Astragalus-containing Chinese herbal combinations for advanced non-small-cell lung cancer: a meta-analysis of 65 clinical trials enrolling 4751 patients

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Background: Non-small-cell lung cancer (NSCLC) is a leading cause of death. Interventions to reduce mortality in patients with NSCLC represent a patient-important field of research. Little is known about interventions used outside the Western world for NSCLC. One intervention widely used in Asia is astragalus-based herbal preparations.

Methods: We conducted a comprehensive systematic review of all published randomized clinical trials (RCTs) evaluating astragalus-based herbal preparations in NSCLC patients. We searched independently, in duplicate, 6 English language electronic databases and 2 Chinese-language databases. We abstracted data independently, in duplicate on studies reporting of methods, survival outcomes, tumor responses, and performance score responses. We applied a random-effects meta-analysis and report outcomes as relative risks (RR) with 95% confidence intervals (CIs).

Results: We included 65 RCTs enrolling 4751 patients. All trials included the herbal preparations plus platinum-based chemotherapy versus chemotherapy alone. We pooled 7 studies (n = 529) reporting on survival at 6 months and found a pooled RR of 0.54 (95% CI, 0.45 to 0.65, \( P \leq 0.0001 \)). We included 20 trials (n = 1520) on survival at 12 months and found a pooled RR of 0.65 (95% CI, 0.54 to 0.79, \( P \leq 0.0001 \)). This effect was consistent at 24 and 36 months. When we applied a composite endpoint of any tumor treatment response, we pooled data from 57 trials and found a pooled RR of 1.35 in favor of herbal treatment (95% CI, 1.26 to 1.44, \( P \leq 0.0001 \)). Statistical heterogeneity was low across trials.

Limitations: The quality of reporting the RCTs was generally poor. There is also reason to believe that studies reported as randomized may not be.

Conclusions: We found a large treatment effect of adding astragalus-based herbal treatment to standard chemotherapy regimens. There is a pressing need for validation of these findings in well-conducted RCTs in a Western setting.

Keywords: astralagus, non-small-cell lung cancer, herbal preparations

Introduction
Lung cancer is the leading cause of cancer death worldwide.1,2 In the United States, lung cancer is the leading cause of death, where it is estimated that 219,440 new cases of lung and bronchus cancer will be diagnosed in 2009; leading to 159,390 lung cancer-related deaths.3 Only 15% of all lung cancer patients are alive 5 years or more after diagnosis.3

The World Health Organization divides lung cancer into 2 major classes: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts
for over 85% of all lung cancer cases, and it includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types) and (2) squamous cell (epidermoid) carcinoma.  

The clinical guidelines for patients with NSCLC include combinations of cytotoxic chemotherapy and targeted biologic therapies, such as bevacizumab and erlotinib. Unfortunately, these current treatments involve non-specific, non-selective cytotoxic chemotherapy, which results in only a modest increase in survival and causes significant toxicity to the patient. According to a meta-analysis of 33 Phase III randomized controlled trials (RCTs), platinum-based chemotherapy offers symptomatic relief and modest improvements in survival (rarely >2 months). Data from 3 RCTs showed that platinum-based chemotherapy provided a median survival time of approximately 7 to 10 months.

In China, traditional Chinese medicines (TCM), which are herbal and/or animal/insect-based combinations, are frequently combined with chemotherapy for the treatment of cancer. One commonly used herbal compound, astragalus, appears to have a number of immunomodulatory properties. Astragalus appears to have antitumor activity where its potentiates LAK cell activity in vitro when used in combination with IL-2. Astragalus appears to restore in vitro T-cell function, which is suppressed in cancer patients. A meta-analysis of 34 RCTs found that Chinese medicines containing the herb astragalus (Astragalus membranaceus) may increase effectiveness of platinum-based chemotherapy when combined with chemotherapy. When compared to chemotherapy alone, astragalus-based Chinese medicines reduced risk of death at 12 months (risk ratio [RR] = 0.67; 95% confidence interval [CI], 0.52 to 0.87), improved tumor response data (RR = 1.34; 95% CI, 1.24 to 1.46), reduced risk of death at 24 months (RR = 0.58; 95% CI, 0.49 to 0.68), increased tumor response (RR = 1.76; 95% CI, 1.23 to 2.53) and stabilized or improved Karnofsky performance status (RR = 1.28; 95% confidence interval [CI], 1.12 to 1.46).

There are a large number of published RCTs on astragalus-based Chinese medicines combined with platinum-based chemotherapy. Although a meta-analysis was conducted on NSCLC treatments using astragalus-based Chinese medicines along with platinum-based chemotherapy, this study did not include Chinese language studies in its search strategy. In a previous meta-analysis on TCM treatments for hepatocellular carcinoma, 44/45 RCTs extracted were in Chinese compared to 1/45 RCTs in English; thereby illustrating the importance of including Chinese manuscripts in the analysis.

Our objective is to systematically review the scientific literature for RCTs on astragalus-based Chinese medicines combined with platinum-based chemotherapy and to meta-analyze the pooled data from these RCTs. Should the results be favorable, astragalus-chemotherapy combination treatment may provide an important step forward for new interventions for patients with NSCLC.

**Methods**

**Study inclusion criteria**

We included any study that randomized patients with advanced NSCLC, provided the treatment group with Chinese herbal medicines containing the herb astragalus in combination with standard platinum-based chemotherapy, provided the control group with platinum-based chemotherapy alone, and reported data on at least one of our outcomes of interest (survival, tumor response, or performance status) with sufficient detail to permit calculation of the risk ratios of each outcome. We excluded pharmacokinetic studies and non-randomized trials. We excluded studies that reported only laboratory values rather than clinical responses. We also excluded direct comparisons of TCM formulations.

**Search strategy**


In addition, PW and YL, both fluent in Mandarin and Cantonese, searched the Chinese databases CNKI (1979 to June 2009) and Wan Fang (1994 to June 2009) independently. No language restrictions were placed on the searches.

Three reviewers (PW, EM and YL) assessed eligibility based on the full text papers and conducted data extraction, independently, using a standard pre-piloted form. Disagreements were resolved by consensus or by a third reviewer. If the required information was not available in the published article, we obtained additional information in correspondence with the authors. We included all evaluated outcome measures including: survival at 6, 12, 24, and 36 months, disease stage, Karnofsky performance (KP), and the response evaluation criteria in solid tumors (RECIST).

The response is categorized as complete response (CR), partial response (PR) outcomes, stable disease (SD), progressive disease (PD) and as CR + PR as a composite for response rate.
In addition, we extracted data on trial quality, protocol, and outcomes assessed. We assessed quality through the reporting of the following criteria: sequence generation and allocation concealment. We also noted the language in which the paper was written and the setting the studies were conducted. These criteria were not used for weighting covariates in the meta-analysis; instead, these were considered *a priori* explanations for study heterogeneity.

All inclusion and exclusion criteria and the categorization of outcomes were made before any meta-analysis of the data. Our decision to group together for this meta-analysis those studies using platinum-based chemotherapy was based on the fact that this therapy is currently a standard treatment for advanced NSCLC. Following the example set by D’Addario et al.\(^{17}\) and the Cochrane Collaboration’s Non–Small-Cell Lung Cancer Collaborative Group,\(^{18}\) platinum-based
chemotherapy was grouped together as a therapeutic class when assessing efficacy of treatment for NSCLC. Each stage of the planning, design, analysis, and reporting of this meta-analysis was conducted in accordance with the QUOROM Statement guidelines.\(^\text{19}\)

### Analysis of outcomes

#### Survival

Given that all of the studies identified in our systematic search reported crude survival data as the number of patients in each treatment group who died by 6, 12, 24, or 36 months, we calculated the probability of failure (death) as the number of patients who had died by each time point divided by the total number of patients enrolled at the start of the trial for each treatment group. This approach is intentionally conservative: if some patients dropped out of the study, retaining them in the denominator as we have done would lower the estimate of effectiveness. This is analogous to an intention-to-treat analysis.\(^\text{20}\) The risk ratios of treatment failure (death) at each time point was calculated as the proportion who died in the astragalus-based herbal medicine plus platinum-based chemotherapy treatment group, compared to the proportion in the platinum-based chemotherapy group. Thus, RR less than 1 favors the combination regimen.

#### Objective tumor response

Given that most of the studies identified in our systematic search used RECIST,\(^\text{21}\) we calculated the probability of tumor response as the number of patients experiencing any response (complete response plus partial response) divided by the total number of patients in each treatment group (complete response plus partial response plus no change plus progressive disease). The RR of tumor response was calculated as the proportion of tumor response in the astragalus-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR more than 1 favors the combination regimen. This is the approach for meta-analysis of tumor response recommended by Sutton et al.\(^\text{22}\)

#### Performance status

Many of the studies identified in our systematic search reported performance status using the Karnofsky performance scale,\(^\text{23}\) with most using a 10-point change as the cutoff for improved or worse performance status, and a few others using a 20-point change as the cutoff. We therefore calculated the probability of improved or stable performance status as the proportion of improved or stable performance status: (\(>10\)-point increase plus no change) divided by the total (\(>10\)-point increase, plus no change, plus \(>10\)-point decrease). The RR of improved or stable performance status was calculated as the proportion of improved or stable performance status in the astragalus-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR more than 1 favors the combination regimen.

### Analysis

We used the random-effects model of DerSimonian and Laird\(^\text{24}\) to estimate the summary RR for each of the four outcomes: risk of death (at 6, 12, 24, and 36 months), tumor response, performance status, and severe chemotherapy toxicity. We used the I\(^2\) statistic to assess between-study heterogeneity and interpreted the outcome as \(<50\%\) as non-problematic heterogeneity. To assess publication bias, we used the Begg-Mazumdar test, which examines the association between the effect estimates of individual studies and their variances; significant correlation between these two factors identifies publication bias.\(^\text{25}\)

We applied the RR and 95% CI as our primary effect measure in this analysis. For analysis examining response, favorable results for the TCM intervention are in the direction greater than 1. In circumstances of zero outcome events in either arm of a trial, we used the Haldane method and added 1 to each arm, as suggested by Sheehe.\(^\text{26}\) We first pooled studies on all interventions versus all controls using the DerSimonian-Laird random-effects method.\(^\text{27}\) This method recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability. We calculated the I\(^2\) statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.\(^\text{28}\) Forest plots are displayed for the primary analysis, showing individual study effect measures with 95% CIs and the overall DerSimonian-Laird pooled estimate. We conducted a meta-regression analysis using the unrestricted maximum likelihood method to determine if the \textit{a priori} covariates of TCM formulation yielded differing effects. We examined publication bias visually and through the Begg-Mazumdar tests. We calculated the optimal information size (OIS) required to determine adequate power across trials. We used Stats Direct and Comprehensive Meta-Analysis (Version 2) for all statistical procedures. All \(P\) values are 2-sided and a \(P\) value \(< 0.05\) was considered significant. PW and EM conducted the analysis.
Results

Included studies

Our systematic search identified 1484 potentially relevant abstracts, of which 164 were identified as requiring full-text article retrieval (Figure 1). Close screening of these 221 studies identified 65 studies that met our inclusion criteria, containing a total of 4751 patients. Most studies were small (median 67, interquartile range 56 to 83). Studies poorly reported methodological issues including sequence generation (25%), allocation concealment (3%), and reporting of adverse events (67%). Table 1 provides the study characteristics.

Survival

We pooled 7 studies \(^ {29-35} \) (n = 529) reporting on survival at 6 months and found a pooled RR of 0.54 (95% CI, 0.45 to 0.65, \( P \leq 0.0001 \), \( I^2 = 0\% \), 95% CI, 0% to 58%, \( P = 0.74 \), see Figure 2). We included 20 trials \(^ {36-49} \) (n = 1520) in our analysis of survival at 12 months and found a pooled RR of 0.65 (95% CI, 0.54 to 0.79, \( P \leq 0.0001 \), \( I^2 = 74\% \), 95% CI, 57% to 82%, \( P < 0.0001 \), see Figure 3). As 12-month survival was our primary outcome, we applied the publication bias assessment and found no evidence of publication bias (Kendall’s tau = −0.157, \( P = 0.31 \)). We included 13 trials \(^ {32,34,35,40-49} \) (n = 1090) with survival rates reported at 24 months and found a pooled RR of 0.74 (95% CI, 0.66 to 0.84, \( P \leq 0.0001 \), \( I^2 = 64\% \), 23% to 78%, \( P = 0.0008 \), see Figure 4). We included data from 10 trials \(^ {45,46,48,49} \) (n = 878) reporting on survival at 36 months and found a pooled RR of 0.86 (95% CI, 0.80–0.92, \( P \leq 0.0001 \), \( I^2 = 29\% \), 95% CI, 0% to 65%, \( P = 0.17 \), see Figure 5).

Tumor response

We were able to include data from 27 trials \(^ {37,39-43,50-70} \) (n = 1759) reporting on complete responses to treatment and found a pooled RR of 1.43 in the direction of favorable outcomes for herbal-based treatment (95% CI, 0.98 to 2.10, \( P = 0.07 \), \( I^2 = 0\% \), 95% CI, 0% to 42%, \( P \leq 0.99 \)). The same 27 trials reported on partial response to treatment and found a pooled RR of 1.35 favoring herbal treatment (95% CI, 1.19 to 1.53, \( P \leq 0.0001 \), \( I^2 = 0\% \), 95% CI, 0% to 38%, \( P = 0.99 \)). When we applied a composite endpoint of any treatment response we pooled data from 57 trials \(^ {30,32-35,37,39-45,48-50,87-90} \) and found a pooled RR of 1.35 in favor of herbal treatment (95% CI, 1.26 to 1.44, \( P \leq 0.0001 \), \( I^2 = 0\% \), 0% to 28%, \( P = 0.99 \), see Figure 6).

Performance status

We included data from 35 trials \(^ {15,37,43,48-53,55,56,58-64,66-72,77,80,84,85,87,88,91-94} \) (n = 2650) assessing stable or improved Karnofsky scores and found a pooled RR of 1.58 (95%, 1.39 to 1.81, \( P \leq 0.0001 \), \( I^2 = 69\% \), 55% to 78%, \( P \leq 0.0001 \), see Figure 7).

Discussion

Our findings should be of interest to cancer researchers and funding agencies. We found consistent evidence of improved survival and tumor response in astragalus-based herbal medicine therapy combined with platinum-based chemotherapy compared with platinum-based chemotherapy alone, the standard of care. While there is reason to be cautious of the quality of the included clinical trials, due to their small sample sizes and inadequate reporting of methodological issues, there has been a consistent direction of treatment effect that warrants further examination by experienced clinical trialists in a transparent manner.

Our study has both strengths and limitations to consider. Strengths include our extensive searching and identification of Chinese clinical trials that few systematic review groups may be able to accomplish. Our analysis used a broad approach that considered all astragalus containing herbal combinations as comparatively similar, thus allowing much greater power to detect an effect over a single trial. It is possible that specific combination exert a differing therapeutic effect; however we were unable to identify such specific formulations. The limitations of our study are predominantly related to the need for caution in interpreting the clinical trials. There is consistent evidence that publication bias may exist in Chinese medical journals and thus, only positive trials are published. Although we recognize favorable outcomes may be more likely to be published, our analysis actually does not find that only positive trials are published. If one examines the forest plots, on average, most trial are negative, but when pooled, become positive. A recent evaluation, by Wu et al, found that many studies labelled as RCTs with Chinese journals were, in fact, not randomized. In our own experience, we recognize many Chinese clinical trialists have not been exposed to appropriate clinical epidemiology training. Yet even if our analysis includes predominantly non-randomized studies, the consistency of therapeutic effect warrants further examination. Other systematic reviews of published studies from Chinese journals have identified specific journals with better study quality, and also found trends in improvement of study quality over time. We assessed publication bias in our primary outcome (survival at 12 months) and did not find statistical evidence of bias, although funnel plots and statistical tests cannot identify the absence of publication bias.
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<td>Astragalus, Atractylodes, Dried longan pulp, Rehmannia praeparatum, white peony root, Radix rhin manniae, dry orange peel, costusroot, hemlock parsley</td>
</tr>
<tr>
<td>Mao</td>
<td>2014</td>
<td>60</td>
<td>MVP + TCM</td>
<td>Astragalus, Chinese angelica, Atractylodes, Poria, polygonatum, Ligustrum, paris [root], ornus, dried orange peel</td>
</tr>
<tr>
<td>Shen</td>
<td>2014</td>
<td>80</td>
<td>NP + TCM</td>
<td>Stragalis, Atractylodes, Adenophora, asparagus, Liriope, almond, Radix stemona, Trichosanthes rind, raw arisaema [root], Shizandra berry, Chinese sage, Oldenlandia diffusa, prunella, raw oyster shell, Bulbus Fritillariae</td>
</tr>
<tr>
<td>Shen</td>
<td>2014</td>
<td>72</td>
<td>NP + TCM</td>
<td>Astragalus, Atractylodes polygonatum, Adenophora, Liriope, umbilicaria, ligustrum, babchi seed, Spatholobus stem, Oldenlandia diffusa</td>
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</table>

(Continued)
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<tr>
<th>Study</th>
<th>No of patients</th>
<th>Protocol*</th>
<th>Ingredients</th>
<th>Disease stage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Su²⁵⁹</td>
<td>80</td>
<td>MVP + Astragalus combination</td>
<td>Lillium brownii, Rehmannia glutinosa, Scrophularia ningpoensis, Angelicae sinensis, Ophiopogonis japonicies, Paonia lactiflora, Adenophora verticillata, Astragalus, Ligusticum lucidum, Paris polyphylla, Oldenlandia diffusa, Hou touynia cordata, Fritillaria cirrhosa, Crenastra variabilis (with individualized additions)</td>
<td>II, III or IV</td>
</tr>
<tr>
<td>Sun²⁶</td>
<td>74</td>
<td>CE-CAP/MVP/TC + Astragalus combination</td>
<td>Gomospermae lucidum, Pseudostellaria heterophylla, Coix lachryma, Atractylodis macrocephala, astragalus, Lycium chinense, Curcuma zeodoaria, Scutellaria barbata, Salviae miltiorrhiza, Morus alba, Thunberg Fritillary Bulb, wild buckwheat rhizome, Ziziphus jujube, Lepidium apetalum, Atractylodis macrocephala, Poria cocos, Pinellia ternata, Citrus reticulata, Eleutherococcus senticosus, Mylabris cichoi (with individualized additions)</td>
<td>III/IV</td>
</tr>
<tr>
<td>Tian⁹³</td>
<td>40</td>
<td>NP + Fu Zhen Jie Du</td>
<td>Astragalus, Adenophora, asparagus, Liriopy, Liguistrum, epimedium, Oldenlandia diffusa</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang¹⁰</td>
<td>32</td>
<td>NP/MVP + Ai Di injection</td>
<td>Panax ginseng, astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang⁷⁰</td>
<td>98</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang⁶⁴</td>
<td>93</td>
<td>MOP + astragalus combination</td>
<td>Adenophora verticillata, Asparagus cochinchinensis, Ophiopogonis japonicies, Pseudostellaria heterophylla, Astragalus, Curcuma zeodoaria, Atractylodis macrocephala, C. aromatica, Paonia rubra, Paonia lactiflora, Oldenlandia diffusa, Scutellaria barbata</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang⁴¹</td>
<td>58</td>
<td>Cisplatin + astragalus combination</td>
<td>Astragalus, Panax ginseng, Lillium brownii, Adenophora verticillata, Ophiopogonis japonicies, Fritillaria cirrhosa, Morus alba, Trichosanthes kirilowii, Scutellaria baicalensis, Paris polyphylla, Scutellaria barbata, Solanum nigrum, Lepidium apetalum, Atractylodis macrocephala, Poria cocos, Pinellia ternata, Citrus reticulata, Eleutherococcus senticosus, Mylabris cichoi (with individualized additions)</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang⁴⁰</td>
<td>60</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang⁴⁰</td>
<td>46</td>
<td>GP/TP + TCM</td>
<td>Astragalus, polygonatum, umbilicaria, babchi seed, Atractylodes</td>
<td>II–IV</td>
</tr>
<tr>
<td>Wen⁷⁷</td>
<td>78</td>
<td>NP + TCM</td>
<td>Astragalus, Campanumanae pille, Polygonatum Ligustrum, Spaltholbus stem, as hide glue (melt), Pinellia</td>
<td>II–IV</td>
</tr>
<tr>
<td>Weng⁷⁵</td>
<td>34</td>
<td>CAP + astragalus combination</td>
<td>Codonopsis pilosulae, astragalus, Atractylodis macrocephala, Poria cocos, Pinellia ternata, Citrus reticulata, Dioscorea opposita, Oldenlandia diffusa, Houtouya cordata, Patrinia villosa, Scutellaria barbata, Agrimonia pilosa, Ziziphus jujube</td>
<td>II–IV</td>
</tr>
<tr>
<td>Xie⁶⁸</td>
<td>60</td>
<td>NP + TCM</td>
<td>Ginseng, Atractylodes, Poria, liquorice root, astragalus, Chinese angelica, Spaltholbus stem, Pyrospinae leaf, Barbed skullcap herb</td>
<td>III/IV</td>
</tr>
<tr>
<td>Xu²⁷</td>
<td>40</td>
<td>TP + Ke Liu Wan</td>
<td>Curcuma, Mylabris, Geckko, Vietnamese Sophora Root, leech, ground beetle, astragalus</td>
<td>II–IV</td>
</tr>
<tr>
<td>Xu⁵⁰</td>
<td>72</td>
<td>GP/TP + TCM</td>
<td>Astragalus, Adenophora, Liriopy, apricot kernel, Thunberg Fritillary Bulb, wild buckwheat rhizome, curcuma, Chinese honeycomb fruit, coix seed, Oldenlandia diffusa</td>
<td>IV</td>
</tr>
<tr>
<td>Xue⁷³</td>
<td>72</td>
<td>GP + TCM</td>
<td>Astragalus, Pseudostellaria Root, Atractylodes, Poria, Pinellia, dry orange peel, mulberry root bark, Rehmanniae vaporata, heartleaf Houtouya herb, Oldenlandia diffusa</td>
<td>IIb/IV</td>
</tr>
<tr>
<td>Yang⁶¹</td>
<td>56</td>
<td>GP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
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<tr>
<td>Yang⁶⁴</td>
<td>40</td>
<td>GP + Ke Liu Wan</td>
<td>Astragalus, Mylabris, leech</td>
<td>III/IV</td>
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<tr>
<td>Yu⁶⁴</td>
<td>92</td>
<td>MAP + radiation + astragalus combination</td>
<td>Astragalus, Pseudostellaria heterophylla, Poria cocos, Amomum xanthioides, Salvia miltiorrhiza, Paonia rubra, Spaltholbus suberecutes, Schisandra chinensis, Glycyrrhizae uralensis (with individualized additions)</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zhang⁷⁶</td>
<td>50</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
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</tr>
<tr>
<td>Zhang⁷³</td>
<td>98</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Treatment Combination</td>
<td>Ingredients</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------</td>
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<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------------------</td>
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<tr>
<td>Zhang</td>
<td>31</td>
<td>EP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutheroxoccus senticosus, Mylabris pachyi</td>
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</tr>
<tr>
<td>Zhang</td>
<td>35</td>
<td>GP + Jian Pi Zi Yin</td>
<td>Astragalus, Atractylodes, Pinellia, Hovenia dulcis, sweetflag, Hovenia dulcis</td>
<td>II/IV</td>
</tr>
<tr>
<td>Zhang</td>
<td>39</td>
<td>MVP + Bu Qi Huo Xue</td>
<td>Astragalus, Radix pseudostellariae, Atractylodes, amomum fruit, Pinellia</td>
<td>II/IV</td>
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<tr>
<td>Zhong</td>
<td>48</td>
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<td>Panax ginseng, Astragalus, Eleutheroxoccus senticosus, Mylabris pachyi</td>
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<tr>
<td>Zhou</td>
<td>53</td>
<td>NP + Fu Zhen Bu Xu</td>
<td>Astragalus, Campanumaea piliosa, Panax, Atractylodes, Dioscoreae, Chinese</td>
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<tr>
<td>Zhou</td>
<td>64</td>
<td>CAP + astragalus combination</td>
<td>Panax ginseng, Atractylis macrocephala, Pinellia, Paeonia lactiflora,</td>
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<tr>
<td>Zhou</td>
<td>65</td>
<td>Cisplatin + astragalus</td>
<td>Panax ginseng, Atractylis macrocephala, Pinellia, Paeonia lactiflora,</td>
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</tr>
<tr>
<td>Zou</td>
<td>69</td>
<td>MAP + astragalus</td>
<td>Astragalus</td>
<td>III/IV</td>
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</tbody>
</table>

*In studies that included stage II patients, all patients received systemic therapy, and no patients received surgery.

*In studies in which patients received radiation in addition to chemotherapy, all patients in both groups received radiation and chemotherapy. The only difference between the two groups was whether they received astragalus-based herbal medicine.

**Abbreviations:** CAP, cyclophosphamide, doxorubicin, cisplatin; NP, vinorelbine, cisplatin; FDH, hydroxy camptothecin, fluorouracil, leucovorin, cisplatin; EAP, etoposide, doxorubicin, cisplatin; MVP, mitomycin-C, vindesine, cisplatin; TC, paclitaxel, carboplatin; GCN, gemcitabine, cisplatin, vinorelbine; CE, cisplatin, etoposide; MAP, mitomycin, doxorubicin, cisplatin; EP, etoposide, cisplatin; MOR, mitomycin, vinorelbine, cisplatin.
Figure 2 Six-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

Relative risk meta-analysis plot (random effects)

- Wang
- Weng
- Wang
- Chen
- Su
- Liu
- Liu
- Combined [random]

Relative risk (95% confidence interval)

0.69 (0.43, 1.11)
0.53 (0.24, 1.12)
0.51 (0.34, 0.69)
0.57 (0.25, 1.25)
0.52 (0.32, 0.79)
1.08 (0.40, 3.12)
0.46 (0.31, 0.67)
0.54 (0.45, 0.65)

Figure 3 Twelve-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

Relative risk meta-analysis plot (random effects)

- Shen
- Xue
- Hong
- Zhang
- Wang
- Shen
- Lu
- Luo
- Wang
- Weng
- Wang
- Chen
- Sui
- Zhou
- Jin
- Yu
- Liu
- Liu
- Combined [random]

Relative risk (95% confidence interval)

0.76 (0.52, 1.08)
0.63 (0.39, 0.96)
0.91 (0.57, 1.42)
0.73 (0.40, 1.31)
0.79 (0.32, 1.93)
0.57 (0.37, 0.85)
0.32 (0.14, 0.69)
0.83 (0.60, 1.17)
0.36 (0.24, 0.50)
0.90 (0.70, 1.21)
0.90 (0.71, 1.11)
0.95 (0.44, 2.07)
0.52 (0.32, 0.79)
0.72 (0.45, 1.15)
0.21 (0.09, 0.42)
0.31 (0.14, 0.62)
1.00 (0.66, 1.52)
0.62 (0.41, 0.86)
2.04 (0.84, 5.45)
0.46 (0.31, 0.67)
0.65 (0.54, 0.79)
Astragalus-containing Chinese herbal combinations for NSCLC

Relative risk meta-analysis plot (random effects)

- Wang\(^{30}\): 0.69 (0.36, 1.29)
- Shen\(^{31}\): 0.80 (0.62, 1.00)
- Lu\(^{32}\): 0.62 (0.42, 0.88)
- Luo\(^{33}\): 0.86 (0.70, 1.07)
- Wang\(^{34}\): 0.85 (0.63, 1.13)
- Chen\(^{35}\): 0.91 (0.69, 1.14)
- Zhou\(^{36}\): 0.86 (0.64, 1.14)
- Jin\(^{37}\): 0.49 (0.32, 0.69)
- Yu\(^{38}\): 0.66 (0.46, 0.92)
- Liu\(^{39}\): 0.94 (0.77, 1.14)
- Zou\(^{40}\): 0.75 (0.55, 0.95)
- Liu\(^{41}\): 0.53 (0.39, 0.68)
- Liu\(^{42}\): 0.61 (0.48, 0.76)
- Combined [random]: 0.74 (0.66, 0.84)

Relative risk (95% confidence interval)

**Figure 4** Twenty-four-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

Relative risk meta-analysis plot (random effects)

- Wang\(^{43}\): 0.75 (0.48, 1.14)
- Shen\(^{44}\): 0.90 (0.76, 1.06)
- Lu\(^{45}\): 0.76 (0.59, 0.95)
- Luo\(^{46}\): 0.92 (0.78, 1.08)
- Wang\(^{47}\): 0.91 (0.72, 1.14)
- Zhou\(^{48}\): 0.93 (0.73, 1.15)
- Jin\(^{49}\): 0.65 (0.50, 0.80)
- Liu\(^{50}\): 0.92 (0.78, 1.05)
- Zou\(^{51}\): 0.89 (0.70, 1.09)
- Liu\(^{52}\): 0.79 (0.66, 0.92)
- Combined [random]: 0.86 (0.80, 0.92)

Relative risk (95% confidence interval)

**Figure 5** Thirty-six-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
Relative risk meta-analysis plot (random effects)

Figure 6  Tumor response with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
Relative risk meta-analysis plot (random effects)

The reporting of quality features including how trials were randomized and how allocation concealment was achieved adds further caution to our study interpretation. While the inadequate reporting of these items is undesirable, there is, as yet, conflicting evidence that the reporting of these issues affects the magnitude of treatment effect.58–100

Given the consistency of treatment effect, large number of trials, importance of the disease and the caution about study quality it seems only reasonable that a clinical trial should be conducted in a Western setting that can ensure adequate sample size and concealed allocation to study arms. Such a clinical trial would provide strong inferences into the believability of our meta-analysis findings and could massively impact drug development. However, until a trial is conducted, we recommend counseling interested patients to maintain cautious optimism on any treatment effect and
discuss with their oncology physician about potential costs and harms.

Our study builds on an existing collaboration between researchers in China and in North America. We recognize that important and effective drugs have been discovered by examining the Chinese medical literature for existing clinical trials. Artemisinin-based therapy for malaria and oseltamivir (Tamiflu®) for influenza are two compelling examples. We have previously used this approach for examining potentially effective interventions for hepatocellular cancers and found evidence of existing interventions that have never been evaluated in the West, despite compelling evidence of effectiveness. We believe that this approach represents a low-cost approach to identifying potentially effective new opportunities for drug development.

Additional research is needed to further understand the specific immunologic and cytotoxic mechanisms that astragalus may affect as an adjunct to chemotherapy for the treatment of advanced NSCLC.

Acknowledgments
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Disclosure
The authors declare no potential conflicts of interest.

References


