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# Traditional herbal medicine for cancer pain: A systematic review and meta-analysis



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Available online 19 February 2015

## KEYWORDS

Traditional herbal medicine;  
Cancer pain;  
Systematic review;  
Meta-analysis

## Summary

**Background:** The effectiveness of traditional herbal medicine (THM) as an adjunctive therapy for cancer pain is unclear.

**Objective:** To assess the effectiveness of THM as an adjunctive therapy for cancer pain using randomized controlled trials (RCTs).

**Methods:** Five electronic databases, including those from the UK and China, were systematically searched for the period before September 2013. All RCTs involving the use of THM in combination with conventional cancer therapy for cancer pain were included.

**Results:** Twenty-four RCTs involving 4889 patients with cancer pain were systematically reviewed. Among them, nine studies of 952 patients reported a significant decrease in the number of patients with cancer pain in the treatment group. Four studies of 1696 patients reported a significant decrease in the degree of pain in the treatment group.

**Conclusion:** The results of these studies suggest that THM combined with conventional therapy is efficacious as an adjunctive therapy for patients with cancer pain. However, more research, including well-designed, rigorous, and larger clinical trials, are necessary to address these issues.

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## Introduction

The International Association for the Study of Pain (IASP) is an international professional organization promoting research, education, and policies related to pain management. The often-quoted IASP definition of pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” is derived from a 1964 definition by Harold Merskey. Although cancer encompasses multiple physical symptoms, the symptom of pain is often cited as most critical. Pain is one of the most common symptoms of cancer, and its intensity increases as the stage of cancer advances. A meta-analysis reported cancer pain in 64% of patients with metastatic disease, 59% of patients receiving antineoplastic therapy, and 33% of patients who had received curative cancer treatment.<sup>1</sup> In Asia, traditional herbal medicine (THM) is frequently combined with Western approaches to treat cancer, usually in regimens that combine various traditional Asian herbs into one treatment strategy. Alternative medicine has been used to meet patient needs in lieu of or as an adjunct to conventional medicine.<sup>2</sup> More than half of patients treated with traditional Asian herbs report effective relief of their symptoms, including pain.<sup>3</sup> About 41–62% of patients with cancer use traditional Asian herbs as an alternative therapy.<sup>4,5</sup> Clinical trials suggest that Asian THM may alleviate cancer pain with no adverse effects. However, a scientific evaluation of the effect of traditional Asian herbs on pain is lacking, and safety and toxicity are concerns.

The effectiveness of traditional Asian herbs is controversial among current practitioners of complementary alternative medicine. To date, no systemic review of the oral administration of traditional Asian herbs for cancer pain has been conducted. Thus, we conducted this systemic review to summarize and critically assess the evidence from randomized controlled trials (RCTs) showing that traditional Asian herbs are effective for reducing cancer pain. Indeed, several RCTs have reported that Asian THM is effective against cancer pain. Thus, we conducted this study as a follow-up to the systematic review conducted by Ling et al.<sup>6</sup> to update research in this area.

## Materials and methods

### Search strategy

The following sources were searched from their inception to September 2013: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, the Allied and Complementary Medicine Database, and the Cumulative Index to Nursing and Allied Health Literature.

The reference lists of the articles were checked for further relevant publications, and experts were asked for information concerning any additional trials. An additional manual search for relevant journals, symposia, and conference proceedings was performed, and all identified publications were cross-referenced. When necessary, personal contact was made with the authors of the published studies to request additional data.

The search terms used were cancer pain [TIAB] OR cancer patient [TIAB] OR cancer patients [TIAB] OR ((Neoplasms[MeSH] OR Neoplasms\*[TI] OR Cancer\*[TI] OR Tumor\*[TI] OR Tumor\*[TI] OR Carcinoma[MeSH] OR Carcinoma\*[TI] OR Adenocarcinoma[MeSH] OR Adenocarcinoma\*[TI] OR adenomatous[TI] OR Lymphoma[MeSH] OR lymphom\*[TI] OR lymphedema\*[TI] OR Sarcoma[MeSH] OR Sarcoma\*[TI] OR “Antineoplastic agents”[MeSH] OR antineoplas\*[TI] OR ((adenom\*[TI] OR adenopath\*[TI]) AND malignant\*[TI])) AND (PAIN[MeSh] OR PAIN MEASUREMENT[MeSh] OR PAIN CLINICS[MeSh] OR ANALGESIA\*[MeSh] OR ANALGESICS\*[MeSh] OR pain\*[TIAB] OR analges\*[TIAB])). Each database was searched independently, as each database searched for this review possessed its own subject headings. No language restrictions were imposed.

### Study selection

We selected only articles on RCTs; quasi-randomized or non-randomized trials were excluded. We also excluded articles on animal or *in vivo* experiments. Studies in which THM was not orally administered were also excluded.

Studies using THM combined with conventional cancer therapy for the treatment group were included. We selected patients receiving conventional treatment such as radiotherapy or chemotherapy, placebos or microwave treatment, or no treatment as the control group.

## Quality assessment

We (JWL and WBL) independently selected the endpoint data on the major outcome measures from each trial in studies evaluating THM. Details of this procedure have been explained elsewhere.<sup>7</sup> We prefer continuous to binary data because most of the eligible trials reported continuous outcomes. We referenced the previous reviews<sup>8,9</sup> in an open discussion. Summaries and quality assessments of all studies were completed by two reviewers following the detailed descriptions of these categories provided in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>10</sup> The following questions were assessed and answered by reviewers: (a) Was the allocation sequence adequately generated? (b) Was allocation adequately concealed? (c) Was knowledge of the allocated interventions adequately prevented during the study? (d) Were procedures to ensure blindness regarding outcome assessment adequate? (e) Were incomplete outcome data adequately addressed? (f) Were the results of the study free of selective outcome reporting? (g) Was the study apparently free of other problems that could put it at a risk for bias? This review used "Y," "U," and "N" to code responses to these questions; "yes" (Y) indicated a low risk of bias, "unclear" (U) indicated an uncertain risk of bias, and "no" (N) indicated a high risk of bias.

## Statistical analysis

Study data were summarized using basic statistics and simple counts and means. The main purpose of the analyses was to quantify and compare the effects of THM combined with conventional cancer therapy (treatment group) with those of conventional cancer therapy alone (control group) on patients with cancer pain using only RCTs. The statistical analysis was performed using Review Manager 5.1 for Windows (The Nordic Cochrane Center). The odds ratios (ORs) for improvement on the visual analog scale (VAS) by number of persons, degree, and number of pain occurrences per day, with their 95% confidence intervals (CI), are presented individually for each trial. An OR <1 indicates a lower risk for the treatment than for the control group, and an OR >1 indicates a greater risk for the treatment than for the control group.

## Results

### Study description

An initial search identified 331 potentially relevant articles. Of these, only 24<sup>11–34</sup> met our inclusion criteria and, thus, were subjected to our systematic review. Nine articles<sup>11,12,14,19,20,22,23,27,34</sup> were in English, and 15 articles<sup>13,15–18,21,24–26,28–33</sup> were in Chinese.

A total of 307 articles were initially excluded because they did not meet our inclusion criteria. Of these, 87 were excluded because they were duplicates of other articles or their titles clearly reflected their irrelevance. Additionally, 196 articles were excluded after an Abstract review. Ten additional articles were included after the review of references. Thirty-four additional articles were excluded after a more detailed evaluation of each article. Six studies were not RCTs, and 28 did not meet our inclusion criteria. As a result, 24 RCTs<sup>11–34</sup> on THM orally administered for cancer pain were reviewed. The total number of subjects evaluated was 4889. Fig. 1 summarizes the search results based on a quality of reporting of meta-analyses flow diagram.<sup>35</sup>

Various cancers (breast, gastric, lung, colorectal, non-small cell lung, pancreatic, esophageal, stomach, cervical, uterine, kidney, leukemia, prostate, ENT, esophagus, bladder, submaxillary gland, bone, primary hepatic carcinoma, ovarian, gallbladder, renal, large intestine and middle/advanced stage of lung) were included in RCTs.

The intervention varied considerably across the trials. There are four kinds of comparisons. Herbs vs western therapy,<sup>16,21–24,26–28,31,33</sup> herbs + western therapy vs herbs,<sup>13,15,17–20,32,34</sup> herbs vs western therapy vs herbs + western therapy,<sup>12,14,25,29,30</sup> and herbs vs none.<sup>11</sup>

All studies based the THM elections on Traditional Chinese Medicine theory. According to the Chinese medicine treatment method, strengthening Qi and eliminating pathogens often use botanicals, promoting blood circulation and removing stasis often use botanicals and animal products and promoting cytotoxic effect often use minerals. Various herbal medicines were used in the included RCTs; the botanical was commonly used, processed animal products were second commonly used and processed minerals were the less common. Key data are summarized in Table 1.

### Traditional herbal medicine used for pain management

Three major kinds of traditional herbal medicine are usually used to control pain

1. Botanicals such as *Corydalis Rhizoma*, *Ligusticum Rhizoma*, *Libanotus*, *Myrrha*, *Cynanchum Paniculatum Radix*, *Clematis Radix*, *Aconitum Radix*, *Aconitum Kusnezoffi Radix*, *Paeoniae Alba Radix*, *Carthami Flos*, *Paeoniae Rubra Radix*, and *Angelicae Pubescentis Radix*.
2. Processed animal products such as *Venenum Bufonis*, *Scorpion*, *Scolopendra*, *Eupolyphaga Seu Steleophag*, and *Lumbricus*.
3. Processed minerals such as *Borneolum Syntheticum* and *Realgar*.

Most of these are known in THM to relieve pain by promoting blood flow and qi circulation.

### VAS improvement by number of persons

An analysis of improvement on the VAS based on nine<sup>13,15,17,18,20,28,30,32,33</sup> of the 23 controlled trials revealed that a total of 495 (81.8%) patients in the treatment group ( $n=605$ ) and 169 (48.7%) members of the control group

**Table 1** Characteristics of randomized controlled trials (RCTs) on the use of traditional herbal medicine (THM) for cancer pain.

Reference	Type of cancer pain	Participants (n)/mean age (SD)/male (%) /country	Comparison treatment vs control/treatment frequency (treatment period)	Drugs	Outcome reported	Quality assessment <sup>a</sup>
Jeong et al. <sup>11</sup>	Breast cancer, gastric cancer, lung cancer, colorectal cancer, other cancer	40/52.6 (11.4)/37.5/Korea	Herbs vs none/3 per day (2 weeks)	None	VAS $p < 0.05$ prefer treatment	Y-U-N-U-Y-Y
Tian et al. <sup>12</sup>	Non-small cell lung cancer	60/over 60 were 35%/50/China	Herbs vs herbs + chemotherapy vs chemotherapy/herbs: 2 per day (2 moths); chemotherapy: vinorelbine or gemcitabine 2 per month, cisplatin 1 per month (2 months)	Vinorelbine plus cisplatin, gemcitabine plus cisplatin	No significant difference	U-U-N-U-Y-Y
Chen et al. <sup>13</sup>	Lung, liver, breast, gastric, pancreatic, esophageal, colorectal cancer	50/Treat: 54.6 (11.35), Control: 53.2 (10.28)/66/China	Western medicine + herbs vs western medicine/herbs: 3 per day (2 weeks); western medicine: 2–3 per day (2 weeks)	Indomethacin, tramal, morphine	VRS: $p < 0.05$ prefer treatment VAS: $p < 0.05$ prefer treatment Karnofsky: $p > 0.05$ no significant difference	U-U-N-N-Y-Y
Wu et al. <sup>14</sup>	Lung, liver, colorectal, stomach, cervical, uterine, kidney, leukemia, prostate, ENT, breast, pancreas, esophagus, bladder, others cancer	2466/40–79 were 87%/50.7/China	Herbs + Taiwan herbal tonic vs hospital meals vs Taiwan herbal tonic/3 per day (1 week)	None	Hospital meals group, Taiwan herbal tonic group: pain $p < 0.05$ significantly reduced herbs + Taiwan herbal tonic group: pain $p < 0.01$ significantly reduced. 10 days after treatment herbs + Taiwan herbal tonic group, hospital meals group: pain $p < 0.01$ reduced, Taiwan herbal tonic group: pain $p < 0.05$ reduced. Analgesic effect $p < 0.05$ prefer treatment duration of analgesia $p < 0.01$ prefer treatment Side effect $p < 0.01$ prefer treatment	U-U-N-U-Y-Y
Lin et al. <sup>15</sup>	Esophageal, gastric, liver, lung, breast, rectal cancer	60/Treat: 57.2 (14.6), Control: 55.8 (15.7)/61.7/China	Western medicine + herbs vs western medicine/4 per day (1 month)	Aspirin, tramal tablet, pethidine	Analgesic effect $p < 0.05$ prefer treatment duration of analgesia $p < 0.01$ prefer treatment Side effect $p < 0.01$ prefer treatment	U-U-N-N-Y-Y
Shi et al. <sup>16</sup>	Liver, lung, gastric cancer	180/Treat: 48.9 (15.5), Control: 46.7 (14.8)/65/China	Herbs vs western medicine/2 per day (2 weeks)	Tramal	Time to pain relief $p < 0.01$ prefer treatment	U-U-U-U-Y-Y

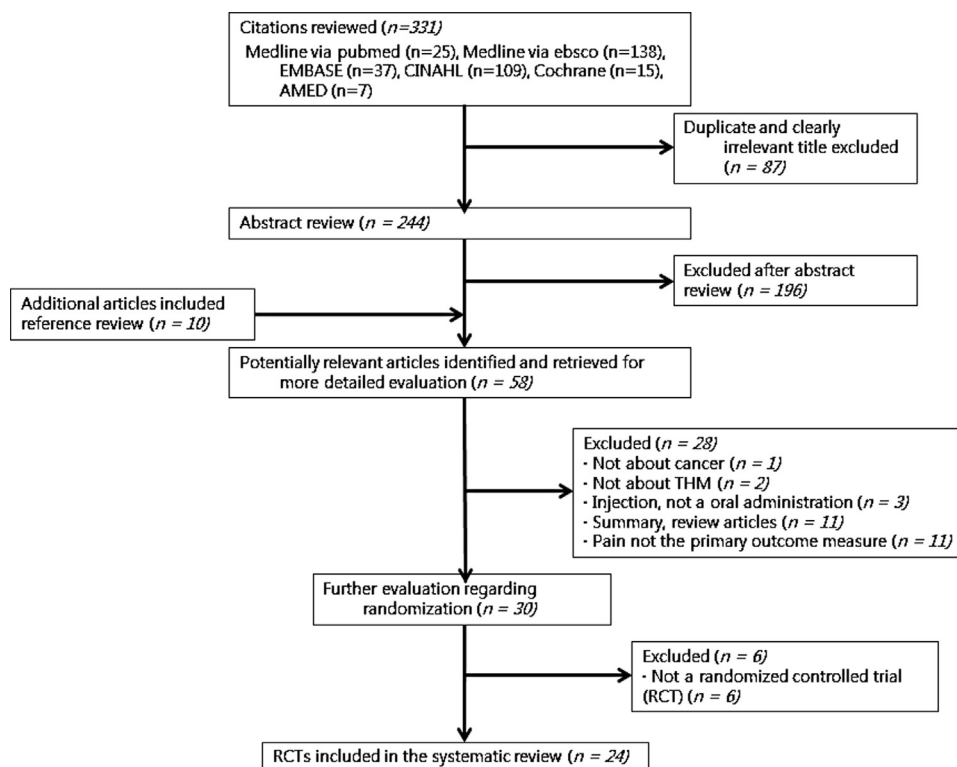
Zhang et al. <sup>17</sup>	Stomach, liver, lung, breast, colon, pancreatic, and submaxillary gland cancer (most metastatic)	110/62.4/NA/China	Herbs + western medicine vs western medicine/herbs: 3 per day; western medicine: 2 per day (3 weeks)	Indomethacin, pethidine	Effect of pain relief $p > 0.05$ no significant difference	U-U-U-U-Y-Y
Cao et al. <sup>18</sup>	Bone cancer	82/Treat: 59.5, Control: 57.4/62.2/China	Western medicine + herbs vs western medicine/4 per day (1 month)	Aspirin, tramal tablet, pethidine	Experimental group's percentage of reduction of pain 97.56%, control group's percentage of reduction of pain 92.68% $p < 0.05$ prefer treatment.	U-U-N-N-Y-Y
Tian et al. <sup>19</sup>	Primary hepatic carcinoma	97/Treat: 51.4 (10.5), Control: 52.4 (10.8)/83.5/China	Herbs + HACE VS HACE + chemotherapy + western medicine/herbs: 1 per day (4 weeks)	MMC, THP, 5-Fu	Pain $p < 0.05$ significant difference	U-U-N-Y-Y-Y
Lin et al. <sup>20</sup>	Primary hepatocellular carcinoma	72/Treat: 51.3 (4.5) Control: 49.1 (5.3)/66.7/China	Microwave + herbs vs microwave/herbs: 3 per day (1 month), microwave: 1 per week (2 weeks)	None	Liver pain $p < 0.01$ prefer treatment	Y-U-N-U-Y-Y
Li et al. <sup>21</sup>	Liver, colon, head, pancreas, prostate, stomach, ovarian, gallbladder, renal, bladder cancer	84/46–84/71.4/China	Herbs vs western medicine/3 per day	Indomethacin	Effect of pain relief, duration of pain relief $p > 0.05$ no significant difference	U-U-U-U-Y-Y
Wan et al. <sup>22</sup>	Cancer	65/Treat: 59.6, Control: 59.7/52.3/China	Herbs + acupuncture vs western medicine/eastern medicine: 1 per day (1 week), western medicine: i.m. 3 per day (1 week)	Bucinnazine	Percentage of reduction of pain no difference. But pain relief $p < 0.05$ significant difference effect about strong pain $p < 0.05$ prefer treatment. Time to pain relief no difference. Time to be cured $p < 0.05$ prefer treatment	U-U-N-U-Y-Y
Zhang et al. <sup>23</sup>	Lung, gastric, liver, esophagus, large intestine cancer	84/Treat: 56.2 (8.4), Control: 52.7 (9.5)/63.1/China	Herbs + opioid analgesics vs opioid analgesics/2 per day (2 weeks)	Morphine hydrochloride sustainedrelease tablets	Frequency of pain, period of pain relief, time to pain relief $p < 0.05$ prefer treatment	Y-U-N-U-Y-Y

Table 1 (Continued)

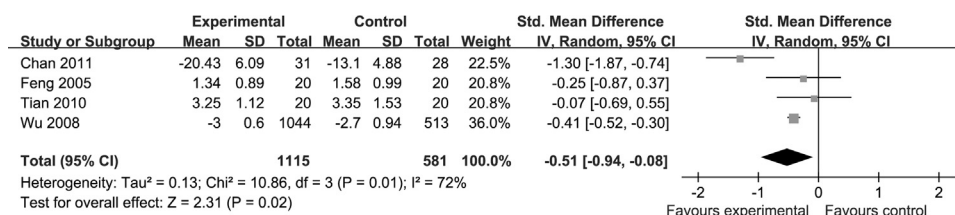
Reference	Type of cancer pain	Participants (n)/mean age (SD)/male (%)/country	Comparison treatment vs control/treatment frequency (treatment period)	Drugs	Outcome reported	Quality assessment <sup>a</sup>
Wu et al. <sup>24</sup>	Lung, liver, gastric, colon, pancreatic cancer	60/Treat: 58.2 (7.3), Control: 58.9 (5.2)/58.3/China	Herbs vs western medicine/3 per day (1 week)	Diclofenac	Experimental group: percentage of pain reduction 90%, Control group: percentage of pain reduction 83.3% no significant difference. But degree of pain reduction, duration of pain, time to pain relief, extension of pain relief, tenderness etc. prefer treatment	U-U-N-U-Y-Y
Liu et al. <sup>25</sup>	Middle-late stage malignant tumor	81/30–75/37/China	Chemotherapy + herbs vs chemotherapy + herbs + moxibustion vs chemotherapy/herbs: 2 per day (1 week); moxibustion: 10 min per day (1 week)	CE-CAP, PVM, FAM, 5-FU + CF, CHOP, CMF, CAF	Chemotherapy group pain $p < 0.05$ significantly reduced. chemotherapy + herbs group pain $p > 0.05$ no significant difference. Herbs + moxibustion group pain $p < 0.05$ significantly reduced. When compared with other group Chemotherapy group $p < 0.01$ , chemotherapy + herbs group $p < 0.05$ prefer treatment	U-U-N-U-Y-Y
Ma et al. <sup>26</sup>	Gastric cancer	62/Treat: 53.1, Control: 52.8/79/China	Herbs vs western medicine/herbs: 3 per day (15 days); western medicine: 2 per day (15 days)	Analgesic drug	Effect of pain relief, duration of pain relief, VRS, Karnofsky $p > 0.05$ no significant difference	U-U-U-U-Y-Y
Bao et al. <sup>27</sup>	Lung, liver, intestinal, breast, stomach, pancreas, esophagus, kidney, others cancer	124/Treat: 69, Control: 67/39.5/China	Herbs compression + 3 L analgesia vs 3 L analgesia + western medicine/herbs compression: 8–12 h per day	Analgesic drug	Time to pain relief significant difference	Y-U-N-U-Y-Y
Zhang et al. <sup>28</sup>	Advanced pancreatic cancer	65/Treat: 54.6 (6.8), Control: 53.2 (7.6)/55.4/China	Herbs + arterial perfusion + chemotherapy vs chemotherapy/herbs: 1 per day (2 months); arterial perfusion: 1 per month (2 months)	Vinorelbine	No significant difference	U-U-N-U-Y-Y

Feng et al. <sup>29</sup>	Primary liver cancer	80/53.8/68.8/China	Dexamethasone vs ginsenosides vs dexamethasone + ginsenosides vs placebo/2 per day	Dexamethasone	Both experimental group $p < 0.05$ prefer treatment dexamethasone + ginsenosides group: effect about (duration of symptoms, low bone mineral density) reported	U-U-Y-Y-Y-Y
Pan et al. <sup>30</sup>	Middle/advanced stage of lung cancer	250/59.6/76.4/China	Herbs + western medicine + Zhiling capsule vs western medicine + Zhiling capsule VS herbs + Zhiling capsule vs Pingxiao capsule/3 per day (2 weeks)		Herbs + western medicine + Zhiling capsule chest pain $p < 0.05$ , 0.01 prefer treatment	U-U-Y-Y-Y-Y
Wei et al. <sup>31</sup>	Liver, lung, gastric cancer	200/Treat: 55.2 (10.1), Control: 54.2 (10.4)/60.5/China	Herbs vs western medicine/3 per day (5 days)	Paracetamol codeine phosphate, placebo drug	Effect of pain relief, duration of pain relief $p > 0.05$ no significant difference	U-U-Y-Y-Y-Y
Wang et al. <sup>32</sup>	Middle-advanced pancreatic cancer	58/Treat: 48.2 (5.7), Control: 49.7 (4.1)/74.1/China	Radiation therapy + herbs vs radiation therapy/radiation: 5 per week (6 weeks); herbs: 2 per day (9 weeks)	None	Experimental group: abdominal pain 25 people among 30 people cured Control group: abdominal pain 16 people among 28 people cured $p < 0.05$ prefer treatment	U-U-N-U-Y-Y
Pan et al. <sup>33</sup>	Liver, stomach, esophagus, liver, kidney, breast, nasopharyngeal, colorectal	400/Treat: 55.4 (12.6), Control: 57.5 (15.1)/66.8/China	Zhiling capsule vs Pingxiao capsule/3 per day (2 weeks)		Experimental group's percentage of reduction of pain 83.9%, control group's percentage of reduction of pain 11.6% $p < 0.001$ significant difference QOL no difference	U-U-N-U-Y-Y
Chan et al. <sup>34</sup>	Ovarian cancer	59/Treat: 52.9, Control: 51.5/0/China	Chemotherapy + herbs vs chemotherapy + placebo/herbs: 2 per day (6 cycles); chemotherapy: 3 weekly cycles (6 cycles)	Placebo, carboplatin, paclitaxel (Taxol)		Y-Y-Y-Y-Y-Y

<sup>a</sup> (1) Was the allocation sequence adequately generated? (2) Was allocation adequately concealed? (3) Was knowledge of the allocated interventions adequately prevented during the study? (4) Were incomplete outcome data adequately addressed? (5) Were reports of the study free of suggestion of selective outcome reporting? (6) Was the study apparently free of other problems that could put it at risk of bias? Key: Y, 'yes'; U, 'unclear'; N, 'no'. The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: <http://www.textcheck.com/certificate/z9r5Zl>.



**Figure 1** Flow diagram showing the number of studies included and excluded from the systematic review. RCT, randomized controlled trial.



**Figure 2** Meta-analysis of combination cancer therapy versus conventional cancer therapy; effect of traditional herbal medicine (THM) combined with standard therapy on visual analog scale (VAS) by number of persons.

( $n = 347$ ) reported a complete or partial response. The percentage (%) of VAS decrease was evaluated by: (difference between VAS before and after treatment/VAS before treatment)  $\times$  100. Complete response and partial response was defined as scoring 91–100% and 61–90.9%. The results showed that concomitant THM therapy was significantly and positively correlated with VAS improvement in terms of number of persons reporting positive results (OR, 1.60; 95% CI, 1.05–2.43). The randomized-effects model was used because of the inter-trial heterogeneity of the results ( $\chi^2$ , 172.01 with 8 df;  $p < 0.00001$ ) (Fig. 2).

### VAS improvement by degree

We identified four trials<sup>12,14,29,34</sup> (1696 patients) reporting improvement on the VAS in terms of degree of change. The pooled analysis showed that THM in combination with Western therapy significantly increased the degree of improvement on the VAS compared with Western therapy alone (MD,  $-0.51$ ; 95% CI,  $-0.94$  to  $-0.08$ ;  $p = 0.02$ ).

The randomized-effects model was used because of the inter-trial heterogeneity of the results ( $\chi^2$ , 10.86 with 3 df;  $p = 0.01$ ) (Fig. 3).

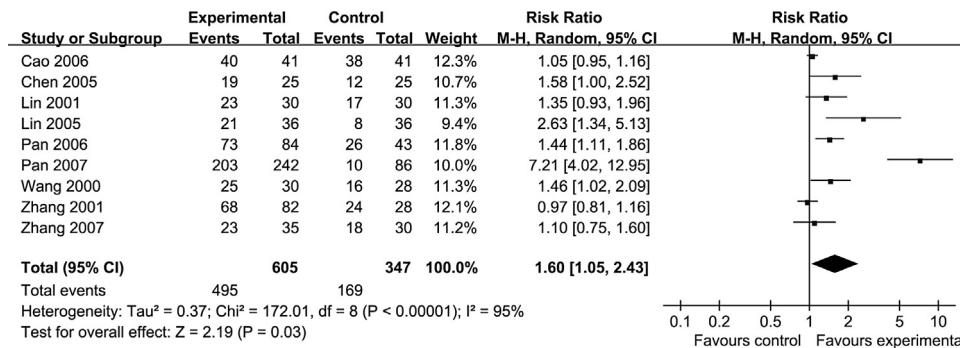
### Discussion

This systematic review of 24 RCTs investigated the efficacy of treatment with both THM and conventional therapy for patients with cancer. This is the first systematic review including only RCTs that investigated the effect of THM as adjunct therapy for cancer pain. We conducted this systematic review after systematically reviewing the work of Ling et al.<sup>6</sup> who included both non-RCTs and RCTs.

This systematic review investigated the effect of adjunct THM therapy on a variety of cancers. Significant evidence has previously demonstrated the effect of THM in this regard.

The treatment group differed significantly from the control group when improvement on the VAS was measured by number of persons reporting decreased pain; this was not





**Figure 3** Meta-analysis of combination cancer therapy versus conventional cancer therapy; effect of traditional herbal medicine (THM) combined with standard therapy on visual analog scale (VAS) by degree.

clear in the review conducted by Ling et al.<sup>6</sup> as it was not a meta-analysis. A similar result was found when improvement on the VAS was measured by degree. We have not added the funnel plot in this review because the meta-analyzed RCTs were not enough to exclude potential publication bias.

We reviewed two articles that investigated the effect of THM on the number of pain occurrences/day in patients with cancer. Although the results were positive, the number of trials was too small to draw firm conclusions. Thus, these results should be interpreted with caution, and further investigation is necessary.

This systematic review had several limitations. First, the quality of the studies was not assessed completely. We used the “Risk-of-Bias” assessment tool included in the Cochrane Handbook<sup>10</sup> to assess the quality of the studies included in this systematic review. As it is difficult to justify the subtle differences in each item using a qualitative method,<sup>36</sup> we tried to assess each trial with regard to seven critical domains: randomization, allocation concealment, blindness of participants and personnel, blindness of outcome assessment, reporting of incomplete outcome data, selective-outcome reporting, and other biases. However, the risk-of-bias assessment may not be entirely objective.<sup>37</sup>

Second, of 24 articles, only nine<sup>11,12,14,19,20,22,23,27,34</sup> were written in English. The remaining 15<sup>13,15–18,21,24–26,28–33</sup> were written in Chinese, making it difficult for other researchers to follow up on the results of these studies.

The quality of the trials in this systematic review was generally weak; thus, further high-quality trials are needed to assess the effectiveness of THM for patients with cancer pain. And as treatment regimens varied in the studies included in the review this is an important limitation.

### Conclusions

In conclusion, this systematic review demonstrated the significant effect of THM treatment combined with standard therapy versus standard therapy alone, as the former was associated with increased improvement on the VAS as measured by number of persons reporting improvement, degree of improvement, and number of pain occurrences per day. Additionally, more RCTs should be conducted to determine the role of THM in a variety of cancer therapies.

### Conflict of interest statement

No authors have any conflict of interest to declare.

### Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government [MEST] (No. 2012-0005755).

### References

- van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Quality of life and non-pain symptoms in patients with cancer. *J Pain Symptom Manage* 2009;**38**(2):216–33.
- Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998;**280**(18):1569–75.
- Rao JK, Mihaliak K, Kroenke K, Bradley J, Tierney WM, Weinberger M. Use of complementary therapies for arthritis among patients of rheumatologists. *Ann Intern Med* 1999;**131**(6):409–16.
- Gozum S, Tezel A, Koc M. Complementary alternative treatments used by patients with cancer in eastern Turkey. *Cancer Nurs* 2003;**26**(3):230–6.
- Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol* 2000;**18**(13):2505–14.
- Ling X, Lao LX, Ge A, Yu S, Li J, Mansky PJ. Chinese herbal medicine for cancer pain. *Integr Cancer Ther* 2007;**6**(3): 208–34.
- Schuler MS, Durdak C, Hol NM, Klink A, Hauer KA, Oster P, et al. Acupuncture treatment of geriatric patients with ischemic stroke: a randomized, double-controlled, single-blind study. *J Am Geriatr Soc* 2005;**53**(3):549–50.
- Madsen MV, Gotzsche PC, Hrobjartsson A. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. *BMJ* 2009;**338**:a3115, <http://dx.doi.org/10.1136/bmj.a3115>.
- Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010;(1). CD003974.
- Higgins J, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. The cochrane Collaboration; 2008.

11. Jeong JS, Ryu BH, Kim JS, Park JW, Choi WC, Yoon SW. Bojungikki-tang for cancer-related fatigue: a pilot randomized clinical trial. *Integr Cancer Ther* 2010;9(4):331–8.
12. Tian J, Liu L, Shi Z, Zhou Z, Wang L. A randomized controlled pilot trial of Feiji recipe on quality of life of non-small cell lung cancer patients. *Am J Chin Med* 2010;38(1):15–25.
13. Chen GY, Liu YQ, Gao P, Tai YH. Clinical study of Zhongyaozhitong capsule on 25 cases with cancer pain. *Jiangsu J Tradit Chin Med* 2005;26(1):16–7.
14. Wu TH, Chiu TY, Tsai JS, Chen CY, Chen LC, Yang LL. Effectiveness of Taiwanese traditional herbal diet for pain management in terminal cancer patients. *Asia Pac J Clin Nutr* 2008;17(1):17–22.
15. Lin D, Li F, Chen LS, Lin HS, Chen YB. Treatment of carcinomatous pain by Jiawei Niantong capsule: a clinical observation of 30 cases. *J New Chin Med* 2001;33(7):18–9.
16. Shi HC, Liu XY, Shi KG, Huang ZG. Clinical observation on the treatment of 90 cases of pain caused by malignant tumor with Aitongning. *Guiding J Tradit Chin Med Pharm* 2005;11(2):21–2.
17. Zhang M. Observation of therapeutic effect of "Compound Strychnos Capsules" in treating cancerous. *Acta Univ Tradit Med Sinensis Pharmacol Shanghai* 2001;15(2):31–2.
18. Cao JX, Xu GY. Clinical observation on treatment of 41 cases of pain induced to bone metastasis cancer with Zhuangguzhitongsan and western medicine. *Chin J Tradit Med Sci Technol* 2006;13(1):48–9.
19. Tian H, Li H, Wang B, Liang G, Huang X, Huang Z, et al. Treatment of middle/late stage primary hepatic carcinoma by Chinese medicine comprehensive therapy: a prospective randomized controlled study. *Chin J Integr Med* 2010;16(2):102–8.
20. Lin J, Jin C, Zheng M, Ouyang X, Zeng J, Dai X. Clinical study on treatment of primary hepatocellular carcinoma by shenqi mixture combined with microwave coagulation. *Chin J Integr Med* 2005;11(2):104–10.
21. Li HL, Hao MA, Wang BT, Bai L. The analgesic effect of traditional Tibetan herb *Lamiophlomis rotata* on cancer pain. *Hebei Med J* 2002;26(2):146–7.
22. Wan D, Li P. Study on Tongkuaixiao Babu plaster in treating cancer pain. *Chin J Integr Med* 2004;10(3):175–80.
23. Zhang T, Ma S, Xie G, Deng Q, Tang Z, Pan X, et al. Clinical research on nourishing yin and unblocking meridians recipe combined with opioid analgesics in cancer pain management. *Chin J Integr Med* 2006;12(3):180–4.
24. Wu MH, Zhou XP, Cheng HB. Clinical study on aitongping capsule in treating cancerous pain. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2005;(3):218–21.
25. Liu J, Yu RC, Rao XQ. Study on effect of moxibustion and guben yiliu III combined with chemotherapy in treating middle-late stage malignant tumor. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2001;21(4):262–4.
26. Ma TX, Li XL, Song ZH, She K. Clinical study about the ache caused by stomach tumor treated with Jiaweibaokeli. *Chin J Cancer Prev Treat* 2003;10(3):297–9.
27. Bao YJ, Hua BJ, Hou W, Lin HS, Zhang XB, Yang GX. Alleviation of cancerous pain by external compress with Xiaozheng Zhitong paste. *Chin J Integr Med* 2010;16(4):309–14.
28. Zhang Q, Wang X-M, Chi H-C. Effects of Guben Yiliu II combined with arterial perfusion with chemotherapeutic agent in treating advanced pancreatic cancer. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2007;27(5):400–3.
29. Feng Y-L, Ling C-Q, Li B. Clinical study on integrative medicine for preventing and treating post-transcatheter arterial chemoembolization. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2005;25(6):534–6.
30. Pan YL, Pan YZ. Observation on the effect of zhiling capsule in treating patients with lung cancer of middle/advanced stage. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2006;26(7):604–7.
31. Wei L, Yang CG, Miao WH. Observation of the efficacy and safety of Tian chan capsule in the treatment of cancer pains. *Chin J New Drug* 2003;12(8):663–5.
32. Wang B, Liu X, Wu Z. Effect of qi replenishing and blood circulation activating drugs in treatment of middle-advanced pancreatic cancer with radio- and chemotherapy. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2000;20(10):736–8.
33. Pan Y-L, Pan Y-Z. Observation on effects of Zhiling capsule in treating 400 patients with various types of cancer in mid-advanced stage. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2007;27(9):807–9.
34. Chan KKL, Yao TJ, Jones B, Zhao JF, Ma FK, Leung CY, et al. The use of Chinese herbal medicine to improve quality of life in women undergoing chemotherapy for ovarian cancer: a double-blind placebo-controlled randomized trial with immunological monitoring. *Ann Oncol* 2011;22(10):2241–9.
35. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. QUOROM Group. *Br J Surg* 2000;87(11):1448–54.
36. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 1995;16(1):62–73.
37. Ernst E, Resch KL. Reviewer bias: a blinded experimental study. *J Lab Clin Med* 1994;124(2):178–82.