

# Efficacy of ginseng oral administration and ginseng injections on cancer-related fatigue

## A meta-analysis

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### Abstract

**Background:** Up to 90% of patients who are under the active treatment suffer from cancer-related fatigue (CRF). CRF can persist about 10 years after diagnosis and/or treatment. Accumulating reports support that ginseng and ginseng injections are both potential drugs for the treatment of CRF but few studies put them together for analysis.

**Methods:** Two reviewers independently extracted data in 3 databases (PubMed, Cochrane Library and China National Knowledge Infrastructure) from their inception to May 24, 2021. The primary outcome was the effect of ginseng in alleviating CRF. The secondary outcome was ginseng in alleviating emotional or cognitive fatigue. Standardized mean difference (SMD) was employed.

**Results:** Twelve studies were included to evaluate efficacy of ginseng oral administration and ginseng injections on CRF. The pooled SMD was 0.40 (95% confidence Interval [95% CI] [0.29–0.51],  $P < .00001$ ). Six studies were included to evaluate efficacy of ginseng oral administration on CRF and the SMD was 0.29 (95% CI [0.15–0.42],  $P < .0001$ ). The order was 2000mg/d, 3000mg/d, 1000mg/d and placebo from high efficacy to low. Ten studies were included to evaluate efficacy of ginseng injections on CRF and the SMD was 0.74 (95% CI [0.59–0.90],  $P < .00001$ ). Emotional fatigue was reported in 4 studies, ginseng oral administration in 2 and ginseng injections in 2. The pooled SMD was 0.12 (95% CI [–0.04 to 0.29],  $P = .15$ ). Cognitive fatigue was reported in 4 studies focusing on ginseng injections and the SMD was 0.72 (95% CI [0.48–0.96],  $P < .00001$ ).

**Conclusion:** Ginseng can improve CRF. Intravenous injection might be better than oral administration. Ginseng injections may alleviate cognitive fatigue. No evidence was found to support that ginseng could alleviate emotional fatigue.

**Abbreviations:** 95% CI = 95% confidence interval, CRF = cancer-related fatigue, SMD = standardized mean difference.

**Keywords:** cancer-related fatigue, ginseng, ginseng injections, meta-analysis

## 1. Introduction

Cancer-related fatigue (CRF) is one of the most common symptoms in patients with cancer. Up to 90% of patients who are under the active treatment suffer from CRF.<sup>[1]</sup> It can persist months or even years after treatment ends which interferes with usual functioning. Besides, fatigue is rarely an isolated symptom and most commonly occurs with other symptoms and signs, such as pain, emotional distress, anemia, and sleep disturbances, in symptom clusters.<sup>[2]</sup> Unlike typical fatigue, CRF cannot be relieved by additional rest, sleep, reducing physical activity, etc. On the contrary, exercise/

physical activity is likely to be effective in ameliorating CRF. Psychological/psycho-education, mind/body wellness training, nutritional and dietary supplements may be effective, too. Unfortunately, these interventions yield, at most, moderate benefits in meta-analyses.<sup>[2]</sup> Until now, evidence to date indicates that synthetic drugs are less effective than non-pharmacologic intervention.<sup>[2]</sup>

Ginseng is the root of plants in the genus *Panax*, such as Korean ginseng (*Panax ginseng* C.A. Meyer), Japanese ginseng (*Panax ginseng* C.A. Meyer), and American ginseng (*Panax quinquefolius* L.). Red ginseng is a processed product of Asian ginseng (*Panax ginseng* C.A. Meyer.) by steaming and drying.

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The datasets generated during and/or analyzed during the current study are publicly available.

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Ginseng has been used to treat chronic fatigue as early as 2000 years ago in China. Nowadays, ginseng is not only used in China, but also sold and used in more than 35 countries, such as Japan, South Korea, North Korea, America.<sup>[3]</sup> Preclinical data supports that ginseng may be helpful for fatigue. Animal studies have reported that ginseng can improve the endurance and swimming duration time of mice.<sup>[4]</sup> Besides, ginseng is mentioned as a dietary supplement for CRF treatment in the NCCN Guidelines based on 1 randomized, double-blind clinical trial using American ginseng which indicated that American ginseng of 2000 mg improved CRF symptom.<sup>[5]</sup> There are several types of ginseng and they were deemed to have same active pharmaceutical ingredients, for example, Rg1 and Rb1. However, other types of ginseng were not discussed in the Guidelines.<sup>[6]</sup>

In addition to oral administration, several types of injections whose main components are ginseng extractions have been approved by Chinese National Medical Products Administration to be used in clinic. The common ones are Kangai injection, Shenfu injection, Shenmai injection, Shenqi Fuzheng injection. Kangai injection (China Food and Drug Administration approval number Z20026868) consists of the extracts from *Astragalus membranaceus* (Fisch.) (Bunge), *Panax ginseng* C.A. Meyer. and *Sophora flavescens* Aiton. Shenfu injection (China Food and Drug Administration approval number Z20043117) consists of the extracts from Red ginseng and *Aconitum wilsonii* Stapf ex Veitch. Shenmai injection (China Food and Drug Administration approval number Z2009364) consists of the extracts from Red ginseng and *Ophiopogon japonicus* (Linn. f.) Ker-Gawl.. Shenqi Fuzheng injection (China Food and Drug Administration approval number Z19990065) consists of the extracts from *Codonopsis pilosula* (Franch.) Nannf. and *Astragalus Membranaceus* (Fisch.) Bunge. Some studies have shown that ginseng injections are of great help in improving the quality of life and reducing the side effects of radiotherapy and chemotherapy in cancer patients.<sup>[7,8]</sup> Therefore, ginseng and ginseng injections are both potential drugs for the treatment of CRF but few studies put them together for analysis. Here, we employed standardized mean difference (SMD) to conduct a meta-analysis to evaluate the efficacy of ginseng and ginseng injections in the treatment of CRF and the quality of the evidence. Emotional and cognitive fatigue were evaluated, too. Besides, in our study, subgroup analyses were conducted to compare the efficacy of cancer types, cancer stages, basic strategies for treatment of cancer and so on.

## 2. Methods

### 2.1. Study registration

The protocol of this meta-analysis is registered in PROSPERO, under the registration number CRD42021228094 on February 18, 2021. It is available at <http://www.crd.york.ac.uk/PROSPERO/>.

### 2.2. Literature search

PubMed, Cochrane Library, China National Knowledge Infrastructure were systematically searched from the database inception to May 24, 2021. The following keywords were used for the Chinese database search: (shen or renshen or gaolishen or xiyangshen or hongshen or baishen or shuishen or yeshan-shen or Kangai zhushuye or Shenqi Fuzheng zhushuye or Shenfu zhushuye or Shenmai zhushuye) and (pilao or pifa or pijuan or pibei or juandai or fali). The following keywords were used for the English database search: (Ginseng or Ginsengs or *P. quinquefolius* or *Panax* or ginsenosides or ginsenoside or Kangai injection or Shenqi fuzheng injection or Shenfu injection or Shenmai injection) and (fatigue or lethargy or exhaustion or tiredness or weariness or physical performance or exercise performance) (Table S1, <http://links.lww.com/MD/H734> for details).

### 2.3. Inclusion/exclusion criteria

For inclusion in the review, studies were required to meet the following criteria: Experimental design: randomized controlled trials; Type of participants: subjects with CRF, regardless of age, sex, type of cancer, pathological type, cancer treatment; Type of interventions: drugs with ginseng or ginseng injections; Control: unlimited treatment method; Language types: Chinese and English studies. Studies without enough data (The duration of treatment or fatigue score is unknown) or studies whose participants were subjectively selected were excluded from analysis.

### 2.4. Selection of relevant studies and quality assessment

Two reviewers independently extracted data based on the predetermined criteria, and discrepancies were resolved by consensus. From studies included in the final analysis, the following data were extracted: the name of first author, year of publication, geographic location, types of cancer, basic strategies for treatment of cancer (surgery, chemotherapy or radiotherapy), species and dose of ginseng and ginseng injections in the intervention group, treatment regimen of the control group, duration of treatment, tool name used to assess CRF and type of dimensions used for main outcomes measured. The Cochrane Handbook was used for systematic reviews of interventions to evaluate the quality of the included studies.<sup>[9,10]</sup> This approach requires studies to be assessed across 6 special domains that were subjected to potential bias, including sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. There are 3 biases of judgment: Yes (Low risk), No (High risk), Not clear (Unclear risk).

### 2.5. Outcomes of interest

The primary outcome was the effect of ginseng and ginseng injections in alleviating CRF. The secondary outcome was emotional or cognitive fatigue alleviated by ginseng and ginseng injections.

### 2.6. Statistical analysis

RevMan5.3 (Review Manager (RevMan), Computer program, version 5.3. Cochrane Collaboration, Copenhagen, Denmark) was used for our statistical analysis.<sup>[9,10]</sup> STATA v.16.0 (College Station, TX) was used for network meta-analysis. Because clinical indices to assess clinical response/remission differed among studies, SMD was used as a main effect size to calculate those differences.<sup>[11]</sup> The calculation formula of SMD is as follows:

$$\text{SMD} = \text{M1} - \text{M2/pooled SD}$$

Where M1 is the mean of fatigue reduction in the intervention group, M2 is the mean of fatigue reduction in the control group, and pooled SD is a pooled intervention specific standard deviation.<sup>[8]</sup> If the value of SMD is positive and  $P < .05$ , it shows that the effect of the intervention group is better than that of the control group.

### 2.7. Assessment of heterogeneity

Chi<sup>2</sup> test combined with I<sup>2</sup>-test was used to test the heterogeneity between studies. If  $P < .1$  or  $I^2 > 50\%$ , it suggested significant heterogeneity and we would use random-effects model for meta-analysis; otherwise, a fixed-effects model would be used. Wherever feasible, a meta-regression analysis would be conducted to explore the source of significant heterogeneity. Sensitivity analyses would be undertaken to assess the robustness of our findings by excluding studies with high risk of bias.<sup>[12]</sup>

## 2.8. Assessment of reporting biases

Funnel plots were performed to assess reporting bias with more than 10 trials. Egger's regression intercept was calculated by STATA v.16.0 to do a test of asymmetry. A 2-tailed  $P$  value  $< .05$  was considered statistically significant.<sup>[13]</sup>

## 2.9. Summarizing and interpreting results

GRADE approach was used to interpret findings. We assessed the outcomes with reference to the overall risk of bias of the included studies, the inconsistency of the results, the directness of the evidence, the precision of the estimates, and the risk of publication bias. The quality of the body of evidence for each assessable outcome were categorized as follows: no reason to downgrade the quality of evidence, serious reason (downgraded by one) or very serious reason (downgraded by two).<sup>[14]</sup>

## 3. Results

### 3.1. Selection and general characteristics of the included studies

A total of 1764 studies were identified from the 3 electronic databases. Seventy-one duplicate studies were excluded by using Endnote X9. On review of the title and abstract, 1631 studies were excluded. After further careful review of 62 articles of the full text, a further 40 studies were excluded. Finally, 22 papers with a total of 2086 participants were included. Patients were treated with ginseng oral administration in 7 papers and with ginseng injections in 15 (Fig. 1 and Table 1). They were published between 2010 and 2020 and were conducted in China ( $n = 16$ ), America ( $n = 3$ ), Korea ( $n = 2$ ) and Italy ( $n = 1$ ). Six studies were randomized, double-blind, placebo-controlled design trials, and the rest of 16 studies used randomized design (Table 1). The detailed information was summarized in Table 1 and Table S2, <http://links.lww.com/MD/H735> and 3, <http://links.lww.com/MD/H736>.

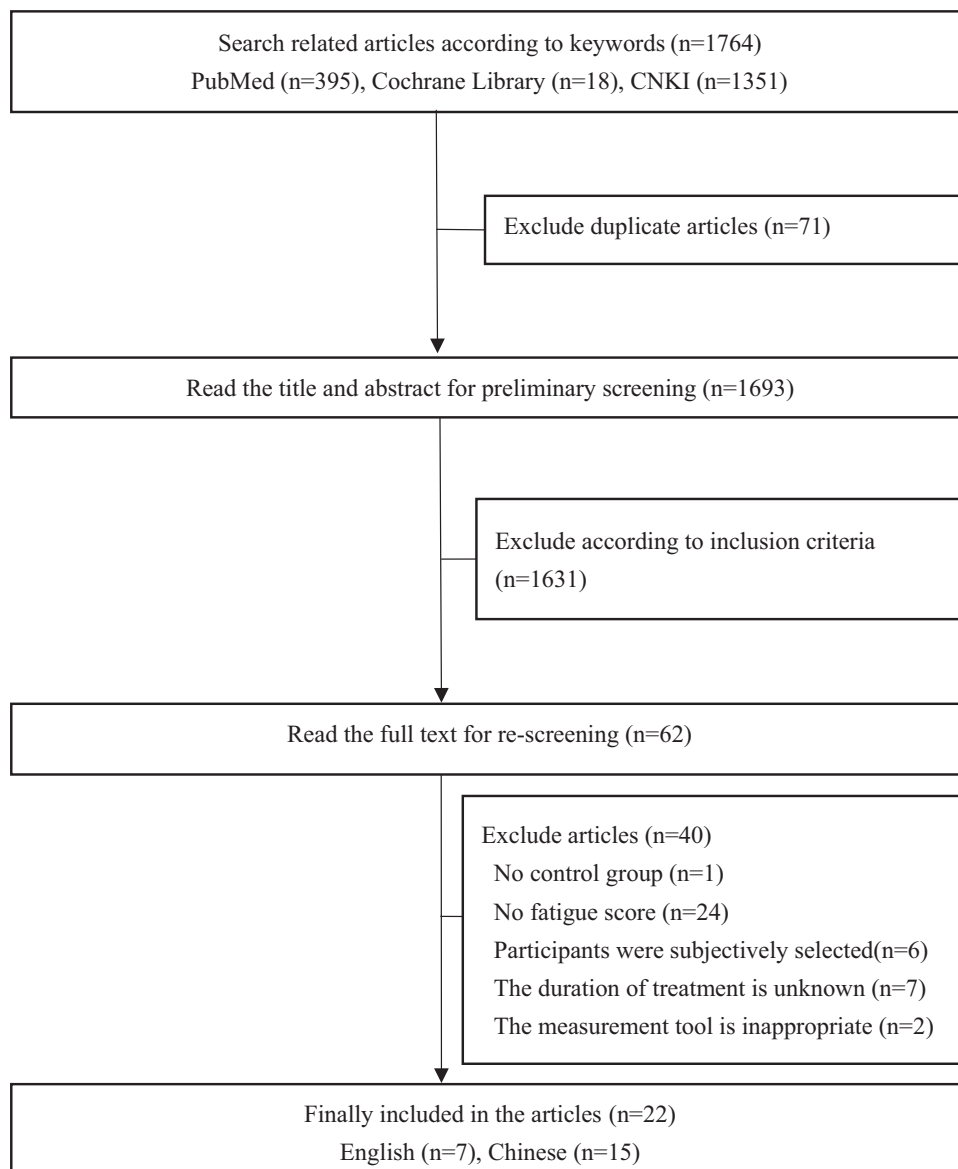
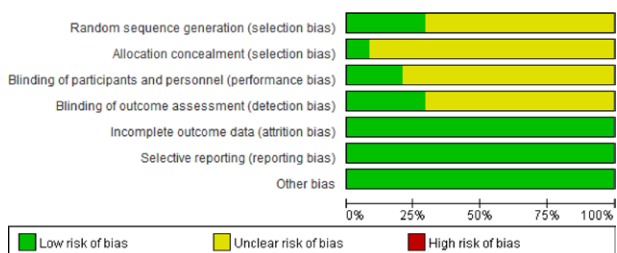


Figure 1. Flow chart.

**Table 1**  
**Characteristics of studies included in the systematic review and meta-analysis.**

First author (yr)	Intervention/dose	Control	Follow-up period/sample size (intervention/control)	Main outcome measures used type of dimensions	Measurement tools
Barton et al (2010)	American ginseng 2000 mg/d	Placebo	8 wk (48/39)	Usual fatigue	BFI
Barton et al (2013)	American ginseng 2000 mg/d	Placebo	4 wk (147/153) and 8 wk (138/133)	General subscale of the (MFSI-SF)	MFSI-SF
Guglielmo et al (2020)	American ginseng 1000 mg/d	Placebo	8 wk (16/16)	The mean value of BFI score	BFI
Kim et al (2017)	Red ginseng 3000 mg/d	Placebo	12 wk (15/15)	The severity of fatigue: Worst fatigue score	BFI
Shulong Jiang (2017)	Red ginseng extract 3000mg/d	None	60 days (34/26)	Total score	FSI
Kim et al (2020)	Red ginseng 2000 mg/d	Placebo	8 wk (161/169) and 16 wk (161/169)	Fatigue subscale score	FACIT-F
Yennurajalingam et al (2017)	Panax ginseng extract 400 mg/d	Placebo	15 days (52/54) and 29 days (56/56)	Fatigue subscale score	FACIT-F
Shengsong Yin (2014)	Kangai injection (Panax ginseng) 40 mL/d	None	3 wk (20/20)	Total score	BFI
Fang Shi (2017)	Kangai injection (Panax ginseng) 40 mL/d	None	6 wk (45/45)	Total score	PFS
Danni Shan (2020)	Kangai injection (Panax ginseng) 40–60 mL/d	None	2 wk (45/45)	Total score	PFS
Hongchen Li (2011)	Shenfu injection (Red ginseng) 30 mL/60 mL/d	None	12 wk (62/58)	Physical fatigue score	PFS
Yibing Feng (2014)	Shenfu injection (Red ginseng) 60 mg/d combined with Dexamethasone	Dexamethasone	12 wk (31/32)	Physical fatigue score	PFS
Jing Wu (2014)	Shenmai injection (Red ginseng) 50–100 mL/d	None	4 wk (47/47)	Behavior fatigue score	PFS
Xiaomu Tang (2016)	Shenmai injection (Red ginseng) 50 mL/d	None	9 wk (43/43)	Behavior fatigue score	PFS
Yinshui Zou (2014)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d	None	3 wk (35/35)	Total score	BFI
Qi Zhang (2016)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d	None	4 wk (26/26)	Behavior fatigue score	PFS
Zhiyong Liu (2016)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d combined with Megestrol acetate	Megestrol acetate	3 wk (30/30)	Total score	PFS
Jia Li (2018)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d combined with Letrozole	Letrozole	16 wk (20/20)	Total score	BFI
Qingying Wang (2018)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d	None	6 wk (20/20)	Behavior fatigue score	PFS
Cong Chen (2019)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d	None	8 wk (33/33)	Physical fatigue score	CFS
Jianbing Luo (2019)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d	None	2 wk (107/86)	Total score	PFS
Xiao Li (2020)	Shenqi fuzheng injection (Codonopsis pilosula) 250 mL/d	None	2 wk (31/29)	Physical fatigue score	PFS

BFI = brief fatigue inventory, CFS = cancer fatigue scale, FACIT-F = functional assessment of chronic illness therapy-fatigue subscale, FSI = fatigue symptom inventory, MFSI-SF = multidimensional fatigue symptom inventory-short form, PFS = piper fatigue scale.



**Figure 2.** Risk of bias graph.

**3.2. Methodological quality of studies**

All included 22 studies were randomized controlled trials. Two were dynamically allocated by computer,<sup>[5,15]</sup> and 4 used

random number table method.<sup>[7,16–18]</sup> Those 6 were rated as low risk. One study used stratified block randomization allocation and bias risk was not clear.<sup>[19]</sup> The other 15 studies didn't describe the method of random sequence generation. Of 6 double-blind studies, only 1 mentioned double-blind method but did not describe the specific implementation process.<sup>[20]</sup> Two studies were multicenter and 6 used placebo as control.<sup>[5,19]</sup> All included studies had low risk of bias regarding incomplete outcome data, had low risk of bias regarding selective reporting and none claimed conflict of interest, early termination of the trial (Figs. 2 and 3).

**3.3. Outcome of heterogeneity text**

For the primary outcome, all intervention groups' data was combined, regardless of the types and stages of cancer and so



Figure 3. Risk of bias summary.

on. Consequently, our analyses were subject to high potential risk of between-study heterogeneity. A meta-regression was conducted, we found that placebo may be a source of heterogeneity. In 6 studies that used placebo, ginseng oral administration was in 6 and ginseng injections in 0, so analysis was conducted separately. We did not find other sources of heterogeneity (Table 2).

Sensitivity analyses were undertaken by excluding studies with high risk of bias. Compare the 2 results, we still ca not explain the source of heterogeneity (Fig. S1, <http://links.lww.com/MD/H737;2>, <http://links.lww.com/MD/H738;3>, <http://links.lww.com/MD/H739>). Therefore, whether heterogeneity taken into account or not, results were all presented and discussed in the manuscript, respectively. The same as the secondary outcome (Table 2).

3.4. Outcome of publication bias text

Egger linear regression was conducted to text symmetry of funnel plots. No publication bias was found in each outcome (Fig. S4, <http://links.lww.com/MD/H740;6>, <http://links.lww.com/MD/H742;7>, <http://links.lww.com/MD/H744>).

3.5. Outcome of GRADE rating

Table 3 for details.

3.6. Efficacy of ginseng oral administration and ginseng injections on CRF

Fatigue was reported in 22 studies and 10 were excluded because of heterogeneity. Of included 12 studies, ginseng was used in 5 studies and ginseng injections in 7. The number of patients in the ginseng group is 656 and 646 in control. Efficacy was assessed between 2 weeks and 12 weeks. The pooled SMD was 0.40 (95% confidence interval (95% CI) [0.29–0.51],  $P < .00001$ ) (Fig. 4). If heterogeneity was not taken into account, the pooled SMD was 0.89 (95% CI [0.60–1.18],  $P < .00001$ ) (Fig. S4, <http://links.lww.com/MD/H740>). Those indicate that ginseng can alleviate CRF.

3.7. Network meta-analysis between ginseng oral administration and ginseng injections

Network meta-analysis to compare the relative efficacy of ginseng oral administration and ginseng injections was done (Fig. 5 and Table 4). The order was ginseng injections, ginseng oral administration and placebo from high efficacy to low.

Table 2

Outcome of meta-regression.

Oral and injectable ginseng for CRF	
SMD	P > t
Mode of administration	.556
Ginseng/ginseng extract	.733
Oral/different injections	.334
Types of ginseng	.697
Cancer types	.783
Basic strategies for treatment of cancer.	.381
With or without placebo	.041
Measurement tools	.201
Mode of administration	.556
Injectable ginseng for CRF	
Different injections	.523
Types of ginseng	.396
Duration of treatment	.685
Cancer types	.298
Basic strategies for treatment of cancer	.989
With or without hormone	.543
Measurement tools	.149

CRF = cancer-related fatigue.

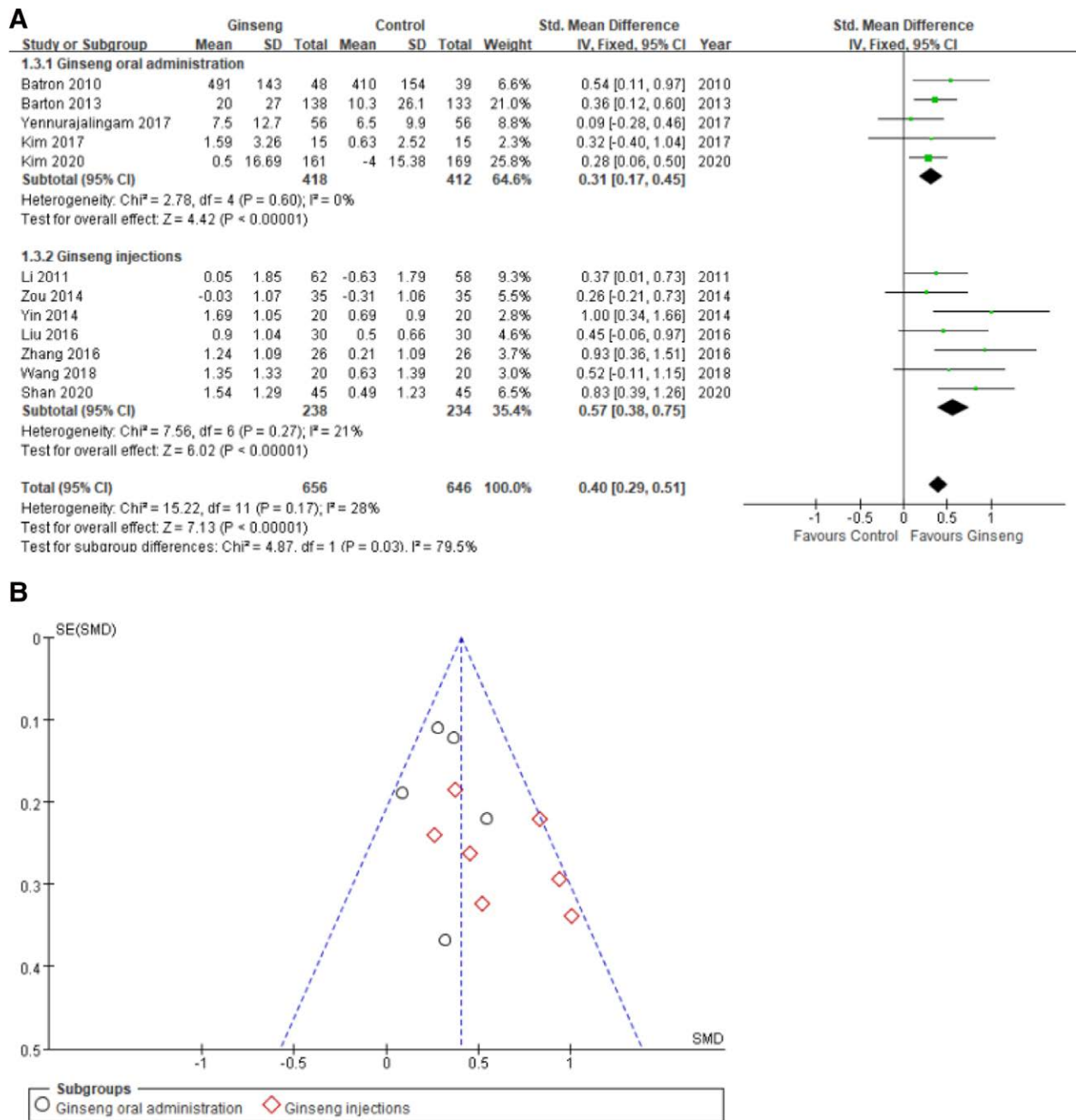
**Table 3**  
Outcome of GRADE rating.

	Certainty assessment										Effect	Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Relative Absolute (95% CI)	Effect		
<b>Ginseng oral administration and ginseng injections</b>	22	randomized trials	not serious	serious <sup>*</sup>	not serious	not serious	none	1063	1023	-	SMD <b>0.89 higher</b> (0.6 higher to 1.18 higher)	⊕⊕⊕○ Moderate
<b>Ginseng oral administration for CRF</b>	7	randomized trials	not serious	not serious	not serious	not serious	none	468	454	-	SMD <b>0.46 higher</b> (0.1 higher to 0.82 higher)	⊕⊕⊕⊕ High
<b>Ginseng injections for CRF</b>	15	randomized trials	not serious	serious <sup>*</sup>	not serious	not serious	none	595	569	-	SMD <b>1.08 higher</b> (0.73 higher to 1.44 higher)	⊕⊕⊕○ Moderate
<b>Ginseng oral administration and ginseng injections for emotional fatigue</b>	10	randomized trials	not serious	serious <sup>*</sup>	not serious	not serious	none	500	484	-	SMD <b>0.67 higher</b> (0.13 higher to 1.21 higher)	⊕⊕⊕○ Moderate
<b>Ginseng oral administration for emotional fatigue</b>	3	randomized trials	not serious	not serious	not serious	not serious	none	228	215	-	SMD <b>0.34 lower</b> (1.12 lower to 0.43 higher)	⊕⊕⊕⊕ High
<b>Ginseng injections for emotional fatigue</b>	7	randomized trials	not serious	serious <sup>*</sup>	not serious	not serious	none	272	269	-	SMD <b>1.12 higher</b> (0.5 higher to 1.74 higher)	⊕⊕⊕○ Moderate
<b>Ginseng oral administration and ginseng injections for cognitive fatigue</b>	8	randomized trials	not serious	serious <sup>*</sup>	not serious	not serious	none	410	402	-	SMD <b>0.8 higher</b> (0.31 higher to 1.29 higher)	⊕⊕⊕○ Moderate
<b>Ginseng oral administration for cognitive fatigue</b>	1	randomized trials	not serious	very serious <sup>†</sup>	not serious	not serious	none	138	133	-	SMD <b>0.04 SD lower</b> (0.28 lower to 0.2 higher)	⊕⊕⊕○ Low
<b>Ginseng injections for cognitive fatigue</b>	7	randomized trials	not serious	serious <sup>*</sup>	not serious	not serious	none	272	269	-	SMD <b>0.93 higher</b> (0.44 higher to 1.42 higher)	⊕⊕⊕○ Moderate

CI = confidence interval, CRF = cancer-related fatigue, SMD = standardized mean difference.

<sup>\*</sup>There was substantial heterogeneity among studies, meta-regression and sensitivity analyses of each outcome were conducted but we didn't find the sources of heterogeneity.

<sup>†</sup>Small sample size and wide confidence interval.



**Figure 4.** Efficacy of ginseng oral administration and ginseng injections on CRF. CRF: cancer-related fatigue.

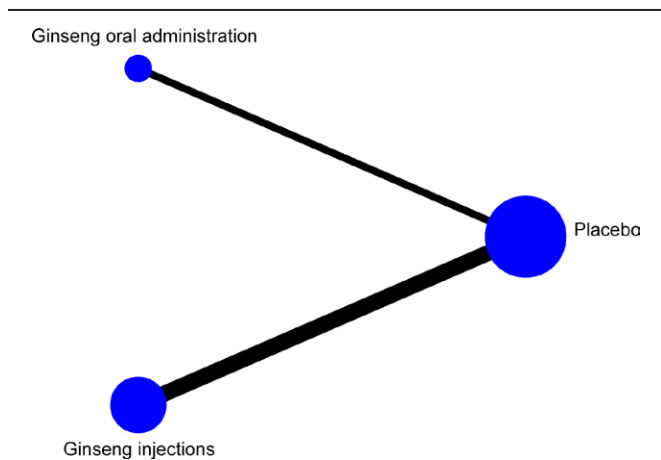
**3.8. Efficacy of ginseng oral administration on CRF**

Seven papers reported the efficacy of ginseng oral administration on CRF and 1 was excluded because of heterogeneity.<sup>[16]</sup> Six studies included 862 patients, 434 received ginseng and 428 received placebo.<sup>[5,15,19–22]</sup> Efficacy was assessed between 29 days and 12 weeks. The pooled SMD was 0.29 (95% CI [0.15–0.42], *P* < .0001) (Fig. 6). If heterogeneity was not taken into account, the pooled SMD was 0.46 (95% CI [0.10–0.82], *P* = .01) (Fig. S5, <http://links.lww.com/MD/H741>). Those indicate that ginseng oral administration can alleviate CRF.

Efficacies of different doses were explored. Sixteen patients were treated with 1000mg/day ginseng and 16 with placebo in 1 study.<sup>[20]</sup> The pooled SMD was -0.29 (95% CI [-0.98 to 0.41], *P* = .42). Three hundred and forty-seven patients were treated with 2000mg/d ginseng and 341 with placebo in 3

studies.<sup>[5,15,19]</sup> The pooled SMD was 0.35 (95% CI [0.19–0.50], *P* < .00001). Fifteen patients were treated with 3000mg/d ginseng and 15 with placebo in 1 study.<sup>[21]</sup> The SMD was 0.32 (95% CI [-0.40 to 1.04], *P* = .38). Those indicate that 2000 or 3000mg/d ginseng should be effective to treat CRF. There is no significant difference between 3000mg/d ginseng group and control group and that might be due to the small sample size (Fig. 7). Network meta-analysis to compare the relative efficacy of different doses was done. The order was 2000mg/d, 3000mg/d, placebo and 1000mg/d from high efficacy to low. But there was no significant difference (Fig. 8 and Table 5).

Efficacies of different duration were also explored. One hundred and six patients, 52 in ginseng group and 54 in control, were treated for 2 weeks in 1 study.<sup>[22]</sup> The SMD was 0.10 (95% CI [-0.28 to 0.48], *P* = .62). Four hundred and twelve patients, 203 in ginseng group and 209 in control, were treated



**Figure 5.** Network of 2 types of administration routes on CRF. CRF: cancer-related fatigue.

**Table 4**  
**Network meta-analysis between ginseng oral administration and ginseng injections.**

Fatigue reduction		
Placebo	Ginseng-injections	Ginseng-oral-administration
-1.09 (-1.46, -0.71)	0.61 (-0.04, 1.26)	
-0.47 (-1.01, 0.06)		

SMD for comparisons are in the cell in common between the column-defining and row-defining treatment. SMD < 0 favors row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

SMD = standardized mean difference.

for 4 weeks in 2 study.<sup>[5,22]</sup> The pooled SMD was 0.20 (95% CI [0.00–0.39],  $P = .05$ ). Seven hundred and twenty patients, 363 in ginseng group and 357 in control, were treated for 8 weeks in 4 study.<sup>[5,15,19,20]</sup> The pooled SMD was 0.32 (95% CI [0.17–0.46],  $P < .0001$ ). Thirty patients, 15 in ginseng group and 15 in control, were treated for 12 weeks in 1 study.<sup>[21]</sup> The SMD was 0.32 (95% CI [-0.40 to 1.04],  $P = .38$ ). Three hundred and thirty patients, 161 in ginseng group and 169 in control, were treated for 16 weeks in 1 study. The SMD was 0.24 (95% CI [0.02–0.45],  $P = .03$ ). It seems that 4 to 8 weeks is enough for ginseng oral administration to alleviate CRF (Fig. 9).

**3.9. Efficacy of ginseng injections on CRF**

Four types of injections (Kangai injection, Shenfu injection, Shenmai injection and Shenqi Fuzheng injection) whose main components are ginseng extractions have been approved by Chinese National Medical Products Administration to be

used in clinic. Fifteen studies reported these 4 on CRF and 5 papers were excluded because of heterogeneity.<sup>[17,18,23–25]</sup> Three hundred and forty-four patients were in the ginseng injection group and 338 in the control group. Efficacy was assessed between 2 weeks and 16 weeks. The pooled SMD was 0.74 (95% CI [0.59–0.90],  $P < .00001$ ) (Fig. 10). If heterogeneity was not taken into account, the pooled SMD was 1.08 (95% CI [0.73–1.44],  $P < .00001$ ) (Fig. S6, <http://links.lww.com/MD/H742>). Those indicate that ginseng injections can alleviate CRF.

Efficacies of the 4 types of injections were also explored, respectively. The SMD of Kangai injection, Shenfu injection, Shenmai injection or Shenqi Fuzheng injection was 1.12 (95% CI [0.67–1.58],  $P < .00001$ ), 1.54 (95% CI [-0.79 to 3.87],  $P = .20$ ), 1.02 (95% CI [0.71–1.33],  $P < .00001$ ), 1.00 (95% CI [0.42–1.57],  $P = .0007$ ), respectively (Fig. S6, <http://links.lww.com/MD/H742>). Those indicate that Kangai injection, Shenmai injection or Shenqi Fuzheng injection can alleviate CRF.

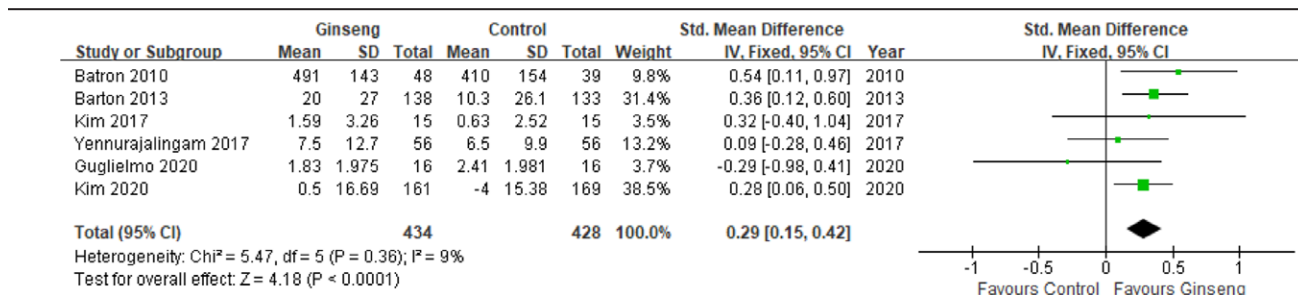
**3.10. Efficacy of ginseng oral administration and ginseng injections on emotional fatigue**

Ten studies reported the efficacy of ginseng oral administration or ginseng injections on emotional fatigue and 6 were excluded because of heterogeneity.<sup>[7,16,18,23,26,27]</sup> The number of patients in the experimental group was 286 and 277 in the control group. The pooled SMD was 0.12 (95% CI [-0.04 to 0.29],  $P = .15$ ) (Fig. 11). If heterogeneity was not taken into account, the pooled SMD was 0.67 (95% CI [0.13–1.21],  $P = .02$ ) (Fig. S7, <http://links.lww.com/MD/H744>). It seems that whether ginseng could alleviate emotional fatigue is uncertain.

Ginseng oral administration was employed in 3 studies and 1 study was excluded because of heterogeneity.<sup>[16]</sup> The pooled SMD was 0.10 (95% CI [-0.10 to 0.30],  $P = .32$ ) (Fig. 11). If heterogeneity was not taken into account, the pooled SMD was -0.34 (95% CI [-1.12 to 0.43],  $P = .38$ ) (Fig. S7, <http://links.lww.com/MD/H744>). Those indicate that ginseng oral administration may not alleviate emotional fatigue.

Seven studies explored efficacies of ginseng injections on emotional fatigue and 3 were excluded because of heterogeneity. The pooled SMD of the 4 studies was 0.79 (95% CI [0.55–1.03],  $P < .00001$ ) (Fig. 12). If heterogeneity was not taken into account, the pooled SMD was 1.12 (95% CI [0.50–1.74],  $P = .0004$ ) (Fig. S8, <http://links.lww.com/MD/H749>).<sup>[7,18,23,26–29]</sup> Those results suggest that ginseng injections may be effective in alleviating emotional fatigue.

Efficacies of the 3 types of injections were also explored, respectively. The SMD of Shenfu injection, Shenmai injection or Shenqi Fuzheng injection was 1.16 (95% CI [-0.98 to 3.30],  $P = .29$ ), 0.84 (95% CI [0.53–1.14],  $P < .00001$ ), 1.34 (95% CI [0.13–2.55],  $P = .03$ ), respectively (Fig. S8, <http://links.lww.com/MD/H749>). Those indicate that Shenmai injection or Shenqi Fuzheng injection can alleviate emotional fatigue.



**Figure 6.** Forest plot of ginseng oral administration on CRF. CRF: cancer-related fatigue.



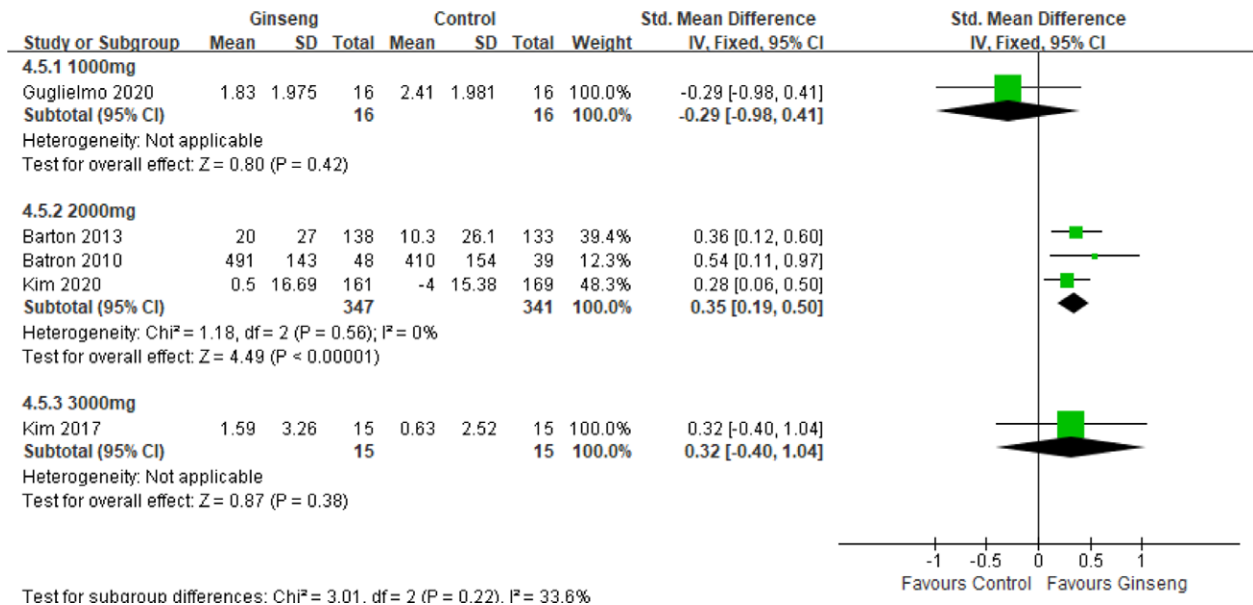


Figure 7. Forest plot of different doses of ginseng oral administration on CRF. CRF: cancer-related fatigue.

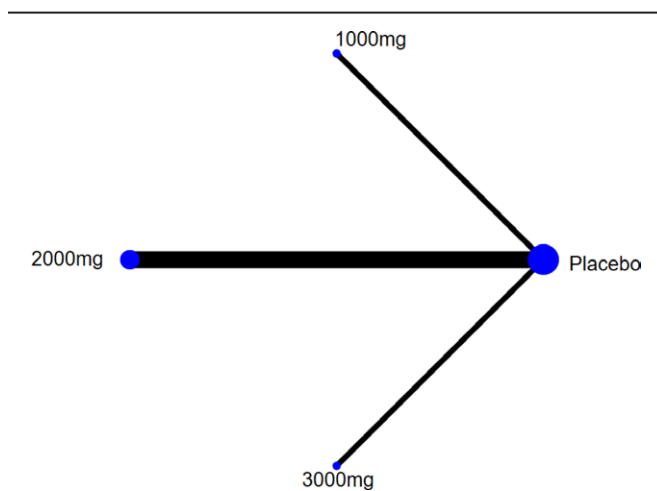


Figure 8. Network of different doses of ginseng oral administration on CRF. CRF: cancer-related fatigue.

**Table 5**  
Network meta-analysis of different dose.

Fatigue reduction			
Placebo			
-0.32 (-1.04, 0.40)	3000 mg		
-0.35 (-0.50, -0.19)	-0.02 (-0.76, 0.71)	2000 mg	
-0.29 (-0.41, -0.98)	0.61 (-0.40, 1.61)	0.63 (-0.08, 1.34)	1000 mg

SMD for comparisons are in the cell in common between the column-defining and row-defining treatment. SMD < 0 favors row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

SMD = standardized mean difference.

**3.11. Efficacy of ginseng oral administration and ginseng injections on cognitive fatigue.**

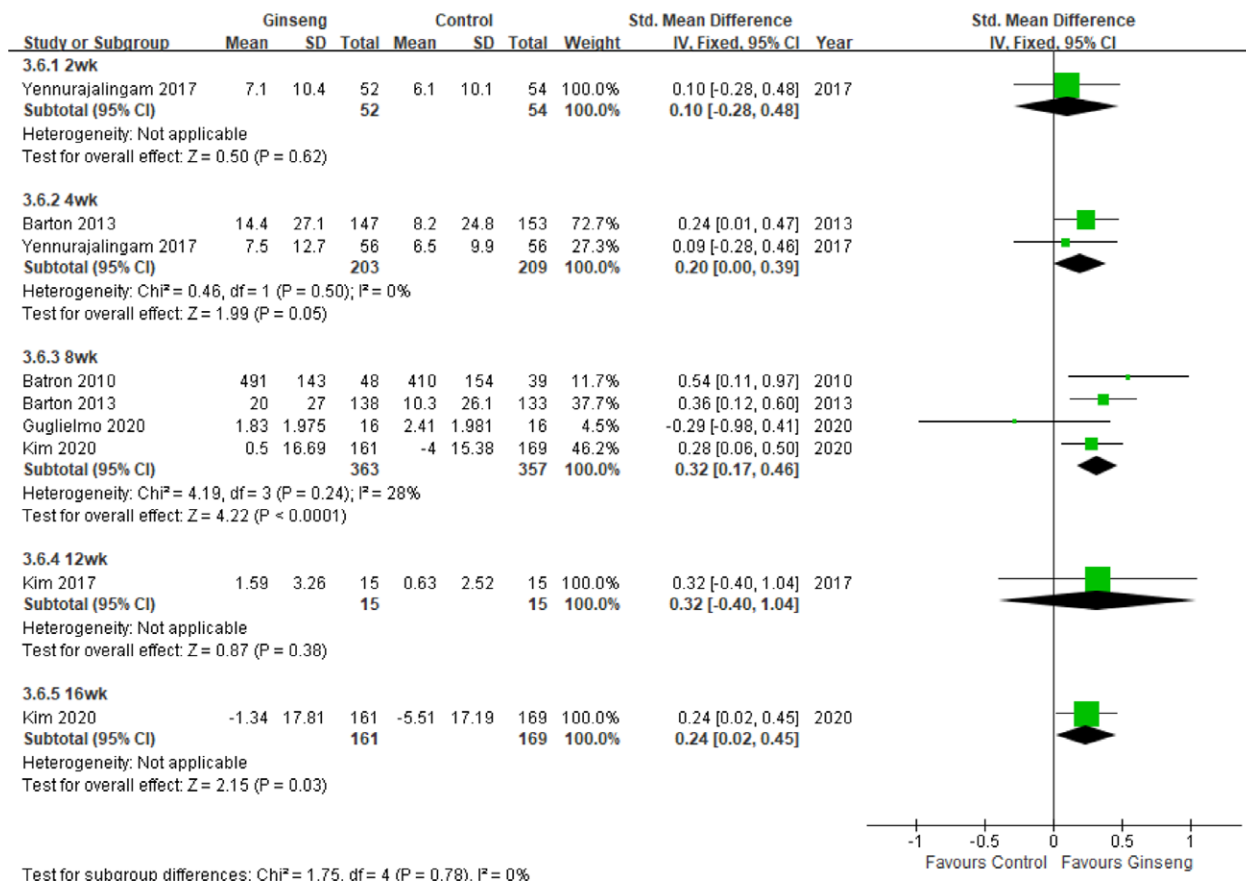
Cognitive fatigue is a psychological state characterized by the subjective feelings of tiredness, and impaired ability to think,

memorize, and concentrate.<sup>[30,31]</sup> Cognitive fatigue is strongly associated with CRF. Eight studies reported the efficacy of ginseng oral administration and ginseng injections on cognitive fatigue. Four studies, 1 on ginseng oral administration and 3 on ginseng injections, were excluded because of heterogeneity.<sup>[5,18,23,29]</sup> Finally, 4 studies on ginseng injections were included. The pooled SMD was 0.72 (95% CI [0.48–0.96], P < .00001) (Fig. 13). If heterogeneity was not taken into account, the pooled SMD of all 8 studies was 0.80 (95% CI [0.31–1.29], P = .001) (Fig. S9, <http://links.lww.com/MD/H750>) and the pooled SMD of 7 studies on ginseng injections was 0.93 (95% CI [0.44–1.42], P = .0002) (Fig. S10, <http://links.lww.com/MD/H751>).<sup>[7,16,17,23,26,27,29,32]</sup> Ginseng oral administration was employed in 1 study and the SMD was -0.04 (95% CI [-0.28 to 0.20], P = .76) (Fig. S9, <http://links.lww.com/MD/H750>). Taking together, those results suggest that ginseng injections may be effective in alleviating cognitive fatigue while ginseng oral administration may not be beneficial to cognitive fatigue relieving.

Efficacies of the 3 types of injections were also explored, respectively. The SMD of Shenfu injection, Shenmai injection or Shenqi Fuzheng injection was 0.79 (95% CI [-0.50 to 2.09], P = .23), 0.83 (95% CI [0.53–1.14], P < .00001), 1.13 (95% CI [0.00–2.25], P = .05), respectively (Fig. S10, <http://links.lww.com/MD/H751>). Those indicate that Shenmai injection or Shenqi Fuzheng injection can alleviate cognitive fatigue.

**3.12. The effect of cancer types on efficacy of ginseng and ginseng injections on CRF**

CRF may associate with cancer types.<sup>[16]</sup> The effect of cancer types on efficacy of ginseng on CRF was explored here. Nine studies evaluated the efficacy of ginseng on the treatment of lung cancer.<sup>[7,16,17,23,24,26,27,29,32]</sup> Of the total 725 participants, 519 had undergone chemotherapy prior to participation, 245 were non-small cell lung cancer patients, 86 were lung adenocarcinoma patients and 425 were advanced lung cancer patients. If heterogeneity was not taken into account, those results supported the benefit of Red ginseng, Kangai injection, Shenfu injection, Shenmai injection and Shenqi Fuzheng injection on fatigue relief. Those results support CRF improvement of ginseng injections



**Figure 9.** Forest plot of different duration of ginseng oral administration on CRF. CRF: cancer-related fatigue.

on lung cancer including the pathological types of non-small cell lung cancer, and TNM staging of advanced lung cancer. At the same time, ginseng may also benefit patients with colorectal cancer and nasopharyngeal carcinoma, and may have little effect on patients with head and neck cancer (Table 6).

### 3.13. Incidences of treatment-related adverse events between different drugs and cancer types

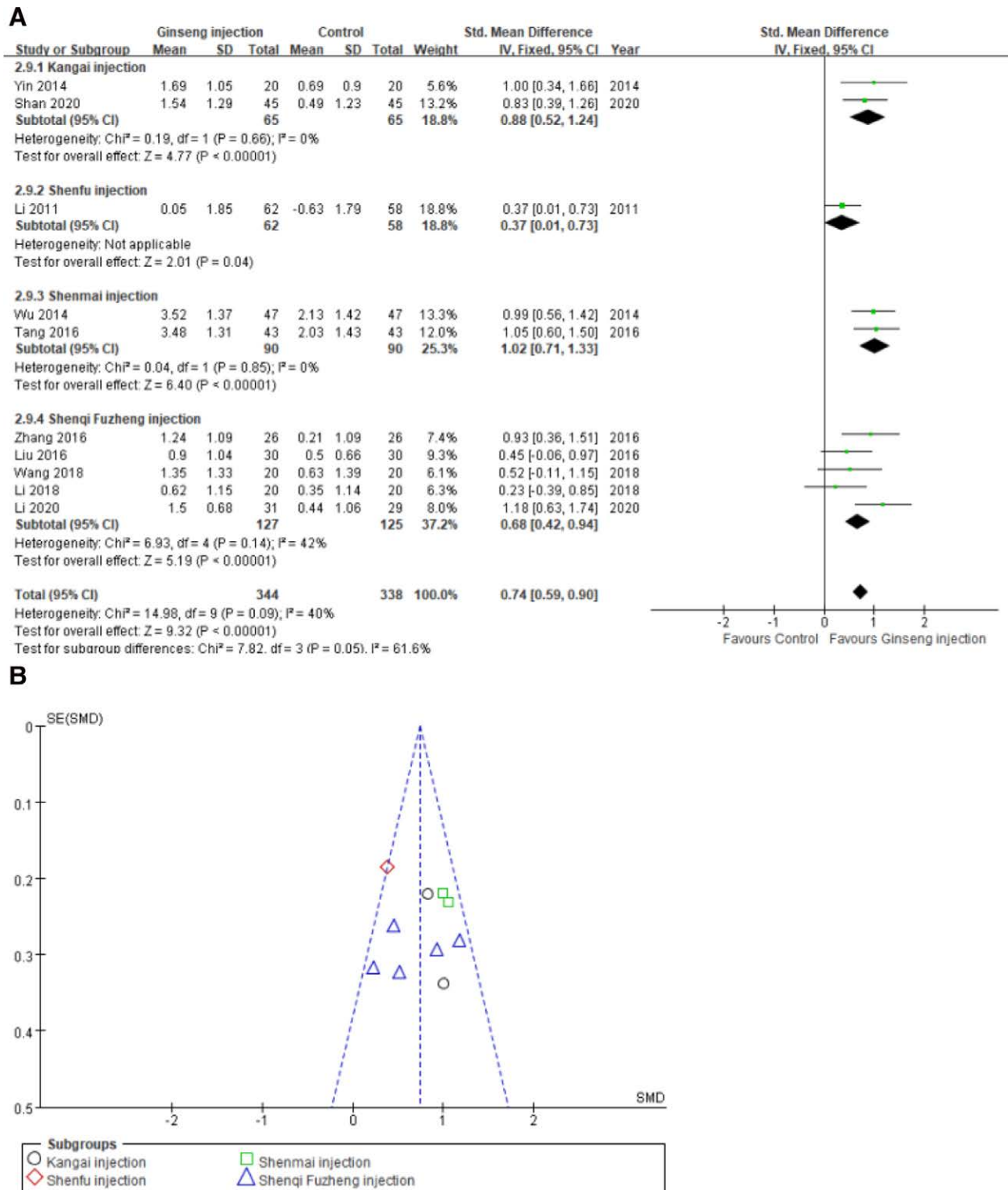
Adverse events were collected and summarized in Table 7. It seems that ginseng has no discernible adverse reactions.

## 4. Discussion

Panax ginseng root is widely used in Asia owing to its therapeutic anti-oxidative, immunomodulatory properties as well as other numerous pharmacologic activities. It has a good safety profile and minor incidence of adverse effects.<sup>[33]</sup> In China, ginseng has been used to treat chronic fatigue as early as 2000 years ago. Several meta-analyses and systematic reviews focusing on the efficacy of ginseng on fatigue were published recently and they reported that ginseng benefits fatigue, such as chronic fatigue syndrome, idiopathic chronic fatigue, physical fatigue in human beings and animals.<sup>[34,35]</sup> At the same time, the number of studies focusing on efficacy of ginseng on CRF is growing. Several types of injections whose main components are ginseng extractions have been approved by Chinese National Medical Products Administration to treat patients. Therefore, hundreds of papers focusing on ginseng on CRF were written in Chinese. Here, we conducted a meta-analysis of papers written in Chinese and in English to evaluate the efficacy of ginseng and ginseng injections in the treatment of CRF.

The primary outcome was the effect of ginseng and ginseng injections in alleviating CRF. SMD was employed here because clinical indices to assess CRF differed among studies. The data indicate that ginseng treatment, including oral administration and injection, yield benefits CRF whether heterogeneity taken into account (SMD = 0.40; 95% CI [0.29–0.51],  $P < .00001$ ) or not (SMD = 0.89; 95% CI [0.60–1.18],  $P < .00001$ ). Several other drugs have been found to be effective in CRF. Methylphenidate may be accepted more widely and be recommended more frequently. But the results of several trials indicated that methylphenidate, compared with placebo, may not improve CRF.<sup>[36,37]</sup> Dr Moraska et al conducted a randomized, double-blind, placebo-controlled study but did not find evidence that methylphenidate improved the primary end point of CRF.<sup>[36]</sup> Dr Centeno's paper indicated that methylphenidate was not more efficient than placebo to treat CRF.<sup>[37]</sup> Among 22 included studies on ginseng/ginseng injections, results of 21 showed or showed a trend that there was a reduction in CRF in the ginseng/ginseng injections group compared with the control group. Those concordantly indicate that ginseng is effective to treat CRF. So, it seems that ginseng is a promising drug to alleviate CRF.

Emotional fatigue or/and cognitive fatigue is an important part of CRF. Ten papers explored efficacy of ginseng on emotional fatigue. If heterogeneity not taken into account, data supported the conclusion that ginseng could alleviate emotional fatigue (SMD = 0.67; 95% CI [0.13–1.21],  $P = .02$ ). But if heterogeneity taken into account, the data show a trend that ginseng might alleviate emotional fatigue (SMD = 0.12; 95% CI [-0.04 to 0.29],  $P = .15$ ). Efficacy of ginseng on cognitive fatigue was also explored and the data indicated that ginseng injections can alleviate cognitive fatigue whether heterogeneity taken into account (SMD = 0.72; 95% CI [0.48–0.96],  $P < .00001$ ) or not



**Figure 10.** Efficacy of ginseng injections on CRF. CRF: cancer-related fatigue.

(SMD = 0.93; 95% CI [0.44–1.42], *P* = .0002). So, ginseng can alleviate CRF and might be beneficial to treat emotional fatigue or/and cognitive fatigue. At the same time, several papers suggested that the combination treatment of ginseng/ginseng injections and methylphenidate or dexamethasone showed potential clinical benefit in CRF without discernible associated toxicities.<sup>[23,38]</sup>

Two types of administration routes were included in this study: oral and intravenous injection. Maybe it's because that the efficacy of intravenous injection is faster than oral administration, ginseng injections have other ingredients besides ginseng, the results of network meta-analysis showed that

intravenous injection was better. But there was no evidence that ginseng oral administration, as compared with placebo, could improve emotional fatigue whether heterogeneity taken into account (SMD = 0.10; 95% CI [-0.10 to 0.30], *P* = .32) or not (SMD = -0.34; 95% CI [-1.12 to 0.43], *P* = .38). It is similar for cognitive fatigue (SMD = -0.04; 95% CI [-0.28 to 0.20], *P* = .76).

Four types of injections, Kangai injection, Shenqi fuzheng injection, Shenfu injection and Shenmai injection whose main components are ginseng extractions, have been used in clinic in China. The pooled SMD of the 4 injections indicates that

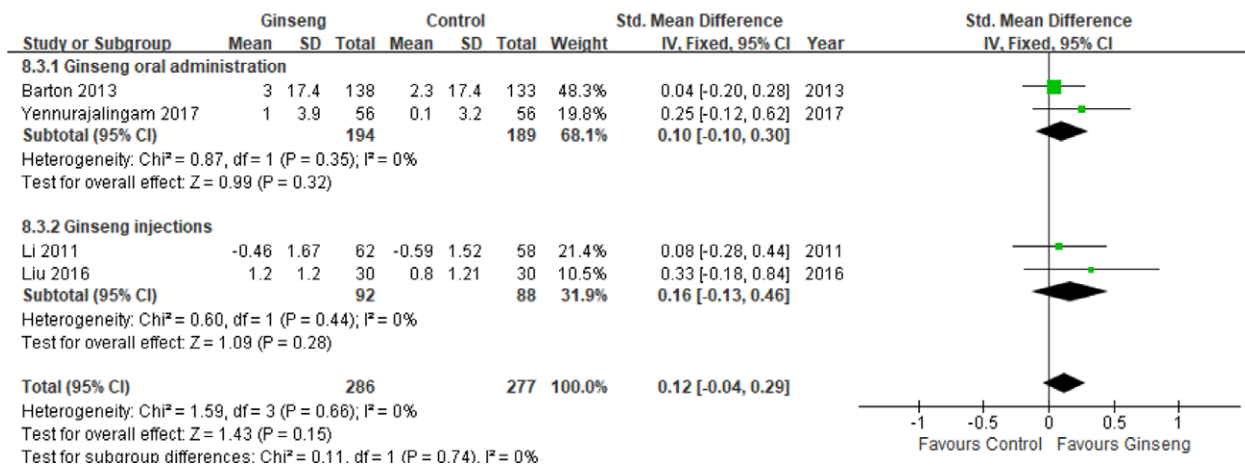


Figure 11. Forest plot of ginseng oral administration and ginseng injections on emotional fatigue.

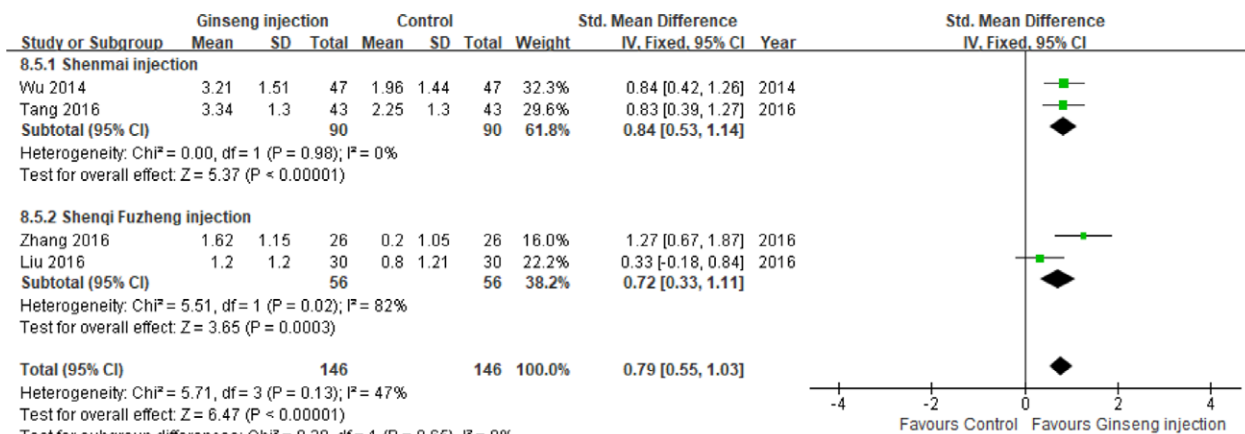


Figure 12. Forest plot of ginseng injections on emotional fatigue.

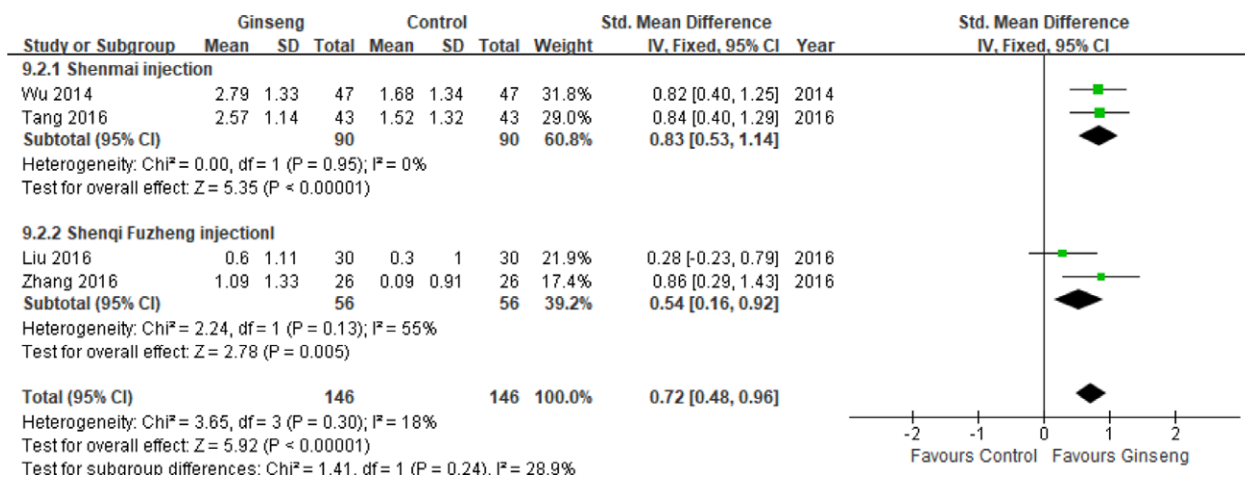


Figure 13. Forest plot of ginseng injections on cognitive fatigue.

ginseng injections are effective in alleviating CRF and cognitive fatigue whether heterogeneity taken into account or not. Data supported that each type of injections may alleviate CRF. Besides, Shenmai injection and Shenqi fuzheng injection may be effective to alleviate both emotional fatigue and cognitive fatigue. Cancer types were taken into account in some of the included papers focusing on ginseng injections, hence the effect

of cancer types on efficacy was meta-analyzed here. It seems that ginseng injections could alleviate CRF caused by non-small cell lung cancer, colorectal cancer, malignant melanoma and nasopharyngeal carcinoma (Table 6). Therefore, ginseng injections can alleviate CRF and may be beneficial to treat emotional fatigue and cognitive fatigue, particularly caused by some types of cancer. Due to limited studies, it is unknown whether ginseng

**Table 6**  
**Efficacy of ginseng and ginseng injections on CRF alleviating by various factors.**

Factors	No. of trails	Total number	SMD(95%CI)	P value	Heterogeneity I <sup>2</sup> (%)	Model used
Fatigue						
Types of drugs						
Ginseng	7	922	0.46 (0.10–0.82)	.01	83%	Random-effects
Kangai injection	3	220	1.12 (0.67–1.58)	<.00001	58%	Random-effects
Shenfu injection	2	183	1.54 (–0.79 to 3.87)	.20	97%	Random-effects
Shenmai injection	2	180	1.02 (0.71–1.33)	<.00001	0%	Fixed-effects
Shenqi fuzheng injection	8	581	1.00 (0.42–1.57)	.0007	90%	Random-effects
Major constituent						
American ginseng	3	390	0.35 (0.15–0.55)	.0007	50%	Fixed-effects
Red ginseng	7	783	1.08 (0.51–1.66)	.0002	92%	Random-effects
Panax ginseng	4	332	0.85 (0.19–1.50)	.01	87%	Random-effects
Codonopsis radix	8	581	1.00 (0.42–1.57)	.0007	90%	Random-effects
Dose of intervention						
Ginseng						
1000 mg/d						
2000 mg/d	1	32	–0.29 (–0.98 to 0.41)	.42		
3000 mg/d	3	688	0.35 (0.19–0.50)	<.00001	0%	Fixed-effects
Duration of intervention						
Ginseng						
2 wk	1	106	0.10 (–0.28 to 0.48)	.62		
4 wk	2	412	0.20 (0.00–0.39)	.05	0%	Fixed-effects
8 wk	4	720	0.32 (0.17–0.46)	<.0001	28%	Fixed-effects
12 wk	1	30	0.32 (–0.40 to 1.04)	.38		
16 wk	1	330	0.24 (0.02–0.45)	.03		
Tumor types						
Lung cancer						
Total	9	725	1.16 (0.71–1.61)	<.00001	87%	Random-effects
Non-small cell cancer	4	245	1.49 (0.38–2.59)	.008	93%	Random-effects
Lung adenocarcinoma	1	86	1.05 (0.60–1.50)	<.00001		
Advanced lung cancer	6	425	1.31 (0.68–1.94)	<.0001	88%	Random-effects
Ginseng	1	60	2.08 (1.44–2.72)	<.00001		
Kangai injection	2	180	1.17 (0.48–1.86)	.0009	78%	Random-effects
Shenfu injection	2	183	1.54 (–0.79 to 3.87)	.20	97%	Random-effects
Shenmai injection	2	180	1.02 (0.71–1.33)	<.00001	0%	Fixed-effects
Shenqi fuzheng injection	2	122	0.57 (–0.08 to 1.23)	.09	68%	Random-effects
Ovarian cancer	1	30	0.32 (–0.40 to 1.04)	.38		
Gastric cancer	2	106	1.48 (–0.41 to 3.37)	.12	94%	Random-effects
Colon cancer	1	330	0.28 (0.06–0.50)	.01		
Head and neck cancer	1	32	–0.29 (–0.98 to 0.41)	.42		
Nasopharyngeal carcinoma	1	40	1.00 (0.34–1.66)	.003		
Brest cancer	1	40	0.23 (–0.39 to 0.85)	.47		
Treatment						
Lung cancer						
Chemotherapy						
Total	7	579	1.23 (0.65–1.81)	<.0001	90%	Random-effects
Kangai injection	2	180	1.17 (0.48–1.86)	.0009	78%	Random-effects
Shenfu injection	2	183	1.54 (–0.79 to 3.87)	.20	97%	Random-effects
Shenmai injection	1	86	1.05 (0.60–1.50)	<.00001		
Shenqi fuzheng injection	1	70	0.26 (–0.21 to 0.73)	.28		
Emotional Fatigue						
Types of drugs						
Ginseng	3	443	–0.34 (–1.12 to 0.43)	.38	92%	Random-effects
Shenfu injection	2	183	1.16 (–0.98 to 3.30)	.29	97%	Random-effects
Shenmai injection	2	180	0.84 (0.53–1.14)	<.00001	0%	Fixed-effects
Shenqi fuzheng injection	3	178	1.34 (0.13–2.55)	.03	92%	Random-effects
Cognitive fatigue						
Types of drugs						
Ginseng	1	271	–0.04 (–0.28 to 0.20)	.76		
Shenfu injection	2	183	0.79 (–0.50 to 2.09)	.23	93%	Random-effects
Shenmai injection	2	180	0.83 (0.53–1.14)	<.00001	0%	Fixed-effects
Shenqi fuzheng injection	3	178	1.13 (0.00–2.25)	.05	92%	Random-effects

can alleviate CRF caused by other types of cancer. Future rigorous clinical trials and published results will provide deeper insight.

Besides inherent limitations of individual trials, there are limitations to our analyses. First, different types of studies were

included. There are great differences in doses, duration, routes of administration, types of drugs among studies. Those make a great risk of bias in the implementation of the meta-analysis. Second, the sample size in each trial is small. Most of them were about 100. Consequently, confidence levels were very wide and

**Table 7**  
**Adverse events.**

First author (yr)	Type of ginseng	Side effects	Grade	Incidence rate (%)	
				Intervention	Control
Barton et al (2010)	American ginseng	Agitation	2–3	2	0
		Anxiety	2–3	4	5
		Insomnia	2–3	8	10
		Nausea	2–3	13	7
		Vomiting	2–3	5	10
Barton et al (2013)	American ginseng	Agitation	2–3	1	2
		Anxiety	2–3	2	3
		Insomnia	2–3	6	7
		Nausea	2–3	3	2
		Vomiting	2–3	1	1
Kim et al (2017)	Red ginseng	Nausea	1	6.7	13.3
		Insomnia	1	6.7	6.7
		Palpitation	1	6.7	0
		Headache	1	6.7	13.3
		Urticaria	1	6.7	6.7
		Total		13.3	20
Shulong Jiang (2017)	Red ginseng	Leukopenia	1–4	18	62
		Thrombocytopenia	1–4	18	50
		Decreased hemoglobin	1–4	18	12
		Nausea and/or vomiting	1–4	26	81
		Diarrhea	1–4	24	23
		Alopecia	1–4	38	38
		Liver damage	1–4	21	23
		Renal dysfunction	1–4	15	19
		Neurotoxicity	1–4	21	46
		Nausea	>0	28	31
		Decreased appetite	>0	18	15
Kim et al (2020)	Red ginseng	Neutropenia	>0	19	10
		Diarrhea	>0	14	13
		Aspartate	>0	11	11
		aminotransferase increase			
		Alanine	>0	12	10
		aminotransferase increase			
		Fatigue	>0	9	9
		Constipation	>0	9	7
		Thrombocytopenia	>0	8	1
		Peripheral neuropathy	>0	15	19
		Leukopenia	>0	8	4
		Insomnia	>0	6	5
		Dyspepsia	>0	6	5
		Stomatitis	>0	4	5
		Cough	>0	5	5
		Headache	>0	7	2
		Vomiting	>0	6	3
		Upper respiratory tract infection	>0	6	2
		Yennurajalingam et al (2017)	Panax ginseng extract	Allergic reaction	3–5
Appendicitis	3–5			0	2
Dyspnea	3–5			0	2
Fatigue	3–5			0	3
Hyperglycemia	3–5			0	2
Hypokalemia	3–5			0	2
Infections and infestations	3–5			2	0
Lung infection	3–5			0	2
Thrombotic Thrombocytopenic purpura	3–5			0	2
Total	3–5			2	15
Yibing Feng (2014)	Shenfu injection			Myelosuppression	>0
		Gastrointestinal reaction	>0	22.58	34.38
		Cardiovascular side effects	>0	6.45	25.00
		Fatigue	>0	12.90	43.75
		Abnormal liver function	>0	9.68	21.88
Xiaomu Tang (2016)	Shenmai injection	Skin reaction	>0	16.13	18.75
		Leukopenia	>0	60.47	90.70
		Thrombocytopenia	>0	69.76	88.37
Jianbing Luo (2019)	Shenqi Fuzheng injection	Gastrointestinal reaction	>0	69.76	90.70
		fever	-	1.87	5.81
		lethargy	-	2.80	6.98
		Stomatitis	-	0.93	0.65

there was a great variability. Third, there are great differences in cancer types, stages, basic strategies for treatment of cancer. Some trials even enrolled several types of cancer in different stages. Some patients were at stage III to VI, some were cancer survivors who remained free of disease. Some were treated with chemotherapy, radiotherapy or others, some were not. Because CRF is associated with cancer types, stages and basic strategies for treatment of cancer (for example, chemotherapy, radiotherapy),<sup>[2,16]</sup> those confounders play a role in CRF and affect the efficacy of ginseng treatment more or less. Fourth, clinical indices to assess clinical response differed among studies. Brief Fatigue Inventory, Multidimensional Fatigue Symptom Inventory–Short Form, Fatigue Symptom Inventory, Piper Fatigue Scale, et al were employed in different trials. Though those correlate with each other and have been well accepted to assess CRF, little variability among studies might be unavoidable. Fifth, the methodological quality and quality of evidence of the literature included in this study were rated low (Table 3). Although our findings support the effectiveness of ginseng and ginseng injections in the treatment of CRF, the GRADE approaches were rated low. Sixth, some database, such as Web of Science, et al, were not included in the databases searched because we do not have access.

## 5. Conclusion

Ginseng, ginseng oral administration or ginseng injections, may improve CRF. Intravenous injection might be better than oral administration. It seems that ginseng injections may alleviate cognitive fatigue. No evidence was found to support that ginseng could alleviate emotional fatigue. More high-quality randomized, double-blind, placebo-controlled studies with homogeneous samples, large sample sizes, fixed protocol are warranted to identify effectiveness of ginseng on CRF caused by specific type of cancer.

## Author contributions

**Data curation:** Tianwen Hou, Jing Huang.

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**Project administration:** Shijiang Sun.

**Resources:** Xueqi Wang.

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**Supervision:** Jianming He.

**Validation:** Xi Liang, Haiyan Bai.

**Visualization:** Tianhe Zhao, Jingnan Hu, Jianli Ge.

**Writing – original draft:** Huijing Li.

**Writing – review & editing:** Jianming He.

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