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REVIEW

Dietary supplements and fatigue in patients with breast cancer: a systematic review

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Abstract

Purpose Cancer-related fatigue (CRF) is defined as a distressing, persistent, and subjective sense of physical or emotional and/or cognitive exhaustion. The treatment of CRF includes pharmacological and non-pharmacological therapies; dietary strategies with promising results have also been used. This study aimed to identify dietary supplements that improve fatigue in patients with breast cancer.

Methods A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Data were obtained from PubMed, Scopus, MEDLINE, CENTRAL, and CINAHL databases using the following MeSH terms: breast neoplasms, dietary supplements, diet, and fatigue. In addition, the Google and Google Scholar search engines were used to find grey literature. Methodological quality was evaluated using the risk of bias in randomised clinical trials in the systematic Cochrane reviews, and the quality of the evidence was also analysed using the GRADE system.

Results A total of 893 studies were assessed, of which eight were included in the review, with 932 women diagnosed with breast cancer. The most commonly used supplements that improve fatigue were guarana, acetyl-L-carnitine, and co-enzyme Q10. Two studies had a low risk of bias in all categories and three had high-quality evidence.

Conclusions Dietary supplements or diet patterns are seldom used to treat fatigue in patients with breast cancer. The results of this review showed that guarana extract and a diet rich in whole foods, omega-3 fatty acids, fruits, and vegetables could be used to treat CRF in patients with breast cancer. The studies had a low risk of bias with high-quality evidence on the efficacy of the interventions in treating fatigue in the study population.

Keywords Breast neoplasms · Dietary supplement · Diet · Fatigue · Adverse effects

Background

Anti-neoplastic therapy includes one or more associated treatments such as surgery, radiotherapy, chemotherapy, and hormone therapy. However, several adverse effects are reported to be associated with its use [1]. Fatigue is extremely common, and it does not occur in isolation because it is associated with symptoms such as pain, sleep disorders, anaemia, and depressive symptoms [2].

Cancer-related fatigue (CRF) is defined by the National Comprehensive Cancer Network (NCCN) as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [2].

The cause of CRF is still unknown, and several factors may be involved, such as changes in cytokine levels, circadian rhythm dysfunction, decreased 5-hydroxytryptophan concentration, changes in the metabolism of adenosine triphosphate and its reduced concentration in muscle cells, imbalance in afferent vagal activation, and changes in the hypothalamic pituitary-adrenal axis [3].

Polymorphism in the Met/Met genotype catechol-o-methyltransferase (COMT) gene contributes to higher cortisol concentrations, increased α-amylase activity, and fatigue in patients with breast cancer. This genotype may lead to an imbalance in the pituitary-adrenal hypothalamic

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axis due to reduced COMT activity, higher catecholamine concentrations, and increased pain due to the activation of β-adrenergic receptors, thus contributing to fatigue [4].

In addition to anti-neoplastic treatment, factors such as disease stage are associated with CRF. A meta-analysis that included 27 studies with 12,237 breast cancer survivors showed that disease stage (II and III) and treatments such as chemotherapy increased the risk of intense fatigue. Moreover, an increased risk of severe fatigue has been observed in patients who underwent surgery along with chemotherapy, radiotherapy, or chemotherapy and radiotherapy, either alone or in combination with hormone therapy [5].

CRF is diagnosed after excluding reversible causes such as anaemia, climacteric syndrome, and hypothyroidism. However, it must be emphasised that health professionals often do not have sufficient knowledge on fatigue and its impact on the patient's quality of life. On the other hand, patients consider fatigue unavoidable during cancer therapy [6]. Patients and families should be informed that fatigue management is an integral part of health care and that this symptom may persist during and after cancer treatment [2].

The treatment of CRF includes both pharmacological and non-pharmacological strategies. A recent meta-analysis of 11,525 patients with cancer showed that physical exercise and psychological interventions were effective in reducing CRF during and after cancer treatment and were significantly better than the available pharmaceutical treatments [7].

The use of dietary supplements is a non-pharmacological strategy commonly used by cancer patients with the aim of improving difficult-to-control symptoms such as fatigue [8]. However, the effects are inconsistent and should be interpreted with caution, because many studies of dietary supplements present bias in their methods, which may compromise the results [9]. Dietary supplements include a variety of products such as vitamins, herbs, amino acids, and other botanical compounds [10].

In breast cancer, randomised clinical trials of dietary strategies have shown promising results in improving fatigue [11, 12]. However, there is a lack of studies that synthesise these results to assess the methodological quality of the clinical trials. Until now, there has been no systematic work in the literature evaluating the improvement of fatigue with the use of dietary supplements in patients with breast cancer. This information would be useful for guiding future research in addition to generating a recommendation for the use of dietary supplements. Thus, this study aimed to evaluate which dietary supplements improve fatigue among patients with breast cancer. Furthermore, the adverse effects of supplementation were investigated.

Methods

Protocol

The study protocol was submitted and approved in PROSPERO (CRD42017075782). A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Eligibility criteria

Participants

We included studies on patients aged 18 years and older who were diagnosed with breast cancer and evaluated for fatigue and those who used dietary supplements and/or diet to treat fatigue. Moreover, only clinical trials were included.

The exclusion criteria were as follows: repeated articles, use of another intervention along with supplements and/or diet, pregnant women, men, and patients with cachexia.

Information sources

The articles were obtained from the following databases: PubMed, Scopus (Elsevier), MEDLINE, CENTRAL, and CINAHL. Google and Google Scholar search engines were used to identify grey literature that was not readily available in the databases. The articles were obtained on 31 August 2017. There was no language restriction or time delimitation.

Search strategy

The search was conducted in accordance with the Patient, Intervention, Control, and Outcome strategy [14] by a team of trained evaluators who used the filter Clinical Trial when it was available at the database, and the following Medical Subject Headings (MeSH) with the Boolean operators *AND* and *OR* were also utilised: breast neoplasms (MeSH) AND dietary supplements (MeSH) OR diet (Mesh) AND fatigue (MeSH). The search aimed to answer the following research question: Which dietary supplement improves fatigue in women with breast cancer? Only studies that used fatigue as the primary or secondary outcome were included.

Selection of studies

The title and abstract of the studies were analysed independently, simultaneously, and in pairs, and then they were

read in full. The evaluation was conducted by two reviewers, with discrepancies resolved by a third researcher.

Data items

The following information was obtained:

1. Characteristics of the studies: author, publication year, country, number of groups, loss to follow-up, studied variables, and instrument used to evaluate the outcome of fatigue.
2. Patient characteristics: age, race, clinical history of cancer treatment, tumour stage, and oestrogen receptor status.
3. Characteristics of the intervention: description of the intervention and the placebo, time of intervention, number of evaluations, and primary results.

Risk of bias in each study

To analyse the risk of bias, we used the risk of bias evaluation for randomised clinical trials in the systematic Cochrane reviews [15]. Two reviewers conducted the assessment, and a third reviewer resolved the discrepancies.

Data analysis

Review Manager (RevMan) version 5.3 was used to construct the risk of bias graph. No quantitative statistical analysis was performed (meta-analysis).

Evidence quality analysis

The quality of the evidence was evaluated and the strength of recommendations was assessed using the Grading System of Recommendations Assessment, Development, and Evaluation (GRADE). The study quality was classified into three groups: high quality, moderate quality, low quality, and extremely low quality [16]. The level of evidence was assessed in pairs, and the differences were resolved by a third reviewer.

Results

A total of 893 studies, including published articles and other documents, were identified. Of the 893 articles, 108 were duplicated. Thus, 782 studies were identified after removing the duplicates. The exclusion criteria were as follows: absence of breast cancer ($n=690$), fatigue not used as an outcome ($n=45$), absence of intervention with supplements or diet ($n=3$), and other type of study ($n=14$). In total, 22 of the 30 full-text articles that were selected for eligibility evaluation were excluded. There were eight studies on men, and 14 studies used another intervention along with dietary supplements/diet. Finally, eight studies (seven articles and one dissertation) were included for review (Fig. 1).

Review studies published within the last 6 years (2011–2017) were conducted in the following countries: Brazil [11, 17], the United States [12, 18, 19], Japan [20, 21], and Malaysia [22]. All 932 women who were

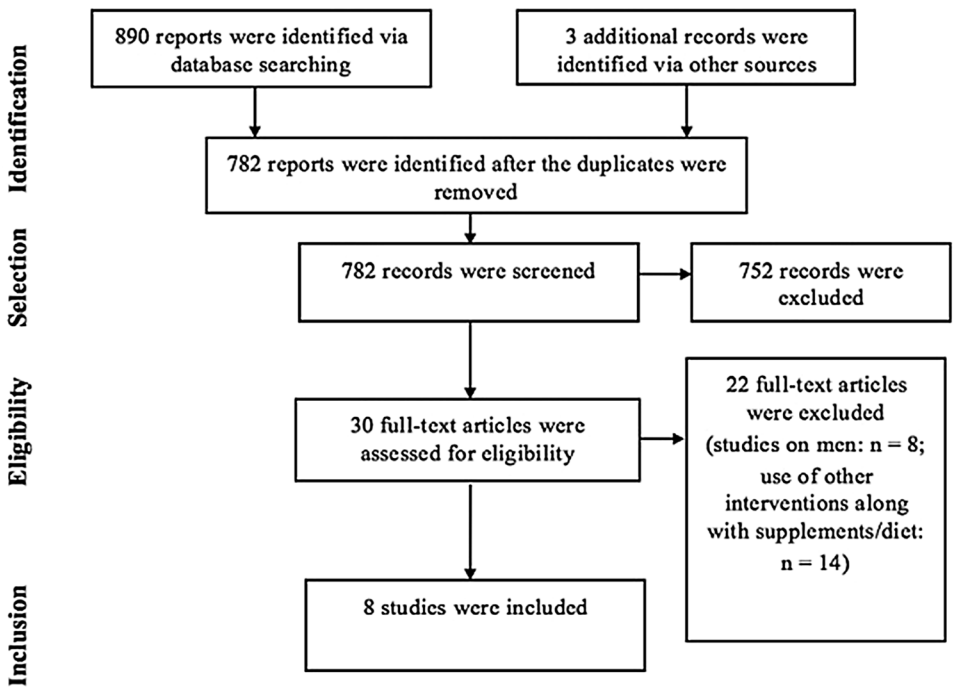

Fig. 1 PRISMA flow diagram

diagnosed with breast cancer or were cancer survivors were included in the review. The sample size of the studies ranged from 30 to 409. One study used two intervention groups (IGs) and one control group (CG) [21], and one study did not report loss to follow-up [22]. Meanwhile, other studies reported from one to 97 patients lost to follow-up [12, 19]. The primary variables were fatigue, quality of life, anxiety and depression, and adverse effects. The Brief Fatigue Inventory was the primary tool used for assessing fatigue (Table 1).

The age of the patients ranged from 20 to 85 years, and two studies did not describe race. The most frequent treatment was chemotherapy ($n=6$), and the most reported tumour stages were grades I–III. In most studies ($n=6$), the hormone receptor status was not described (Table 2).

The main supplements used were the following: guarana extract, acetyl-L-carnitine, and co-enzyme Q10 (CoQ10). These supplements were administered alone or in combination with other supplements. Only one study used diet as the sole intervention. The groups for comparison were diverse, and five articles included a placebo group that used innocuous substances or vitamins. Exercise guidelines or general health care was used in two surveys, and only one study did not use a placebo or exercise guidelines in their CG. The intervention period ranged from 3 to 24 weeks, and the number of evaluations ranged from 2 to 8 (Table 3).

Five of the eight studies that were analysed reported an improvement in fatigue after the intervention period [11, 12, 17, 20, 21]. Studies that used supplementation with chlorella and guarana extract [11, 17] or with branched-chain amino acids, CoQ10, and acetyl-L-carnitine [20] or a fatigue reduction diet [12] reported effects on the overall fatigue and dimensions and feeling of fatigue after the intervention. Supplements such as acetyl-L-carnitine, when administered alone, did not improve fatigue. Moreover, they increased peripheral neuropathy and decreased functional status after 24 weeks of use.

Coconut oil improved the quality of life on a functional and global scale in the CG, but fatigue did not decrease [22]. However, an average decrease in fatigue severity after the intervention period was reported. Supplementation with CoQ10 combined with 300 IU vitamin E was not associated with improvement of fatigue, depression, or quality of life after the study period [19] (Table 3).

The U.S. National Cancer Institute's Common Toxicity Criteria (CTC) were used in five studies. Four studies reported the effects as the number of patients who presented the symptom per event, and one [20] evaluated the frequencies of symptom occurrence (Table 4).

The use of guarana extract was associated with the following effects: palpitation, nausea, insomnia, anxiety, diarrhoea, xerostomia, dry skin, and headache, with grade 2 as

Table 1 Characteristics of the studies included in the review

Author, year	Country	Sample	Number of groups	Lost to follow-up	Studied variables	Instrument used to evaluate fatigue
Albarnaz, 2017 [17]	Brazil	42	2	3	Fatigue, pain, sleep quality, anxiety and depression, adverse effects	Revised piper fatigue scale
de Oliveira Campos et al., 2011 [11]	Brazil	60	2	15	Fatigue, sleep quality, symptoms of menopause, anxiety and depression, adverse effects	FACT-F, chalder fatigue scale, and brief fatigue inventory
Hershman et al., 2013 [18]	USA	409	2	14	Functional evaluation of cancer therapy, fatigue	FACT-F
Iwase et al., 2015 [20]	Japan	59	2	2	Fatigue, quality of life, anxiety and depression	Brief fatigue inventory
Law et al., 2014 [22]	Malaysia	60	2	0	Quality of life (fatigue)	EORTH QLQ-30 and EORTH QLQ-23
Lesser et al., 2013 [19]	USA	236	2	97	Fatigue, overall quality of life, depression, social support	POMS-F, FACT-F, and LASA-fatigue
Noguchi et al., 2014 [21]	Japan	36	3	9	Quality of life, abdominal symptoms, favourable effects on physical condition (fatigue)	None
Zick et al., 2017 [12]	USA	30	2	1	Fatigue, sleep quality, food consumption, plasma carotenoid levels	Brief fatigue inventory

FACT-F functional assessment of chronic illness therapy-fatigue, *FACT-Taxane* functional assessment of cancer therapy-taxane, *EORTH QLQ* European organisation for research and treatment of cancer core quality of life questionnaire, *POMS-F* profile of mood states-fatigue, *LASA-Fatigue* linear analog scale assessment-fatigue, *FACT-B* functional assessment of cancer therapy-breast

Table 2 Analysis of the biological, ethnic, and clinical characteristics of the study participants

Author, year	Age (years)	Race	Clinical treatment period	Tumour stage	Oestrogen receptor status
Albarnaz, 2017 [17]	37–58	White and non-White	Patients with breast cancer undergoing exclusive chemotherapy	I–IV	Not applicable
de Oliveira Campos et al., 2011 [11]	22–60	White and non-White	Patients with breast cancer after the first cycle of chemotherapy	I–III	Not applicable
Hershman et al., 2013 [18]	26–80	White, Black, Asian, Native American, and multiple races	Patients with breast cancer with programmed adjuvant taxane-based chemotherapy	I–III	Not reported
Iwase et al., 2015 [20]	20–80	Not reported	Women with breast cancer undergoing chemotherapy	0–IV	60.7 and 64.5% were positive in the IG and CG, respectively
Law et al., 2014 [22]	30–73	Malaysian, Chinese, and Indian	Patients with breast cancer at the start of the chemotherapy cycle	III–IV	Not reported
Lesser et al., 2013 [19]	28–85	Hispanic, Black, and White	Women with newly diagnosed breast cancer and scheduled to start adjuvant therapy (chemotherapy)	Not reported	Not reported
Noguchi et al., 2014 [21]	36–64	Not reported	Survivors of breast cancer who completed the curative treatment (surgery and/or radiotherapy) or undergoing chemotherapy and/or hormone therapy	Not reported	Not reported
Zick et al., 2017 [12]	47–81	White	Women with breast cancer who completed the treatment except for hormone therapy and Herceptin	0–IIIa	80% were positive in the FRDG; 80% were positive in the CG; and 7% have unknown status

IG intervention group, *CG* control group, *FRDG* fatigue reduction diet group

the highest magnitude of the effect [17]. However, grade 1 adverse events have been reported in another study on guarana extract [11] according to the CTC.

The main grade 3 symptoms resulting from the use of acetyl-L-carnitine were vomiting (IG) and insomnia (CG). Neuropathy was observed in eight patients, with grades 3–4 in the IG and grade 1 in the CG [18]. Studies on the supplements of branched-chain amino acids, CoQ10, and acetyl-L-carnitine reported grade 3 or higher leukopenia in the IG and CG. Other adverse grade 3 effects were observed in the same study, such as anaemia and arthralgia, in one patient from the IG and febrile neutropenia, oral mucositis, and lip infection in one patient from the CG [20].

Law et al. [22] did not use any specific questionnaire to identify adverse effects with coconut oil; however, the questionnaire used to assess the quality of life (European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire) has a specific dimension for cancer treatment-related symptoms. No changes were observed between the groups after six cycles of chemotherapy. Grades 3 and 4 toxicity was observed by Lesser et al. [19]. However, no severe toxicity was attributed to the use of CoQ10. No statistically significant difference was observed between the IG and CG in terms of the degree of toxicity.

The Izumo scale (specific scale for abdominal symptoms) was used in the study by Noguchi et al. [21], and no significant changes were observed during the post-intervention period in any of the study groups who used chlorella granules, chlorella extract, or a mix of vitamins. Adverse effects were not evaluated by Zick et al. [12], and no symptoms were observed in the group using a fatigue reduction diet or in the health care group 12 weeks after the intervention.

The risk of bias analysis showed that two studies [18, 19] had a selection bias for random sequence generation and two had a performance and detection bias [20, 21]. One study showed attrition bias, and two studies showed other types of bias, such as sample size bias [11, 20]. The studies by Albarnaz [17] and Zick et al. [12] showed a low risk of bias for all categories (Fig. 2).

High-quality evidence as assessed using GRADE was observed in three studies [11, 12, 17]. Moderate-quality

Table 3 Characteristics of the intervention (supplementation/diet) used in the studies

Author, year	Supplementation/diet (characteristics)	Control/placebo (characteristics)	Intervention period	Number of evaluations	Main results
Albarnaz, 2017 [17]	50 mg dried guarana extract (1 capsule twice daily, after lunch and dinner)	50 mg crystalline microcellulose (1 capsule twice daily, after lunch and dinner)	± 13 weeks	3	Reduction of total fatigue and the dimensions of fatigue in the guarana group; no changes observed in the placebo group
de Oliveira Campos et al., 2011 [11]	50 mg dried guarana extract every 12 h (twice daily)	Placebo capsules with cellulose every 12 h (twice daily)	14 weeks	3	Improvement in overall fatigue with guarana before and after crossing compared with CG
Hershman et al., 2013 [18]	3,000 mg/day ALC	600 mg cellulose	24 s	6	Increased peripheral neuropathy in ALC group and reduced functional status after 24 weeks
Iwase et al., 2015 [20]	2500 mg Inner Power® (branched-chain amino acids), 30 mg CoQ10, and 50 mg ALC (once daily)	Proper exercises and relaxation techniques were recommended to the CG	± 3 weeks	4	Improved fatigue within the last 24 h; overall fatigue status and change in feeling of fatigue in the IG compared with CG
Law et al., 2014 [22]	10 mL coconut oil (twice daily)	Did not undergo intervention or placebo	3 cycles of chemotherapy	5	Increase in functional and overall QL of IG compared to CG
Lesser et al., 2013 [19]	300 mg CoQ10 combined with 300 IU vitamin E (divided into 3 doses with meals)	Placebo combined with 300 IU vitamin E (divided into 3 doses with meals)	24 weeks	4	CoQ10 was not associated with improvement of fatigue, depression, and LF after 24 weeks or at any time during the study
Noguchi et al., 2014 [21]	Group 1: chlorella granule 6000 mg 4 sticks/day (2 after breakfast, 1 after lunch, and 1 after dinner); Group 2: beverage with extract of chlorella 3 times daily (morning, afternoon, and night), 2400 mg chlorella extract	Mix of vitamins containing 5 mg vitamin B1, 12 mg vitamin B2, 10 mg vitamin B6, 15 mg vitamin B12, 10 mg niacin, 10 mg pantothenic acid, 200 mg folic acid, and 30 mg biotin once daily after breakfast	4 weeks	2	Improvement of QL using the breast cancer subscale and fatigue. Clinical examination showed reduced fatigue and improvement of abdominal symptoms, dry skin, and capillary brightness
Zick et al., 2017 [12]	FRDG: (1) 1/2 of the whole grain intake; (2) 5 servings of vegetables (1 leafy green, 1 tomato, and 1 yellow or orange); (3) 2 servings of fruits (1 high in vitamin C); (4) 1 serving of fatty fish, and (5) 1 serving of nuts, seeds, or oils rich in omega-3 fatty acids	HCCG. The 8 topics were as follows: (1) oral health, (2) healthy vision, (3) discarding of over-the-counter and prescription drugs, (4) healthy skin and hair, cell phones, and health, (6) hearing loss, (7) colorectal cancer screening, and (8) prevention of colds and flu	12 weeks	3 on-site and 8 via telephone	Decreased calorie intake in the HCCG; increase in food intake from the different food groups in the FRDG, except non-citrus fruits and maintenance in the HCCG; reduction of fatigue in the FRDG compared to HCCG; sleep quality increased in the FRDG and decreased in the HCCG; increase in the total carotenoid and omega-3 fatty acid levels in the FRDG and increase in c-tocopherol levels in the HCCG

ALC acetyl-L-carnitine, *CoQ10* co-enzyme Q10, *IG* intervention group, *CG* control group, *QL* quality of life, *FRDG* fatigue reduction diet group, *HCCG* health care control group

Table 4 Adverse effects and symptoms from the use of supplementation or diet

	Albarnaz 2017 [17][a]		de Oliveira Campos et al. 2011 [11][a]		Hershman et al. 2013 [18][a]		Iwase et al. 2015 [20][b]	
	IG	CG	IG	CG	IG	CG	IG	CG
Insomnia	2	3	22	31	22	24	0	0
Palpitation	2	5	10	12	0	0	3.6	0
Nausea	1	2	25	35	21	22	64.3	51.6
Anxiety	2	2	17	25	0	0	0	0
Dermatological	2	1	1	3	0	0	0	0
Diarrhoea	1	2	0	0	0	0	14.3	3.2
Xerostomia	1	3	0	0	0	0	0	0
Allergic reaction	0	0	0	0	0	0	0	0
Anaemia	0	0	0	0	0	0	25	32.3
Constipation	0	0	0	0	0	0	17.9	3.2
Dehydration	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	85.7	87.1
Fever	0	0	0	0	0	0	3.6	6.5
Hot flushes	0	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	0
Left ventricular dysfunction	0	0	0	0	0	0	0	0
Leukopenia	0	0	0	0	0	0	39.3	41.9
Neutropenia	0	0	0	0	0	0	42.9	35.5
Febrile neutropenia	0	0	0	0	0	0	0	3.2
Thrombocytopenia	0	0	0	0	0	0	7.1	3.2
Pain	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	7	4	28.6	12.9
Reflux	0	0	0	0	0	0	0	0
Fullness	0	0	0	0	0	0	0	0
Gastritis	0	0	0	0	0	0	10.7	0
Arthralgia	0	0	0	0	0	0	21.4	22.6
Myalgia	0	0	0	0	0	0	25	19.4
Watery eyes	0	0	0	0	0	0	14.3	3.2
Oedema of the limbs	0	0	0	0	0	0	14.3	12.9
Alopecia	0	0	0	0	0	0	92.9	83.9
Phlebitis	0	0	0	0	0	0	10.7	0
Anorexia	0	0	0	0	0	0	3.6	0
Sensory peripheral neuropathy	0	0	0	0	0	0	10.7	3.2
Motor peripheral neuropathy	0	0	0	0	9	10	0	0
Involuntary movement	0	0	0	0	8	3	0	0
Oral mucositis	0	0	0	0	0	0	17.9	3.2
Dysgeusia	0	0	0	0	0	0	7.1	0
Lip infection	0	0	0	0	0	0	0	3.2

	Law et al. 2014 [22]		Lesser et al. 2013 [19][a]		Noguchi et al. 2014 [21][c]			Zick et al. 2017 [12][d]	
	IG	CG	IG	CG	IG[e]	IG[f]	CG	IG	CG
Insomnia	–	–	0	0	0	0	0	–	–
Palpitation	–	–	0	0	0	0	0	–	–
Nausea	–	–	0	0	0	0	0	–	–
Anxiety	–	–	0	0	0	0	0	–	–

Table 4 (continued)

	Law et al. 2014 [22]		Lesser et al. 2013 [19][a]		Noguchi et al. 2014 [21][c]			Zick et al. 2017 [12][d]	
	IG	CG	IG	CG	IG[e]	IG[f]	CG	IG	CG
Dermatological	–	–	0	0	0	0	0	–	–
Diarrhoea	–	–	0	0	3 (0–4.5)	0 (0–3)	0 (0–2)	–	–
Xerostomia	–	–	0	0	0	0	0	–	–
Allergic reaction	–	–	1	0	0	0	0	–	–
Anaemia	–	–	1	0	0	0	0	–	–
Constipation	–	–	1	1	2.5 (0.3–3)	2 (0.5–4.5)	1 (0–3)	–	–
Dehydration	–	–	3	2	0	0	0	–	–
Dizziness	–	–	1	0	0	0	0	–	–
Fatigue	–	–	1	3	0	0	0	–	–
Fever	–	–	2	1	0	0	0	–	–
Hot flushes	–	–	0	2	0	0	0	–	–
Hypotension	–	–	1	0	0	0	0	–	–
Infection	–	–	5	3	0	0	0	–	–
Left ventricular dysfunction	–	–	0	1	0	0	0	–	–
Leukopenia	–	–	3	2	0	0	0	–	–
Neutropenia	–	–	12	4	0	0	0	–	–
Febrile neutropenia	–	–	0	0	0	0	0	–	–
Thrombocytopenia	–	–	0	0	0	0	0	–	–
Pain	–	–	1	4	0 (0–4)	0 (0–2.5)	0 (0–3)	–	–
Vomiting	–	–	1	1	0	0	0	–	–
Reflux	–	–	0	0	1 (0–6)	2 (0–4)	0 (0–1)	–	–
Fullness	–	–	0	0	1 (0–3)	2 (0–3.5)	0 (0–2)	–	–
Gastritis	–	–	0	0	0	0	0	–	–
Arthralgia	–	–	0	0	0	0	0	–	–
Myalgia	–	–	0	0	0	0	0	–	–
Watery eyes	–	–	0	0	0	0	0	–	–
Oedema of the limbs	–	–	0	0	0	0	0	–	–
Alopecia	–	–	0	0	0	0	0	–	–
Phlebitis	–	–	0	0	0	0	0	–	–
Anorexia	–	–	0	0	0	0	0	–	–
Sensory peripheral neuropathy	–	–	0	0	0	0	0	–	–
Motor peripheral neuropathy	–	–	0	0	0	0	0	–	–
Involuntary movement	–	–	0	0	0	0	0	–	–
Oral mucositis	–	–	0	0	0	0	0	–	–
Dysgeusia	–	–	0	0	0	0	0	–	–
Lip infection	–	–	0	0	0	0	0	–	–

IG intervention group, *CG* control group or placebo

[a]Data expressed as absolute numbers patients who presented the symptom per event

[b]Data expressed as percentage

[c]Data expressed as median, first and third quartiles

[d]Study did not evaluate adverse events

[e]Chlorella granules

[f]Chlorella extract

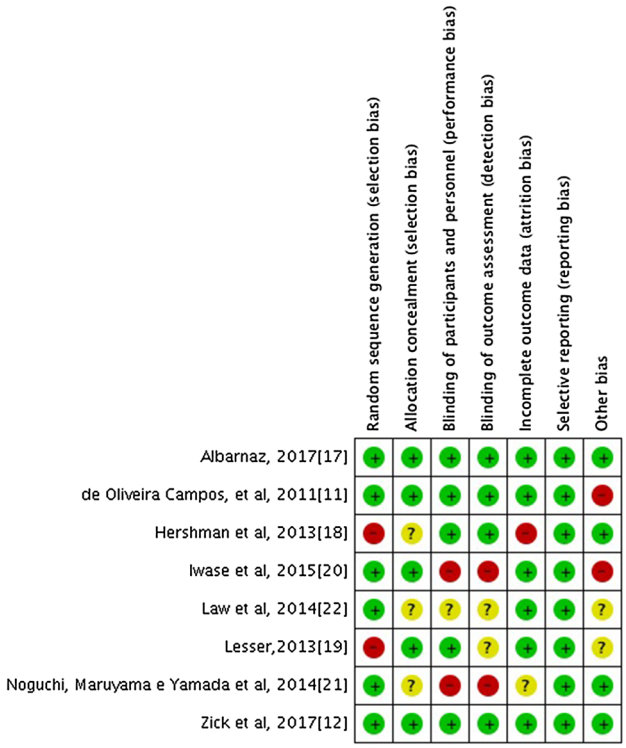

Fig. 2 Summary of the risk bias in each study

evidence was observed in three studies [19, 20, 22], and two studies showed low-quality evidence [18, 21] (Table 5).

Discussion

CRF is an extremely common and persistent symptom in patients with cancer. However, only few studies have investigated the use of dietary supplements to reduce fatigue in patients with breast cancer. The Brief Fatigue Inventory was the most used instrument for evaluating fatigue, and studies that used guarana extract and a fatigue reduction diet for women with breast cancer had a low risk of bias and a high level of evidence.

The main objective of fatigue evaluation is to obtain a complete and detailed history to differentiate its causes in patients with cancer. Several specific, one-dimensional and multidimensional scales were used for fatigue quantification [23]. Only one study did not use a specific instrument for fatigue assessment [22], and one study assessed fatigue by recording favourable effects on the physical condition of patients [21]. The literature has shown that a clinically significant level of fatigue may be efficiently identified using brief screening indices from non-specific questionnaires, such as the Profile of Mood States (POMS). In the same study, the authors reported that the use of only two items from the Fatigue Symptom Inventory could accurately identify a clinically significant level of fatigue, contributing to a decrease in the time of screening for this symptom in patients with breast cancer [24].

Fatigue is a multifactorial symptom, which justifies the use of multiple therapies for its control. The National Comprehensive Cancer Network and the Oncology Nursing Society recommend the following non-pharmacological interventions: physical exercise, psychological intervention, cognitive behavioural therapy, white light therapy for improving sleep, and nutritional monitoring [2].

The use of complementary and integrative therapies to treat and manage breast cancer symptoms has often been considered an alternative to conventional medical treatment [25]. A previous study evaluated the strength of the recommendation, i.e. the emphasis on the adoption or rejection of a particular approach, by considering potential advantages and disadvantages of the use of integrative therapies in breast cancer; the results showed that guarana supplementation had a strength of recommendation D, indicating that it must not be used to treat fatigue [25]. By contrast,

Table 5 Quality evidence rating using GRADE

Intervention/comparison	Number of study participants	Quality evidence (GRADE)
Guarana extract [11, 17]	102 (2 RCTs)	⊕⊕⊕⊕ high
Acetyl-L-carnitine [18]	409 (1 RCT)	⊕⊕⊖⊖ low
Branched-chain amino acids, CoQ10, and acetyl-L-carnitine [20]	59 (1 RCT)	⊕⊕⊕⊖ moderate
Coconut oil [22]	60 (1 RCT)	⊕⊕⊕⊖ moderate
CoQ10 and vitamin E [19]	236 (1 RCT)	⊕⊕⊕⊖ moderate
Chlorella granules [21]	36 (1 RCT)	⊕⊕⊖⊖ low
Chlorella extract [21]	36 (1 RCT)	⊕⊕⊖⊖ low
Fatigue reduction diet [12]	30 (1 RCT)	⊕⊕⊕⊕ high

RCT randomised clinical trial, *CoQ10* co-enzyme Q10, *High quality* other studies may change our confidence in the effect estimate, *Moderate quality* other studies may have a significant impact on our confidence in the effect estimate and may alter it, *Low quality* other studies may have a significant impact on our confidence in the effect estimate and may alter it, *Extremely low quality* great uncertainty about the estimate

guarana supplementation had high-quality evidence using the GRADE system, which means high reliance on the information used to support a given recommendation. Guarana has psychostimulant properties attributed to caffeine. Its benefits in learning, memory, performance, and coordination are evident and related to its action on wakefulness and fatigue [11].

Studies on ginseng have shown that it may improve CRF and has a high strength of recommendation C. In other words, this herbal medicine can be administered in selected individuals. However, the route of administration depends on the recommendation of a professional as there is a moderate certainty that the benefit of the intervention is small [25]. In the same study, acetyl-L-carnitine supplementation received a strength of recommendation D, indicating that its use is not recommended for fatigue control as there is moderate or high evidence that its risks outweigh its benefits.

Similar results were found for the use of acetyl-L-carnitine alone with low-quality evidence. However, acetyl-L-carnitine when used with branched-chain amino acids and CoQ10 had moderate-quality evidence on the reduction of overall fatigue and feeling of fatigue after the intervention period [20]. CoQ10 acts directly on energy generation by regulating oxidative phosphorylation, although other authors did not observe improvement in fatigue when using CoQ10 supplementation along with vitamin E 24 weeks after the intervention [19].

Patients with cancer traditionally use natural products. A decrease in mean fatigue was observed in a study on coconut oil supplementation after six cycles of chemotherapy in patients with breast cancer. The consumption of coconut oil should increase the energy supply that preserves physical function, increasing the functional quality of life and overall health [22].

In addition, alternative/complementary medicine, such as herbs, minerals, or animal parts, have been used by patients with cancer. Green algae, such as chlorella, have been used as a nutritional supplement in healthy individuals and those with cancer. Previous studies have shown that chlorella helps improve the function of the immune system [21]. The supplementation of chlorella granules and extracts reduced fatigue 4 weeks after the intervention, as shown in this review.

Anti-neoplastic therapy affects the nutritional status of patients with breast cancer, thus negatively affecting body weight, waist circumference, and fat mass. These changes could increase the risk of postoperative complications and mortality [26]. A study including 42 patients evaluated the relationship among fatigue, dietary intake, and body composition in breast cancer survivors. The study found a positive association between fatigue and fat percentage and an inverse association between dietary fibre intake and carbohydrate intake. No statistically significant associations were found between fatigue levels and body composition [27]. The association between dietary factors and fatigue levels is in accordance with a study conducted by Zick et al. [12], who stated that a diet rich in whole foods, omega-3 fatty acids, fruits, and vegetables may reduce fatigue in breast cancer survivors.

A recent study used herbal medicines and nutritional supplements to manage the symptoms and adverse effects of breast cancer and emphasised the indiscriminate use of these therapies as there are no clear regulatory norms for their use. Herbal medicine and dietary supplements may have positive and synergistic effects, or these supplements may interact negatively with drugs and may decrease the therapeutic effect of oncologic treatment [28]. In the present study, no serious adverse events associated with the use of supplements have been reported based on the U.S. States National Cancer Institute's CTC or any other instruments. The only article addressing the use of a specific diet for the reduction of fatigue did not assess adverse effects [12].

Bias risk analysis is an essential tool in evaluating the methodological quality of a study. This evaluation provides an appropriate answer to the research question and enables the generalisation and application of the results of the research [15]. Only two studies had a low risk of bias for all categories in this review [12, 17]. The improper treatment of bias can negatively affect health decision-making. Furthermore, clinical trials that used dietary supplements still lacked detailed information on the methods used, and the occurrence of methodological errors compromises their internal validity.

This study has some limitations, and owing to the limited number of studies on supplementation used to treat fatigue in women with cancer and the heterogeneity of the interventions, a systematic review with a meta-analysis was not possible. Another limitation is the number of MeSH terms used, which implies that other studies meeting the eligibility criteria may not have been retrieved from the search. We did not restrict the time period when searching the articles, and specific tools were used to analyse the risk of bias and evidence level. Finally, other relevant texts and grey literature were considered for review. These are some of the positive aspects of this review.

Conclusion

Dietary supplements or diets are seldom used to treat fatigue in patients with breast cancer, and the results of this review show that guarana extract and a diet rich in whole foods, omega-3 fatty acids, fruits, and vegetables can be used to treat fatigue related to cancer, particularly in patients with breast cancer. The studies had a low risk of bias with

high-quality evidence on the efficacy of the interventions in treating fatigue in the study population.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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