

Ginseng for the Management of Cancer-Related Fatigue: An Integrative Review

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Author's disclosure of conflicts of interest is found at the end of this article.

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<https://doi.org/10.6004/jadpro.2021.12.4.5>

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Abstract

Background: Cancer-related fatigue (CRF) is one of the most prevalent, debilitating symptoms affecting a majority of patients with cancer worldwide. It can lead to poor compliance with anticancer therapy and discontinuation of treatment. Current management strategies for CRF center around activity and exercise; however, these strategies can be challenging for many patients undergoing active treatment. Ginseng has been shown to improve CRF and may provide benefit for patients suffering from CRF. **Methods:** A systematic review was completed by searching PubMed and Scopus databases. **Results:** 115 search results were reduced to a final sample of five articles after applying inclusion and exclusion criteria. Published results suggest that 2,000 mg of American ginseng once daily improves symptoms of CRF. Minimal side effects or drug interactions are observed. Additional research is needed to further evaluate the role of ginseng for CRF. **Conclusion:** There are data to support the use of American ginseng to treat CRF. Large-scale randomized controlled trials are needed to validate these findings and determine optimal dosage and duration of therapy.

Cancer-related fatigue (CRF) is one of the most prevalent, debilitating symptoms, affecting a majority of cancer patients (up to 99%) worldwide and potentially persisting for up to 10 years after treatment (Gupta et al., 2007; Liu et al., 2012; Neefjes et al., 2013). The National Comprehensive Cancer Network defines CRF as a “distressing, persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (NCCN, 2019). While the etiology of CRF is not fully understood, it is believed to be multifactorial and can be attributed to cancer biology as well as anticancer treatment (Neefjes et al., 2013). Cancer-related fatigue can be devastating, affecting all aspects of a patient’s life, including but not limited to activities of daily living (ADLs), productivity, sleep, relationships, and caregivers. Furthermore, CRF may lead to poor compliance with anticancer therapy and discontinuation of treatment (Liu et al., 2012).

Current management strategies for CRF center around activity and exercise (NCCN, 2019). Complementary therapies such as tai chi, yoga, acupuncture, massage therapy, and cognitive behavior therapy have been researched; however, rigorous data are lacking and early findings have yet to be replicated (Arring et al., 2019). While pharmacological interventions, such as psychostimulants and steroids, have been investigated, many have been found to be ineffective in randomized controlled trials (RCT; Bruera et al., 2006; Ruddy et al., 2014). Ginseng has long been touted as a valued herbal remedy in Chinese traditional medicine, and more recently has gained favor in Western cultures for several different ailments, including fatigue, cancer, and diabetes (Attele et al., 1999; Kiefer & Pantuso, 2003).

Ginseng products are commonly referred to as “adaptogens” in alternative medicine realms; a term that denotes an agent that has the ability to restore balance and increase resistance to physical, chemical, and biological stress (Kiefer & Pantuso, 2003). There are two primary species of ginseng; Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*). The most important active ingredients in both species are ginsenosides (Bach et al., 2016; Kiefer & Pantuso, 2003). Chemically, ginsenosides are considered glycosides that have been reported to affect a wide range of biological processes, resulting in hypoglycemia and anti-inflammatory and cardioprotective effects (Szczyka et al., 2019). Both species have been widely used worldwide with a belief that ginseng will improve overall quality of life (QOL), including fatigue.

While the pharmacology is not completely understood, there are recognized differences between the drug metabolism of American and Asian ginseng, although neither appear to have clinically significant drug interactions (Davis & Behm, 2019). In a report investigating herbal supplements and tinctures for potential inhibitory effects of the cytochrome P450 3A4 system, American ginseng was found to be noninhibitory (Budzinski et al., 2000). Furthermore, few side effects are observed with both American and Asian ginseng supplementation, although patients taking high doses of American ginseng, defined as greater than 2.5 grams per day, have reported in-

somnia, tachyarrhythmias, hypertension, and nervousness (Mancuso and Santangelo, 2017).

There are a number of RCTs that have reported on the efficacy of ginseng supplementation on fatigue reduction, although there are fewer that focus on CRF (Bach et al., 2016). The aim of this review is to present an integrative examination of available research on ginseng’s role in improving CRF. Due to the scarcity of data available on American ginseng alone or Asian ginseng alone, this article examines current evidence for using both species of ginseng for the management of CRF.

METHODS

The electronic databases of PubMed and Scopus were searched using the following keywords: ginseng, cancer-related fatigue, Asian ginseng, American ginseng, quality of life, and fatigue. One hundred fifteen studies with human participants published from January 2009 to April 2019 were identified and reviewed for ginseng as an intervention for CRF (see Figure 1). The identified studies were further examined for those relevant to patients with CRF treated with ginseng. Five studies were identified for this integrative review: four RCTs and one retrospective review (see Table 1).

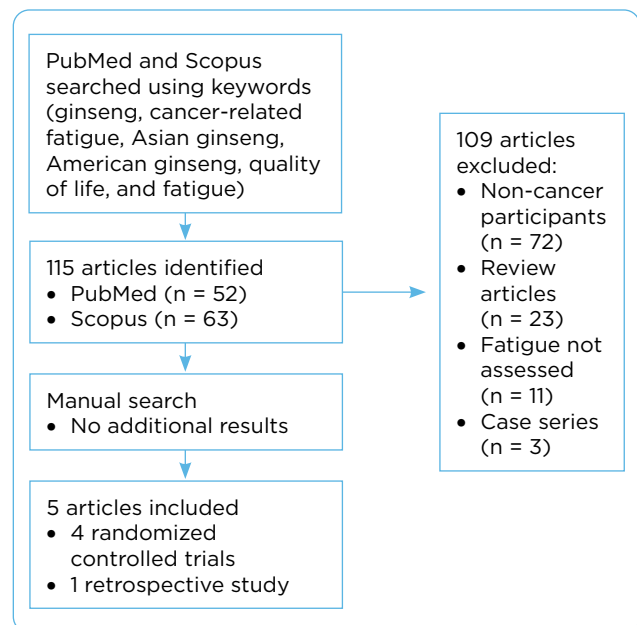


Figure 1. Selection of studies examining ginseng.

Table 1. Summary of Literature Review

Article	No. of patients	Cancer types	On active cancer treatment, n (%)	Dose of ginseng	Duration of tx	Measures of fatigue	Results (p value)
Barton et al., 2010 (RCT; American Ginseng [W1])	Total: 282	Breast: 109 Colon: 29 Lung: 35 Combination/Other /Unknown: 160	Chemotherapy: 160 (57%) Radiation therapy: 51 (18%)	750 mg qd 1,000 mg qd 2,000 mg qd	8 weeks	<ul style="list-style-type: none"> Primary outcome measure: Brief Fatigue Inventory (BFI) Secondary outcome measures: Vitality subscale of the Medical Outcome Scale Short Form-36 (SF-36); The Pittsburgh Sleep Quality Index (PSQI); Global Impression of Benefit Scale; Linear analogue self-assessment scale 	No significant difference of activity interference or usual fatigue between placebo and collective ginseng arms Subset analyses revealed trend for greater positive effects on ginseng 2,000 mg daily dosing
Barton et al., 2013 (RCT; American ginseng [W1])	Total: 364 Ginseng group: 183 Placebo group: 181	Ginseng arm: Breast: 110 Colon: 20 Hematologic: 8 Prostate: 6 Combination/unknown/other: 22	Ginseng arm: 83 (49%) Placebo arm: 83 (49%)	2,000 mg qd	8 weeks	<ul style="list-style-type: none"> Primary outcome measure: Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) Secondary outcome measures: Profile of Mood States (POMS); Brief Fatigue Inventory (BFI) 	Statistically significant improvement in fatigue in ginseng arm (p = .003)
Yennurajalingam et al., 2017 (RCT; Asian ginseng)	Total: 127 Ginseng group: 63 Placebo group: 64	Ginseng arm: Breast cancer: 15 GI cancer: 4 GU cancer: 31 Thoracic cancer: 9 Other: 4	NR	400 mg bid	29 days	<ul style="list-style-type: none"> Primary outcome measure: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Secondary outcome measures: Edmonton Symptom Assessment System (ESAS); Hospital Anxiety and Depression Scale (HADS); Global Symptom Evaluation (GSE) 	No significant difference in ginseng vs. placebo group (p = .67)

Note. RCT = randomized controlled trial; R = retrospective; NR = not reported; W1 = Wisconsin; GI = gastrointestinal; GU = genitourinary; QOL = quality of life.

Table 1. Summary of Literature Review (cont.)

Article	No. of patients	Cancer types	On active cancer treatment, n (%)	Dose of ginseng	Duration of tx	Measures of fatigue	Results (p value)
Chang, et al., 2018 (R; American ginseng)	Total: 15	Breast cancer: 3 Carcinoid tumor: 1 Colon cancer: 3 Endometrial cancer: 1 Melanoma: 1 Multiple myeloma: 2 Lung cancer: 1 Pancreatic cancer: 1 Head and neck cancer: 1 T-cell lymphoma: 1	15 (100%)	2,000 mg qd (12 patients took in combination with methylphenidate 10-40 mg/day)	Reported mean of 30.5 days	<ul style="list-style-type: none"> Edmonton Symptom Assessment System (ESAS) 	Significant reduction in fatigue score ($p < .0002$)
Pourmohamadi et al., 2018 (RCT; Asian ginseng)	Total: 114 Ginseng group: 54 Placebo group: 60	Nonmetastatic colon cancer: 114	All participants received 1 prior cycle of chemotherapy	100 mg qd	30 days	<ul style="list-style-type: none"> Beck questionnaire Short-form inventory for assessing and recording the symptoms of fatigue (researcher-built test) 	Ginseng associated with significant improvement in QOL and mood ($p < .0001$)

Note: RCT = randomized controlled trial; R = retrospective; NR = not reported; WI = Wisconsin; GI = gastrointestinal; GU = genitourinary; QOL = quality of life.

RESULTS

Sample Characteristics

Sample sizes of included studies ranged from 15 to 364 participants, and all patients had a cancer diagnosis. Cancer types included were breast cancer, colon cancer, lung cancer, combination/other, hematologic, prostate cancer, gastrointestinal (GI) cancer, genitourinary (GU) cancer, carcinoid tumor, endometrial cancer, melanoma, multiple myeloma, pancreatic cancer, head and neck cancer, and T-cell lymphoma. A majority of participants were reported to be on active cancer treatment either in the form of systemic therapy or radiation, although Yennurajalingam and colleagues (2017) did not report this data. Duration of treatment with ginseng ranged from 29 to 56 days (Barton et al., 2010, 2013; Chang et al., 2018; Pourmohamadi et al., 2018; Yennurajalingam et al., 2017).

American Ginseng (*Panax quinquefolius*)

Three of the included studies explored American ginseng for management of CRF. Barton and colleagues (2010) completed a pilot study evaluating three different doses (750 mg, 1,000 mg, and 2,000 mg) of daily American ginseng (specifically Wisconsin ginseng, a common type of American ginseng), as compared with placebo. The duration of treatment was 8 weeks for each treatment arm. Patients included in this study were varied regarding treatment history and cancer type. Across all cohorts, 57% were undergoing active chemotherapy and 18% were receiving current radiation therapy; cancer types in the study consisted of breast (n = 109), colon (n = 29), lung (n = 35), and “combination/unknown/other” (n = 109; Barton et al., 2010). No significant difference in activity interface or usual fatigue between placebo and treatment arms was significant; however, a subset analysis reported a trend towards improvement of fatigue in the cohort using a daily dose of 2,000 mg (Barton et al., 2010).

Barton and colleagues (2013) went on to complete a multisite, double-blind trial assessing 2,000 mg American ginseng (specifically Wisconsin ginseng) as compared with placebo for a duration of 8 weeks. Study participants included those with breast (n = 206), colon (n = 22), hematologic (n = 10), prostate (n = 9), gynecologic (n = 7) and combination/unknown cancer (n =

32), and 49% in both the control and treatment arm were undergoing active treatment. A statistically significant improvement in fatigue was reported in the ginseng arm ($p = 0.003$); subset analysis comparing those on active cancer therapy with those who had completed treatment reported a statistically significant improvement in fatigue at 4 weeks ($p = 0.02$) and 8 weeks ($p = .01$) in participants receiving active treatment as compared with those in the placebo arm (Barton et al., 2013). To note, there were no statistically significant differences in toxicities between arms per Common Terminology Criteria for Adverse Events (CTCAE) grading.

Chang and colleagues (2018) completed a retrospective study assessing 2,000 mg of American ginseng dosed daily. A majority of participants (n = 12) were also prescribed concurrent methylphenidate at doses of 10 to 40 mg daily. Multiple cancer types were included in this trial, specifically breast cancer (n = 3), carcinoid tumor (n = 1), colon cancer (n = 3), endometrial cancer (n = 1), melanoma (n = 1), multiple myeloma (n = 2), lung cancer (n = 1), pancreatic cancer (n = 1), head and neck cancer (n = 1), and T-cell lymphoma (n = 1). All participants were on active cancer treatment. The mean duration of treatment was reported to be 30.5 days. The authors report a statistically significant reduction in participants' fatigue scores ($p < .0002$). 11% (n = 2) of patients reported grade 2 adverse events of anxiety and diarrhea per CTCAE grading (Chang et al., 2018).

Asian Ginseng (*Panax Ginseng*)

Two studies examined the impacts of Asian ginseng on CRF. Yennurajalingam and colleagues (2017) completed a RCT comparing 400 mg of twice daily Asian ginseng with placebo for a duration of 29 days. The authors did not report on whether patients were undergoing active treatment. Study participants included those with breast (n = 22), GI (n = 4), GU (n = 78), gynecologic (n = 1), and other cancers (n = 8; Yennurajalingam et al., 2017). There was no statistically significant difference in fatigue measures between the placebo or ginseng arm ($p = 0.67$; Yennurajalingam et al., 2017). One participant in the ginseng arm reported a grade 3 to 5 adverse event, specifically an infection.

Pourmohamadi and colleagues (2018) completed an RCT comparing 100 mg of daily Asian ginseng for a duration of 30 days. Unique to this trial, all participants (n = 113) shared a diagnosis of nonmetastatic colon cancer and had received one prior cycle of chemotherapy. The authors did not report specifically on improvement in fatigue in the ginseng arm as compared with placebo; rather, they reported on other QOL measures and reported a statistically significant improvement in mood and “sleeping abilities” in the ginseng arm ($p < .0001$) as compared with placebo. No toxicity data were reported.

Side Effects and Ideal Dosage

Few side effects were reported across the five studies included in this review. Chang and colleagues (2018) reported 11% of patients experienced grade 2 diarrhea; however, this was attributed to methylphenidate and not ginseng. Yennurajalingam and colleagues (2017) reported one patient treated with ginseng had an arm infection, although the correlation with ginseng is unknown. Pourmohamadi and colleagues (2018) did not report adverse events; furthermore, neither Barton and colleagues (2010) nor Barton and colleagues (2013) reported a significant difference in toxicities between treatment and placebo arm (see Table 2).

Doses of both American and Asian ginseng varied in the included studies. Yennurajalingam and colleagues (2019) evaluated a dose of 400 mg twice daily Asian ginseng, which did not yield a significant improvement in fatigue. Similarly, Pourmohamadi and colleagues (2018) evaluated a dose of 100 mg of daily Asian ginseng and re-

ported no significant improvement in fatigue. Both Chang and colleagues (2018) and Barton and colleagues (2013) reported a significant reduction in fatigue for patients taking 2,000 mg of American ginseng daily with few reported side effects. Therefore, 2,000 mg daily of American ginseng could be considered as a possible starting point for future trials, as there are not enough data available at the time of this publication to make definitive dosing recommendations for standard-of-care practice.

Measures of CRF

As a greater understanding of the complexity of CRF is appreciated among cancer researchers, multiple tools have been developed to assess the range of symptoms CRF manifests. The studies included in this review employed many different measures of fatigue as the primary endpoint. Barton and colleagues (2010) used the Brief Fatigue Inventory (BFI) for primary outcome assessment. The BFI is a short-form survey that assesses fatigue in the present moment, usual fatigue in the last 24 hours, and worst fatigue in the last 24 hours, as well as other interface items, including general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life. This tool was developed by Mendoza and colleagues (1999) for use in cancer patients and is considered a reliable instrument to rapidly assess fatigue level in cancer patients.

In Barton’s follow-up RCT in 2013, investigators used the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) to assess the primary endpoint. The MFSI-SF is a valid and reliable measure of CRF that includes 30 items

Table 2. Reported Toxicities of Ginseng

Article	Dosage of ginseng	Toxicities
Barton et al., 2010	750 mg qd, 1,000 mg qd, 2,000 mg qd	No statistically significant difference in toxicities between treatment and placebo arms
Barton et al., 2013	2,000 mg qd	No statistically significant difference in toxicities between arms
Yennurajalingam et al., 2017	400 mg bid	1 patient in ginseng arm reported infection
Chang et al., 2018	2,000 mg qd (12 patients took in combination with methylphenidate 10–40 mg/day)	11% of patients developed grade 2 adverse effect of anxiety or diarrhea
Pourmohamadi et al., 2018	100 mg qd	Not reported

to assess the multidimensional nature of fatigue (Stein et al., 2004). Patients are asked to rate each item on a four-point Likert scale of 0 “not at all” to 4 “extremely” based on their experience from the past 7 days. Items assessed include statements such as “I am fatigued,” “I am worn out,” “I have trouble paying attention,” and “I am forgetful” (Stein et al., 2004).

Yennurajalingam and colleagues (2017) assessed fatigue using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). The FACIT-F consists of 27 QOL questions divided into four domains: physical, social, emotional, and functional, with a 13-item fatigue subscale. The 13-item fatigue subscale was the primary outcome of this study (Yennurajalingam et al., 2017). Patients are asked to rate the intensity of their fatigue on a four-point Likert scale of 4 “not fatigued at all” to 0 “very much fatigued” as experienced over the prior 7 days (Webster et al., 2003).

Chang and colleagues (2018) used the Edmonton Symptom Assessment System (ESAS) as the primary assessment of fatigue. This tool is widely used by palliative care providers and assesses the intensity of symptoms over a 24-hour period, including an 11-point numerical rating system for fatigue, where 0 represents no symptom and 10 represents worst symptom (Chang et al., 2018). Hui and colleagues report that the ESAS tool is responsive to change, with the optimal cutoff for improvement being equal or greater to one and the optimal cutoff for deterioration being less than or equal to 1 for each of the 10 symptoms assessed (Hui et al., 2015).

Finally, Pourmohamadi and colleagues (2018) developed a “customized questionnaire” for study participants, which included the Beck questionnaire and a researcher-built test (Pourmohamadi et al., 2018). The short-form, researcher-built inventory assessed fatigue based on three QOL metrics: muscular pain, degree of happiness, and sleep quality. These were coded on a three-point Likert scale of 1 “mild,” 2 “moderate,” and 3 “severe” (Pourmohamadi et al., 2018). The Beck questionnaire is a widely used tool for assessing the severity of both cognitive and somatic aspects of depression; little data exist on the validity of this questionnaire to measure CRF (Aalto et al., 2012).

DISCUSSION

Cancer-related fatigue is a pervasive toxicity of multiple different anticancer therapies across the cancer care continuum. Clinicians in medical oncology, radiation oncology, and survivorship encounter this side effect on a regular basis. Besides exercise, which is not always feasible for many patients, few other evidence-based options exist to help patients manage CRF. Early data suggest American ginseng can improve CRF, although further studies are needed to validate these early findings.

The studies included in this review were varied in terms of cancer types included. The most commonly included cancer type was breast cancer (n = 237) followed by colon cancer (n = 166). Given the high incidence of these malignancies in the United States, this is perhaps not surprising, although the paucity of data for other neoplasms is a limitation. Given the heterogeneity of treatment regimens across different malignancies, it is important to recognize the degree and etiology of CRF can also vary, which might cause one cancer type to be more responsive to ginseng than others. It is for this reason that prospective trials are needed to target specific populations to fully understand the potential benefit. One area of immediate need is prostate cancer; given the high incidence of this malignancy, as well as the long-term treatment trajectory many of these patients face, it is an ideal population in which to assess the efficacy of ginseng for CRF. Furthermore, in the era of immunotherapy and targeted therapies, the differences in the pathogenesis of CRF as compared with cytotoxic chemotherapy and radiotherapy warrant further investigation.

Another limitation of this review is the diversity of patient samples regarding timing of treatment course and stage of disease. For example, Pourmohamadi and colleagues (2018) included only participants with nonmetastatic colon cancer, while other researchers included survivors, those on active treatment, those with localized disease, as well as patients with advanced or metastatic disease. Stage of cancer warrants stratification as CRF is often worse in later stages of the disease. Additionally, none of the studies included used the same measure of CRF, making the results difficult to compare. Given the numerous tools available to researchers and clinicians for measuring CRF, a consensus is needed as to the best available assessment.

The studies included in this review reported few toxicities. Prior preclinical studies have demonstrated American ginseng does not interfere with many chemotherapy agents used in breast cancer patients, suggesting an appropriate safety profile (Duda et al., 1999). However, because herbal supplements, including ginseng, are not regulated by the U.S. Food & Drug Administration, potency between crops is variable and manufacturing processes are not standard. This makes it difficult to know the exact percentage of ginsenosides in different products. Therefore, close attention is warranted to determine quality and potency of ginseng to be used by patients and in future studies.

IMPLICATIONS FOR ADVANCED PRACTITIONERS

Fatigue should be screened and assessed for in any patient with a current diagnosis or history of cancer at regular intervals. Advanced practitioners are well adapted to assess CRF and develop practice guidelines on the best management and assessment strategies. Furthermore, RCTs assessing ginseng in specific cancer populations are warranted. Advanced practitioner researchers are well suited to carry out such research given their expertise in symptom management.

CONCLUSIONS

Early data support the use of American ginseng to treat CRF; the ideal dosing remains to be well defined. As compared with American ginseng, trials that utilized Asian ginseng failed to observe meaningful benefit in improvement of CRF. Large-scale RCTs are needed to replicate these early findings and determine optimal dosage and duration of therapy. Further trials with disease-specific and treatment-specific focus will help clinicians tailor recommendations to different patient populations. ●

Disclosure

The author has no conflicts of interest to disclose.

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