REVIEW ARTICLES

Ginseng as a Treatment for Fatigue: A Systematic Review

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Abstract

Background: Millions of people with chronic illness suffer from fatigue. Fatigue is a complex, multidimensional symptom with poorly understood causes, wide variations in severity among individuals, and negative effects on multiple domains of daily life. Many patients with fatigue report the use of herbal remedies. Ginseng is one of the most widely used because it is believed to improve energy, physical and emotional health, and well-being.

Objective: To systematically review the published evidence to evaluate the safety and effectiveness of the two types of *Panax ginseng* (Asian [*Panax ginseng*] and American [*Panax quinquefolius*]) as treatments for fatigue.

Design: PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), Ovid MEDLINE, and EM-BASE databases were searched using Medical Subject Heading and keyword terms, including ginseng, *Panax*, ginsenosides, ginsenoside* (wild card), fatigue, fatigue syndrome, cancer-related fatigue, and chronic fatigue. Studies were included if participants had fatigue, had used one of the two *Panax ginseng*s as an intervention, and had scores from a self-report fatigue measure. Two reviewers independently assessed each article at each review phase and met to develop consensus on included studies. Risk of bias was assessed using version 5.3 of the Cochrane Collaboration Review Manager (RevMan), and results were synthesized in a narrative summary.

Results: The search strategy resulted in 149 articles, with 1 additional article located through review of references. After titles, abstracts, and full text were reviewed, 139 articles did not meet inclusion criteria. For the 10 studies reviewed, there was a low risk of adverse events associated with the use of ginseng and modest evidence for its efficacy.

Conclusions: Ginseng is a promising treatment for fatigue. Both American and Asian ginseng may be viable treatments for fatigue in people with chronic illness. Because of ginseng's widespread use, a critical need exists for continued research that is methodologically stronger and that includes more diverse samples before ginseng is adopted as a standard treatment option for fatigue.

Keywords: complementary and integrative health, herbal, *Panax*, symptom management

Introduction

MILLIONS OF PEOPLE in the United States experience fatigue as a symptom of chronic illness or as an adverse event (AE) of the treatment of chronic illness, or both.^{1,2} Fatigue is a complex, multidimensional symptom with poorly understood causes, wide variations in severity among indi-

viduals, and negative effects on multiple domains of daily life.³ Negative effects include decreased work productivity, physical activity, social interaction, and recreational activity, as well as feelings of loss and sadness.⁴

Over 32% of the population of the United States uses complementary and alternative medicine,⁵ with ginseng being on the top-10 list of the most-used natural products.⁶ People

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who experience fatigue often report the use of herbal remedies,⁷ and one of the most commonly used is ginseng. Traditional Chinese Medicine and herbal medicine philosophies consider ginseng to be an adaptogen that helps restore balance to the body. Ginseng is believed to improve energy, physical and emotional health, and well-being.^{8–10} In the *Panax* genus (Asian [*Panax ginseng*] and American [*Panax quinquefolius*]), the root is the part of the plant with medicinal properties.

Asian and American ginseng both contain ginsenosides, which are the active compounds believed to act on the central nervous system¹¹ and to have antioxidant¹² and anti-inflammatory properties,⁸ as well as cortisol-modulating effects.⁸ These are some of the reasons why researchers have considered *P. ginseng* to be a potential treatment for fatigue in multiple populations with chronic illness, including cancer survivors, patients with fibromyalgia, and patients with multiple sclerosis. The accepted and studied dosages of *Panax ginseng* range from 500 to 2000 mg.⁸ Knowing whether ginseng is a safe and effective treatment for fatigue in people with physical illness is important for clinicians and patients.

We located one published meta-analysis of the efficacy of ginseng supplements by using our search strategy and limiting it to reviews that assessed ginseng as a treatment for fatigue.¹³ The meta-analysis included 12 randomized controlled trials designed to determine whether ginseng reduced fatigue and improved physical performance. However, the analysis was limited by its broad scope. The studies reviewed included subjects who were not experiencing fatigue or who did not have physical illness, included outcomes based on self-report and physical performance, and combined all results into a single outcome for the analysis. Therefore, we aimed to expand on this work by evaluating the safety and effectiveness of the two types of *Panax ginseng* (*P. ginseng* and *P. quinquefolius*) as treatments for fatigue, focusing only on studies that included fatigued participants with a chronic illness and employed a self-report measure for fatigue, to assess the state of knowledge about the safety and effectiveness of Asian and American ginseng in managing fatigue in people with chronic illness.^{14,15}

Methods

The National Library of Medicine's (NLM) PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), Ovid MEDLINE, and EMBASE databases were searched with no start date limit to April 2016 and limited to English language, clinical trials. The search was conducted using MeSH (Medical Subject Heading) and keyword terms, including ginseng, *Panax*, ginsenosides, ginsenoside* (wild card), fatigue, fatigue syndrome, cancer-related fatigue (CRF), and chronic fatigue (Box 1 includes the detailed search strategy). Studies were included if participants had fatigue, one of the two *Panax ginseng* were used as an intervention, either as a single agent or in combination with other natural products, and scores from self-report measures of fatigue outcomes were reported.

Studies that did not use a self-reported fatigue measure or that included only participants without fatigue (healthy subjects), or both, were excluded because the aim of this review was to assess the impact of ginseng as a treatment for those experiencing fatigue associated with chronic illness.

BOX 1. SEARCH STRATEGY

For the literature search, the following databases were used: the National Library of Medicine's PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), Ovid MEDLINE, and EMBASE. All searches were limited to English language and the following types of studies: clinical trials, controlled clinical trials, randomized controlled trials, meta-analyses, and systematic reviews. The search results were as follows: PubMed, 22 citations; CINAHL, 27 citations; Ovid MEDLINE, an additional 24 citations; and EMBASE, an additional 127 citations—total, 200 citations. All results were put into an EndNote file and 52 duplicate citations were removed, leaving 148 citations.

Subject headings used: *panax ginsenosides*; fatigue; fatigue syndrome, chronic; neoplasms.

Key/text words used: ginseng, ginsenosides, fatigue, chronic fatigue, cancer-related fatigue, cancer.

Additionally, self-reported measures of fatigue aligned with the accepted definition that fatigue is a subjective, multidimensional symptom.^{16,17} Studies that reported results of non-*Panax ginseng* (e.g., Siberian ginseng) were excluded because they have different compositions of active ingredients and do not contain ginsenosides.¹⁸

Results

The search strategy found 149 articles after 52 duplicates were removed, and 1 additional article was located through review of references (Fig. 1). Two assessors (N.M.A. and L.M.N.) independently reviewed each article at each review phase and met to develop consensus on included studies. After reviewing titles and abstracts, 134 articles did not meet inclusion criteria, resulting in 15 articles retrieved for review. Five of the articles retrieved were excluded for not including a *Panax ginseng* (2), not reporting fatigue as an outcome (1), or including only subjects without fatigue (2). Therefore, 10 articles were included in this review (Table 1).^{8,11,12,19–25}

These studies are too heterogeneous to conduct a meaningful meta-analysis (doses, populations, and length of treatment vary widely). This review is not limited to randomized controlled trials or single-agent studies to assess the current state of evidence for ginseng as a treatment for fatigue. Risk of bias was assessed using version 5.3 of the Cochrane Collaboration Review Manager (RevMan), and results were synthesized in a narrative summary categorized by the type of ginseng tested: four American ginseng (*P. quinquefolius*),^{8,19–21} and six Asian ginseng (*P. ginseng*).^{11,12,22–25}

American ginseng (*P. quinquefolius*)

American ginseng is native to Canada and the United States. Four trials evaluated the impact of American ginseng on fatigue.^{8,19–21} One study evaluated the impact of American ginseng within a natural product combination (Immune No. 2) on symptoms, which included fatigue.²¹ Each study used a different fatigue measure, including the Brief Fatigue Inventory, Multidimensional Fatigue Symptom Inventory–Short Form, Fatigue Severity Scale, and the Scores of Symptoms and Signs.^{8,19–21}

FIG. 1. PRISMA flow diagram.

Design

All four American ginseng trials used bias controls, including double-blinding and a placebo.^{8,19–21} Three trials ranged from 8 weeks to 6 months.^{8,19,21} One study was a crossover trial that ran 6 weeks followed by a 2-week wash-out, and then the crossover for an additional 6 weeks.²⁰ Two of the studies had primary aims of evaluating the safety of ginseng and included multiple dosages of ginseng in the trials.^{19,20} Two of the studies included 2000 mg per day as their highest dose of American ginseng,^{8,19} and one study had a maximum dose of 400 mg per day of American ginseng.²⁰ The study testing the Immune No. 2 combination did not include information about the ginseng dose used.²¹

Sample

Three of the four studies were conducted in the United States,^{8,19,20} and one was conducted in China.²¹ The sample consisted of cancer survivors in two studies, patients with multiple sclerosis in one study, and patients with HIV in the combination study. All participants were adults.^{8,19–21} Three studies included only those who reported fatigue for 1 month or more.^{8,19,20} Sample sizes ranged from 56 to 364. One study with 282 participants was described as a pilot study; however, it was powered at 80%, with an effect size of 0.41.¹⁹ The smallest sample ($n=56$) was from a study that employed a crossover design and was powered at 80%, with an effect size of 0.8.²⁰ Three studies included mostly white women.^{8,19,20} One study had mostly male participants (62%).²¹ Attrition ranged from 12% to 39%, with the largest attrition rate occurring in the cancer survivors' pilot study.¹⁹

Safety and efficacy

All dosages of American ginseng were tolerated well, with no serious AEs reported. Three of the four studies showed no

differences in AE rates between the ginseng and placebo groups,^{8,19,21} two of which used 2000 mg of ginseng as the highest dose.^{8,19} None reported serious AEs (i.e., life-threatening events, death, or inpatient hospitalization). AEs reported included nausea, insomnia, headache, rash, and flu-like symptoms.^{8,19,20} All four studies showed improvements in fatigue over time; however, only the 8-week 2000-mg trial and the 6-month American ginseng combination (Immune No. 2) demonstrated significant improvements in the primary fatigue outcome in the intervention group compared with that in the control group.^{8,21} However, the 400-mg trial did show a statistically significant improvement in the real-time digital fatigue scale for those who received ginseng compared with controls, but the study's authors did not believe this result was clinically meaningful.²⁰

Appraisal of the reviewed American ginseng research

Overall, the study designs were strong because they controlled for multiple types of bias (Figs. 2 and 3). Three trials were powered at 80% or greater.^{8,19,20} Three of the four studies demonstrated significant improvements in fatigue in the intervention group compared with the control group.^{8,20,21} One study's authors did not believe their results to be clinically meaningful, but this was difficult to assess because they reported only a combined baseline (intervention and control groups together) fatigue score.²⁰ The valid and reliable digital fatigue scale that tracked self-reported fatigue in real time by using a watch-like device²⁰ has the potential to inform our understanding of fatigue patterns because it provides more data than the traditional self-report approach, which requires participants to think back over days, weeks, or months.

In one study, it was not clear if the fatigue evaluation was valid or reliable, which could undermine the results.²¹ One study completed a per-protocol analysis because two

TABLE 1. CHARACTERISTICS OF INCLUDED STUDIES

Study	Location	Type of ginseng	Daily dose per arm	Diagnosis	N	Gender	Study design	Primary fatigue assessment	Length	Results	Power size	Effect Attrition, %	Reported AEs ^a
Barton et al. ¹⁹	United States	American	Ginseng: 750, 1000, 2000 mg	CRF	282	Women (66%)	Pilot double-blind placebo controlled RCT	Brief Fatigue Inventory	8 Weeks	Nonsignificant findings but data showed decreasing CRF with the use of ginseng at two higher doses.	0.8	0.41	38 Placebo ^b : Grade ≥3, 750 mg, Grade ≥3, 11%, 1000 mg, Grade ≥3, 4%, 2000 mg, Grade ≥3, 7%. Most reported AE: anxiety, insomnia, nausea.
Barton et al. ⁸	United States	American	Ginseng: 2000 mg	CRF	364	Women (78%)	Multisite, double-blind placebo controlled RCT	Multidimensional Fatigue Symptom Inventory-Short Form	8 Weeks	Significant improvement in fatigue scores in intervention group compared with placebo.	0.9	0.38	22 Placebo ^b : Grade 3, 1%, ginseng: 2000 mg, Grade 3, 1%. Most reported AE: anxiety, insomnia, nausea.
Braz et al. ¹¹	Brazil	<i>Panax ginseng</i> C.A. Meyer	Amitriptyline: 25 mg, ginseng: 100 mg	Fibromyalgia	52	Women ^c (100%)	Double-blind placebo controlled RCT, comparative (amitriptyline, placebo, <i>P. ginseng</i>)	Fatigue VAS	12 Weeks	Fatigue decreased for all three groups, with no significant differences between groups.	NR	NR	27 AEs not reported. Each group had three participants drop out because of adverse effects.
Etemadifar et al. ²³	Iran	Korean	Ginseng: 500 mg	MS	52	Women ^c (100%)	Double-blind placebo controlled RCT	Modified Fatigue Impact Scale	3 Months	Total fatigue was significantly different in favor of ginseng. Physical dimension on the fatigue scale was significantly different for the ginseng group.	NR	NR	0 Reported no serious AEs. Did not report AEs in detail. Only reported one patient who had constipation, which resolved.
Jeong et al. ²⁴	Korea	Combination, including <i>Panax ginseng</i>	Bojungikki-Tang, ginseng dose: 1252.5 mg	CRF	40	Women (60%)	Placebo controlled RCT with waitlist	VAS of Global Fatigue	2 Weeks	Intervention group had significantly improved fatigue compared with placebo.	0.8	0.2	10 No serious AEs reported. Reported 10% AEs but did not clarify if intervention or placebo group. Most reported AEs: flatulence, Dyspepsia.
Kim et al. ²⁰	United States	American	Ginseng: 400 mg	MS	53	Women (94%)	Double-blind placebo crossover	Fatigue Severity Scale	6 Weeks	Both groups improved. No significant difference between groups. Mixed modeling showed significantly improved RDFS; however, authors do not believe this was clinically significant.	0.8	0.8	11 Placebo, 26 ^d , ginseng, 29 ^d , no serious AEs reported. Most reported AEs: nausea, insomnia, headache, rash, flu-like syndrome.

(continued)

TABLE 1. (CONTINUED)

Study	Location	Type of ginseng	Daily dose per arm	Diagnosis	N	Gender	Study design	Primary fatigue assessment	Length	Results	Power size	Effect Attrition, %	Reported AEs ^a
Kim et al. ¹²	Korea	<i>P. ginseng</i> C.A. Meyer	Ginseng: 1000, 2000mg	Idiopathic chronic fatigue	90	Women (76%)	Double-blind placebo controlled RCT	Fatigue Numeric Rating Scale (NRS) and VAS	4 Weeks	NRS questions decreased for all three groups, with no significance between groups. ^c VAS scores declined for all groups, with <i>P. ginseng</i> (2g) arm scores significantly lower than control. ^c	0.9	0.53	2 AEs not reported.
Le Gal et al. ²⁵	France	Combination with <i>P. ginseng</i> C.A. Meyer	Pharmaton, ginseng dose: 80mg	Functional fatigue	232	Women (65%)	Multicenter, double-blind placebo controlled RCT	Investigator developed self-report tool	6 Weeks	Intervention group had significantly improved fatigue over placebo.	NR	NR	5.6 Placebo: 9% Pharmaton: 17%, AE grades not reported. One serious AE reported in placebo group. Most reported AEs: nausea/ vomiting, sleep disorders, abdominal pain. AEs not listed. ^b
Wang et al. ²¹	China	Combination containing American ginseng	Immune No. 2, ginseng dose NR	HIV after highly active antiretroviral therapy	264	Men (62%)	Double-blind placebo controlled RCT	Fatigue item in Scores of Symptoms and Signs	6 Months	Intervention group had significantly improved fatigue than placebo.	NR	NR	12 AEs not listed. ^b
Yemurajalingam et al. ²²	United States	<i>P. ginseng</i> C.A. Meyer	Ginseng: 800mg	CRF	30	Women (50%)	Single arm pre/post	Functional Assessment of Chronic Illness Therapy Fatigue	29 Days	Significantly improved fatigue scores at days 15 and 29 from baseline.	NR	NR	20 No AEs attributed to the study. Grade >3, 6%. These were not attributed to the study. Most reported AEs: pain, nausea.

^aGrade 3 or higher.^bNo significant differences in reported AEs between intervention and placebo groups.^cOnly recruited women.^dRaw numbers because of inability to calculate a rate.

AE, adverse event; CRF, cancer-related fatigue; MS, multiple sclerosis; NR, not reported; RCT, randomized controlled trial; RDFS, real-time digital fatigue scale; VAS, Visual Analog Scale.

FIG. 2. Overall risk of bias: American ginseng. The authors’ judgments about each risk-of-bias item are shown as percentages across all included studies of American ginseng.

participants were removed for not taking their ginseng,²¹ which could have led to a bias in missing data. Furthermore, one study found significant results testing a combined treatment (Immune No. 2) that included American ginseng.²¹ Testing a combination of ingredients produces results that cannot be attributed to any of the individual components. None of the study reports revealed any significant safety concerns.

Asian ginseng (*P. ginseng*)

Asian ginseng is found in China, Korea, and Russia and is believed to be one of the most-researched species of ginseng.²⁶ Six studies evaluated Asian ginseng as a treatment for fatigue. Four trials tested Asian ginseng (*P. ginseng* C.A. Meyer^{11,12,22} or *P. ginseng* [Korean ginseng]).²³ Two studies tested Asian ginseng as part of a combination of natural products (Bojungikki-tang and Pharmaton).^{24,25} Multiple fatigue assessments were utilized, including a Visual Analog Scale,^{11,12,24} the Modified Fatigue Impact Scale,²³ a Numeric Self-Rating Scale,¹² the Functional Assessment of Chronic Illness Therapy–Fatigue,²² and one investigator-developed, self-report tool.²⁵

Design

Four of the six studies were double-blind, placebo-controlled trials.^{11,12,23–25} One study was a randomized controlled trial with a waitlist control.²⁴ One study was a single-arm, prospective, open-label trial.²² Overall, risk of bias was found to be unclear to high (Figs. 4 and 5). Study durations ranged from 4 weeks to 3 months.^{11,12,22–25} Daily doses ranged from 80 to 2000 mg of *P. ginseng*,^{11,12,22–25} with the longest trial using a 250-mg dose twice daily, for a total daily dose of 500 mg, for 3 months.²³ Five of the six studies were designed to evaluate the efficacy of ginseng as a treatment for fatigue,^{11,12,23–25} and one was designed to evaluate the safety and tolerability of ginseng as a treatment for fatigue.²²

Sample

The six studies were conducted in different countries.^{11,12,22–25} Study participants had the following diagnoses: cancer,^{22,24} fibromyalgia,¹¹ chronic fatigue,¹² multiple sclerosis,²³ and functional fatigue.²⁵ All studies included only adults. Four of six studies required participants to report fatigue as an inclusion criteria.^{12,22,24,25} Sample sizes ranged from 30 to 232. The trial with the smallest sample ($n = 30$) was reported as a preliminary study.²² One study that was reported as a pilot study ($n = 40$) was powered at 80%, with an effect size of 0.2.²⁴ None of the other studies reported the power of the study to detect change. Two of the six studies included only women.^{11,23} Three additional studies included mostly women: 60%, 76%, and 65%, respectively.^{12,24,25} The study conducted in the United States was the only one to report race; most participants were white (84%).²² The lowest attrition rate was 0%,²³ with attrition rates in the other five studies reported as a minimum of 2% and a maximum of 27%.^{11,12,22,24,25}

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Barton et al. 2010	+	+	+	?	+	+
Barton et al. 2013	+	+	+	?	+	+
Kim et al. 2011	?	?	?	?	?	–
Wang et al. 2013	+	+	+	+	–	+

FIG. 3. Risk of bias: American ginseng. The authors’ judgments about each risk-of-bias item are shown for each included study of American ginseng. +, Indicates low risk of bias; –, high risk of bias; ?, unclear risk of bias.

FIG. 4. Overall risk of bias: Asian ginseng. The authors' judgments about each risk-of-bias item are shown as percentages across all included studies of Asian ginseng.

Safety and efficacy

No study reported serious AEs in the intervention group.^{11,12,22–25} One study that tested ginseng in a natural product combination (Pharmaton) reported a single, serious AE in the control group; a participant had to be admitted to the hospital for edema of the uvula that resolved after corticosteroid therapy.²⁵ The single-arm study reported a 6% rate for serious AEs; however, none was attributed to ginseng.²² One study did not report any AEs, but the investigators noted that nine participants (three from each arm) dropped out be-

cause of AEs.¹¹ Only three of the six studies reported AEs in detail, with rates that ranged from 10% to 53%.^{22,24,25} In the study that reported the largest AE rate (53%), none of the AEs was attributed to the intervention.²² The most-reported AEs included nausea/vomiting, sleep disorders, abdominal pain, and bowel disorders.^{12,22–25} Fatigue decreased in all six studies, with five studies reporting significant differences in fatigue measures in the invention group.^{12,22–25}

Appraisal of reviewed Asian ginseng research

Most (four of six) of the studies were double-blind, placebo-controlled trials; however, they did not report how they mitigated bias (Figs. 4 and 5).^{11,12,23,25} Four of the six studies showed that the intervention group had significantly improved fatigue outcomes compared with the placebo group^{12,22–25}; the single-arm prospective, open-label trial showed significantly improved fatigue scores at 15 and 29 days compared with fatigue at baseline.²² The single-arm trial also had the highest risk of bias.²² Because this study did not have a control group, it is possible that the improvement over time resulted from something other than the ginseng treatment.²²

Three studies excluded participants from the analysis if they did not adhere to the study protocol, thus a per-protocol analysis was done rather than an intent-to-treat analysis.^{22,23,25} A per-protocol analysis may result in bias related to missing data.²⁷ However, one study reported no attrition, but it is not clear if the attrition count was defined as including participants who were excluded for not following the study protocol.²³ One study used an investigator-developed fatigue measure, but did not report validity or reliability of the measure.²⁵ If the fatigue measure was not valid and reliable, this would challenge the validity of the results.²⁵ Furthermore, two studies tested Asian ginseng in a combination with other natural products, making it difficult to ascertain the relative contribution of the ingredients to the study outcomes.^{24,25} None of the studies reported significant safety concerns for the intervention group.

Cancer-related fatigue

A subanalysis was conducted for the studies of CRF because they made up the largest illness group in this review. Four of the 10 studies evaluated ginseng's impact on CRF.^{8,19,22,24} Two studies included both active treatment and post-treatment cancer survivors.^{8,19} One study included only results at 2 months after treatment,²⁴ and the other included only active-treatment cancer survivors.²²

FIG. 5. Risk of bias: Asian ginseng. The authors' judgments about each risk-of-bias item for each included study of Asian ginseng. +, Indicates low risk of bias; –, high risk of bias; ?, unclear risk of bias.

FIG. 6. Risk of bias: the authors’ judgments about each risk-of-bias by percentage across all included studies.

Ginseng doses ranged from 800 to 2000 mg. Ginseng doses in three of the four studies were >1000 mg, and intervention periods ranged from 2 to 8 weeks.^{8,19,24} Three of the four CRF studies reported significant results.^{8,22,24} Two showed that ginseng (one, *P. quinquefolius*; one, *P. ginseng*) improved fatigue significantly in the study groups versus the controls,^{8,24} whereas the other study showed that *P. ginseng* significantly improved participants’ fatigue scores from those at baseline.²²

Although the studies were promising for their effectiveness in decreasing CRF, the results should be approached cautiously. Two of the four studies had sample sizes of fewer than 50 participants.^{22,24} Three had mostly women participants.^{8,19,24} Both the sample size and sample composition may have impacted the generalizability of the results. To date, none of the positive results of the CRF ginseng studies has been replicated.

Discussion

This review aimed to evaluate the safety and effectiveness of the two types of *Panax ginseng* (Asian [*P. ginseng*] and American [*P. quinquefolius*]) as a treatment for fatigue through examining study designs, samples, safety, and efficacy. Key strengths of the studies included the study designs and the safety and efficacy results. Most of the studies (8/10) were double-blind, randomized controlled trials,^{8,11,12,19–21,23,25} which allows for control of multiple types of bias; however, mitigating detection and attrition bias would increase the overall strength of the evidence (Figs. 6 and 7). Four (4/10) studies reported being powered at 80% or greater, which can add to the strength of the studies to detect the effects of the treatment.^{8,19,20,24}

None of the studies reported significant AEs attributed to ginseng. One study did report a serious AE attributed to the placebo.²⁵ Reported rates of grade ≥3 AEs ranged from 1% to 11%.^{8,19,22,24,25} Three of 10 studies showed no significant differences in AEs between the ginseng and placebo groups.^{8,19,21} The most common, nonserious AEs reported were nausea/vomiting, sleep disorders, abdominal pain, and bowel disorders.

Most (7/10) studies showed significant improvements in fatigue scores in the intervention group compared with the control group.^{8,12,20,21,23–25} Additionally, one single-arm study showed significant improvement in fatigue scores from baseline at 15 and 29 days²²; however, this study did not have a control group. Therefore, there could be plausible explanations other than treatment with ginseng for the improvement in fatigue over time.²² Furthermore, one study’s

authors interpreted their findings as not being clinically meaningful; however, because the authors reported a combined (placebo and intervention) baseline for fatigue, it was difficult to assess the rationale for their conclusion.²⁰

Five of the six studies reporting significant differences in fatigue between the ginseng and placebo groups may have

FIG. 7. Risk of bias. The authors’ judgments about each risk-of-bias item for each included study. +, Indicates low risk of bias; -, high risk of bias; ?, unclear risk of bias.

been biased from missing data, because they completed per-protocol analyses and/or did not seem to adhere to intention-to-treat analysis.^{12,21–23,25} This type of analysis limits the ability to overcome biases related to attrition or missing data, or both, which could favor the intervention group.²⁷ Two studies did not show significant improvements in fatigue: one was a dose-finding pilot study,¹⁹ and the other was a three-arm randomized controlled trial with 52 participants that tested the second lowest dose of ginseng (100 mg).¹¹

Most of the studies (6/10) were conducted in Western countries.^{8,11,19,20,22,25} Sample sizes ranged from 30 to 364.^{8,11,12,19–25} Three (3/10) studies were either pilot or preliminary studies.^{19,22,24} Cancer was the most common (4/10) condition studied.^{8,19,22,24} Eight (8/10) of the studies included mostly women participants.^{8,11,12,19,20,23–25} Two studies' inclusion criteria specified that participants had to be women.^{11,23} Because of the preponderance of women participants, the study results cannot necessarily be generalized to men—possibly because women may be more likely to seek alternative treatments, such as ginseng, or because the conditions studied primarily impacted women (e.g., fibromyalgia and multiple sclerosis).^{28,29}

No consistent dosage for ginseng was used. Study interventions varied from 80 to 2000 mg daily.^{8,11,12,19–25} Three of the 10 studies used 2000 mg as the maximum dose.^{8,12,19} All but two (six of eight) studies that demonstrated significant improvements in fatigue in the intervention group tested ginseng doses of 400 mg or more.^{8,12,20,22–24} Study durations for treatment ranged from 2 weeks to 6 months.^{8,11,12,19–25} Most (seven of eight) studies that showed significant improvements in fatigue were trials that lasted 4 weeks or more.^{8,12,20–23,25}

Limitations

One limitation of this review is limiting the studies to English language only, which could have led to a language bias. However, in a meta-analysis, Morrison et al.³⁰ showed that although limiting to English only in reviews is perceived to lead to a language bias, a language limitation in search strategy did not result in systematic bias. Additionally, not limiting this review to single-agent use of ginseng may have confounded the results regarding efficacy of ginseng as a treatment for fatigue. However, limiting the studies to single-agent use of ginseng would have ignored the traditional uses of ginseng (often multiagent combinations) and would have narrowed the assessment of the state of evidence on the effectiveness of ginseng for fatigue in people with chronic illness.

Conclusion and clinical implications

Overall, there was modest support for ginseng as a treatment for fatigue. Both American and Asian ginseng may be viable treatments for fatigue in people with chronic illness because of the low risk associated with its use, coupled with modest evidence for its efficacy. However, it is critical that future research build on the evidence provided by the studies reviewed about ginseng dose and duration of treatment, be methodologically strong, and include more diverse samples before ginseng, which is already in widespread use, is adopted as a standard treatment option for fatigue.

Future research recommendations

Future research should focus on developing safe and effective interventions for fatigue. We found three obvious gaps in the literature regarding American and Asian ginseng as treatments for fatigue in people with chronic illness that should be considered for additional research. First, future research reports should include a clear presentation of the statistical methods used and specify how missing data were handled to address attrition bias. Second, larger and more diverse samples are needed to increase the generalizability and statistical power of the studies. Third, future studies should be designed for a regimen of 400 mg or more of ginseng for at least 4 weeks. Finally, the results of current studies with significant findings should be replicated by future studies to assure that the findings can be reproduced.

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