzheng injections (two basic constituents): Radix Astragalus and Codonopsis pilosula), 250 mL/day, by intravenous drip for 10 days while receiving the NE chemotherapy regimen Control group: NE (epirubicin) chemotherapy regimen alone: NVB (vinorelbine) 25 mg/m ² intravenously on days 1 and 8; EADM (epirubicin/pharmorubicin) 90 mg/m ² on day 2 intravenously for a 28-day cycle; 3 cycles administered (total 84 days)
Outcomes	1. Quality of life (based on Karnofsky performance status) 2. Toxicity, including; marrow suppression; vomiting and nausea; reaction of gastric tract, liver and kidney; alopecia; leukocyte reduction; phlebitis (based on WHO criteria for toxicity) 3. T-lymphocyte subsets (results compared before and after treatment)
Notes	Shenqi Fuzheng injections were developed by Lizhu Pharmaceutical Company Mainly composed of: Dangshen (Radix Codonopsis) Huangqi (Radix Astragali)
Allocation concealment	D – Not used

Study Liu 2000

Methods	Generation of allocation sequence: not stated Blinding: not stated Sample size estimation: no information Withdrawals/dropouts: no information ITT analysis: no
Participants	Ethnicity: Chinese Setting: inpatients 80 female patients

Characteristics of included studies (Continued)

40 in treatment group (age: 29 to 70 years; disease duration: not stated)
40 in control group (age: 30 to 69 years; disease duration: not stated)
Inclusion: female postoperative breast cancer patients without other chronic diseases (such as diabetes, hypertension, heart attack, stroke etc.)
Exclusion: breast cancer patients with the above chronic diseases

Interventions

Treatment group:
Shenmai injections commenced 1 day after surgery, 60 mL/day for 7 days intravenously
After wound healing, commenced first chemotherapy treatment with CMF (n = 18), CAF (n = 15), CAP (n = 7); duration 4 weeks, then stopped for 2 weeks, followed by 2 more treatments
Control group:
Given only chemotherapy after surgery, as in the treatment group: CMF (n = 18), CAF (n = 16), CAP (n = 6)

Outcomes 1. Immune system: T-lymphocyte subsets (CD3, CD4, CD8); study did not specify how to measure these
2. WBC count ($>3 \times 10^9/L$ = improved)

Notes Shenmai injections produced by Hangzhou Qing Chun Bao Yao Pharmaceutical Company of Zhejiang Province
Mainly composed of:
Renshen (Radix Ginseng)
Maidong (Radix Ophiopogonis)

Allocation concealment D – Not used

Study **Situ 2005**

Methods

Generation of allocation sequence: random table
Blinding: not stated
Sample size estimation: no information
Withdrawals/dropouts: no information
ITT analysis: no

Participants

Ethnicity: Chinese
Setting: inpatients and outpatients
120 patients
61 in treatment group (age: 30 to 65 years, mean: 49; disease duration: not stated)
59 in control group (age: 30 to 65 years; mean: 49; disease duration: not stated)
Inclusion: female breast cancer patients aged between 18 and 65, after surgery plus chemotherapy with CMF or CTF regimen
Exclusion: patients with heart disease, cerebral vessel disease, liver or kidney disease, hematological disease or mental disorder, and those patients who could not keep complicate to receive traditional Chinese medicine after surgery

Interventions

Treatment group:
Aifukang capsules (mixture of 7 Chinese herbs) were administered 2 days after surgery, 4 capsules 3 times/day up to the end of the sixth chemotherapy course
Control group:
No Aifukang capsules given; CMF or CTF treatment alone

Outcomes 1. Quality of life (based on the EuroQLQ-BR23 questionnaire)
2. Fatigue
3. Nausea and vomiting

Notes	<p>Aifukang capsules were developed by the Academy of Traditional Chinese Medicine of Guangdong</p> <p>They are mainly composed of:</p> <p>Huangqi (Radix Astragali)</p> <p>Baisu (Rhizoma Atractylodis macrocephalae)</p> <p>Fu Lin (Poria)</p> <p>Taizi Sheng (Radix Pseudostellariae)</p> <p>Shan Zhuyu (Fructus Corni)</p> <p>Nu Zengzi (Folicum Ligustri lucidi)</p> <p>Eshu (Rhizoma Curcumae)</p> <p>Banzhi Lian (Herba Scutellariae barbatae)</p> <p>Yiyi Ren (Semen Coicis)</p> <p>Huaishan (Rhizoma Dioscoreae)</p> <p>Zhishou Wu (Herba Cistanches)</p> <p>Each capsule includes 2 g crude herb medicine</p>
Allocation concealment	D – Not used
Study	Yang 2004
Methods	<p>Generation allocation sequence: random table</p> <p>Blinding: not stated</p> <p>Sample size estimation: no information</p> <p>Withdrawals/dropouts: no information</p> <p>ITT analysis: no</p>
Participants	<p>Ethnicity: Chinese.</p> <p>Setting: inpatients.</p> <p>59 female patients</p> <p>31 in treatment group (age: 32 to 69 years, mean: 54.2; disease duration: not stated)</p> <p>28 in control group (age: 31 to 70 years, mean: 53.5; disease duration: not stated)</p> <p>Inclusion: female patients diagnosed with stage IV (advanced) breast cancer according to the diagnostic criteria of Tumour Treatment Standardization of China</p> <p>Exclusion: not stated</p>
Interventions	<p>Treatment group:</p> <p>Aidi injections (basic compound of at least 4 herbs), 50 mL/day, adding crude herbs 0.3 g/mL, by intravenous drip for 15 days, stopping for 6 days, followed by the next course of treatment; mean duration, at least 30 days/patient</p> <p>Navelbine (25 mg/m²) administered concurrently on days 1 and 8, plus intravenous infusion of Pirarubicin (40 to 50 mg/m²) on day 1, for 21 days</p> <p>Control group: Navelbine (25 mg/m²) on days 1 and 8, plus intravenous infusion of Pirarabican (40 to 50 mg/m²) on day 1, for 21 days</p>
Outcomes	<p>1. Quality of life (based on a score of quality of life for tumor patients and Karnofsky performance status)</p> <p>2. Toxicity, including marrow suppression, reaction of gastric tract and phlebitis (based on WHO criteria)</p> <p>3. T-lymphocyte subsets (did not specify how to measure these)</p>
Notes	<p>Aidi injections developed by Guizhou Yibao Pharmaceutical Company. Mainly composed of:</p> <p>Renshen (Radix Ginseng)</p> <p>Huangqi (Radix Astragali)</p> <p>Cijia Wu (Radix Acanthopanaxis senticosi)</p> <p>Banmao (Mylabris)</p> <p>Each 1 mL contains 0.3 g crude herbs</p>
Allocation concealment	D – Not used

Characteristics of included studies (Continued)

CAF, cyclophosphamide, Adriamycin, fluorouracil
CAP, cyclophosphamide, Adriamycin, Platino
CMF, cyclophosphamide, methotrexate, fluorouracil
CTF, cyclophosphamide, pirarubicin, 5-fluorouracil
ITT, intention-to-treat
TNM, tumor, nodes, metastasis (tumor staging)
WBC, white blood cell(s)
WHO, World Health Organization

Characteristics of excluded studies

Study	Reason for exclusion
Hou 2000	Randomised study, but compared one herbal medicine after chemotherapy versus another herbal medicine after chemotherapy. This did not meet the inclusion criteria.
Huang 2003	Random sampling study testing a compound herb formula combined with chemotherapy in 32 breast cancer patients.
Li 2000	Randomised controlled trial testing a compound herb formula combined with conventional treatment for 85 cancer patients after chemotherapy and radiotherapy. The outcome was reported as global improvement for all cancer patients including 11 breast cancer patients. We could not extract the data we needed.
Liang 1999	Randomised controlled trial testing Shenqi fuzheng injections combined with conventional treatment for 48 cancer patients. The objective was to assess efficacy of the injections for treatment of cancer.
Wang 1990	Not a randomised controlled study. Tested a compound herb formula combined with chemotherapy in 62 breast cancer patients.
Wang 2003	Randomised controlled trial studying the effect of a Bazhen decoction in the treatment of leukocytopenia caused by postoperative chemotherapy in 20 breast cancer patients. Different outcome indexes and inconsistency make it difficult to extract the data we needed.
Weng 2003	Not a randomised controlled study. Tested a compound herb formula for relief of the toxic and negative effects of chemotherapy in 60 breast cancer patients.
Wu 1997	Randomised controlled trial testing Yiqibuxuetang for leukocyte reduction caused by chemotherapy in 38 cancer patients. The outcome was reported as global improvement for all cancer patients. We could not extract the data we needed.
Yuan 1997	Randomised controlled trial testing a compound herb formula combined with conventional treatment for leukocyte reduction after chemotherapy in 58 cancer patients. The outcome was reported as global improvement for all cancer patients, including 21 with breast cancer. We could not extract data we needed.
Zhang 1997	Chemotherapy was given preoperatively in this study, presumably to reduce tumor size before surgery. It did not meet the criteria for this review.

ADDITIONAL TABLES

Table 01. 01 The five compound herbal formulae and one single herb administered to breast

Number	Chinese Herb	Formula	Pharmacological acti	Route	Duration	Times/d	Dose	Total dose	Type of the dosage
1	Shenmai	Renshen Saponim (Panax ginseng (CA Mey)) 0.1 g Mai dong Saponim (Ophiopogon japonicus (Thunb) Ker-Gawl 0.1 g and a small amount of polysaccharide are added to these two herbs Renshen Saponim (Panax ginseng (CA Mey)) 0.1 g Mai dong Saponim (Ophiopogon japonicus (Thunb)) Ker-Gawl 0.1 g and a small amount of polysaccharide are added to these two herbs Mai dong Saponim (Ophiopogon japonicus (Thunb)) Ker-Gawl 0.1 g and a small amount of polysaccharide are added to these two herbs Renshen Saponim (Panax ginseng (CA	Increases energy and improves recovery of immunity Reduces toxicity and tumor complications, relieves fatigue and is anti-inflammatory Increases energy and improves recovery of immunity Reduces toxicity and tumor complications, relieves fatigue and is anti-inflammatory	Intravenous injection	7days	1	60mL	420mL	Injection liquid

Table 01. 01 The five compound herbal formulae and one single herb administered to breast (Continued)

Number	Chinese Herb	Formula	Pharmacological acti	Route	Duration	Times/d	Dose	Total dose	Type of the dosage
		Mey)) 0.1 g Mai dong Saponim (Ophiopogon japonicus (Thunb)) Ker-Gawl 0.1 g and a small amount of polysaccharide are added to these two herbs Renshen Saponim (Panax ginseng (CA Mey)) 0.1 g Mai dong Saponim (Ophiopogon japonicus (Thunb)) Ker-Gawl 0.1 g and a small amount of polysaccharide are added to these two herbs							
2	Yiqiyangxue compound	Huangqi (Radix Astragalus membranaceus) Dangshen (Radix Codonopsis pilosula) Mai dong (Ophiopogon japonicus (Thunb)) Ker-Gawl Bai shao (Paeonia lactiflora pall) Dang gui (Angelica sinensis) Bai he (Lilium	Modulates the endocrine system, stimulates the blood circulation, clears heat, aids detoxification, and improves the state of the spleen and stomach	Oral	30days	1	250mL	7500mL	Decotions

Table 01. 01 The five compound herbal formulae and one single herb administered to breast (Continued)

Number	Chinese Herb	Formula	Pharmacological acti	Route	Duration	Times/d	Dose	Total dose	Type of the dosage
3	Yiqiyanxue compound	brownii FE Brown var. viridulum Baker) Ban xia (Pinellia ternata (Thunb)) Breit and other plants Huangqi (Radix Astragalus membrancers) Dang shen (Radix Codonopsis pilosula) Dang gui (Angelica sinensis) Nv zeng zi (Ligustrum lucidum ait) Danshen and other plants	Modulates the endocrine system, stimulates the blood circulation, balances the level of Yin and Yang, increases energy, and harmonises the spleen and stomach	Oral	30days	3	9 g	250-315 g	Compound pill
4	Pishentang	Dangshen (Radix Codonopsis pilosula) 30 g Huang qi (Radix Astragalus membrancers) 30 g Bai shu (Atractylodes macrocephala (Koidz)) 12 g Fu lin (Sclerotium Poria cocos (Schw)) 10 g Gan cao (Glycyrrhizin) 6 g Dang gui (Angelica sinensis) 15 g Shu di 20 g	Improves the function of the spleen and stomach, modulates the state of the liver and kidneys, stimulates the blood circulation, and balances energy and blood		21days	1	60mL	1260mL	Water liquid

Table 01. 01 The five compound herbal formulae and one single herb administered to breast (Continued)

Number	Chinese Herb	Formula	Pharmacological acti	Route	Duration	Times/d	Dose	Total dose	Type of the dosage
5	Fuzheng sheng xue tiao yuan tang	Zhi he ze (Homo sapiens Linnaeus) 10 g Gou ji zi (Lycium barbarum L) 12 g Nv zeng zi (Ligustrum lucidum ait) 12 g Tu shi zi 10 g Ba ji tian (Morinda officinalis (How)) 15 g Bu gu zhi 15 g Dangshen (Radix Codonopsis pilosula) 15 g Shou wu 10 g Ji xue ten (Spatholobus suberectus (Dunn)) 15 g Mai ya (Hordeum vulgare) 10 g Bai shu (Atractylodis macrocephala (Koidz)) 15 g Gu cui bu 10 g Huang jing (Polygonatum sibiricum (Red)) 15 g	Increases immunity, protects the blood system and bone marrow against depression, harmonises the spleen and stomach, relieves fatigue and induces diuresis	Oral	30days	1	200mL	6000mL	Decotions of herbs
6	Huangqi	Huangqi (Radix Astragalus membraners)	Huangqi (Radix Astragalus membraners)	enous dripping	84days	1	20mL	1680mL	Injection liquid

Table 01. 01 The five compound herbal formulae and one single herb administered to breast (Continued)

Number	Chinese Herb	Formula	Pharmacological acti	Route	Duration	Times/d	Dose	Total dose	Type of the dosage
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Table 02. Formulation for each trial

Study ID	Formulation
Fang 1996	Oral decoction of Chinese herbs (Radix Paeoniae alba, Bulbus Lilii, Rhizoma Pinelliae, Radix Astragali, Radix Codonopsis, Radix Ophiopogonis, Radix Angelicae sinensis, Radix Salviae miltiorrhizae, Rhizoma Curculiginis, Pericarpium Citri reticulatae)
Hong 2005	Erxian Dan (Carapax et Plastrum testudinis 50 g, Colla Comus cervi 12 g, Colla Corii asini 12 g, Fructus Lycii 15 g, Radix Panacis quinquefolii 15 g, Radix Glehniae 30 g)
Huo 2003	Shenmai injection (mainly Radix Ginseng, Radix Ophiopogonis)
Li 2002	Shenqi fuzheng injection (mainly Radix Codonopsis, Radix Astragali)
Situ 2005	Aifukang capsule (Radix Astragali, Poria, Rhizoma Atractylodis macrocephalae, Radix Pseudostellariae, Rhizoma Dioscoreae, Fructus Corni, Folicum Ligustri lucidi, Rhizoma Curumae, Herba Scutellariae, Semen Coicis)
Yang 2004	Aidi injection (mainly Radix Ginseng, Radix Astragali, Radix Acanthopanax senticosi, Mylabris)
Liu 2000	Shenmai injection (mainly Radix Ginseng, Radix Ophiopogonis)

ANALYSES**Comparison 01. Chinese medicinal herbs plus chemotherapy versus chemotherapy alone**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Nausea and vomiting			Relative Risk (Fixed) 95% CI	Totals not selected
02 Nausea and vomiting improved			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Alopecia			Relative Risk (Fixed) 95% CI	Totals not selected
04 Fatigue			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
05 Phlebitis			Relative Risk (Fixed) 95% CI	Totals not selected
06 White blood cell reduction			Relative Risk (Fixed) 95% CI	Totals not selected
07 White blood cell change after treatment			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
08 Percentage change of CD3-positive cells (Tlymphocyte subsets)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
09 Percentage change of CD4-positive cells (Tlymphocyte subsets)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
10 Percentage change of CD8-positive cells (Tlymphocyte subsets)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
11 Thrombocytopenia			Relative Risk (Fixed) 95% CI	Totals not selected
12 Quality of life: EuroQLQ-BR23 symptoms scores			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
13 Quality of life: improvement in Karnofsky performance status			Relative Risk (Fixed) 95% CI	Totals not selected
14 Liver toxicity			Relative Risk (Fixed) 95% CI	Totals not selected
15 Kidney toxicity			Relative Risk (Fixed) 95% CI	Totals not selected

COVER SHEET

Title Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients (Review)

25

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Authors	Zhang M, Liu X, Li J, He L, Tripathy D
Contribution of author(s)	Zhang MM: Designed the review, developed the search strategy and drafted the review. Liu XM: Conceived the idea, co-developed the search strategy and revised the review. Li Jing: Reviewed the draft review and revised changes. He L: Helped develop the search strategy. Debu Tripathy: Provided clinical input to the protocol and revised the review.
Issue protocol first published	2004/3
Review first published	2007/2
Date of most recent amendment	21 February 2007
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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	15 February 2007
Date authors' conclusions section amended	Information not supplied by author
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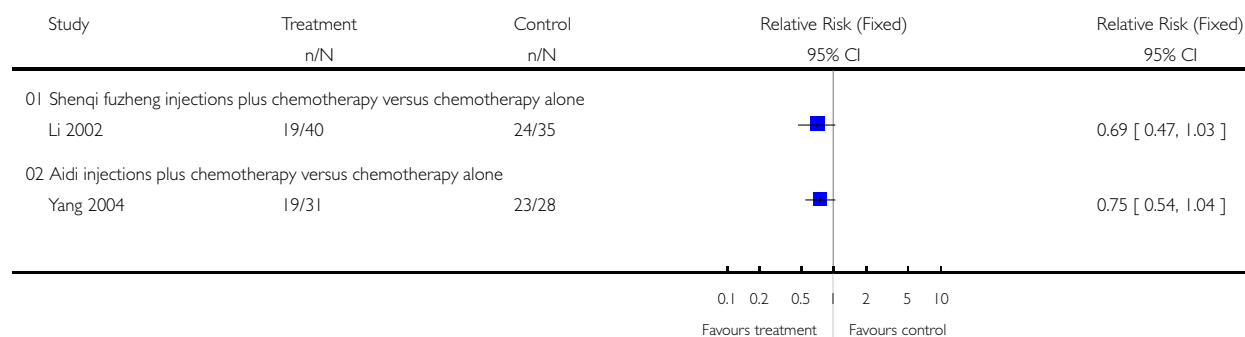
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 01 Nausea and vomiting

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 01 Nausea and vomiting

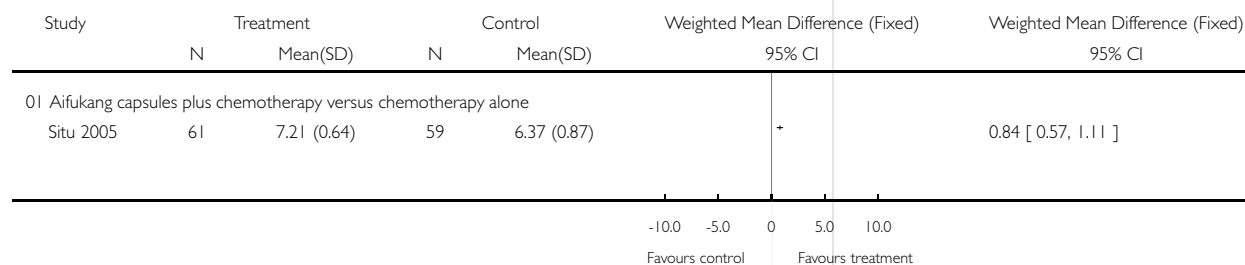


Analysis 01.02. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 02 Nausea and vomiting improved

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 02 Nausea and vomiting improved

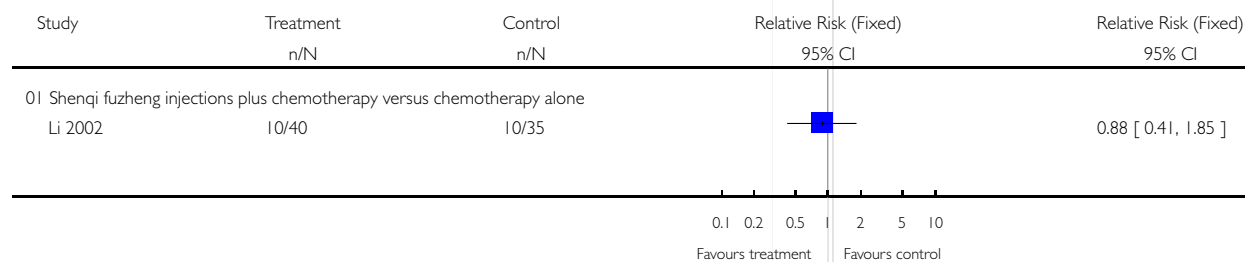


Analysis 01.03. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 03 Alopecia

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 03 Alopecia

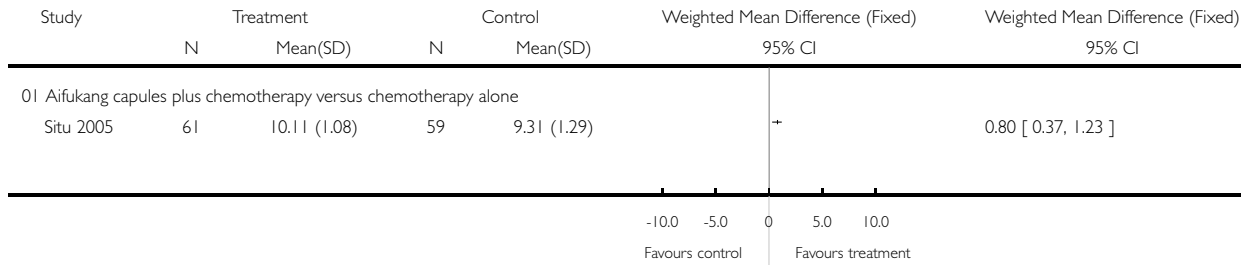


Analysis 01.04. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 04 Fatigue

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 04 Fatigue

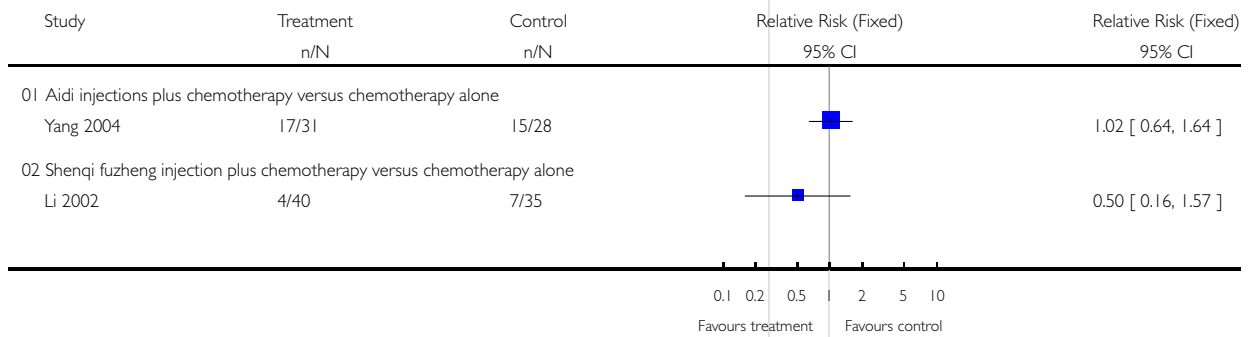


Analysis 01.05. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 05 Phlebitis

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 05 Phlebitis

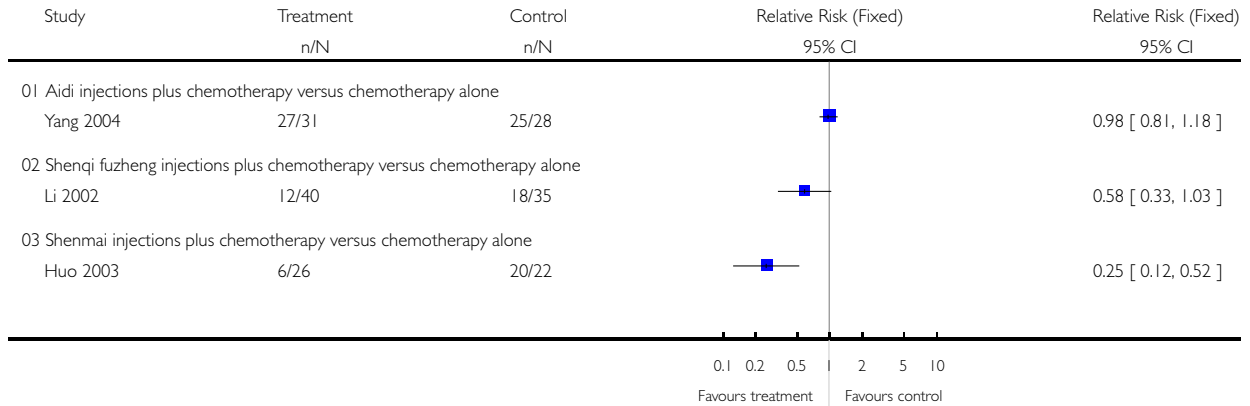


Analysis 01.06. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 06 White blood cell reduction

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 06 White blood cell reduction

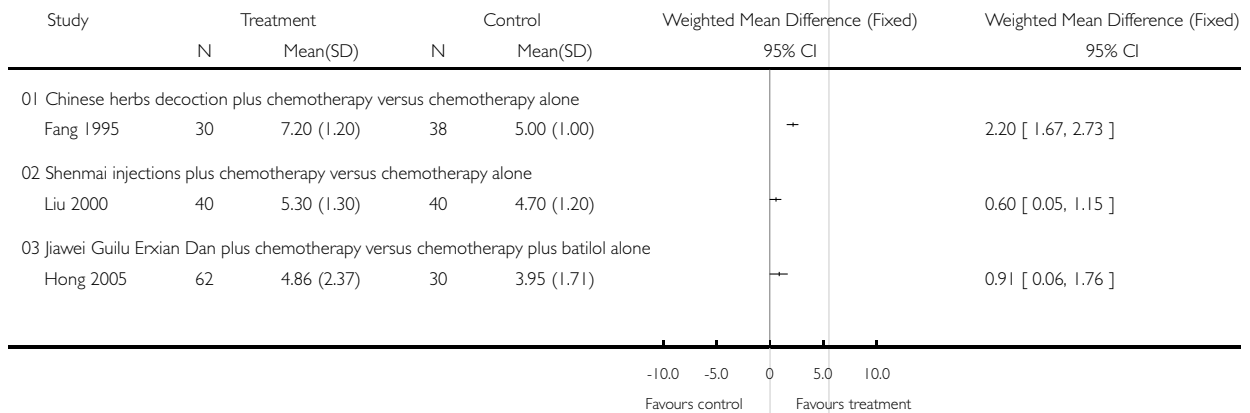


Analysis 01.07. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 07 White blood cell change after treatment

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 07 White blood cell change after treatment

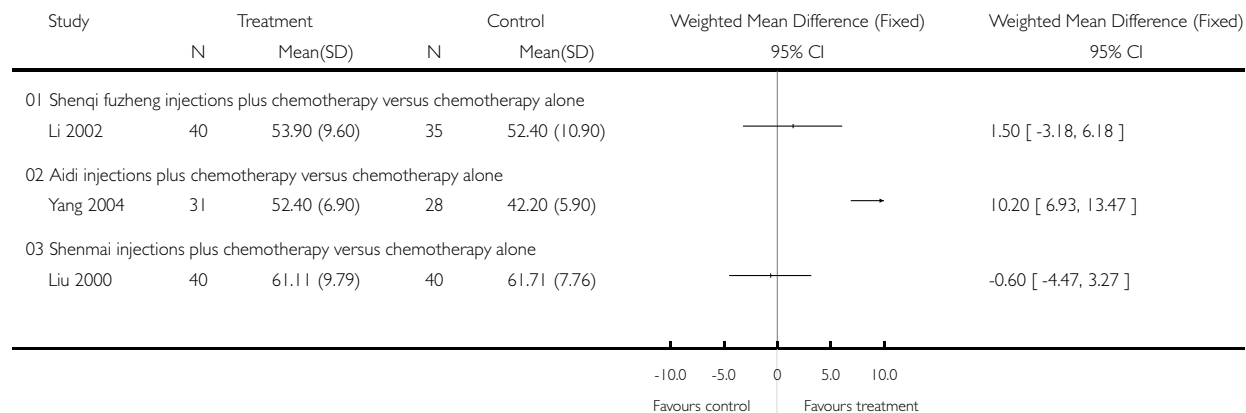


Analysis 01.08. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 08 Percentage change of CD3-positive cells (Tlymphocyte subsets)

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 08 Percentage change of CD3-positive cells (Tlymphocyte subsets)

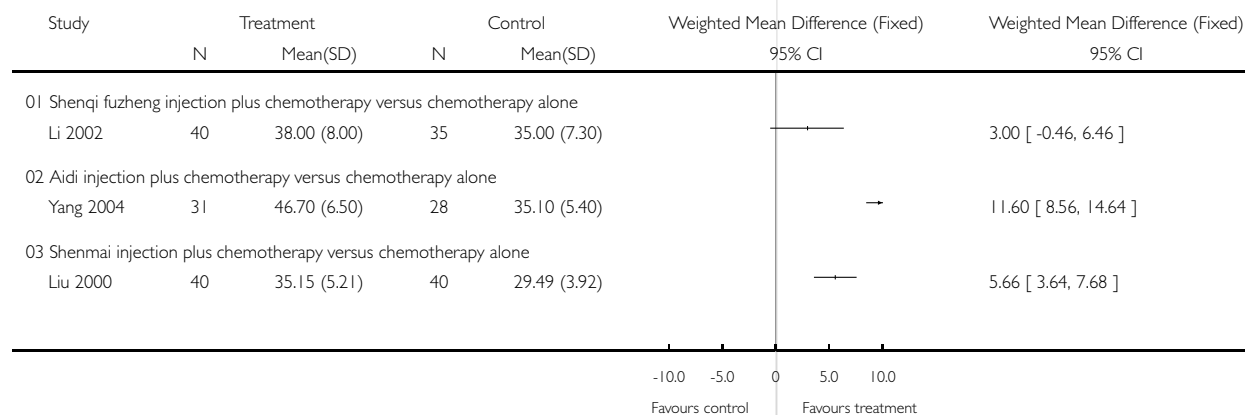


Analysis 01.09. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 09 Percentage change of CD4-positive cells (Tlymphocyte subsets)

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 09 Percentage change of CD4-positive cells (Tlymphocyte subsets)

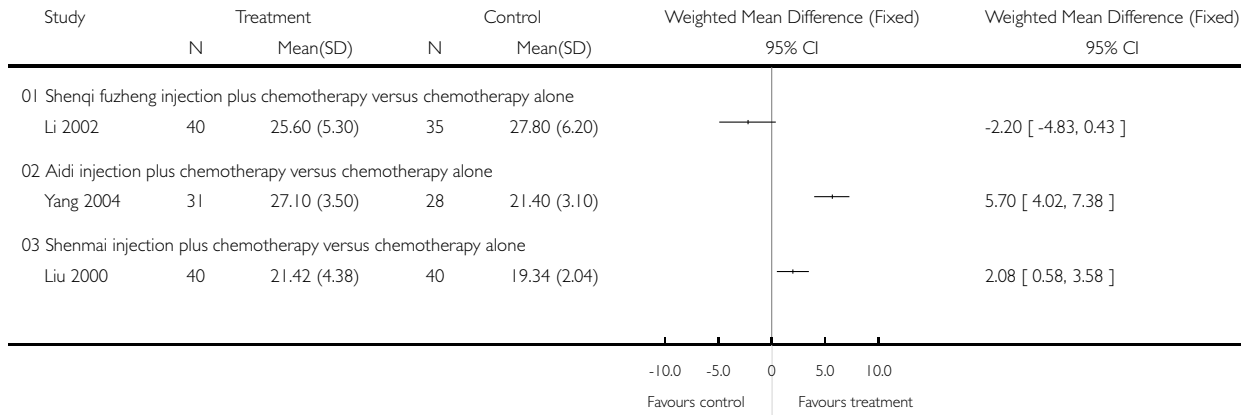


Analysis 01.10. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 10 Percentage change of CD8-positive cells (Tlymphocyte subsets)

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 10 Percentage change of CD8-positive cells (Tlymphocyte subsets)

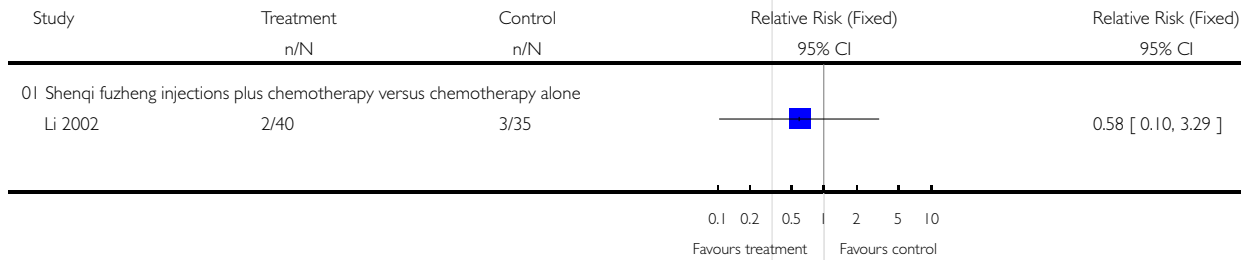


Analysis 01.11. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 11 Thrombocytopenia

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 11 Thrombocytopenia

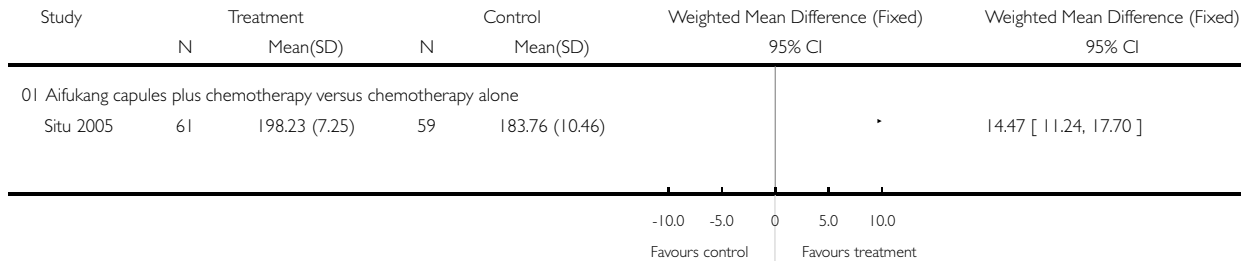


Analysis 01.12. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 12 Quality of life: EuroQLQ-BR23 symptoms scores

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 12 Quality of life: EuroQLQ-BR23 symptoms scores

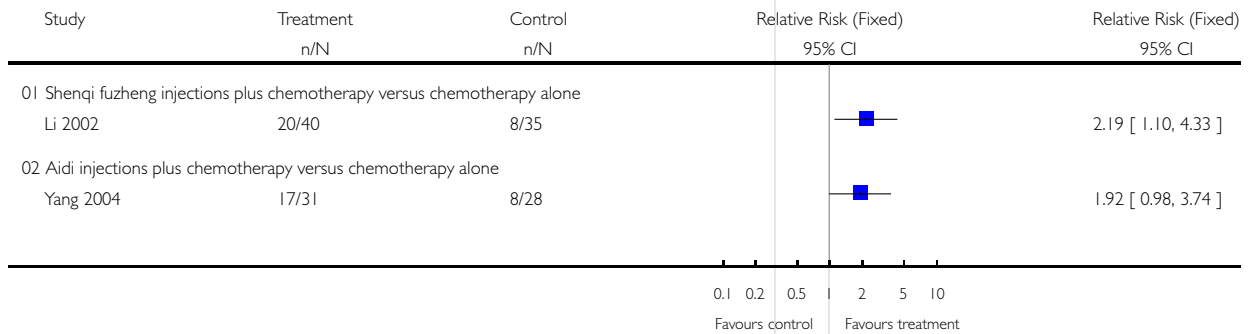


Analysis 01.13. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 13 Quality of life: improvement in Karnofsky performance status

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 13 Quality of life: improvement in Karnofsky performance status

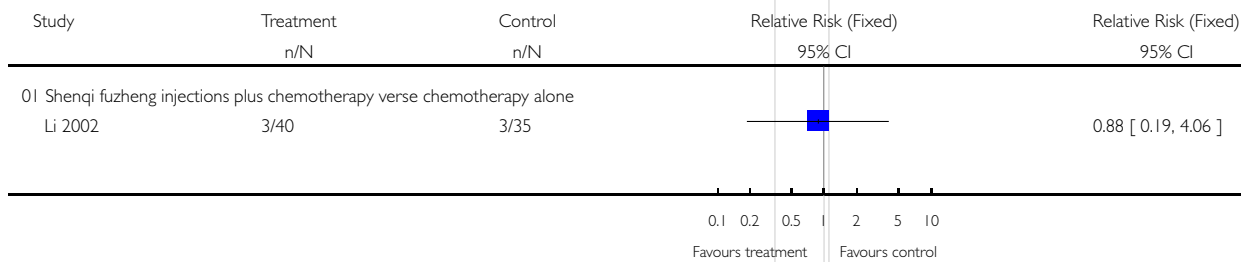


Analysis 01.14. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 14 Liver toxicity

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 14 Liver toxicity



Analysis 01.15. Comparison 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone, Outcome 15 Kidney toxicity

Review: Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients

Comparison: 01 Chinese medicinal herbs plus chemotherapy versus chemotherapy alone

Outcome: 15 Kidney toxicity

