


# Benefit of Adjuvant Traditional Herbal Medicine With Chemotherapy for Resectable Gastric Cancer

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## Abstract

**Introduction:** Stomach cancer, historically, has a low survival rate advances in curative resection procedures. **Objectives:** To assess the potential benefits of traditional herbal medicines in conjunction with chemotherapy in postoperative gastric cancer patients in terms of overall survival and disease-free survival. **Data Sources:** We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, a Chinese database (CNKI), a Korean database, a Japanese database, AMED, and CINAHL up to September 2016. We summarized survival data from all RCTs. **Study Selection:** All RCTs of oral traditional medicines for resectable gastric cancer compared with chemotherapy alone were eligible. **Data Extraction:** Thirteen eligible trials with survival data (1075 patients) were deemed eligible for inclusion. **Results:** There were 217 documented deaths of the 574 patients assigned to adjuvant traditional medicines groups and 319 documented deaths of the 501 patients assigned to the chemotherapy-only groups. Adjuvant traditional medicines were associated with a statistically significant benefit in terms of overall survival rate (hazard ratio = 0.56; 95% confidence interval = 0.47-0.66;  $P < .00001$ ) and disease-free survival (hazard ratio = 0.54; 95% confidence interval = 0.43-0.66;  $P < .00001$ ). **Conclusion:** Among the RCTs included, the inclusion of postoperative adjuvant traditional medicines was associated with reduced risk of death in gastric cancer patients, when survival rates were compared with the group of patients who received chemotherapy alone. However, most of the included studies utilized are thought to be of low quality, so it would certainly appear that more trials are both advisable and necessary to arrive at correct and convincing conclusions.

## Keywords

traditional herbal medicine, gastric cancer, randomized controlled trials, systematic review, meta-analysis

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## Introduction

Gastric cancer is the fifth most common cancer diagnosed and continues to represent the most common cause of gastrointestinal cancer-related death (causing more than 800 000 fatalities annually).<sup>1</sup>

Gastric cancer diagnosed at an early stage will often respond to surgical intervention with curative intent. However, the high rate of recurrence and poor survival after surgery would suggest a firm therapeutic basis for implementation of other, adjuvant treatments.<sup>2,3</sup>

Postoperative adjuvant chemotherapy has been associated with reduced risk of death in gastric cancer patients.<sup>3</sup> However, adjuvant chemotherapy or adjuvant radiotherapy, when used alone, do not seem to significantly improve the survival rate following surgery.<sup>2,4</sup>

In recent years, the effect of natural products (when incorporated into traditional medicine) has demonstrated

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material and beneficial effects in improving available cancer therapeutics.<sup>5</sup> Traditional medicine has been used and has been shown to increase the survival rate of gastric cancer patients (when combining therapy with conventional medicines) in East Asia.<sup>6</sup> Also, traditional medicines have been often used to treat patients suffering from anemia or chronic exhaustive symptoms.<sup>7</sup> It has been documented, in this regard, that traditional medicines have served to increase intestinal motility and decrease the negative postoperative symptoms of gastrectomy patients,<sup>8</sup> and traditional medicines have been regularly prescribed to improve the postoperative quality of life of patients.<sup>9</sup>

Numerous studies have indicated that the combination of traditional medicine with chemotherapy can be used to enhance the efficacy of and diminish the side effects and complications of medical procedures.<sup>10</sup> Yang et al reported that limited, weak evidence showed that traditional medicine improved leukopenia and decreased adverse events of chemotherapy in the short-term remission of advanced or late gastric cancer.<sup>11</sup>

However, there has been no comprehensive review of the randomized controlled trials (RCTs) on the benefit of adjuvant traditional medicine for resectable gastric cancer. In view of the foregoing, it was deemed important to assess the overall survival (OS) rate and overall disease-free survival (DFS) of adjuvant traditional medicine with chemotherapy quantitatively by means of a meta-analysis from all relevant trials.

## Methods

### Information Sources and Search Strategy

For this systematic literature review, several health care databases including Medline, CINAHL, a Chinese database (CNKI), a Korean database (Oriental Medicine Advanced Searching Integrated System), and a Japanese database (J-STAGE) were explored following the procedure suggested in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1).<sup>12</sup> Language differences were no constraint, and foreign-language articles were translated.

Searches were conducted up to September 2016, using the following search terms (“stomach cancer” or “stomach neoplasm” or “gastric cancer” or “gastric tumor” and “herb” or “traditional medicine” or “Traditional Chinese medicine” or “Chinese medicine” or “Kampo” or “plants”).

The results of these literature were investigated, and then the titles and abstracts of all articles were reviewed. The irrelevant articles and duplicates were eliminated. Finally, the references of all eligible full-text articles were examined for potentially relevant RCTs.

### Eligibility Criteria and Study Selection

Two reviewers evaluated the inclusion criteria independently. Disagreements between reviewers about inclusion and exclusion were solved by discussion. Identified abstracts and citations were evaluated for the following inclusion criteria.

**Types of Studies.** Data from RCTs were sought electronically. Quasi-randomized trials were also included. The RCTs comparing the inclusion of adjuvant traditional medicine in conjunction with chemotherapy alone after surgery for resectable gastric cancers were included.

**Types of Participants.** Patients undergoing partial or total gastrectomy for gastric cancer with any overall TNM (tumor, node, and metastasis) stage, overall stage grouping system, or performance status (World Health Organization or Karnofsky Index). Patients of any age were included.

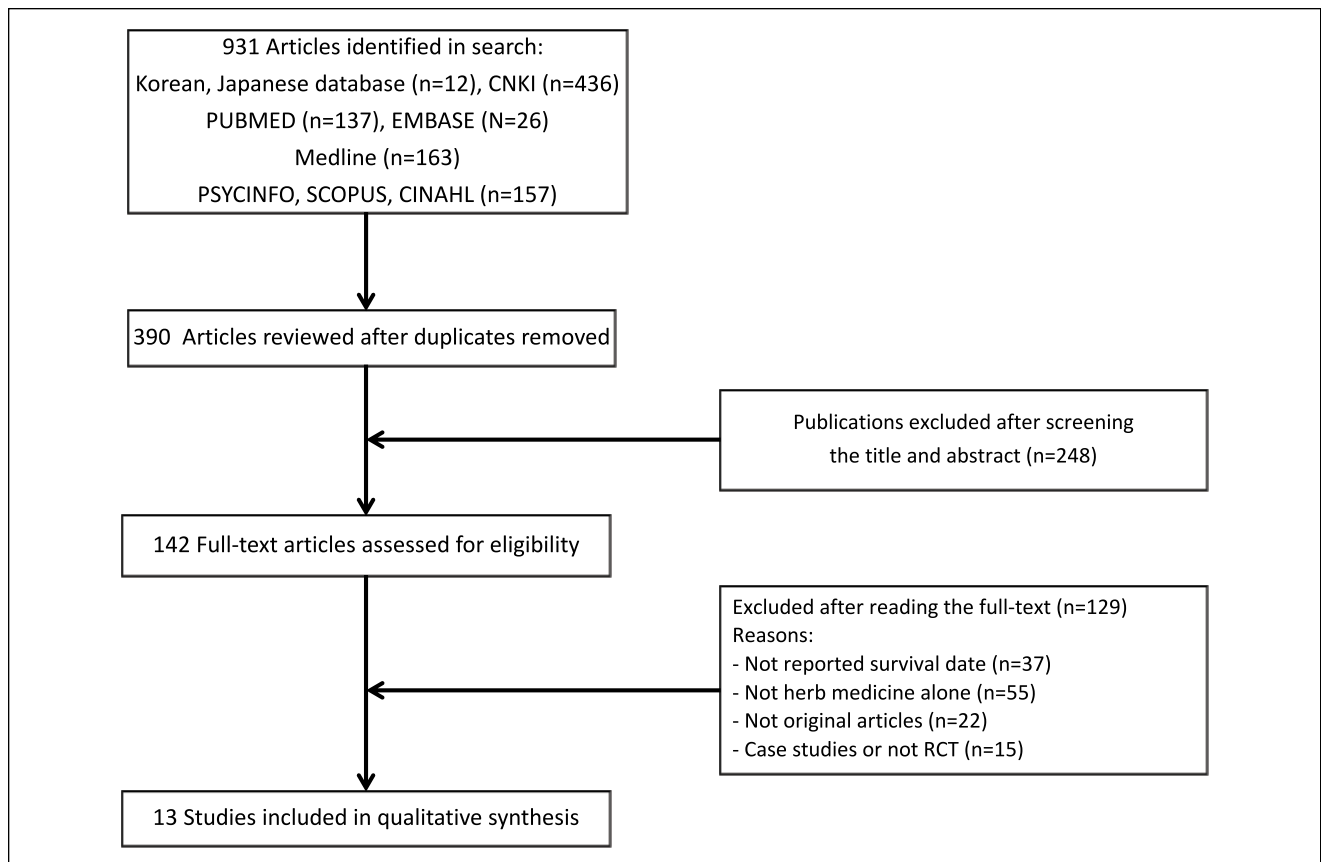
**Types of Interventions.** Studies that examined oral traditional medications with postsurgical chemotherapy versus postsurgical chemotherapy alone were included. We defined traditional medicines as any orally ingested product of any type (such as decoctions, capsules, and tablets) from plants, animal parts, and mineral medicines.

Drugs requiring intravenous administration were excluded. Combination of presurgical chemotherapy in patients were also excluded. Trials with radiotherapy were excluded. Chemotherapy included any protocol such as monochemotherapy, fluorouracil, motomyacin C, or any other polychemotherapy regimens.

**Types of Outcome Measures.** We included studies that reported survival data as mortality, OS, and DFS. OS was defined as the survival rate from trials to the documented date of death from any cause or the last follow-up that was used as a censoring date. DFS was defined as the rate to relapse, metastasis, second cancer, or death from any other cause. OS and DFS were analyzed through hazard ratios (HRs). Secondary outcomes were adverse events.

### Assessment of Risk of Bias

The authors individually evaluated risk of bias with the Cochrane Collaboration’s Tool for evaluating risk of bias.<sup>13</sup> This tool supports consideration of “how the sequence was generated, how allocation was concealed, the integrity of blinding, the completeness of outcome data, selective reporting, and other biases.” If the raters disagreed, the final rating was made by consensus. The risk of bias in each domain was evaluated and categorized into 3 groups: (1) “low risk of bias,” “plausible bias unlikely to seriously alter the results”; (2) “high risk of bias,” “plausible risk of



**Figure 1.** Flow diagram for the study selection on resectable gastric cancer.

bias that seriously weakens confidence in the results”; and (3) “unclear risk of bias,” “plausible bias that raises some doubt about the results.”

### Data Collection and Synthesis of Results

Data from the included studies in the review were individually recorded by each reviewer. Disagreements between reviewers were resolved by consensus. Trials were coded by 2 raters for reliability, and results were compared confirm accuracy. Trials were coded for the following characteristics (sample size, UICC [Union for International Cancer Control] stage of patients with gastric cancer, regimens of chemotherapy, schedule of interventions, and main components of traditional treatment).

OS and DFS were analyzed through the software package RevMan 5 provided by the Cochrane Collaboration. These statistics were entered directly into RevMan using the “O-E and Variance” outcome type. To calculate “O-E” and “V” statistics, a log-rank approach was applied for a HR. Fixed-effect meta-analysis methods were used in RevMan for “O-E and Variance” outcomes. Forest plots were used to display HRs with trials

and overall. Subgroup analyses were examined according to the main components of traditional treatment. Heterogeneity between trials and subgroups of trials with different regimens of chemotherapy was calculated using  $\chi^2$  statistics and analyzed with the  $I^2$  statistics. Sensitivity analysis was conducted. The treatment effects were examined according to high-/medium-quality studies, versus low-quality studies.

## Results

### Study Characteristics

The search of several health care databases including Medline, CINAHL, a Chinese database (CNKI), a Korean database, and a Japanese database provided a total of 931 citations. After extracting results that were missed in the initial vetting of duplicates, 390 articles remained. Of these, 248 studies were excluded because after reviewing the titles and the abstracts, they did not meet the criteria. Thus, 142 studies remained, which were then assessed more attentively for their eligibility to be included in the present review. The full texts of the remaining references were examined in more detail. The 37 studies without survival

**Table I.** Characteristics of Included Randomized Trials.

Source	Traditional Treatment (Main Components)	Chemotherapy, Dosage	Schedule	UICC Stage (No. of Patients)
<i>Hedyotis diffusa</i> + <i>Scutellaria barbata</i>				
Meng 2015 <sup>25</sup>	Decoction ( <i>Scutellaria barbata</i> 30 g, <i>Hedyotis diffusa</i> 10 g, etc); 300 mL/day for 3 months	Fluorouracil 500 mg/m <sup>2</sup> IV  Calcium folinate 100 mg/m <sup>2</sup> IV, 5 days Oxaliplatin 130 mg/m <sup>2</sup> IV, 1 day Fluorouracil 600 mg/m <sup>2</sup> IV, 2-6 days	Every 4 weeks (6 cycles) for 2 years	I, 8; II, 36; III, 42; IV, 14
Yue 2009 <sup>19</sup>	Pill ( <i>Scutellaria barbata</i> 30 g, <i>Hedyotis diffusa</i> 30 g, etc) 45 g/day for 3 months	Adriamycin 30 mg/m <sup>2</sup> IV, 1-8 days Mitomycin 10 mg/m <sup>2</sup> IV, 1 day Tegafur 0.6 g/day orally	Every 3-4 weeks (3-4 cycles)	II, 101; III, 57
Shi 2008 <sup>18</sup>	Decoction ( <i>Scutellaria barbata</i> 10-20 g, <i>Hedyotis diffusa</i> 15-30 g, etc); 20 days every year for 3 years	Mitomycin 6-8 mg/m <sup>2</sup> IV Tegafur 0.6 g/day orally	Every week for 2 months, 1 month for next year	NA 67
<i>Hedyotis diffusa</i> + <i>Semen Coicis</i>				
He 2014 <sup>24</sup>	Decoction ( <i>Semen Coicis</i> 30 g, <i>Hedyotis diffusa</i> 30 g, etc); 300 mL/day for 6 months	Docetaxel 75-85 mg/m <sup>2</sup> IV, 1 day  Cisplatin 75 mg/m <sup>2</sup> IV, 1 day Fluorouracil 750 mg/m <sup>2</sup> IV, 1-2 days	Every month (6 cycles)	II, 46; III, 53
Cui 2006 <sup>14</sup>	Decoction ( <i>Semen Coicis</i> 30 g, <i>Hedyotis diffusa</i> 24 g, etc); 500 mL/day for 6 months	Oxaliplatin 150 mg/m <sup>2</sup> IV, 1 day  Calcium folinate 200 mg/m <sup>2</sup> IV, 1-3 days Fluorouracil 400 mg/m <sup>2</sup> IV then 600 mg/m <sup>2</sup> IV, 1-3 days	Every 3 weeks (6 cycles)	II, 15; III, 27
<i>Poria</i> + <i>Semen Coicis</i>				
Fu 2016 <sup>26</sup>	Decoction ( <i>Semen Coicis</i> 30 g, <i>Poria</i> 20 g, etc), 200 mL/day	Fluorouracil 500 mg/m <sup>2</sup> IV  Calcium folinate 200 mg/m <sup>2</sup> IV, 5 days Cisplatin 20 mg/m <sup>2</sup> IV, 3 days	Every 4 weeks (6 cycles) for 2 years	I, 7; II, 38; III, 40; IV, 15
Chen 2008 <sup>17</sup>	Decoction ( <i>Semen Coicis</i> 30 g, <i>Poria</i> 12 g, etc)	(Fluorouracil, Calcium folinate, Cisplatin) OR (Epirubicin, Fluorouracil, Cisplatin) OR (Oxaliplatin, Calcium folinate, Fluorouracil)	Every month (4-6 cycles)	III, 90
<i>Poria</i> + <i>Atractylodes macrocephala</i>				
Fang 2013 <sup>22</sup>	Ba Zhen Jiao Nang ( <i>Atractylodes macrocephala</i> , <i>Poria</i> , etc), 12 pills/day for 4 months	Paclitaxel 175 mg/m <sup>2</sup> IV, 1 day	Every 3 weeks (4 cycles)	II-III, 40
Jiang 2011 <sup>20</sup>	Decoction ( <i>Atractylodes macrocephala</i> 30 g, <i>Poria</i> 15 g, etc) for 3 months	Cisplatin 80 mg/m <sup>2</sup> IV, 3 days Fluorouracil 500 mg/m <sup>2</sup> IV, 1-5 days  Calcium folinate 200 mg/m <sup>2</sup> IV, 1-5 days Cisplatin 20 mg/m <sup>2</sup> IV, 3-5 days	Every 4 weeks (6 cycles)	II-III, 96

(continued)

**Table 1. (continued)**

Source	Traditional Treatment (Main Components)	Chemotherapy, Dosage	Schedule	UICC Stage (No. of Patients)
<i>Poria + Atractylodes macrocephala + Radix Pseudostellariae</i>				
Zhou 2007 <sup>16</sup>	Decoction (Radix Pseudostellariae 12 g, Atractylodes macrocephala 12 g, Poria 15 g, etc), every day for 3 months	Calcium folinate 200 mg/m <sup>2</sup> IV, 5 days  Fluorouracil 500 mg/m <sup>2</sup> IV, 5 days Cisplatin 20 mg/m <sup>2</sup> IV, 5 days OR Calcium folinate 200 mg/m <sup>2</sup> IV, 5 days Fluorouracil 500 mg/m <sup>2</sup> IV, 5 days Epirubicin-Adriamycin 50 mg/m <sup>2</sup> IV, 1 days Cisplatin 20 mg/m <sup>2</sup> IV, 5 days	Every 3 weeks (6 cycles)	NA 59
Yang 2003 <sup>15</sup>	Decoction (Radix Pseudostellariae 12 g, Atractylodes macrocephala 12 g, Poria 30 g, etc), every day for 6 months	Fluorouracil 500 mg/m <sup>2</sup> IV, 1-5 days  Epirubicin 50 mg/m <sup>2</sup> IV, 1 day Mitomycin 4 mg/m <sup>2</sup> IV, 1 day	Every 3 weeks (6 cycles)	II, 4; III, 81; IV, 4
<i>Other components</i>				
Cai 2013 <sup>21</sup>	Biejiajian Wan pill, 9 g/day for 6 months	Oxaliplatin 85 mg/m <sup>2</sup> IV, 1 day  Calcium folinate 200 mg/m <sup>2</sup> IV Fluorouracil 400 mg/m <sup>2</sup> IV, then 600 mg/m <sup>2</sup> IV, 1-2 days	Every 2 weeks (12 cycles)	II-IV, 56
Zhang 2013 <sup>23</sup>	Norcantharidin 9 tablets/day for 6 months	Cisplatin 20 mg/m <sup>2</sup> IV, 3 days  Calcium folinate 200 mg/m <sup>2</sup> IV, 5 days Fluorouracil 500 mg/m <sup>2</sup> IV, 5 days	Every 4 weeks (6 cycles) for 2 years	II-III, 82

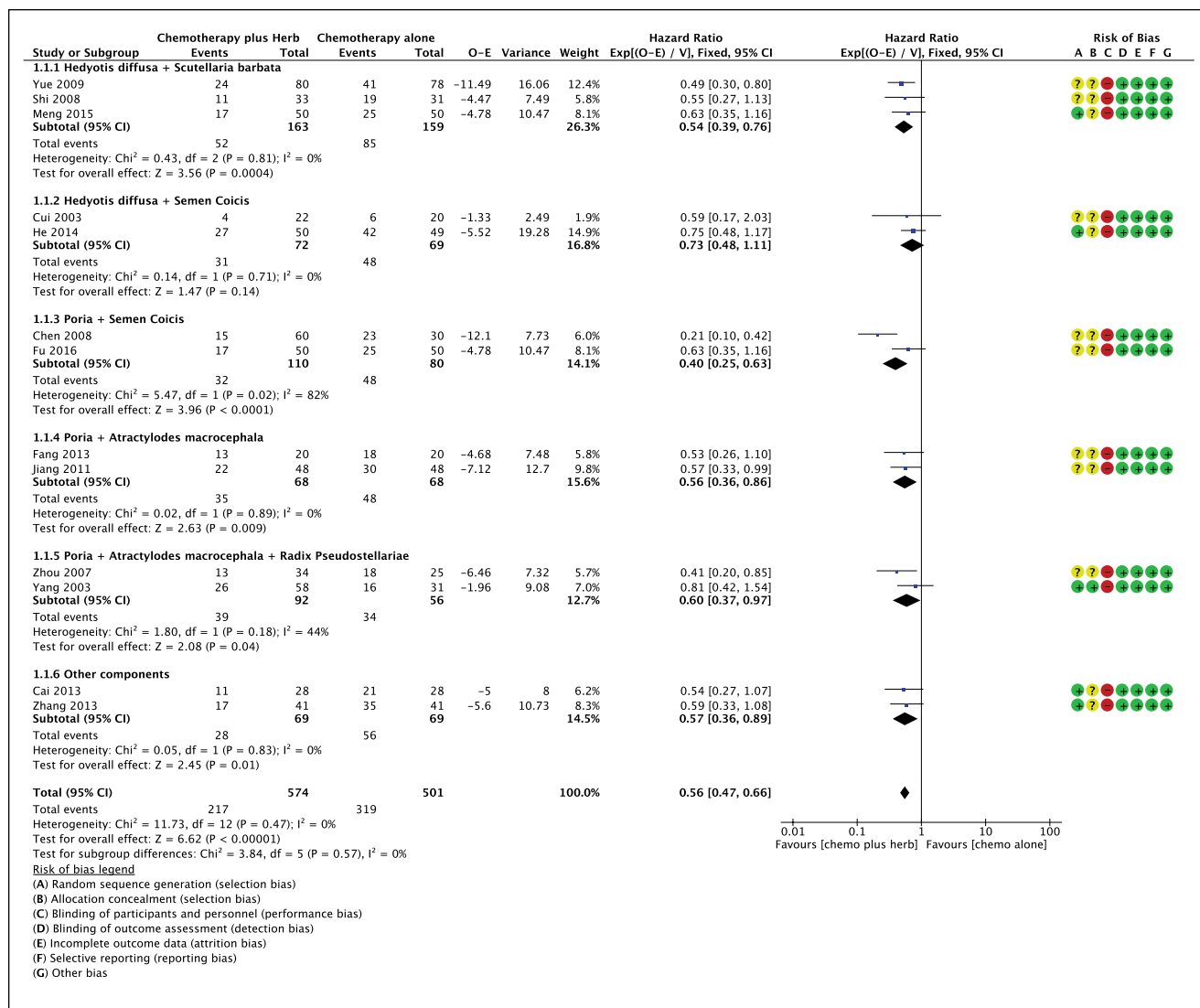
Abbreviations: UICC, Union for International Cancer Control; IV, intravenous; NA, not available.

date were excluded. Finally, 13 trials<sup>14-26</sup> with 1075 patients were identified for inclusion in the review (Figure 1).

The characteristics of the 1075 patients, traditional medicines used, and chemotherapy regimen are listed in Table 1. The main components of tradition medicines were identified as *Hedyotis diffusa*, *Scutellaria barbata*, *Semen Coicis*, *Poria*, *Atractylodes macrocephala*, and *Radix Pseudostellariae*. However, a wide variation was found between trials as for the traditional medicines regimens in all the trials. The methods of preparation of herb formulas were decoctions, pills, or tablets. In all studies, the primary outcome assessed was survival rate. Seven studies reported DFS. None of studies mentioned side effects or adverse events.

### *Risk of Bias in Included Studies*

The methodological quality of the 13 included studies was assessed (Figure 2). Five studies described the method used to generate the allocation sequences or allocation concealment.<sup>15,21,23-25</sup> Two studies used a computer-generated random table.<sup>23,24</sup> Cai and Meng mentioned the random number table for generating a random allocation sequence.<sup>21,25</sup> Two studies reported the use of sealed envelopes.<sup>15,16</sup> None of the studies mentioned blinding of participants and personnel. All studies were silent regarding the blinding of outcome assessment; however, it judged that the outcome measurements of survival data were not likely to be influenced by lack of blinding.



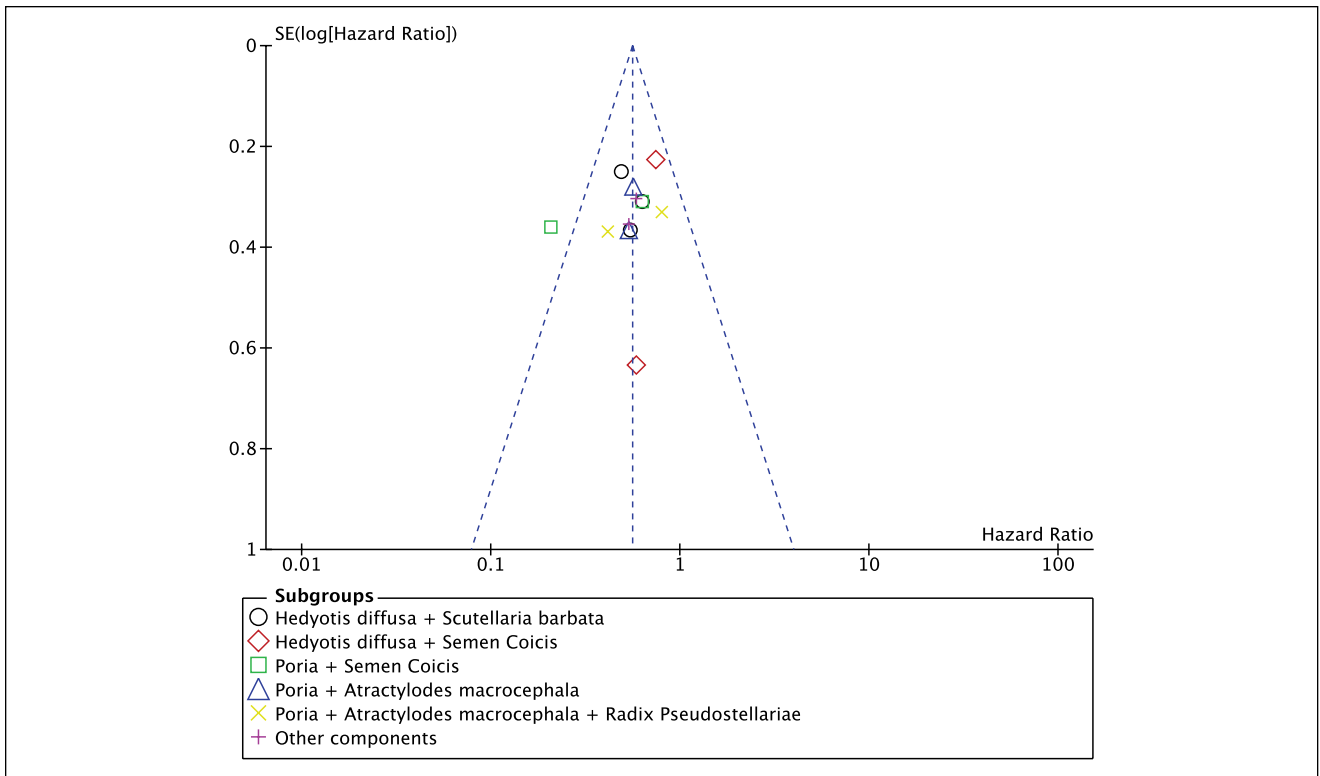
**Figure 2.** Risk of bias, overall survival, and overall hazard ratio for overall survival when comparing traditional medicine versus chemotherapy alone, and risk of bias of 13 included studies.

**Synthesis of Results**

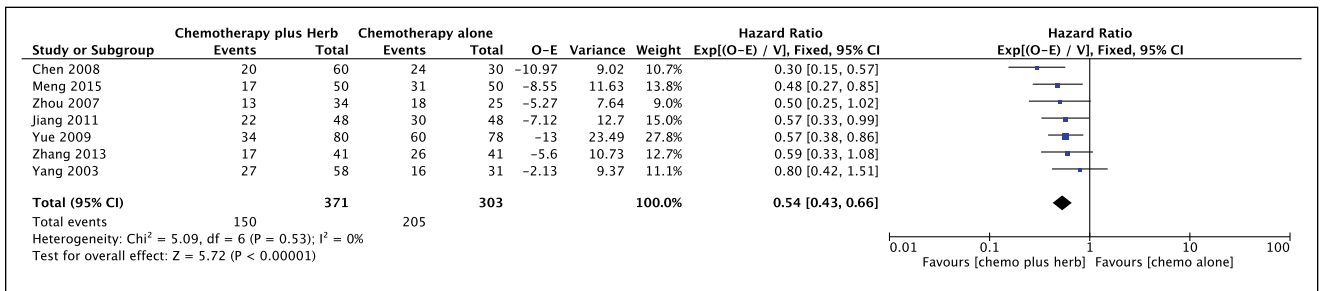
Figure 2 shows the HRs for OS. There was a significant benefit from any traditional medicine plus chemotherapy, when compared with chemotherapy alone with an overall HR of death equal to 0.56 (95% confidence interval [CI] = 0.47-0.66;  $P < .00001$ ). No significant heterogeneity was apparent across the set of trials ( $P = .47$ ).

An interaction test between the type of regimen (Hedyotis diffusa + Scutellaria barbata, Hedyotis diffusa + Semen Coicis, Semen Coicis + Poria, Poria + Atractylodes macrocephala, Poria + Atractylodes macrocephala + Radix Pseudostellariae, and other component) and the treatment effect on OS were not significant ( $P = .57$ ). Three trials involving 322 patients implemented herbal medicine

including Hedyotis diffusa + Scutellaria barbata and a statistically significant benefit for OS was observed (HR = 0.54; 95% CI = 0.39-0.76;  $P = .0004$ ).<sup>18,19,25</sup> Two trials using traditional medicine including Hedyotis diffusa + Semen Coicis had 141 patients with OS data, but no significant effect was detected (HR = 0.73; 95% CI = 0.48-1.11;  $P = .14$ ).<sup>14,24</sup> The other regimens (Semen Coicis + Poria,<sup>17,26</sup> Poria + Atractylodes macrocephala,<sup>20,22</sup> Poria + Atractylodes macrocephala + Radix Pseudostellariae,<sup>15,16</sup> and other component<sup>21,23</sup>) were explored comparing with chemotherapy alone, and they showed a statistically significant benefit of adjuvant traditional medicines over chemotherapy alone for resectable gastric cancer (HR = 0.40, 95% CI = 0.25-0.63,  $P < .0001$ ; HR = 0.56, 95% CI = 0.36-0.86,  $P = .009$ ; HR = 0.60, 95% CI = 0.37-0.97,  $P = .004$ ; HR = 0.57, 95% CI =



**Figure 3.** Funnel plots of 13 trials comparing traditional medicine versus chemotherapy alone.



**Figure 4.** Disease-free survival and overall hazard ratio for disease-free survival when comparing traditional medicine versus chemotherapy alone.

0.36-0.89, *P* = .001, respectively). In sensitivity analyses, the summary overall HR remained statistically significant, including 5 trials with adequate sequence generation or allocation concealment (HR = 0.67, 95% CI = 0.52-0.87; *P* < .003). There was no perceptible asymmetry in funnel plots of these 13 studies (Figure 3).

DFS was available on 7 trials with a total number of 674 patients from the 13 trials.<sup>15-17,19,20,23,25</sup> The implementation of adjuvant traditional medicine improved DFS compared with chemotherapy alone with an overall HR of 0.54 (95% CI = 0.43-0.66; *P* < .00001). HRs for DFS in 7 trials and overall are shown in Figure 4. No significant heterogeneity was detected (*P* = .53).

### Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis of adjuvant traditional herbal RCTs for resectable gastric cancer with OS. Overall, post-operative herbal treatments have not been the standard of care for gastric cancer, but the evidences from the meta-analysis showed the benefit of adjuvant herbal treatment with chemotherapy.

The 13 trials showed a statistically significant benefit associated with adjuvant herbal treatments after curative resection of gastric cancers. Seven trials reported statistically significant difference for the improvement of rate of

remission. Assessments of risk of bias showed potential biases in RCTs. The methods of allocation concealment for only 2 trials were clarified. Only 4 studies mentioned a random method. No blinding of outcome assessment was used; however, the assessment of total mortality may be considered unbiased. There was no perceptible asymmetry in funnel plots; however, the validity has been questioned because of the relatively small number of studies.<sup>27</sup>

Our review is limited by potential heterogeneity and bias from including methodological issues. The heterogeneity appeared at many fields in included studies, such as in the sample group, the herbal treatments, and the chemotherapies. Heterogeneity of study was considered a potential limitation in this systematic review. These trials had limited heterogeneity of studies making it difficult to draw definitive conclusions. Methodological heterogeneity included different components of herb, control interventions, and the stage of the cancer afflicting the particular patients.

Patient-level meta-analyses could not be carried out, so we were unable to address the estimates of the survival curve. Although there was no limitation of language, there were no non-Chinese articles included in the studies. Therefore, we could not reach a cogent conclusion. We suggest that future trials should focus on such methodological quality of the study with standard treatments (components of herb, treatment period, and treatment regimens) in multinational clinic centers.

## Conclusion

In conclusion, our findings suggest that traditional herbal medicines are efficacious in the treatment of resectable gastric cancer. Among the RCTs included, postoperative adjuvant traditional medicines were associated with reduced risk of death (HR = 0.56) and disease (HR = 0.54) in gastric cancer compared with chemotherapy alone, and is recommended for patients with resectable gastric cancer. However, most of the included studies were of low quality with potential heterogeneity so that the conclusion is not convincing. More trials are needed to draw convincing conclusion about the benefits. Future studies based on more precise evaluation will estimate overall survival.

## Authors' Note

This systematic review was formatted according to PRISMA guidelines.

## Declaration of Conflicting Interests


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