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REVIEW ARTICLE

Ginseng and Ginseng Herbal Formulas for Symptomatic Management of Fatigue: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Ginseng has been widely used in fatigue management. However, its efficacy on fatigue remains unclear. This study aimed to assess the efficacy and safety of ginseng and ginseng herbal formulas for fatigue in randomized clinical trials (RCTs).

Methods: The authors searched PubMed, Embase, Cochrane, Web of Science, and Allied and Complementary Medicine Database (AMED) databases from inception to July 6, 2022. Outcomes included fatigue severity, quality of life (QoL), and adverse events (AEs). Quality of evidence was assessed using the Cochrane Risk of Bias Tool. They pooled all included data and performed subgroup analysis by fatigue type, assessment instrument, and ginseng type.

Results: The authors included 19 RCTs. Pooled analyses found no significant reduction in fatigue severity with ginseng versus controls (standardized mean difference [SMD]: −0.36, 95% confidence interval [CI]: −0.82 to 0.11, $p = 0.13$). In subgroup analysis, there was significant fatigue reduction with the ginseng herbal formula (SMD: −0.39, 95% CI: −0.66 to −0.13, $p = 0.004$) and chronic fatigue (CF) (SMD: −0.30, 95% CI: −0.56 to −0.03, $p = 0.03$) compared to controls. Ginseng produced significant reductions in general (i.e., non-disease-specific) fatigue compared to controls (SMD: −0.48, 95% CI: −0.71 to −0.25, $p < 0.0001$). Ginseng was associated with a trend toward QoL improvement ($p = 0.05$) and did not increase AEs compared with controls. Effect sizes were small.

Conclusion: Ginseng herbal formulas improved fatigue severity compared to controls, especially among patients with CF, but with a small effect size. Rigorous RCTs as well as guidelines for standard ginseng usage are needed to further evaluate the effects of ginseng for fatigue and ensure proper use.

Keywords: ginseng, fatigue, herbal medicine, efficacy, safety

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Introduction

FATIGUE IS AMONG the most common and debilitating symptoms and a challenge to public health.[1] Clinically significant fatigue, usually defined in terms of associated disability and persistence, affects 5%–20% of the general population.[2] It has a much higher prevalence in patients with chronic diseases such as stroke and multiple sclerosis (MS), and nearly 100% prevalence in cancer survivors,[3–5] significantly reducing their quality of life (QoL)[6–8] and leading to increased health care costs and loss of productivity.[9] Current clinical practice guidelines for fatigue recommend nonpharmacologic treatments, such as exercise and cognitive behavioral therapy (CBT), as general supportive therapies.[2,10]

However, their application is limited due to lack of access to trained providers, high cost, and difficulty in establishing a routine.[11,12] At the same time, the effects of conventional medications, such as methylphenidate and paroxetine, on fatigue remain unclear, especially for fatigue without a specific cause, which impedes use of these drugs.[13,14] They may also have limiting side effects. Furthermore, regardless of which pharmacologic or nonpharmacologic therapies they received, only half of patients achieve any therapeutic benefit.[15]

Given the gap between symptom burden and available effective therapies, a growing number of patients use complementary and alternative medicine (CAM), including herbal remedies such as ginseng, to help manage fatigue.[16] ''Ginseng'' refers to several species in the Panax genus. Among them, *Panax ginseng* C.A. Mey (Chinese ginseng and Korean ginseng) and *Panax quinquefolium* L. (American ginseng) are two main species that are widely used to treat fatigue in CAM.[17] Chinese and Korean ginsengs differ in their drying processes.[18] Pharmacology research has demonstrated that bioactive chemicals extracted from ginseng, including ginsenosides, ginseng polysaccharides, and ginseng protein, may have antifatigue effects. They help regulate fatigue through antioxidation, anti-inflammatory activity, reduction of toxic metabolite accumulation, or management of energy metabolism by regulating the expression of proinflammatory cytokines (interleukin-6, tumor necrosis factor-α, interleukin-1β) and activating oxidative stress-related pathways, such as Nrf2-ARE and the PI3-K/Akt signaling pathway.[19,20]

In traditional Chinese medicine (TCM), ginseng can be used alone or integrated into multicomponent herbal formulas to alleviate fatigue.[17] Use of ginseng in the United States is widespread and growing rapidly, with projected sales from its use expected to almost double from $6.1 billion in 2020 to $11.7 billion in 2026.[21]

In recent years, clinical trials of ginseng or ginseng-containing formulas for fatigue have yielded contradictory results. One clinical study in patients treated for head and neck cancer showed that American ginseng did not significantly reduce fatigue severity at week 8 compared to placebo as measured by the total Brief Fatigue Inventory (BFI) score; however, ginseng did improve enjoyment of life and interference with relationships.[22] In contrast, several randomized controlled trials (RCTs) in patients with various health conditions have found reduction in fatigue with ginseng compared to placebo.[23–25] However, inconsistency in ginseng types, patient populations, and outcome measures limit interpretation of these results.

Although several systematic reviews have evaluated the effect of ginseng on fatigue,[17,26–28] they focused on a specific underlying disease or a particular type of ginseng, had methodologic flaws, or did not pool data in a meta-analysis. These shortcomings highlight the need for better understanding of the efficacy of ginseng for management of fatigue across populations. Therefore, they performed a systematic review and meta-analysis of RCTs among patients with primary/secondary fatigue to evaluate the efficacy and safety of ginseng compared with controls for patient-reported outcomes of fatigue and QoL across ginseng types and original causes of fatigue. The authors also addressed differences across ginseng type or underlying conditions in subgroup analysis. Their study provides evidence to inform clinical practice for symptomatic control with herbal supplements and identifies gaps for future research.

Materials and Methods

The current systematic review and meta-analysis was carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Supplementary Table S1) and Cochrane guidelines.[29] The study protocol was registered in International Prospective Register of Systematic Reviews (registration no. CRD42021247021).

Criteria for article selection

This review included parallel-group RCTs of ginseng and ginseng herbal formulas for fatigue published in English using any control. No restrictions were placed on the origin of study, publication year, or trial status. Studies with adult patients who presented with the symptom of fatigue were considered eligible for inclusion, regardless of the primary diagnosis, cause of the symptom, or duration. No restrictions were placed on the geographic, socioeconomic, or ethnic backgrounds of the participants. Three types of ginseng (Chinese ginseng, Korea ginseng, and American ginseng) and 14 ginseng-containing herbal formulas, which are classical prescriptions of TCM, were included as interventions (Table 1; Supplementary Table S3). Since ginseng is used in different forms with highly variable dosing, including extractive compounds, granules, or as multicomponent formulas, the authors did not place any restrictions on the doses of ginseng used in each study and planned *a priori* to pool results across dosages.

Studies that used only extractive compounds of ginseng or a combination of unsubstantiated therapies, such as physical therapy and food supplement, were excluded. Also excluded were crossover trials, quasi-RCTs, and studies that compared the efficacy of different ginseng doses without placebo or other control. They included studies that measured one or more of the following clinical outcomes: (1) fatigue measured by validated instruments as a primary or secondary outcome, regardless of whether the instrument measured general or disease-specific fatigue, utilized a single item or multiple items, or was unidimensional or multidimensional; (2) general QoL measured by a validated instrument; and (3) adverse events (AEs) associated with ginseng and ginseng herbal formulas.

Search strategy, data selection, and data extraction

The authors conducted an electronic search of five databases, PubMed, Embase, Cochrane, Web of Science, and

Table 1. Composition of Ginseng Containing Formulas in Included Studies

Study	*Ginseng-containing formulas*	*Composition*
Shin et al[23]	Sipjeondaebo-tang (Shi quan da bu tang)	Ginseng Radix (Panax ginseng C.A. Meyer) 1 g, Astragali Radix (Astragalus membranaceus Bunge) 1 g, Poria Sclerotium (Poria cocos Wolf) 1 g, Atractylodis Rhizoma Alba (Atractylodes japonica Koidzumi or Atractylodes macrocephala Koidzumi) 1 g, Angelicae Gigantis Radix (Angelica gigas Nakai) 1 g, Paeoniae Radix (Paeonia lactiflora Pallas) 1 g, Cnidii Rhizoma (Cnidium officinale Makino or Ligusticum chuanxiong Hort) 1 g, Cinnamomi Ramulus (Cinnamomum cassia J. Presl) 1 g, Rehmanniae Radix Preparata (Rehmannia glutinosa Liboschitz ex Steudel) 1 g, and Glycyrrhizae Radix et Rhizoma (Glycyrrhizauralensis Fischer, Glycyrrhiza glabra Linné, or Glycyrrhiza inflataBatal) 0.5 g
Lee et al[41]	Sipjeondaebo-tang (Shi quan da bu tang)	Astragali Radix (10.5%), Panax ginseng radix (10.5%), Atractylodes Rhizoma Alba (10.5%), Poria sclerotium (10.5%), Rehmanniae Radix (10.5%), Angelicae Gigantis Radix (10.5%), Paeonia Radix (10.5%), Cnidii Rhizoma (10.5%), Glycyrrhizae Radix et Rhizoma (5.3%), and Cinnamomi Ramulus (10.5%)
Moon et al[35]	Cheonwangbosimdan (Tian Wang Bu Xin Dan)	Danggui (Angelica gigas root) 125 mg, Tianmendong (Asparagus tuber) 125 mg, Huanglian (Coptis rhizome) 250 mg, Renshen (Ginseng) 62.5 mg, Fuling (Hoelen) 62.5 mg, Jiegeng (Platycodon root) 62.5 mg, Yuanzhi (Polygala root) 62.5 mg, Shengdihuang (Rehmannia root) 500 mg, Danshen (Salvia miltiorrhiza root) 62.5 mg, Wuweizi (Schisandra fruit) 125 mg, Xuanshen (Scrophularia root) 62.5 mg, Baiziren (Thujae semen) 125 mg, and Suanzaoren (Ziziphus seed) 125 mg
Jeong et al[40]; Hamada et al[44]	Bojungikki-tang (Hochu-ekki-to: TJ-41)	Astragali radix (16.7%), Atractylodis lanceae rhizoma (16.7%), Ginseng radix (16.7%), Angelicae radix (12.5%), Bupleuri radix (8.3%), Zizyphi fructus (8.3%), Aurantii nobilis pericarpium (8.3%), Glycyrrhizae radix (6.3%), Cimicifugae rhizoma (4.2%), and Zingiberis rhizoma (2.0%) with a total daily dose of 7.5 g
Yagi et al[45]	Ninjin'yoeito (Ren Shen Yang Rong Tang)	Rehmannia Root 4.0 g, Japanese Angelica Root 4.0 g, Atractylodes Rhizome 4.0 g, Poria Sclerotium 4.0 g, Ginseng 3.0 g, Cinnamon Bark 2.5 g, Polygala Root 2.0 g, Peony Root 2.0 g, Citrus Unshiu Peel 2.0 g, Astragalus Root 1.5 g, Glycyrrhiza 1.0 g, Schisandra Fruit, 1.0 g

Allied and Complementary Medicine Database (AMED), from database inception to May 12, 2021 (updated on July 6, 2022) for RCTs of ginseng and ginseng herbal formulas for fatigue published in English (Table 1; Supplementary Table S2). They searched the National Institutes of Health clinical trials registry (https://www.clinicaltrials.gov/) and the International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) for ongoing trials. They imported search results from the original databases to EndNote X9. Two authors (X.L. and Y.L.Z.) independently assessed the eligibility of each record according to a study screening standard operating procedure (SOP) to ensure unbiased selection.

Reference lists from relevant systematic reviews and meta-analyses were reviewed to further identify additional eligible trials. They initially reviewed titles, followed by abstracts, excluding nonclinical trial studies and those who did not focus on ginseng and ginseng herbal formulas. The same two authors then performed a full-text article review and recorded the reason for exclusion, with disagreements resolved by another three reviewers (M.Y. [Mingxiao Yang], S.K. [that is SooDam Kim], and Y.N.H.) by consensus.

Two authors used a modified Cochrane data extraction form (X.L. and Y.L.Z.) to independently extract detailed data (study origin, year of publication, patient demographics, intervention, comparator, outcome and results, setting, AEs, etc.) from each study[30] (Supplementary Table S4: Modified Cochrane Data Extraction Form). Discrepancy or disagreement was resolved through discussions with another three reviewers (M.Y., S.K., and Y.N.H). Data required for meta-analysis were transferred from the data extraction form to RevMan software (version 5.4) using a double entry method.

Risk of bias and quality of evidence assessments

Two reviewers (X.L. and Y.L.Z.) assessed risk of bias (RoB) of each included study using the Cochrane revised RoB-2 tool.[31] Discrepancies were resolved through discussions and arbitration by another three reviewers (M.Y., S.K., and Y.N.H). The quality of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation system.[32]

Statistical analysis

The authors planned meta-analysis of all studies that provided efficacy data related to fatigue severity and used placebo, conventional treatment, or usual care as a comparator. They planned to pool data across ginseng types, underlying causes of fatigue, control, and specific fatigue outcome measurements. While the mechanism of fatigue is multifaceted,[33] the symptom itself is targeted by ginseng

regardless of etiology; it is therefore hypothesized that ginseng would have similar efficacy regardless of the underlying cause of fatigue. Similarly, because different fatigue measures fundamentally quantify the same symptom, it is appropriate to pool results across measures. In addition to the main comparison, they performed subgroup analysis based on the specific type of ginseng, fatigue type, and outcome measure to explore differences and serve as a sensitivity analysis. In cases in which only one study existed for a specific comparison, they conducted descriptive analysis instead.

Efficacy data were synthesized and statistically analyzed in RevMan 5.4. Continuous and dichotomous data were summarized using standardized mean difference (SMD) and relative risk or risk ratio (RR) with 95% confidence intervals (CIs), respectively. When rare instances such as zero case in an outcome event were reported, the Peto odds ratio model was used to merge dichotomous data. Chi-square tests were performed in the forest plot using RevMan 5.4 to investigate statistical heterogeneity, and a p-value of <0.10 was considered significant, in accordance with the Cochrane Handbook. The I^2 value was calculated to quantify statistical heterogeneity.

If there was no or low heterogeneity among studies ($I^2 \leq 50\%$), a fixed effects model was applied for meta-analysis; if statistical heterogeneity was high ($I^2 > 50\%$), they analyzed sources of heterogeneity using subgroup or sensitivity analysis, and a random effects model was adopted for meta-analysis. The authors underwent a descriptive analysis if the source of heterogeneity was unclear. They generated funnel plots to assess potential publication bias when more than 10 studies were included.

Quality control

To ensure the consistency and accuracy of the results, including article screening, data extraction, and RoB assessment, each reviewer underwent three systematic

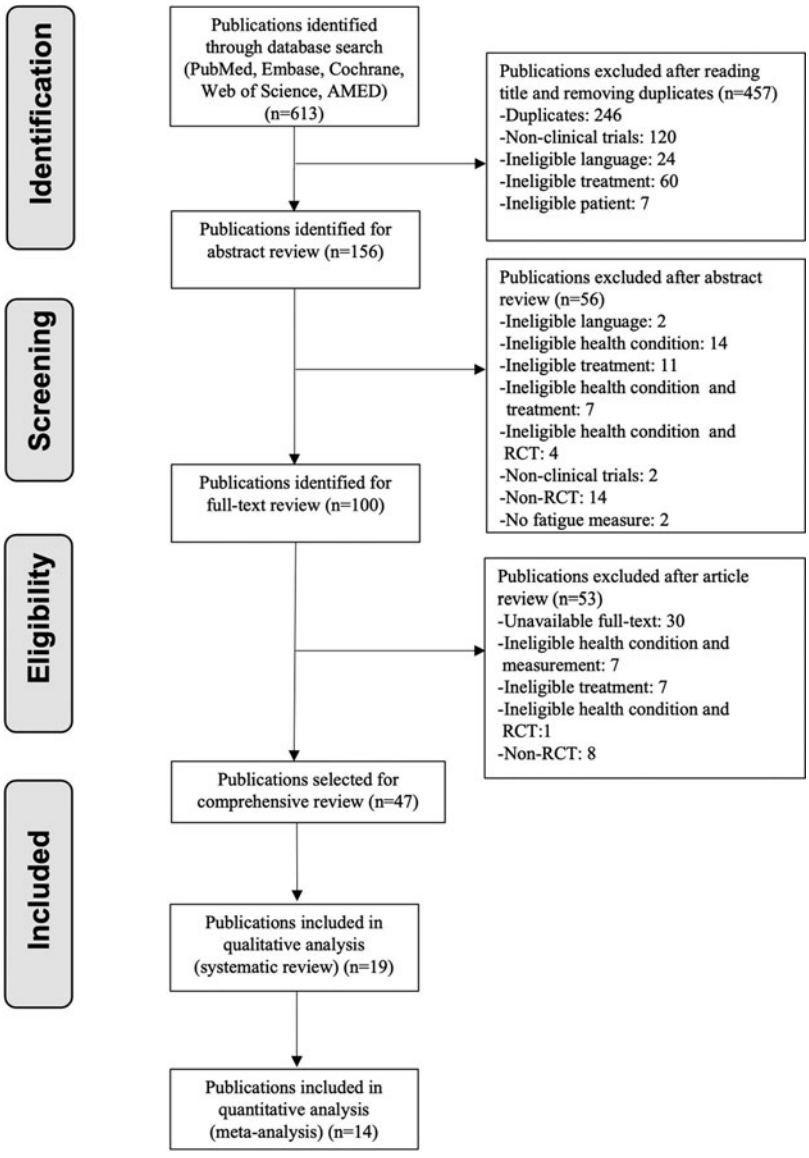

FIG. 1. Flow diagram of systematic review. This chart illustrates the article selection process and selection criteria for the literature review and meta-analysis. RCT, randomized controlled trial.

Table 2. Characteristics of Included Studies

Study	Year/ country	Primary disease	Fatigue subtype	Sample size	Age (years)	Interventions/ dose/duration	Control	Primary outcome	Secondary outcome
Yagi et al[45]	2022/Japan	Gynecologic disease	Disease-related fatigue	E:15 C:15	E:45.1 ± 7.7 C:41.1 ± 8.3	NYT/7.5 g/10 days	Sodium ferrous citrate	CFS VAS-A	AEs[a]
Lee et al[41]	2021/Korea	Malignant cancer	CRF	E:25 C:25	E:56.6 (11.6) C:58.7 (12.5)	Sipjeondaebo-tang/ 9 g/3 weeks	Placebo	BFI	EORTC QLQ-C30 AEs[b]
Shin et al[23]	2021/Korea	Not limited	CFS	E:48 C:48	E:41.5 ± 8.2 C:40.6 ± 9.8	Sipjeondaebo-tang/ 9 g/8 weeks	Placebo	CIS VAS FSS ChFi	EQ-5D-5L Safety assessment[c]
Hong et al[24]	2020/Korea	NAFLD	Disease-related fatigue	E:48 C:46	E:50.0 ± 13.3 C:49.7 ± 13.2	KRG/2 g/4 weeks	Placebo	FSS	
Sung et al[34]	2020/Korea	Not limited	CF	E:25 C:25	E:49.000 ± 8.351 C:47.087 ± 10.795	KRG/3 g/6 weeks	Placebo	VAS FSS CFSQ	EQ-5D-5L (Part 1 EQ-VAS) AEs[d]
Moon et al[35]	2020/Korea	Malignant tumor with insomnia	CRF	E:11 C:11	E:63.0 [53.0–71.0] C:63.0 [54.0–67.0]	Cheonwangbosimdan/ 20 mL/4 weeks	CBT-I	BFI	EQ-5D-5L Safety assessment outcomes AEs[e]
Kim et al[25]	2020/Korea	Colon cancer	CRF	E:219 C:219	E:60 (29–84) C:60 (27–86)	KRG/2 g/16 weeks	Placebo	BFI FACIT-Fatigue survey	AEs[f]
Jung et al[36]	2020/Korea	NAFLD	Disease-related fatigue	E:30; 30 C:30	E:42.83; 45.07 C:42.67	GBCK25/125 mg; 500 mg/12 weeks	Placebo	MFS	AEs[g]
Guglielmo et al[22]	2020/Italy	Head and neck cancer	CRF	E:17 C:15	E:58 [34–73] C:55 [35–79]	American ginseng/ 1 g/8 weeks	Placebo	BFI	AEs[h]
Zhang et al[43]	2019/China	TCM asthenia syndrome	TCM asthenia syndrome	E:60; 60 C:60	E:34.88 ± 11.07; 35.8 ± 0.16 C:37.72 ± 10.88	KRG/1.8 g; 3.6 g/ 4 weeks	Placebo	Fatigue self-assessment scale	Safety assessment[i]
Hamada et al[44]	2018/Japan	COPD	Disease-related fatigue	E:18 C:17	E:75.3 ± 6.1 C:74.7 ± 7.1	TJ-41/7.5 g/ 12 weeks	Untreated with TJ-41	VAS	Acute exacerbations[j]
Yennurajalingam et al[46]	2017/United States	Advanced cancer	CRF	E:63 C:64	E:61.0 (54.0–67.0) C:61.0 (53.3–66.8)	PG/400 mg/28 days	Placebo	FACIT-Fatigue survey ESAS fatigue scale	Toxicity and safety[k]
Kim et al[37]	2017/Korea	EOC	CRF	E:15 C:15	E:55.9 ± 12.1 C:52.9 ± 10.1	Red ginseng/3 g/ 12 weeks	Placebo	BFI	EORTC QLQ-C30 AEs[l]

(*continued*)

TABLE 2. (CONTINUED)

Study	Year/ country	Primary disease	Fatigue subtype	Sample size	Age (years)	Interventions/ dose/duration	Control	Primary outcome	Secondary outcome
Hong et al[38]	2016/Korea	NAFLD	Disease-related fatigue	E:40 C:40	Not reported	KRG/3 g/3 weeks	Placebo	FSS	
Kim et al[39]	2013/Korea	Not limited	ICF	E:30; 30 C:30	E:39.5 (25, 57); 40.5 (22, 59) C:39.5 (24, 60)	PG/1 g; 2 g/4 weeks	Placebo	CFSQ VAS	AEs[m]
Etemadifar et al[42]	2013/Iran	RRMS	Disease-related fatigue	E:26 C:26	E:33.3 ± 7.5 C:34.5 ± 8.9	KRG/250 mg/ 12 weeks	Placebo	MFIS	MSQOL-54 AEs[n]
Barton et al[47]	2013/United States	All cancers, other than brain or CNS lymphoma	CRF	E:183 C:181	E:55.3 (12.7) C:55.9 (11.8)	American ginseng/ 2 g/8 weeks	Placebo	MFSI-SF BFI POMS	Side effects[o]
Jeong et al[40]	2010/Korea	Malignant cancer	CRF	E:20 C:20	E:49.4 (10.8) C:53.4 (8.0)	TJ-41/7.5 g/2 weeks	Waiting list	VAS Trial Outcome Index–Fatigue	FACT-General AEs[p]
Barton et al[48]	2010/United States	Cancer	CRF	E:70; 72; 71 C:69	E:58 (11); 60 (12); 62 (11) C:62 (13)	American ginseng/ 750 mg; 1 g; 2 g/8 weeks	Placebo	BFI Vitality subscale of the SF-36	SF-36 Self-reported toxicities AEs[q]

[a]AEs include mild liver dysfunction in the E group.
[b]AEs included dyspepsia in the E group and pruritus in the C group.
[c]AEs include hot flashes, headache, heartburn, migraine, dermatitis, nausea, lower abdominal pain, dizziness, heavy stomach, loss of appetite, and muscle pain in both groups.
[d]There were no AEs associated with intervention.
[e]Not reported.
[f]AEs included nausea in 128 patients (E group, 28%; C group, 32%), neutropenia in 62 subjects (E group, 19%; C group, 10%), hypertensive crises at high doses in the E group (G3, 3 cases, 1.40%), and C group (G2, 1 case, 0.47%). Neutropenia equal to and above grade 3 was more frequent in the E group than in the C group (13% vs. 7%). AEs resulting in trial product discontinuation occurred in nine patients (E group, 2%; C group, 2%). AEs resulting in death occurred in one patient in the C group.
[g]No AEs were reported with the intervention.
[h]Not reported.
[i]No moderate or serious AEs were reported.
[j]No patients experienced intervention-related AEs.
[k]Grade 1 to 2 AEs included 27 patients in the E group and 24 patients in the C group; grade 3 to 5 AEs included 1 patient in the E group and 9 in the C group but without details.
[l]Grade 1 AEs included nausea, insomnia, palpitation, headache, and urticaria in the E group and nausea, insomnia, headache, and urticaria in the C group.
[m]AEs included systemic rash and pruritus.
[n]AEs included constipation in the E group.
[o]AEs included nausea, vomiting, insomnia, anxiety, and agitation in both groups.
[p]AEs included increased blood urea nitrogen and creatinine level, flatulence, and dyspepsia but the specific group was not mentioned.
[q]AEs included agitation, anxiety, insomnia, nausea, and vomiting in every group.

AEs, adverse events; BFI, Brief Fatigue Inventory; C, control; CBT-I, cognitive behavioral therapy for insomnia; CF, chronic fatigue; CFS, chronic fatigue syndrome; CFSQ, Chalder Fatigue Severity Questionnaire; ChFi, Chalder Fatigue Scale; CIS, Checklist Individual Strength; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRF, cancer-related fatigue; E, experimental group; EOC, epithelial ovarian cancer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30; EQ-5D-5L, European Quality of Life 5-dimension 5-level Questionnaire; ESAS, Edmonton Symptom Assessment System; FACIT, Functional Assessment of Chronic Illness Therapy; FACT, Functional Assessment of Cancer Therapy; FSS, Fatigue Severity Scale; GBCK25, fermented ginseng powder; ICF, idiopathic chronic fatigue; KRG, Korean red ginseng; MFIS, Modified Fatigue Impact Scale; MFS, Fatigue index based on the Multidimensional Fatigue Scale; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; MSQOL-54, Multiple Sclerosis Quality of Life Questionnaire; NAFLD, nonalcoholic fatty liver disease; NYT, Ninjin'yoeito (Ren Shen Yang Rong Tang); PG, Panax ginseng; POMS, Profile of Mood States; RRMS, relapsing-remitting multiple sclerosis; SF-36, 36-Item Short Form Survey; Sipjeondaebo-tang, Juzentaihoto/shi quan da bu tang; TCM, traditional Chinese medicine; TJ-41, Bojungikki-tang (Hochuekkito/bu zhong yi qi tang); VAS, Visual Analog Scale.

review methodology training sessions on SOPs before each step of the study process. They also conducted quality monitoring, including double entry, data monitoring, and cross-validation.

Results

Search results

The database search yielded 613 records, of which 367 remained after duplicate removal. The authors excluded 267 articles during title and abstract review, respectively, and 53 articles during full-text review, leaving 47 articles for inclusion (Fig. 1). Evaluation of relevant references yielded no additional studies for inclusion. Therefore, a total of 19 studies with a total of 2,413 patients were included in the quantitative analysis, of which 14 were included in the meta-analysis. Data from three of the remaining five studies could not be pooled because of a lack of fatigue-specific outcomes; the other two studies used different comparators (CBT and sodium ferrous citrate).

Characteristics of included studies

The 19 studies were published between 2010 and 2022; 11 were performed in Korea[23–25,34–41] and the remaining eight studies were from Italy,[22] Iran,[42] China,[43] Japan,[44,45] and the United States.[46–48] All studies included adult patients with fatigue. Fourteen studies[22–25,34,38–42,45–48] included fatigue as the primary outcome, and five[35–37,43,44] evaluated fatigue as a secondary outcome. Eight studies included patients with cancer-related fatigue (CRF),[22,25,35,37,40,41,47,48] of which four included patients with any cancer diagnosis and the remaining four focused on patients with a specific type of cancer, including colorectal,[25] head and neck,[22] ovarian cancer,[37] and advanced cancer.[46] In one study[35] in the cancer population, the authors considered fatigue as a secondary symptom resulting from insomnia.

Among noncancer studies, three included patients with chronic fatigue (CF)[23,34,39]; Seven explored fatigue related to particular diseases, including three with nonalcoholic fatty liver disease (NAFLD),[24,36,38] one with chronic obstructive pulmonary disease (COPD),[44] one with MS,[42] and one with preoperative anemia caused by gynecologic disease[45]; and an additional study[43] used the TCM diagnosis of asthenia syndrome to define fatigue. Only nine studies[22,23,34,39–41,46–48] defined the duration or severity of fatigue in their inclusion criteria. Treatment course ranged from 2 to 16 weeks, and three studies[34,41,46] included postintervention follow-ups up to 4 weeks.

Regarding treatments, 13 studies used single ginseng, of which seven included Korean red ginseng (KRG),[24,25,34,37,38,42,43] two original Panax ginseng,[39,46] three American ginseng,[22,47,48] and one fermented ginseng powder (types of ginseng unknown).[36] The remaining six studies used classical ginseng-containing formulas (Table 1).[23,35,40,41,44,45] Ginseng dosage varied from 125 mg to 9 g; however, most studies used a daily

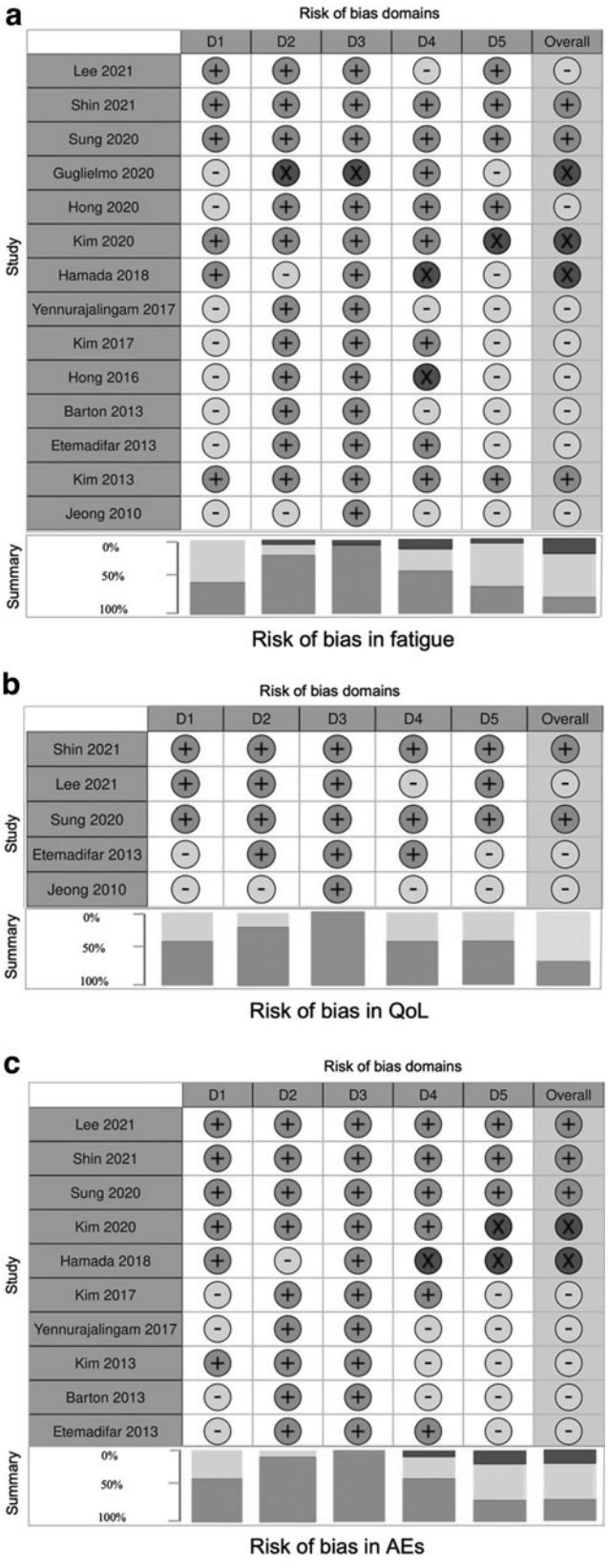

FIG. 2. Risk of bias assessment for each outcome. The **(a)** risk of bias associated with studies reporting fatigue severity; **(b)** risk of bias associated with studies reporting QoL; and **(c)** risk of bias associated with studies reporting AEs. Risk of bias domain definitions: D1 = Bias due to the randomization process; D2 = Bias due to deviation from the intended intervention; D3 = Bias due to missing outcome data; D4 = Bias in measurement of the outcome; D5 = Bias in selection of the reported results. AEs, adverse events; QoL, quality of life.

dosage between 2 and 3 g. Eight studies used ginseng in combination with conventional therapies for primary diseases,[25,38,42,44,45] and two studies did not limit concurrent cancer treatments[35,47] (Table 2).

Among all included studies, 11 two-arm studies[22–25,34,37,38,41,42,46,47] compared ginseng to placebo, 1 two-arm RCT[35] compared ginseng with CBT for insomnia, 1 two-arm RCT[44] compared ginseng to usual care, 1 two-arm RCT[40] compared ginseng to a waiting list group, 1 two-arm RCT[45] compared ginseng plus sodium ferrous citrate to sodium ferrous citrate alone, and 3 three-arm RCTs[36,39,43] and 1 four-arm RCT[48] compared different doses of ginseng to placebo. Sample sizes ranged from 22 to 438. Fourteen different questionnaires were used in the 19 studies to evaluate fatigue severity and its functional interference, 8 studies[23–25,39,40,46–48] of which included multiple instruments.

The most frequently used questionnaires were the Visual Analog Scale (VAS) and BFI, which were used in 12 studies.[22,23,25,34,35,37,39–41,44,47,48] Eight studies also reported general or disease-related QoL using seven different questionnaires, three of which used the European Quality of Life 5-dimension 5-level questionnaire (EQ-5D-5L).[23,24,35] Seventeen articles[22,23,25,34–37,39–48] evaluated AEs. Frequently reported AEs included insomnia, nausea, vomiting, headache, anxiety, agitation, palpitation, and rash (Table 2).

RoB and quality of evidence assessment

RoB ranged from low to high. Major bias was from missing outcome data, deviations from intended intervention, and selection of reported results (Fig. 2a). (1) For fatigue severity, RoB was high in three studies, moderate in eight, and low in three. (2) For QoL, RoB was moderate in three studies and low in two; no studies had high RoB (Fig. 2b). (3) For AEs, RoB was high in two studies, moderate in five, and low in three. Major bias was found in measurement of the outcome and selection of reported results (Fig. 2c). For the outcomes of fatigue severity and safety, quality of evidence was moderate. The main reasons for evidence downgrading were RoB and small effect size. For QoL, the evidence was low quality because of the limited number of included studies and small effect size (Table 3).

Pooled estimates of effects of interventions

Fatigue severity. Pooled data from 14 studies included in the meta-analysis showed that ginseng did not significantly reduce fatigue (SMD: −0.36, 95% CI: −0.82 to 0.11) compared to control (placebo/usual care/waiting list) ($p=0.13$) with significant statistical heterogeneity ($I^2=94\%$) (Fig. 3a). However, sensitivity analysis showed that, excluding one study,[25] it reduced the statistical heterogeneity to 2%, with results showing significant improvement in fatigue (SMD: −0.23, 95% CI: −0.35 to −0.10, $p=0.0003$) (Supplementary Fig. S1).

The excluded study, which had 438 participants, evaluated CRF using the mean area under the curve change from baseline of BFI, whereas other studies used mean value and standard deviation from original levels. That study found that KRG managed CRF more effectively (SMD: −2.20, 95% CI: −2.44 to −1.95) than placebo ($p<0.0001$) in the colon cancer population. The heterogeneity was explained by the large magnitude of effect size and the use of different measurements. The results of the remaining 13 studies showed small to moderate effect size. The funnel plot

Table 3. Quality of Evidence Assessment

Comparison	*Outcomes*	*No. of participants (no. and type of studies)*	*Certainty of the evidence (GRADE)*[a]	*Relative effect (95% CI)*	*Anticipated absolute effects risk with controls*	*Risk difference with Ginseng*[e]
Ginseng vs. controls	Fatigue severity	1413 (14 RCTs)	⊕⊕⊕◯ MODERATE[b]	—	—	SMD 0.36 scores lower (0.82 lower to 0.11 lower)
Ginseng vs. controls	Quality of life	285 (5 RCTs)	⊕⊕◯◯[c] LOW	—	—	SMD 0.23 scores higher (0.00 lower to 0.47 higher)
Ginseng vs. controls	Safety	1287 (10 RCTs)	⊕⊕⊕◯ MODERATE[d]	OR 0.98 (0.89 to 1.08)	400 per 1,000	5 fewer per 1,000 (28 fewer to 19 more)

[a]GRADE Working Group grades of evidence: high certainty, very confident that the true effect is close to the effect estimate; moderate certainty, moderately confident in the effect estimate—the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different; low certainty, confidence in the effect estimate is limited—the true effect may be substantially different from the effect estimate; very low certainty, very little confidence in the effect estimate—the true effect is likely to be substantially different from the effect estimate.

[b]Nine out of 12 studies were associated with moderate to high risk of bias. The results were imprecise due to the confidence intervals, including potential for no effect or benefit and small effect size. One included study contained a dose–response gradient; therefore, the quality of evidence was upgraded one level from low to moderate.

[c]The results were imprecise due to the confidence intervals, including potential for no effect or benefit and small effect size. Funnel plot analysis was not able to be conducted because only four studies reported quality-of-life outcome, three of which reported results that preferred the effect of ginseng and one of which found no significant difference between ginseng and control groups. Publication bias was suspected.

[d]Risk of bias analysis showed moderate to high risk of bias associated with AEs.

[e]The intervention group risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; SMD, standardized mean difference.

(Figs. 2 and 3a) showed asymmetry, indicating high likelihood of publication bias.

Ginseng type. Subgroup analysis by ginseng type (Fig. 3b) showed significant fatigue reduction with ginseng-containing formulas, but not with ginseng as a single herb, with small effect size (study number = 4; SMD: −0.39, 95% CI: −0.66 to −0.13) compared to controls ($p = 0.004$). There was low statistical heterogeneity among included studies ($I^2 = 0\%$). Two studies used the same formula, TJ-41, and showed significant improvements in fatigue severity among patients with COPD (SMD: −0.38, 95% CI: −1.07 to 0.31) and cancer (SMD: −0.48, 95% CI: −1.11 to 0.15) compared to formulas with no ginseng[40,44]; one study showed that the herbal formula Sipjeondaebo-tang was associated with significant improvement in CF compared to placebo (SMD: −0.22, 95% CI: −0.62 to −0.01).[23] One study showed that the herbal formula Sipjeondaebo-tang significantly reduced fatigue in patients with cancer compared to placebo (SMD: −0.68, 95% CI: −1.26 to −0.11).[41]

However, further subgroup analyses did not find significant improvement in fatigue with use of KRG[24,25,34,37,38,42] (six studies included; SMD: −0.50, 95% CI: −1.46 to 0.47), Panax ginseng[39,46] (two studies included; SMD: −0.18, 95% CI: −0.64 to 0.28), or American ginseng[22,47] (two studies included; SMD: 0.05, 95% CI: −0.74 to 0.85), although there was high statistical heterogeneity resulting from different fatigue measurements (all KRG, Panax ginseng, and American ginseng: $I^2 \geq 60\%$).

Fatigue type. Figure 3c shows subgroup analysis by disease type. All three studies of CF in the general population[23,34,39] found that ginseng was effective, including Panax ginseng (SMD: −0.44, 95% CI: −0.88 to 0.01), KRG (SMD: −0.22, 95% CI: −0.79 to 0.36), and Sipjeondaebo-tang (SMD: −0.22, 95% CI: −0.62 to 0.18). In the pooled

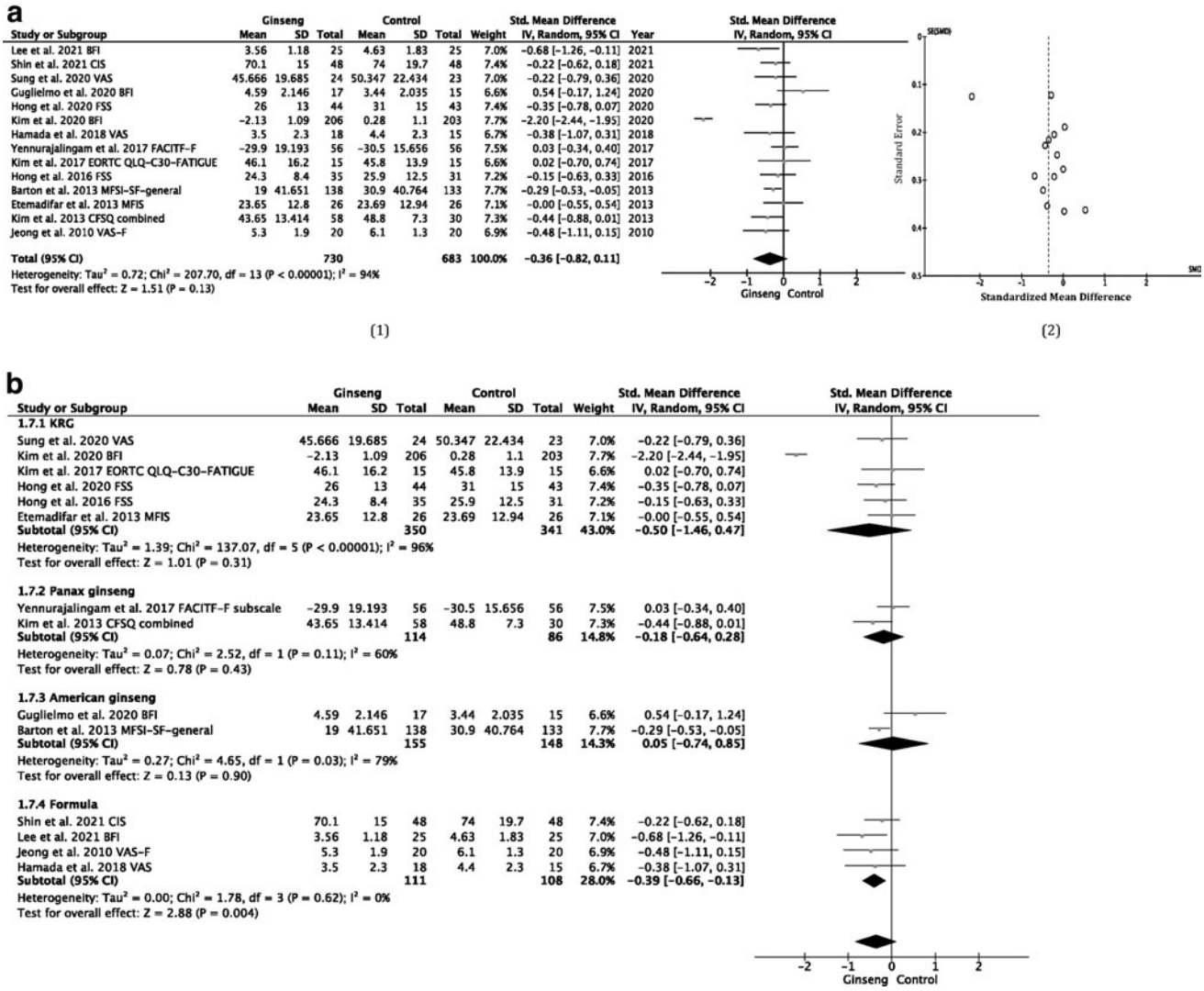

FIG. 3. Forest plot comparing the fatigue severity of the ginseng group versus controls. **(a)** (1) Overall fatigue severity; (2) a funnel plot of the studies included in (1); **(b)** subgroup by ginseng type; **(c)** subgroup by disease type; and **(d)** subgroup by instrument type. CI, confidence interval; SD, standard deviation.

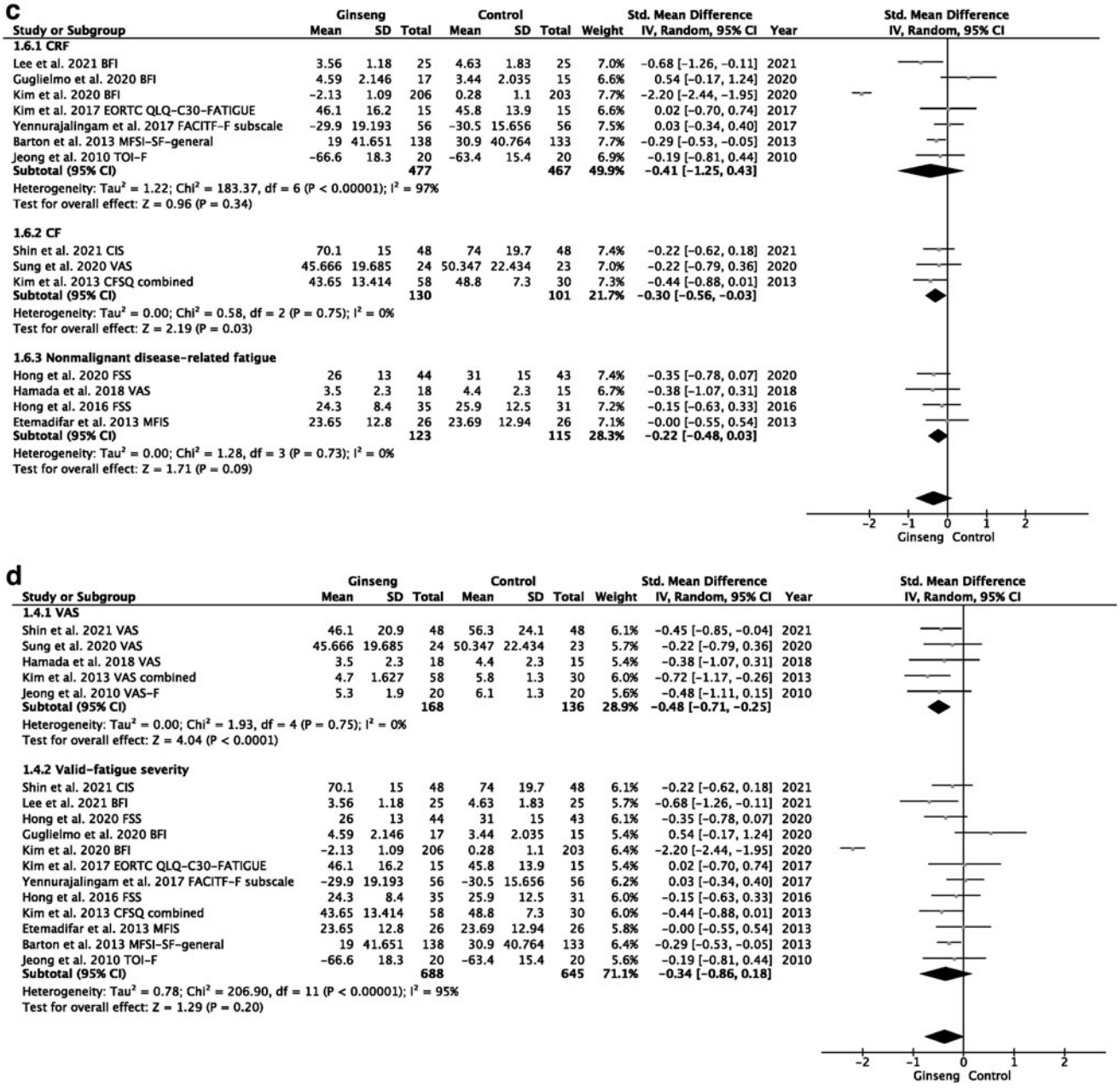

FIG. 3. *(Continued).*

analysis, ginseng significantly reduced CF severity with small effect size (SMD: –0.30, 95% CI: –0.56 to –0.03) compared to placebo ($p = 0.03$), with no heterogeneity. Four studies conducted in nonmalignant disease-related fatigue, including COPD, NAFLD, and MS,[24,38,42,44] found no benefit in fatigue compared to control in the pooled analysis (SMD: –0.22, 95% CI: –0.48 to 0.03, $p = 0.09$).

Results from seven studies in CRF were mixed, with no significant improvement in the pooled analysis (SMD: –0.41, 95% CI: –1.25 to 0.43)[22,25,37,40,41,46,47] compared to controls ($p = 0.34$). Notably, the CRF study with the largest sample size supported the benefit of KRG (2 g daily) over a 16-week period (SMD: –2.20, 95% CI: –2.44 to 0.43) compared to placebo.[25]

Fatigue measurement type. Overall, 5 studies[23,34,39,40,44] measured fatigue severity with VAS and the remaining 14 studies[22–25,37–42,45–47,49] used eight different valid fatigue severity instruments, including the Multidimensional Fatigue Symptom Inventory, Chalder Fatigue Severity Questionnaire, and Fatigue Severity Scale. Pooled analysis across measurement instruments showed inconsistent results: ginseng significantly reduced fatigue compared to controls with no heterogeneity as measured by VAS (moderate effect size) (SMD: –0.48, 95% CI: –0.71 to –0.25, $p < 0.0001$). However, there was no significant improvement in the pooled analysis as measured by valid fatigue instruments (SMD: –0.34, 95% CI: –0.86 to 0.18) compared to controls ($p = 0.20$), with high heterogeneity ($I^2 = 95\%$) (Fig. 3d).

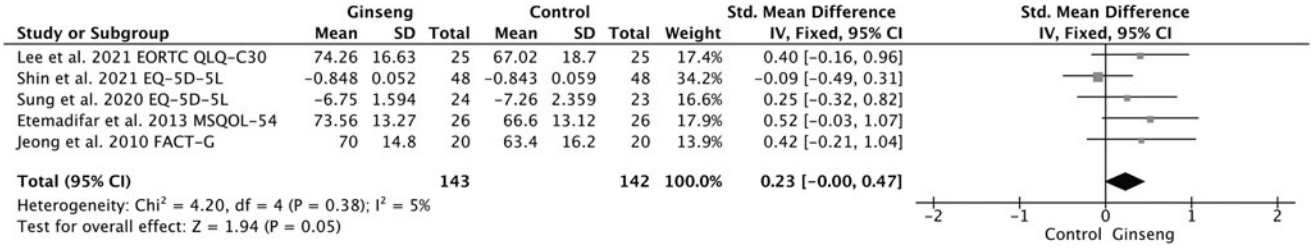

FIG. 4. Forest plot comparing quality of life of the ginseng group versus controls.

Quality of life. Five studies measured QoL changes using the Functional Assessment of Cancer Therapy, Multiple Sclerosis Quality of Life Questionnaire, European Organization for Research, EQ-5D-5L, or Treatment of Cancer-Quality of Life Questionnaire.[23,34,40–42] Four studies found that ginseng improved QoL (Fig. 4).[34,40,42] The largest effect size (moderate) was seen in a study of patients with MS[42] (SMD: 0.52, 95% CI: –0.03 to 1.07), which found that 12-week use of KRG significantly improved MS-related QoL compared to placebo ($p<0.0001$). Similarly, two studies conducted in a cancer population[40,41] found moderate QoL improvement from the use of ginseng formulas, including 2-week use of TJ-41 compared to the wait list group (SMD: 0.42, 95% CI: –0.21 to 1.04) and 3-week use of Sipjeondaebo-tang compared to placebo (SMD: 0.40, 95% CI: –0.16 to 0.96).

However, studies in CF populations had contradictory findings. One study showed that 6-week use of KRG had a small effect size on QoL compared to placebo (SMD: 0.25, 95% CI: –0.32 to 0.82),[34] whereas another study found no benefit of Sipjeondaebo-tang use for 8 weeks (SMD: –0.09, 95% CI: –0.49 to 0.31).[23] In the pooled analysis of the five studies, there was a trend toward improvement in QoL with ginseng (SMD: 0.23, 95% CI: –0.00 to 0.47) compared to controls ($p=0.05$), with low heterogeneity ($I^2=5\%$).[23,34,40–42]

Safety. Ten studies reported the number of AEs in each group (Fig. 5). AEs associated with ginseng were mainly gastrointestinal reactions such as vomiting, nausea, and loss of appetite. Rash, headache, and agitation were also reported in several studies. A pooled analysis of the safety data showed no significant difference in AE occurrence in patients who received ginseng versus control (RR: 0.98, 95% CI: 0.89 to 1.08, $p=0.71$, $I^2=0\%$).

Discussion

This systematic review and meta-analysis evaluated the efficacy and safety of ginseng and ginseng herbal formulas among 2,182 patients in RCTs. The authors found that ginseng was associated with reduction in fatigue, especially when using a ginseng formula and among patients with CF, compared to the placebo/waiting list, without increasing AEs. They also found a trend toward improvement in QoL with ginseng compared to controls. Interpretation of this literature is limited by variable and at times high RoB in the included studies with respect to missing outcomes, data deviations from intended intervention, and selection of the reported result; evidence was rated as moderate quality. Nonetheless, these findings have important clinical and research implications for ginseng in the management of fatigue.

Few remedies for fatigue are supported by strong evidence and clinical practice guidelines do not include specific recommendations regarding standard therapy,[50] although non-pharmacologic interventions such as exercise, yoga, and acupuncture are noted to be effective supportive treatments.[13,50] Herbal medicine, including ginseng, has a long history of use for fatigue management, without robust evidence.[51] The findings suggest that while evidence is imperfect, ginseng is a useful option for treating fatigue. Consistent with other systematic reviews,[17,26–28] it was found that ginseng is associated with improvement in fatigue severity compared with the placebo/waiting list, with a small effect size.

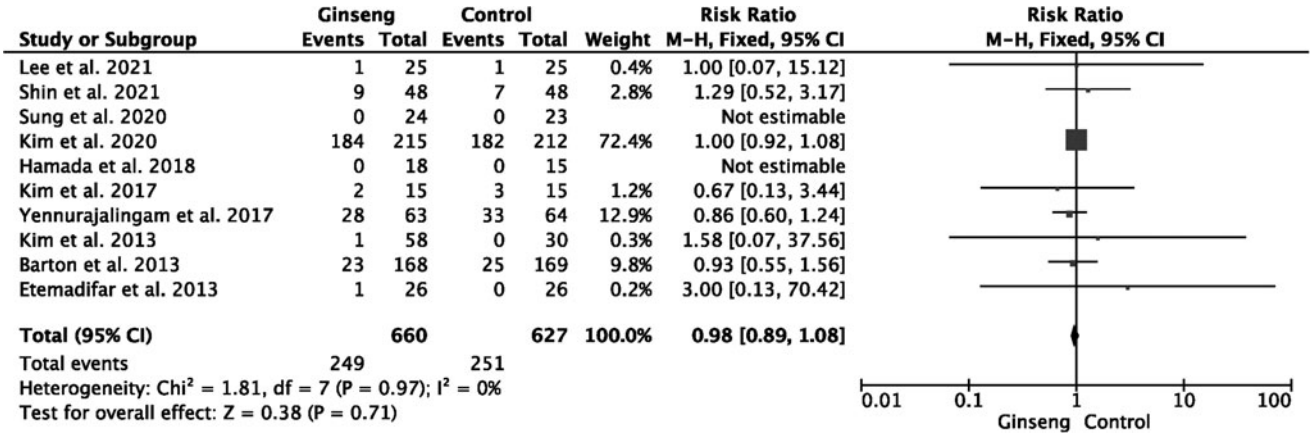

FIG. 5. Forest plot comparing adverse events of the ginseng group versus controls.

The review enhances the prior literature by including multiple types of ginseng and multiple types of fatigue, which broadens applicability of the findings. Without other highly effective evidence-based therapies and with good support that ginseng is safe and at least mildly effective, it is reasonable to include ginseng among the standard supportive approaches for patients experiencing fatigue.

The subgroup analysis suggests that multicomponent ginseng-containing herbal formulas may lead to better fatigue reduction than ginseng alone, although effect sizes were small to moderate. Fatigue is a nonspecific condition with multiple etiologies and multidimensional clinical presentations,[52] so it is not surprising that multimodal therapies that include products with multiple herbs may be more effective than single agents. Their results are consistent with other studies showing that multiple herbs combined in formulas or whole extracts often offer better efficacy than equivalent doses of individual active herbs, especially for complex health conditions.[53,54] The authors also found that patients with secondary forms of fatigue may respond less well to ginseng than those with CF, which is consistent with prior studies.[17] Notably, patients undergoing active cancer treatment derived benefit from ginseng use versus placebo without discernible toxicities.[25,47]

Despite evidence for ginseng's efficacy and likely safety, the evidence in support of its safety had mostly a moderate or high RoB and must be considered with caution. There are potential drug interactions with hormone treatments, central stimulants, antipsychotic drugs,[55–57] and possibly warfarin.[58–60] More evidence regarding these interactions and the overall safety of ginseng is needed, and clinical monitoring in patients using ginseng is prudent.

To advance the field and better inform clinicians and patients, further methodologically rigorous research is needed to provide more reliable evidence of the safety and efficacy of ginseng for fatigue. These studies should clearly define fatigue and apply reasonable inclusion criteria to avoid a floor effect. Their findings are helpful for informing such studies. Because classic ginseng formulas may be more efficacious than single ginseng for fatigue, especially nonspecific fatigue, future randomized trials should focus on evaluating these products. In addition, ginseng is likely to work best in combination with other therapeutic modalities, so studies of combination therapy will be important. Future studies should also utilize validated instruments targeting specific domains of fatigue rather than general instruments such as VAS to reduce the risk of detection bias, especially in patients with secondary fatigue.

Assessment of drug–herb interactions, QoL assessment, and long-term follow-up, which have not been well addressed in included studies, are key components of future trials. Studies comparing various doses are also needed to determine the optimal dose of ginseng for fatigue and active treatment-controlled trials are critical for evaluating the effect of ginseng in both experimental and real-world settings.

Notably, the mechanism of the effect of ginseng on fatigue is not yet fully understood. A recent study demonstrated that the antifatigue mechanism of ginseng may be associated with enhancement of energy metabolism and antioxidant and anti-inflammatory activity.[19] A study using a rat model of postoperative fatigue syndrome indicated that the use of ginsenoside Rb1 may improve energy metabolism in skeletal muscle through an increase in the content of adenosine triphosphate (ATP) and an enhanced activity of energy metabolic enzymes such as Na+-K+-ATPase and succinate dehydrogenase.[61] Another study suggested that the antioxidation effects of ginseng are related to the reaction of water soluble ginseng acidic polysaccharide on physiologic biomarkers of oxidative stress and the morphology of the mitochondria in striated skeletal muscle.[62] Inhibition of inflammatory responses may be related to a water extract of KRG through the suppression of the p38/JNK/TBK1 activation pathway.[63]

In addition, ginseng and ginseng extract may also impact fatigue by ameliorating lipid peroxidation, metabolic disorders of bile acids, amino acids, fatty acids, and lipids, or impacting gut microbiota dysbiosis.[64] Further studies are needed to explore and identify specific antifatigue mechanisms of ginseng that could impact clinical applications.

Limitations

This study has limitations. First, treatment effect was only measured at completion of treatment in included studies, and long-term follow-up data were only available for one study. The authors were also unable to include data from additional ongoing studies. Further, because there is no standard prescription for quantification of ginseng, they could not account for dose or duration in the analysis. In addition, they did not include non-English databases. Finally, they pooled study results across doses of ginseng and fatigue type, hypothesizing that the effect should be similar. They used the Random Effects Model in the presence of statistical heterogeneity. This approach may limit the applicability of the pooled effect estimate in some situations, but they believe that it reflects the true efficacy of ginseng overall.

Despite these limitations, the authors' review was focused on RCTs, the highest form of evidence, and included a diverse global population, thus optimizing applicability. They performed a comprehensive appraisal that included all fatigue populations, in which they pooled data and explored subgroups, providing the most relevant information for patients and clinicians.

Conclusion

In conclusion, this systematic review and meta-analysis found that among patients with fatigue, ginseng is safe and associated with improvements in fatigue severity. The findings support the cautious use of ginseng in patients with fatigue, especially given the lack of other therapeutic options. Further rigorous clinical trials focused on reliable outcome measurements, and long-term effects are warranted to assess the full effects of ginseng for fatigue.

Authors' Contributions

J.J.M. and M.Y. conceived the study. X.L. designed the study protocol. X.L. and Y.L.Z. collected the data. X.L. and M.Y. performed statistical analyses. X.L. wrote the article and created the tables and figures. X.L., M.Y., C.M.S., Y.L.Z., Y.N.H., J.J.M., and D.K. critically revised the article. All authors approved the final version of the article. All data were generated inhouse, and no paper mill was used.

All authors agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Author Disclosure Statement

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Supplementary Material

Supplementary Figure S1
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4

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