Original Article

Efficacy and safety of methylphenidate and ginseng in cancer-related fatigue: a network meta-analysis of randomized controlled trials

Huijing Li[1#], Kaimeng Che[1#], Zheng Zhi[1], Wenzhong Xu[1], Jing Huang[1], Xueqi Wang[1], Xi Liang[1], Tianhe Zhao[1], Jingnan Hu[1], Tianwen Hou[1], Shijiang Sun[1], Jianming He[1,2]

[1]Department of Radiotherapy, Hebei Province Hospital of Chinese Medicine, Hebei University of Chinese Medicine, Shijiazhuang, China; [2]Key Laboratory of Integrated Chinese and Western Medicine for Gastroenterology Research (Hebei), Shijiazhuang, China

Contributions: (I) Conception and design: J He, S Sun; (II) Administrative support: J He, S Sun; (III) Provision of study materials or patients: H Li, K Che; (IV) Collection and assembly of data: H Li, K Che; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jianming He. Department of Radiotherapy, Hebei Province Hospital of Chinese Medicine, Hebei University of Chinese Medicine, Shijiazhuang 050011, China. Email: hjmlovelx@hotmail.com; Shijiang Sun. Department of Radiotherapy, Hebei Province Hospital of Chinese Medicine, Hebei University of Chinese Medicine, Shijiazhuang 050011, China. Email: 173655069@qq.com.

Background: Incidence of cancer-related fatigue (CRF), which can persist 5 to 10 years, is nearly 85% in cancer patients. It severely affects the quality of life and is strongly associated with poor prognosis. As clinical trial data on CRF treated with methylphenidate and ginseng, two potential medicines, has been accumulating, an updated meta-analysis was performed to evaluate and compare the efficacy and safety of the two medicines in CRF.

Methods: Randomized controlled trials that investigated methylphenidate or ginseng in the treatment of CRF were identified through a literature search. The primary outcome was CRF relief. Standardized mean difference (SMD) was used to analyze the effect.

Results: Eight studies on methylphenidate were included and the pooled SMD was 0.18 [95% confidence interval (95% CI): −0.00 to 0.35, P=0.05]. Five studies on ginseng were included and the SMD was 0.32 (95% CI: 0.17–0.46, P<0.0001). Results of network meta-analysis showed that the order was ginseng, methylphenidate, placebo from high efficacy to low and ginseng was significantly better than methylphenidate (SMD =0.23, 95% CI: 0.01–0.45). Incidences of insomnia and nausea caused by ginseng were significantly lower than those caused by methylphenidate (P<0.05).

Conclusions: Both methylphenidate and ginseng can significantly ameliorate CRF. Ginseng may be superior to methylphenidate because ginseng may be more effective and might cause less adverse events. Head-to-head trials with fixed protocol are warranted to identify the optimal medical strategy.

Keywords: Methylphenidate; ginseng; cancer-related fatigue (CRF); meta-analysis

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Introduction

Cancer-related fatigue (CRF) is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer/cancer treatment that is not proportional to recent activity and interferes with usual functioning (1). Approximately 62% to 90% of patients suffer from CRF when they are diagnosed with cancer, during or after cancer treatment (2). CRF can

persist five to ten years after diagnosis and/or treatment (3,4). Alvarez-Bustos found that even among breast cancer survivors who were deemed as completely recovered from the cancer, the prevalence of fatigue interfering with quality of life was 43% (5). CRF is also strongly associated with poor prognosis, at least in some types of cancer, such as colorectal cancer and endometrial cancer (6). However, CRF has been underestimated, as some clinicians overlook CRF. This may be partly due to the lack of satisfactory treatment (4).

Methylphenidate, a psychostimulant, is a widely known medicine to treat CRF, whereas the results are mixed. A few papers reported that methylphenidate might lessen CRF in adult cancer survivors and improve cognitive impairment and social functioning in children brain tumors patients (7,8). However, Butler *et al.* found that prophylactic use of methylphenidate in brain tumor patients undergoing radiation therapy did not result in an improvement in CRF (9). In 2020, a clinical trial reported by Centeno showed that methylphenidate may not reduce CRF compared to a placebo (10).

Ginseng was used to improve chronic fatigue as early as 2000 years ago. In the last two decades, some clinical trials focusing on the efficacy of ginseng in CRF were reported. Barton *et al.* reported in 2013 that the fatigue symptom of CRF patients was improved following treatment with 2000mg of Wisconsin ginseng (3). In 2020, two clinical trials which had been independently conducted were reported and they consistently concluded that ginseng should be beneficial to CRF (11,12). Thus, ginseng may appear to be a promising medicine to treat CRF.

As clinical trial data on CRF treated with methylphenidate and ginseng has been accumulating, an updated meta-analysis was performed to evaluate the efficacy and safety of methylphenidate and ginseng. The two medicines were also compared in the study with the use of a network meta-analysis. We present the following article in accordance with the PRISMA-NMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2303/rc).

Highlight box

Key findings

- Both methylphenidate and ginseng can significantly ameliorate CRF.
- Ginseng may be superior to methylphenidate.

What is known and what is new?

- Methylphenidate and ginseng are potential medicines for the treatment of CRF.
- Ginseng is more effective and cause less adverse events than methylphenidate.

What is the implication, and what should change now?

- Ginseng could be used in clinic to treat CRF because it is effective and safe.

Methods

Literature search

PubMed, Cochrane Library were systematically searched to identify published studies from the database inception to November 13, 2021. The following search terms were used: (methylphenidate or ginseng or ginsengs or *P. quinquefolius* or Panax or ginsenosides or ginsenoside) AND (fatigue or lethargy or exhaustion or tiredness or weariness or physical performance or exercise performance) in any fields.

Study selection

The main purpose of this study was to assess the efficacy and safety of ginseng and methylphenidate in CRF. Studies met the following criteria were included: randomized and placebo-controlled trials investigated methylphenidate or ginseng in the treatment of CRF. The treatment duration, types and stages of cancer were unlimited. Studies with ginseng extract, studies without enough data or studies without placebo in the control group were excluded from the analysis.

Data extraction and quality assessment

Two authors independently selected eligible studies based on the predetermined criteria. If any discrepancies were found, a third author adjudicated. The following data were extracted from the final included studies: types of cancer, cancer treatment protocols, dosage of methylphenidate or ginseng in the intervention group, treatment duration, etc. The literature quality was evaluated according to Cochrane Handbook 5.1.0. using Review Manager 5.3 (13,14). Wherever feasible, sensitivity analyses were undertaken to assess the robustness of our findings by excluding studies with high risk of bias.

Statistical analysis

RevMan 5.3 was used to analyze the effect of randomized treatment while STATA v.16.0 was used for network meta-

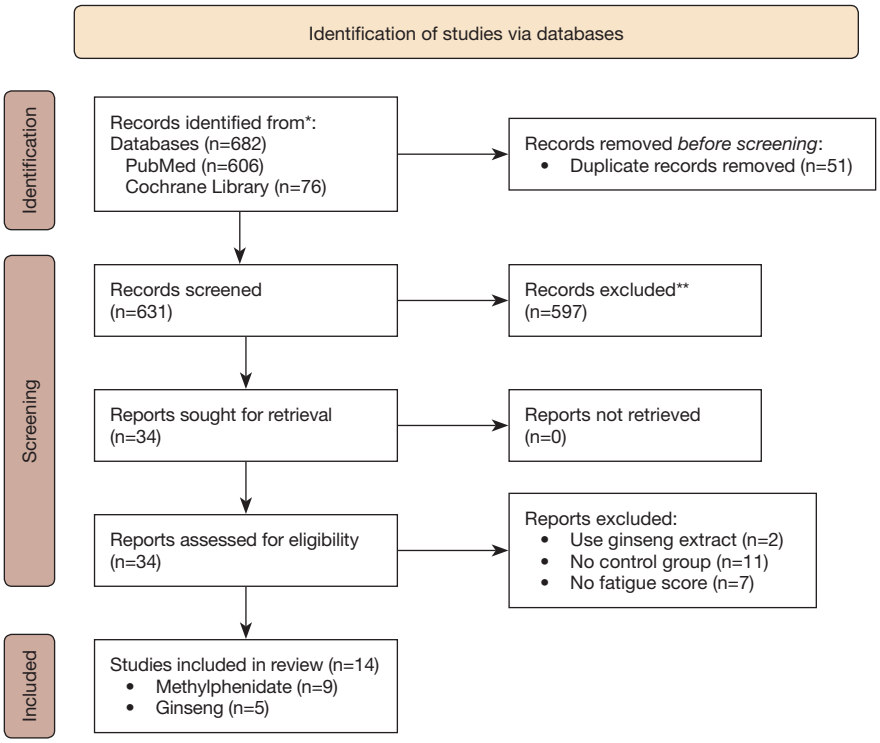

Figure 1 Flow chart. *, consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **, if automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. From: Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

analysis. Cochran's Q test and test of heterogeneity were used to test the heterogeneity. When P<0.10 and I^2>50%, it indicated that there was significant heterogeneity among the studies and a random-effects model was used; otherwise, a fixed-effects model was used. SMD was used as a main effect size and the calculation formula was as follows: SMD = (M1–M2)/pooled SD. Where M1 was the mean of fatigue reduction in the intervention group, M2 was the mean of fatigue reduction in the control group, and pooled SD was a pooled intervention specific standard deviation. When the value of SMD was positive and P<0.05, it indicated that the effect of the intervention group was better than the control group.

Results

Trial characteristics

A total of 682 studies were identified from the two electronic databases. Fifty-one duplicate studies were excluded by using Endnote X9. On review of the title and abstract, 597 studies were excluded. After further careful review of 34 articles of the full text, a further 20 studies were excluded. Finally, 14 papers, nine on methylphenidate and five on ginseng were included (*Figure 1*). They were published between 2006 and 2020 and all were randomized, placebo-controlled trials. The detailed information is summarized in *Table 1*.

Risk of bias assessment for individual randomized controlled trials (RCTs) is shown in Figures S1,S2. And the 14 RCTs were at low risk of bias.

Efficacy of methylphenidate in CRF

Nine RCTs assessed the efficacy of methylphenidate and one was excluded after sensitivity analysis (17) (Figure S3). Eight studies included 498 patients, of whom 252 received methylphenidate and 246 received placebo (9,10,15,16,18-21). Efficacy was assessed between 6 days and 12 weeks. The pooled SMD was 0.18 (95% CI: −0.00 to 0.35, P=0.05) (*Figure 2*). The results suggest that methylphenidate may

Table 1 Characteristics of studies included

Author	Year	Country	Study design	Cancer types of participants	Treatment	Intervention	Duration of treatment	Measurement tools
Bruera *et al.* (15)	2006	USA	Randomized, placebo-controlled	No limit	Surgery and chemoradiotherapy	Methylphenidate 5 mg/2 h (maximum of 20 mg/day)	8 days	FACIT-F
Butler *et al.* (9)	2007	USA	Randomized, double-blind, placebo-controlled	Brain tumor	Radiation therapy	D-threo-methylphenidate 5 mg bid (maximum of 15mg bid)	12 weeks	FACIT-F
Mar Fan *et al.* (16)	2008	Australia	Randomized, double-blind, placebo-controlled	Breast cancer	Chemotherapy	D-methylphenidate 5 mg bid	2 weeks	FACT-F
Lower *et al.* (17)	2009	USA	Randomized, double-blind, placebo-controlled	No limit	Chemotherapy	D-methylphenidate 5 mg bid	8 weeks	FACIT-F
Moraska *et al.* (18)	2010	USA	Randomized, double-blind, placebo-controlled	No limit	Surgery and chemoradiotherapy	Methylphenidate 18–54 mg/day	4 weeks	BFI
Roth *et al.* (19)	2010	USA	Randomized, double-blind, placebo-controlled	Prostate cancer	Surgery and chemoradiotherapy	Methylphenidate 5–10 mg/day (maximum 30 mg/day)	6 weeks	BFI
Bruera *et al.* (20)	2013	USA	Randomized, double-blind, placebo-controlled	No limit	Surgery and chemoradiotherapy	Methylphenidate 5 mg/2 h maximum 20 mg/day + NTI (nursing telephone intervention)	8/15 days	FACIT-F
Richard *et al.* (21)	2015	Canada	Randomized, double-blind, placebo-controlled	Prostate cancer	Hormone	Methylphenidate 5 mg/day for the first 2 weeks followed by 10 mg/day for 8 weeks. 5 mg/day for the last 2 weeks of therapy	6/10 weeks	FACT-F
Centeno *et al.* (10)	2020	Spain	Randomized, double-blind, placebo-controlled	No limit	Surgery and chemoradiotherapy	Methylphenidate 10–25 mg/day	6 days	FACT-F
Barton *et al.* (22)	2010	USA	Randomized, double-blind, placebo-controlled	No limit	Surgery and chemoradiotherapy	American ginseng 2,000 mg/day	8 weeks	BFI
Barton *et al.* (3)	2013	USA	Randomized, multisite, double-blind, placebo-controlled	No limit	Surgery and chemoradiotherapy	American ginseng 2,000 mg/day	4/8 weeks	MFSI-SF
Guglielmo *et al.* (11)	2020	Italy	Randomized, double-blind, placebo-controlled	Head and neck cancer	Surgery and chemoradiotherapy	American ginseng 1,000 mg/day	8 weeks	BFI
Kim *et al.* (23)	2017	Korea	Randomized, double-blind, placebo-controlled	Epithelial ovarian cancer	Surgery and chemotherapy	Red ginseng 3,000 mg/day	12 weeks	BFI
Kim *et al.* (12)	2020	Korea	Randomized, double-blind, parallel, multi-center, placebo-controlled	Colon cancer	Surgery and chemotherapy or palliative therapy	Red ginseng 2,000 mg/day	8/16 weeks	FACIT-F

BFI, brief fatigue inventory; FACT-F, functional assessment of cancer therapy-fatigue; FACIT-F, functional assessment of chronic illness therapy-fatigue subscale; MFSI-SF, multidimensional fatigue symptom inventory-short form.

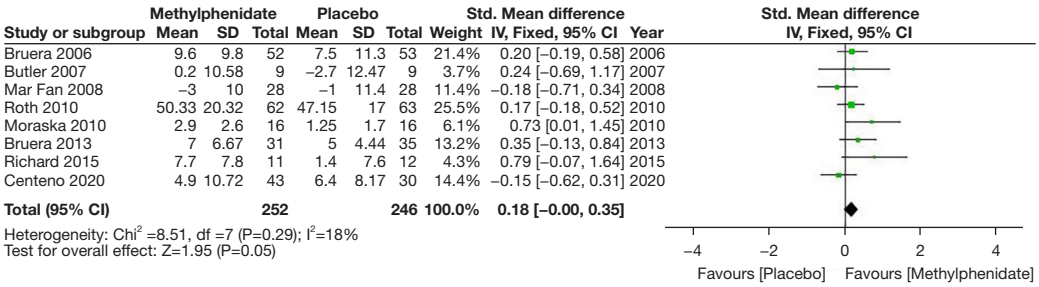

Figure 2 Efficacy of methylphenidate on CRF. CRF, cancer-related fatigue.

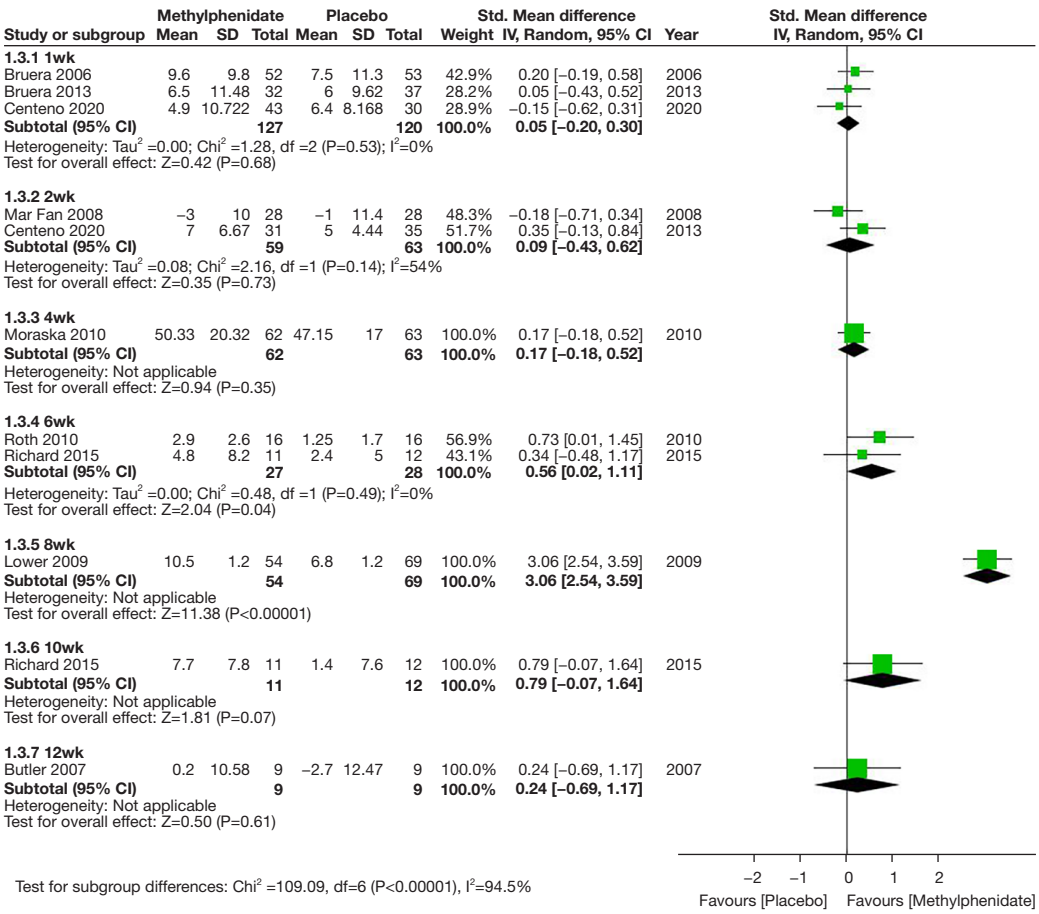

Figure 3 Efficacy of different durations of methylphenidate on CRF. CRF, cancer-related fatigue.

ameliorate CRF.

Efficacy of different durations were explored (*Figure 3*). SMDs for 1, 2, 4, 6, 8, 10 and 12 weeks were 0.05 (95% CI: −0.20 to 0.30, P=0.68), 0.09 (95% CI: −0.43 to 0.62, P=0.73), 0.17 (95% CI: −0.18 to 0.52, P=0.35), 0.56 (95% CI: 0.02–1.11, P=0.04), 3.06 (95% CI: 2.54–3.59, P<0.00001), 0.79 (95% CI: −0.07 to 1.64, P=0.07) and 0.24 (95% CI: −0.69 to 1.17, P=0.61), respectively. The results suggest that 6- to 8-weeks treatment may be significantly effective.

Efficacy of ginseng in CRF

Five papers reported the efficacy of ginseng in CRF. Five studies included 750 patients, of whom 378 received

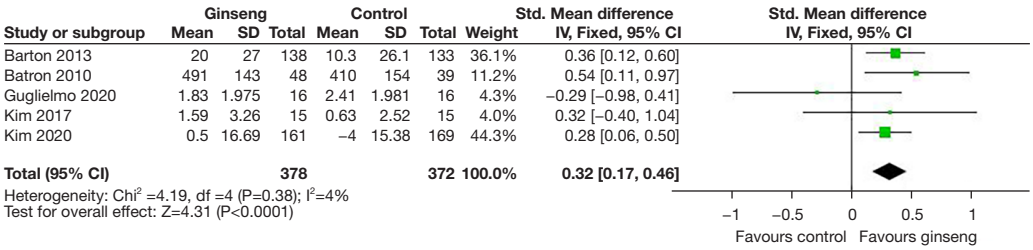

Figure 4 Efficacy of ginseng on CRF. CRF, cancer-related fatigue.

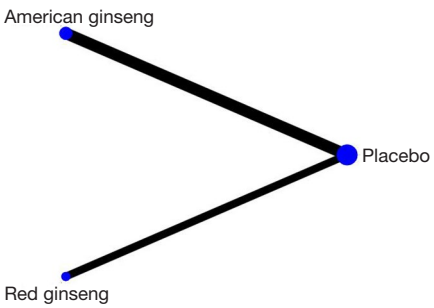

Figure 5 Network of different types of ginseng on CRF. The size of nodes and the thickness of edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively. CRF, cancer-related fatigue.

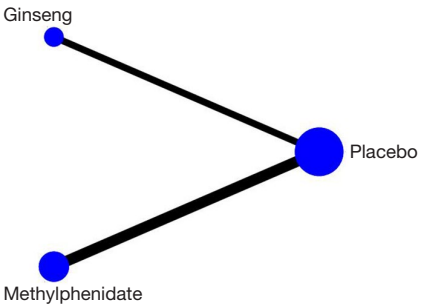

Figure 6 Network of methylphenidate and ginseng on CRF. The size of nodes and the thickness of edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively. CRF, cancer-related fatigue.

Table 2 Network meta-analysis of ginseng types

Insomnia	Placebo		
	−0.35 (−0.55, −0.15)	American ginseng	
	−0.28 (−0.49, −0.08)	0.07 (−0.22, 0.35)	Red ginseng

Comparisons should be read from left to right. SMD for comparisons are in the cell in common between the column-defining and row-defining treatment. SMD <0 favours row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

ginseng and 372 received placebo (3,11,12,22,23). Efficacy was assessed between 8 and 12 weeks. The pooled SMD was 0.32 (95% CI: 0.17–0.46, P<0.0001) (*Figure 4*).

Efficacy of different ginseng types were explored using Network meta-analysis. The order was American ginseng, red ginseng and placebo from high efficacy to low (*Figure 5* and *Table 2*).

Network analysis of methylphenidate and ginseng in CRF

Network meta-analysis was employed to compare relatively efficacy of methylphenidate and ginseng. The order was ginseng, methylphenidate, placebo from high efficacy to low and ginseng was significantly better than methylphenidate (*Figure 6*, *Table 3*).

Incidences of treatment-related adverse events caused by methylphenidate or ginseng

Adverse events were collected and summarized in *Table 4*. Insomnia and nausea were two main adverse events. They were compared using network meta-analysis. The incidence of insomnia or nausea from high to low was methylphenidate, placebo, ginseng (*Figures 7,8*, *Tables 5,6*).

Discussion

Unlike typical fatigue, CRF cannot be relieved by having

Table 3 Network meta-analysis of methylphenidate and ginseng

Fatigue reduction	Placebo		
	−0.32 (−0.46, −0.17)	Ginseng	
	−0.09 (−0.25, 0.08)	0.23 (0.01, 0.45)	Methylphenidate

Comparisons should be read from left to right. SMD for comparisons are in the cell in common between the column-defining and row-defining treatment. SMD <0 favours row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

additional rest, sleep, reducing physical activity, etc. As far as the current evidence is concerned, pharmacologic interventions are far from satisfaction. Several psychostimulants, for example, methylphenidate and modafinil, have been used to treat CRF but they remain controversial. Methylphenidate has conventionally been one of the mainstays of psychostimulants for CRF. It has been used to treat CRF for over 30 years and has been recommended by the National Comprehensive Cancer Network CRF panel. Unfortunately, results of clinical trials are not consistent. Some support that methylphenidate is effective in treating CRF while others do not indicate so. Results of this updated meta-analysis indicate that methylphenidate should be effective to treat CRF (SMD =0.18; 95% CI: −0.00 to 0.35, P=0.05). Even so, results of two did not favor methylphenidate with a relatively large sample size (n=73, 56) (10,16). There are great differences in dosage, duration, cancer treatment protocols, the patient population (different cancer types, stages, etc.), and so on. All those downgrade the quality of evidence.

Panax ginseng has been shown to have a variety of pharmacological activities, including anti-inflammatory, antioxidant, and anticancer effects. Substantial objective evidence supports that ginseng may be helpful for fatigue with mild and reversible adverse effects (24,25). At the same time, a growing body of clinical studies focusing on the efficacy of ginseng in CRF are published. Results of this updated meta-analysis of four articles indicate that ginseng can ameliorate CRF (SMD =0.32; 95% CI: 0.17–0.46, P<0.0001). In addition, results of three out of five articles found that ginseng significantly ameliorates CRF; results of one found that ginseng has a trend to ameliorate CRF; only results of one does not favor ginseng with a small sample size (n=32, P=0.42). These upgrade the quality of evidence.

However, to our knowledge, no article compared methylphenidate and ginseng in CRF. So, a network meta-analysis was conducted to compare the efficacy and safety of the two medicines. The order was ginseng, methylphenidate, placebo from high efficacy to low and ginseng was significantly better than methylphenidate (SMD =0.23, 95% CI: 0.01–0.45). A number of studies have established the safety of ginseng (3,22,26). Insomnia and nausea are the two main adverse events. Results showed that the incidence of insomnia or nausea from high to low was methylphenidate, placebo, ginseng, which means ginseng's adverse events rate may be as low as placebo, if not lower. Collectively, those demonstrate that ginseng may be superior to methylphenidate because ginseng may be more effective and might cause less adverse events.

Besides inherent limitations of individual trials, there are limitations to our analyses. First, studies of different interventions were included. For example, the dosage, duration, etc. may influence the efficacy of these two medicines and strongly increase the heterogeneity of the results. Second, only articles in English were included. Ginseng is sold in over 35 countries, with China as the largest consumer. Studies published in other languages might strengthen or weaken our recommendations. Third, most of included studies are with small samples. Thus, the confidence level was very wide and downgraded the quality of evidence. Fourth, studies with different cancer types, stages, cancer treatment protocols were included. In our study, some trials enrolled several types of cancer patients; some enrolled patients with advanced cancer; some enrolled survivors who were deemed as completely recovered from cancer; some enrolled patients who were getting cancer treatment and some had already completed it. CRF is a complex symptom that greatly differs across cancer settings. One study showed that the incidence of CRF in patients with breast and colorectal cancer (40% and 33%) was higher than that in prostate cancer (17%) (27). Results from a 1-year longitudinal study showed that fatigue of patients with non-metastatic breast cancer undergoing chemotherapy treatment was significantly higher than cancer-free control participants (28). Therefore, these factors may result in an increased heterogeneity and confound the results of this meta-analysis. Fifth, CRF was measured using four distinct instruments. The disparities in sensitivity and specificity of these four scales may affect the results more or less.

Table 4 Main adverse events

Author	Medicant	Adverse event	Incidence rate (%)	
			Intervention	Control
Bruera *et al.* (15)	Methylphenidate	Insomnia	28.8	26.4
		Restlessness	17.3	20.8
		Anorexia	21.2	15.1
Butler *et al.* (9)	D-threo-methylphenidate	Nausea and vomiting	3	0
		Tachycardia	0	1.5
		Increased liver enzymes	1.5	0
Mar Fan *et al.* (16)	D-methylphenidate	Insomnia	1.7	0
		Anxiety	1.7	0
		Dizziness	1.7	1.7
Lower *et al.* (17)	D-methylphenidate	Insomnia	18.4	10.3
		Nausea	27.6	7.7
		Headache	40.8	33.3
Roth *et al.* (19)	Methylphenidate	Increased blood pressure	31	0
		Tachycardia	6	0
Bruera *et al.* (20)	Methylphenidate	Insomnia	18.1	33.3
		Nausea	0	8.3
		Pain	27.2	25
		Mood alteration (depression or anxiety)	18.1	8.3
Richard *et al.* (21)	Methylphenidate	Insomnia	11.8	17.6
		Nausea	5.9	11.8
		Joint pain	23.5	41.2
		Mood alterations	17.6	0
Barton *et al.* (22)	American ginseng	Insomnia	8	10
		Nausea	13	7
		Vomiting	5	10
Barton *et al.* (3)	American ginseng	Insomnia	6	7
		Nausea	3	2
		Anxiety	2	3
Kim *et al.* (23)	Red ginseng	Insomnia	6.7	6.7
		Nausea	6.7	13.3
		Headache	6.7	13.3
Kim *et al.* (12)	Red ginseng	Insomnia	6	5
		Nausea	28	31
		Neutropenia	19	10

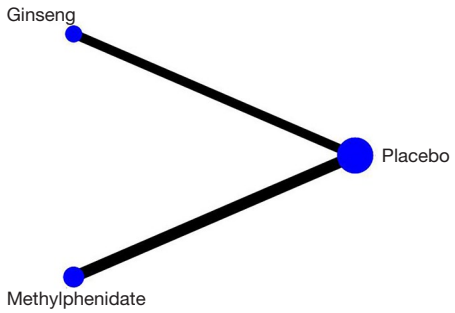

Figure 7 Network of the rate of insomnia. The size of nodes and the thickness of edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively.

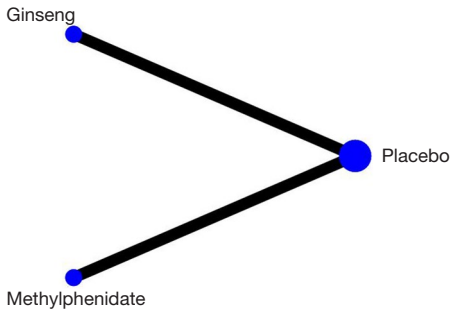

Figure 8 Network of the rate of nausea. The size of nodes and the thickness of edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively.

Table 5 Network meta-analysis of insomnia rate

Insomnia	Placebo		
	0.38 (−0.41, 1.17)	Ginseng	
	−0.09 (−0.91, 0.74)	−0.47 (−1.61, 0.68)	Methylphenidate

Comparisons should be read from left to right. OR for comparisons are in the cell in common between the column-defining and row-defining treatment, OR <0 favour row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

Table 6 Network meta-analysis of nausea rate

Nausea	Placebo		
	0.21 (−0.49, 0.91)	Ginseng	
	−0.93 (−2.18, 0.32)	−1.14 (−2.67, 0.39)	Methylphenidate

Comparisons should be read from left to right. OR for comparisons are in the cell in common between the column-defining and row-defining treatment, OR <0 favour row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

Conclusions

Both methylphenidate and ginseng can significantly ameliorate CRF. Ginseng may be superior to methylphenidate because ginseng may be more effective and might cause less adverse events. Head-to-head trials with fixed protocol are warranted to identify the optimal medical strategy.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-NMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2303/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2303/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

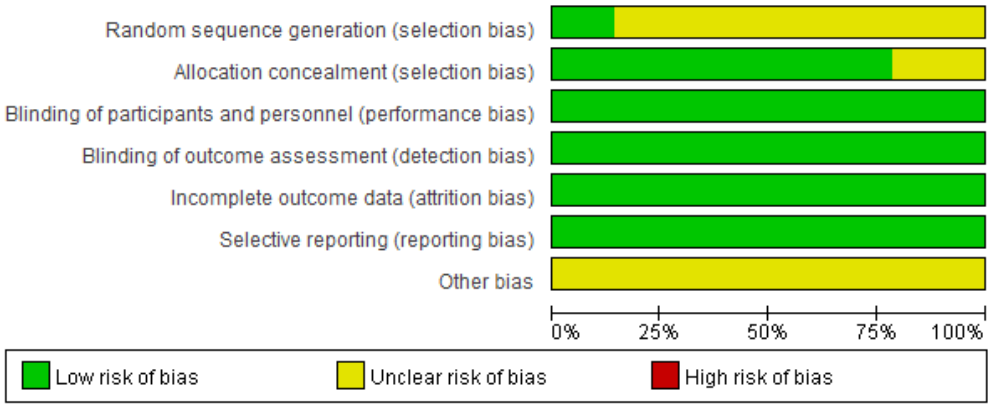

Figure S1 Risk of bias summary.

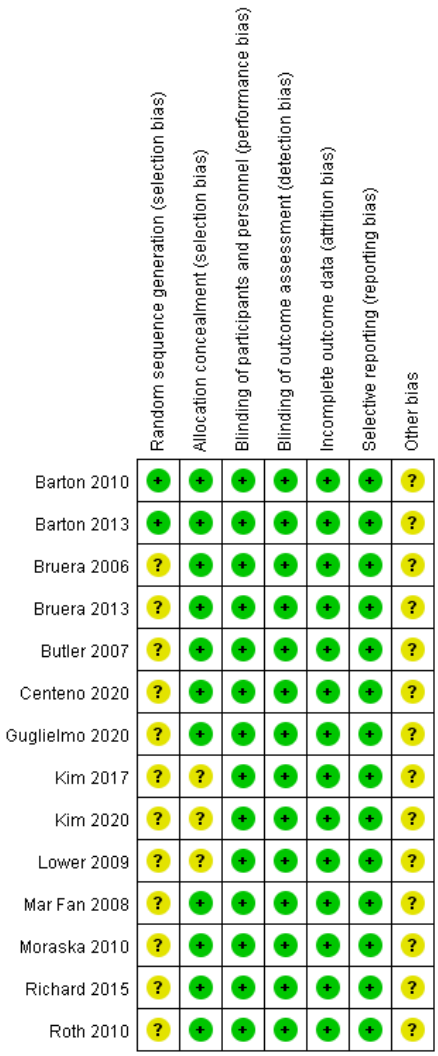

Figure S2 Risk of bias graph.

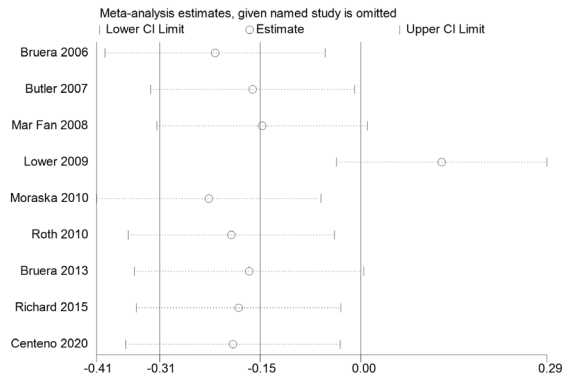

Figure S3 Sensitivity analysis of methylphenidate.

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