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Efficacy of Astragalus Membranaceus (Huang Qi) for Cancer-Related Fatigue: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

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Abstract

Background: Cancer-related fatigue is the most common complication in patients. Astragalus membranaceus is widely used in many countries to treat cancer, but its efficacy and safety is uncertain. **Objectives:** This study aimed to summarize the evidence on Astragalus membranaceus on cancer-related fatigue and quality of life in patients with cancer. **Methods:** Nine electronic databases were explored for the clinical randomized controlled trial of intervention with Astragalus membranaceus alone for cancer-related fatigue and quality of life in cancer patients from inception to July 1, 2022. The risk of bias assessment tool was adopted by Cochrane Handbook 6.1.0. The effect size was estimated using relative risk and mean difference with a corresponding 95% confidence interval. Review Manager 5.4 was used for meta-analysis. The evidence level was assessed using Grading of Recommendation, Assessment, Development and Evaluation (GRADE). **Results:** Eight studies were included. The results of the meta-analysis showed that the addition of Astragalus membranaceus to the control group was effective in reducing cancer-related fatigue (SMD = −1.63, 95% CI [−1.90, −1.36], $P < .00001$) and (RR = 1.55, 95% CI [1.19, 2.02], $P = 0.001$) in patients with cancer and improving quality of life (SMD = 0.86, 95% CI [0.17, 1.55], $P = 0.01$) and (RR = 1.57, 95% CI [1.10, 2.23], $P = 0.01$). **Conclusion:** The current evidence is supportive of the efficacy of Astragalus membranaceus in patients with cancer-related fatigue and their quality of life, but due to the small and low quality of the included literature and the lack of uniformity in terms of cancer type as well as treatment modalities, there is currently insufficient evidence to provide strong support for the clinical use of Astragalus membranaceus in the treatment of cancer-related fatigue. More high-quality evidence is needed in the future to further validate the use of Astragalus membranaceus in the treatment of clinical cancer-related fatigue. **Registration:** A review protocol was developed and registered in the International Prospective Register of Systematic Reviews (PROSPERO). Registration number: CRD42023442277. Registered 20 July 2023.

Keywords

astragalus membranaceus, cancer-related fatigue, CRF, dietary supplements, Huang Qi, meta-analysis, QoL, quality of life, systematic review

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Introduction

According to the American Cancer Society in 2020, the global incidence of cancer is currently increasing, but the cancer mortality rate shows a continuous decline[1] and the number of cancer survivors is steadily increasing. The prevalence of cancer-related fatigue (CRF) among different cancer patient populations is estimated to range from 50% to

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92%, possibly reaching as high as 100%,[2] which has been identified as the most common and distressing complication compared to other symptoms and continues throughout the cancer patient's life cycle.[3] At the same time, insomnia, pain and depression have been shown to be significantly associated with CRF, seriously affecting patients' treatment compliance, recovery process and their quality of life (QoL).[3,4]

CRF is closely associated with tumor development and treatment and its pathogenesis is unclear with mechanisms that have gained more attention and support including skeletal muscle, mitochondrial dysfunction, central nervous system dysfunction, peripheral immune activation, and inflammatory dysfunction.[5] Due to the complexity of the pathogenesis of the disease, there is no clear drug treatment option. The United States National Comprehensive Cancer Network (NCCN) Clinical Guidelines for the treatment of CRF recommends non-pharmacological treatments, such as exercise interventions, sleep therapy, and nutritional supplementation support as the first-choice recommendations for the intervention of patients with CRF.[6]

As early as 1994, federal law had established that herbal supplements could be used as a dietary supplement, independent of drug legislation, containing one or more herbs, plants (except tobacco), algae, fungi, or lichens for the purpose of protecting or restoring health without the use of traditional medicine,[7] and both Astragalus membranaceus and ginseng were listed as legal dietary supplements under the United States Dietary Supplement Health and Education Act. In recent years, the NCCN as well as the Society of Integrative Oncology (SIO) have also recommended that patients with CRF manage symptoms associated with the disease and treatment by adding nutritional supplements,[8] and suggested that some herbal supplements, such as ginseng and A. membranaceus may be helpful in CRF.

A. membranaceus belongs to the family Leguminosae, which is widely used in the United States of America, China, Japan, Korea, Iran, Russia, and some other European countries for daily life care, the treatment of cancer and other immune disorders.[9,10] A. membranaceus is included in the 2021 edition of the Chinese Pharmacopoeia Catalogue[11] and is proposed as one of the herbal and health food supplements with certain safety and multiple biological activities.[12] In recent decades, A. membranaceus has played an important role in the treatment of cancer and is widely used to relieve symptoms associated with CRF, such as pain and insomnia.[13]

Modern pharmacology shows that the chemical composition of A. membranaceus mainly includes polysaccharides, saponins, flavonoids, as well as amino acids, trace elements, and others. It is able to inhibit the proliferation, invasion and migration activity of tumor cells through its active ingredients, promote the apoptosis of tumor cells to shrink or stabilize the tumor, and it can also improve the microenvironment of the tumor and improve the prognosis of the patients with tumors through different mechanisms;[14] it can achieve the goal of inhibiting the development of the tumor and improving therapeutic effect by enhancing the effect of conventional treatments and reduce their toxic and side effects on the organism; it is able to protect the hematopoietic function of bone marrow and slow down the reduction of blood cells by alleviating bone marrow suppression; and achieve anti-inflammatory utility by inhibiting the production of inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) and initiating macrophage-related anti-tumor immune response; and improve mitochondrial autophagy in skeletal muscle cells and alleviate skeletal muscle dysfunction.[12,15] A. membranaceus and its active ingredients may alleviate CRF by inhibiting the proliferation of tumor cells, improving the immune profile of the body, being anti-inflammatory, slowing down the reduction of blood cells and strengthening skeletal muscle. Astragalus polysaccharide has been reported to have antioxidant and anti-inflammatory effects; therefore, astragalus polysaccharide (PG2) injection is now approved in Taiwan as a treatment for cancer-related fatigue in patients with advanced cancer.[16]

CRF belongs to the category of consumptive disease in TCM and should be treated according to the TCM principle of "deficiency should be tonified" by giving it tonic products. A large data study analyzed the pattern of Chinese medicine use in the treatment of CRF over the past 20 years and found that A. membranaceus was used more frequently as a "long tonic." [17] Although several clinical trials have reported the effects of A. membranaceus on CRF and QoL,[16,18] they are mostly small-sample, single-center randomized controlled clinical trials (RCTs) with insufficient evidence. Therefore, this study explores the effect of A. membranaceus on CRF in cancer patients through systematic review, with the aim of providing effective evidence to support the better clinical use of A. membranaceus for nutritional supplementation support in CRF patients.

Method

This systematic review is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines,[19] and it has been registered in the PROSPERO system, with the registration number CRD42023442277. Available at: https://www.crd.york.ac.uk/prospero/displayrecord.php?ID=CRD42023442277.

Search Strategy

Two reviewers (XS and BCH) performed the search independently. The PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, China National Knowledge Infrastructure (CNKI),

Wanfang Database, China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM) were searched from inception to 1 July 2022 to identify RCTs examining the use of A. membranaceus alone for CRF in patients with cancer. The reference lists of published reviews and included articles were also searched manually. Additionally, 2 reviewers (XS and BCH) manually searched the gray literature (www.asco.org/ASCO/Meeting), cancer-related societies such as the Registered Nurses Association of Ontario (RNAO) in Canada, the Scottish Intercollegiate Guidelines Network (SIGN), the World Health Organization (WHO), and clinical trial registry databases (clinicaltrials.gov, www.who.int/ictrp,www.chictr) to extend the search for this study and to ensure that the search information was complete and comprehensive. This review did not set any language limits for the electronic search. The search was conducted using a combination of free words and subject terms. The Chinese search terms were as follows: "黄芪," "癌," "肿瘤," "生活质量," "癌因性疲乏," and others; the English search terms were as follows: "Huang Qi," "Astragalus membranaceus," "neoplasms," "cancer," "quality of life," "QoL," "cancer-related fatigue," "CRF," and so on.

Inclusion Criteria

Based on the principles of PICOS, the inclusion criteria are as follows: (a) patients with pathologically diagnosed malignant tumors, assessed by the 10th revision of the International Classification of Diseases (ICD-10) criteria or scale for CRF, without restriction on age, gender, race, tumor type, cancer severity, cancer duration and fatigue; (b) the trial group administered a single selection of A. membranaceus or A. membranaceus extractions, without restriction of A. membranaceus type, dose, duration of treatment, and usage; (c) The control group consisted of conventional treatment, placebo or other treatment measures; (d) primary outcome indicators are CRF and QoL; secondary outcome indicators include pain, anxiety, depression, laboratory indicators, adverse events and others; and (e) RCTs, blinded or not, regardless of publication type and language.

Exclusion Criteria

Based on the principles of PICOS, the exclusion criteria are as follows: (a) A. membranaceus was used in combination with other types of herbs or ingredients; (b) duplicate publications; (c) missing primary information or incomplete reported data and unsuccessful contact with authors; and (d) incorrect data processing and analysis.

Data Extraction

All literature was imported into the reference management software NoteExpress and screened by the researchers after removing duplicates. The literature was independently screened by 2 researchers (XS and BCH) trained in evidence-based nursing specialties according to pre-determined inclusion and exclusion criteria for the literature, extracting information and cross-checking the results. Any disagreements between researchers were resolved by consulting a third researcher (LY) to determine the study's eligibility. The titles and abstracts of the articles were read first to exclude irrelevant literature before further reading the full text to decide on inclusion. Data were extracted independently by 2 evaluators (XS and BCH), using a standardized data extraction form, with the following information: (a) basic information of the literature including authors, year of publication, country and sample size; (b) patient and disease characteristics including age, tumor type, stage and treatment modality; (c) interventions including intervention protocol, duration, follow-up, and others; and (d) outcome indicators including CRF, QoL, adverse events, and laboratory indicators, and others.

Quality Assessment

The Cochrane Collaboration's Risk of Bias Assessment tool was used to evaluate the methodological quality and risk of bias of the included literature, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting bias and other sources of bias. The evaluation was assessed specifically for each element using "low risk," "unclear," and "high risk." The risk of bias assessment was performed independently by 2 evaluators (XS and BCH), and the results were checked. Any disagreements between researchers were resolved by consulting a third researcher (LY) to determine the study's risk of bias.

Data Analysis

Statistical analysis was performed using RevMan 5.4 software. Dichotomous data were expressed as relative risk (RR) and continuous variables were expressed as standardized mean difference (SMD), both of which were given 95% confidence intervals (CI). The I^2 test was used to test for heterogeneity between the results of the included studies. If $I^2 < 50\%$, the heterogeneity between studies was acceptable and meta-analysis was performed by fixed effects model; if $I^2 \geq 50\%$, the heterogeneity of the studies existed and meta-analysis was performed by random effects model. When large heterogeneity existed, subgroup analysis or sensitivity analysis was performed to identify the source of heterogeneity as appropriate, and if heterogeneity still could not be eliminated but was clinically consistent, random effects models were used for analysis and results are interpreted with caution. Descriptive analysis was used when there was a small amount of literature on an indicator

or when it was difficult to combine data. The results of the meta-analysis were presented by forest plots and publication bias was assessed by Egger's test.[20]

GRADE Evidence Quality Assessment

The quality of evidence was evaluated in the included literature by the GRADEproGDT online tool (https://gradepro.org). Five aspects were evaluated in terms of risk of bias, inconsistency, indirectness, precision, and publication bias, and the level of evidence quality was expressed as high, moderate, low, or very low. The evaluation was performed independently by 2 evaluators (XS and BCH) and cross-checked. In case of disagreement, a third party (LY) was consulted until agreement was reached.

Results

Study Selection

A total of 1798 articles were retrieved, and after the NoteExpress software check, the remaining 1745 articles were included in this study. After 2 researchers (XS and BCH) read the titles and abstracts according to the inclusion and exclusion criteria, 21 studies were included. After reading the full text by 2 researchers (XS and BCH), 8 articles did not meet the inclusion criteria, which included control group design non-compliance, the inclusion of the population with non-CRF patients and other outcome indicators, 6 articles were not randomized controlled trials and 8 articles were finally included[16,18,21-26] in the systematic review. One study was a comparison of efficacy across doses and data could not be combined, so a descriptive systematic review was done,[16] and the remaining 7 studies were subjected to meta-analysis,[18,21-26] as shown in Figure 1.

Study Characteristics

A total of 8 studies[16,18,21-26] were included, with publication years ranging from 2005 to 2022, including 5 in Chinese[22-26] and 3 in English.[16,18,21] The total sample size was 804 participants, including 772 Chinese and 32 Mexican nationals. There were 396 patients in the intervention group and 408 patients in the control group, aged between 18 and 96 years, and 5 studies[16,18,21,24,25] mentioned the gender of the included patients. Different types of malignant tumors were included, with more patients with lung, breast, and gastric cancer. In the tumor stage, 2 studies[23,24] were stage II-IV, 1 study[21] stage III-IV, 1 study[22] advanced stage and the remaining 4 studies[16,18,25,26] did not report the stage. Six studies[16,21-25] reported treatment modalities, including bioimmunotherapy,[23] chemotherapy,[21,24] herbal treatment,[25] or palliative care.[16,22] The mode of administration varied among the included studies, with 6 studies[16,18,21,23-26] administering intravenous infusions and 2 studies injecting the Zusanli acupoint (ST36).[22,26] The included studies were all simple A. membranaceus preparations, but the main ingredients chosen were different; 4 studies[16,18,21,23]used A. membranaceus polysaccharide injection, whose main constituents was A. membranaceus polysaccharide, and 4 studies[22,24-26] used A. membranaceus injection, whose main constituents included saponins, methyl glucosides, and flavonoids. Among the included studies, Ma et al[22] was a randomized crossover controlled trial, and the first phase of which was defined as "Ma 1" and the second phase as "Ma 2". The intervention duration was focused on 10-28 days (4 weeks). For the outcome measures, 7 studies[16,18,22-26] assessed fatigue, 2 studies used the Brief Fatigue Inventory-Taiwan version (BFI-T),[16,18] 1 study[22] used the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30), 1 study[23] used the Chinese Medicine Symptom Classification and Quantification Scale, 1 study[25] used the Fatigue Symptom Inventory(FSI), 1 study[26] used the Piper Fatigue Scale (PFS) and one study[24] did not specify its fatigue assessment scale. Five studies[21,23-26] evaluated QoL, four of which[23-26] used the Karnofsky Performance Scale (KPS) and 1 study[21] used the European Organization for Research and Treatment of Cancer 30-item core instrument and 13-item lung cancer module (EORTC QLQ-LC13). Three studies[23-25] evaluated laboratory markers involving hemoglobin, leukocytes, and T-cell subsets. Five studies[16,18,21,23,24] specifically reported adverse effects such as fever and rash, as well as no adverse effects. Only 1 study[21] had a follow-up. The details are shown in Table 1.

Quality Assessment

Among the 8 included studies, 4 studies[16,22,23,26] adequately described the generation of random sequences, 3 studies[22,23,26] used random number tables, 1 study[16] used computer randomization and 2 studies[18,22] mentioned the term "random" but did not elaborate on the details of the randomization method used. One study[16] described the method of allocation concealment in detail. Three studies[16,18,22] were blinded researchers and participants, and 2 of these studies[16,22] was also blinded outcome assessment and statistical analysis. Eight studies had a low risk of bias for outcome data completeness and selective reporting bias, and other biases were unknown. Information on the methodological quality of the included studies is detailed in Figure 2.

Meta-Analysis Results

Cancer-Related Fatigue (CRF). Among the 8 studies, 7 studies[16,18,22-26] measured CRF in cancer patients, but a total of 6 studies[16,22-26] were included in the meta-analysis as 1 study[18] was on the comparison of the efficacy of different doses of A. membranaceus. Four studies[21,22,25,26] were continuous variables and the combined results were $I^2 = 40\%$,

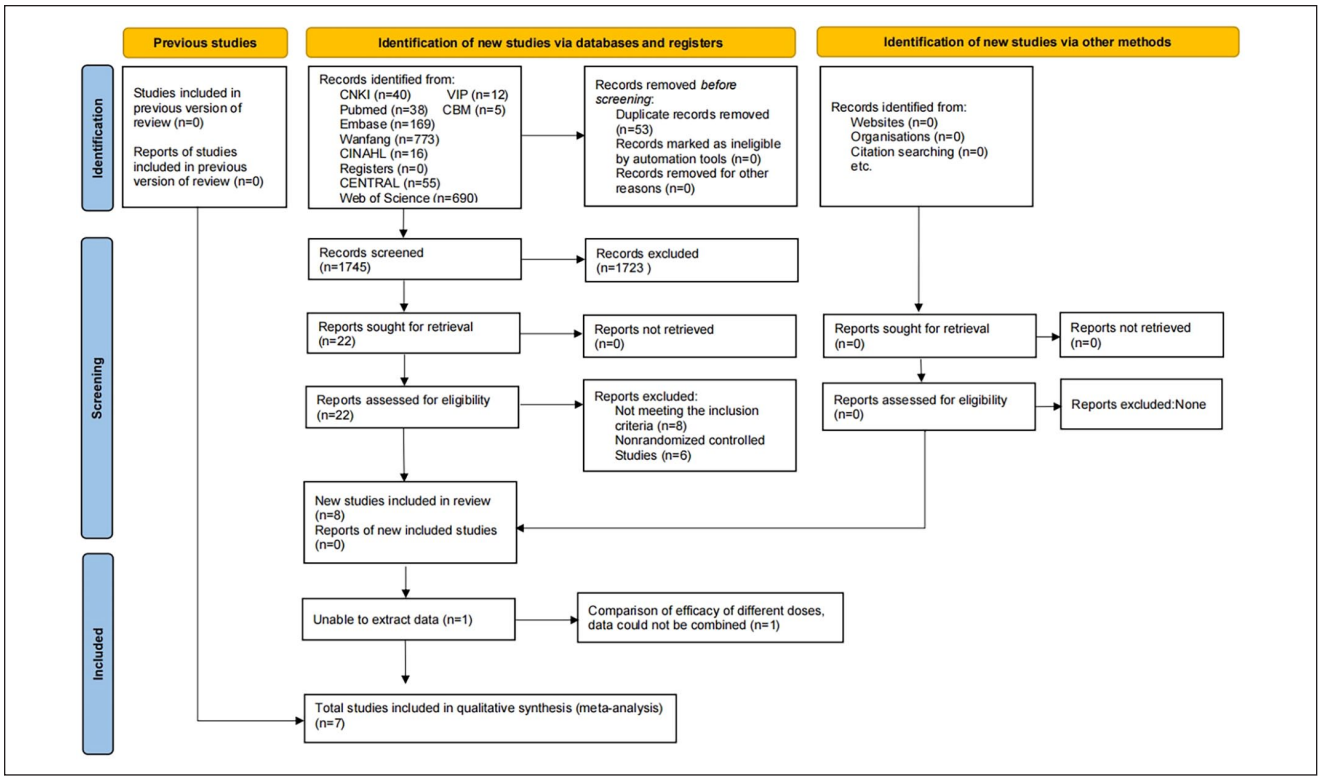

Figure 1. PRISMA flow diagram of study selection.

SMD = −1.63 (−1.90, −1.36), $P < .05$, as shown in Figure 3. Three studies[18,24,26] were dichotomous variables and the combined results were $I^2 = 45\%$, RR = 1.55 (1.19, 2.02), $P = 0.001$, as shown in Figure 4. The results showed that the CRF improvement in the intervention group was significantly better than that in the control group, which suggested that A. membranaceus could effectively improve fatigue in cancer patients. The results of the Wang et al. study[16] showed that both doses of 500 mg and 250 mg were effective in improving fatigue.

Quality of life (QoL). Among the 8 studies, 5 studies[21,23-26] measured the QoL in cancer patients, all of which were included in the Meta-analysis. Two of the studies[21,26] used continuous variables and the combined results were $I^2 = 82\%$, SMD = 0.86 (0.17, 1.55), $P = .01$, as shown in Figure 5. Three studies[23-25] used dichotomous variables and the combined results were $I^2 = 62\%$, RR = 1.57 (1.10, 2.23), $P = .01$. As the number of included studies was too small to perform subgroup analysis, through sensitivity analysis, dichotomous data were removed from the included studies one by one and it was found that after removing the article by the Wang et al. study[24], the heterogeneity decreased from 62% to 0 and the results (RR = 1.37 [1.06, 1.76], $P = 0.02$) were still valid. This suggested that A. membranaceus has a role in improving QoL, as shown in Figure 6.

Pain. One study[26] evaluated the degree of pain and showed that the Visual Analogue Scale (VAS) scores of the 2 treatment groups decreased significantly better than those of the control group after 4 courses of treatment ($P < .05$).

Laboratory indicators. Three[23-25] studies mentioned relevant laboratory indicators, involving hemoglobins, leukocytes, and T-cell subsets. In 2 studies,[24,25] it was observed that the levels of hemoglobin and leukocytes in the treatment group were better than those in the control group ($P < .05$). Two studies[23,24] was found that the proportion of $CD3^+$ and $CD4^+$T cells was significantly higher ($P < .05$) and the proportion of $CD8^+$ T cells was less changed ($P < .05$) in patients after intervention with A. membranaceus polysaccharide injection.

Adverse reactions. Five studies[16,18,21,23,24] specifically reported adverse reactions, of which two[21,23] reported the presence of febrile events in the treatment group, 1 study[23] gave symptomatic treatment of the drug and the fever symptoms disappeared, the other[21] did not write about the specific treatment measures and results. One study[18] reported 3 cases of rash, 2 cases of eczema and 2 cases of pruritus, most of these adverse events were mild and all patients recovered spontaneously without specific treatment within a short period of time. One study[16] showed that more than 90% of the reported adverse

Table 1. The Characteristics of the Included Trials.

Study and setting	Sample (T/C)	Age (yr) (T/C)	Gender M/F (T/C)	Type of cancer	Cancer stage	Treatment modalities	Intervention/Dose		Mode of intervention	Duration of intervention	Outcome/Scale	Adverse events	Follow-up
							Intervention group	Control group					
S1:Chen et al., 2007, China	16/20	63.2/65.8	T:7/9 C:8/12	Multiple Tumors	NR	Kushen prescription	Astragalus Injection + kushen prescription injection /250 mg	Kushen prescriptio n injection	Intravenous injection	Once a day, 2 W	①Fatigue/FSI ②QoL/KPS ③Hemoglobin, leukocytes and T-cell subsets	NR	NR
S2:Chen et al., 2012, China	35/30	64 ± 15.65/ 56.9 ± 11.89	T:14/21 C:11/19	Multiple Tumors	NR	NR	PG2/500 mg	Normal saline	Intravenous injection	Three times a week, 4 W	①Fatigue/BFI-T	Rash, eczema, pruritus	NR
S3:Guo et al, 2012., China	68/68	NR	T:40/28 C:44/24	Lung cancer	Ⅲ-Ⅳ	Chemotherapy	PG2 + VC /250 mg	VC	Intravenous injection	Once a day, 4 W	①QoL/QLQ-C30,QLQ-L C13	Febrile	Regular contact
S4:Ma et al., 2022, China	13/19	39-96	NR	Multiple Tumors	Advanced Tumor	Palliative care	Astragalus Injection/2 ml	Normal saline	Acupoint Injection	Once a week, 3 W	①Fatigue/QLQ-C30	NR	NR
S5:Wang et al., 2005, China	34/34	52.4	T:19/15 C:20/14	Multiple Tumors	Ⅱ-Ⅳ	Chemotherapy	Astragalus Injection+Chem otherapy /60 mg	Chemothe-rapy	Intravenous injection	Once a day, 10 D	①QoL/KPS ②Hemoglobin and leukocytes	No	NR
S6:Wang et al., 2019, China	111/103	62.2 ± 10.69/62 .86 ± 11.5	T:55/56 C:66/37	Multiple Tumors	NR	Palliative care	PG2/500 mg	PG2 /250 mg	Intravenous injection	Three times a week, 4 W	①Fatigue/BFI-T	No	NR
S7:Xu et al., 2022, China	30/30	68.55 ± 10.68/6 6.47 ± 7.86	NR	NR	NR	NR	Astragalus Injection+RN /0.5ml	RN	Acupoint Injection	4 W	①Fatigue/PFS ②QoL/KPS ③Pain/VAS	NR	NR
S8:Zhang et al., 2018, China	36/36	18-65	NR	Lung cancer	Ⅱ-Ⅳ	Bioimmunothe-rapy	PG2 + CIK /250 mg	CIK	Intravenous injection	Once a day, 20 D	①Fatigue/Classification quatification of qi deficiency syndrome of TCM ②QoL/KPS ③T-cell subsets	Febrile	NR

Abreviations: T, Intervention group; C, Control group; M, Male; F, Female; NR, Not reported; W, Week; FSI, Fatigue Symptom Inventory; QOL, Quality of life; KPS, Karnofsky Performance Status; PG2, Astragalus Polysaccharides; BFI-T, Brief Fatigue Inventory-Taiwan version; VC, Vinorelbine and Cisplatin; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QLQ-LC13, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire -Lung Cancer 13; D, day; RN, routine nursing; PFS, Piper Fatigue Scale; VAS, Visual Analogue Scale; CIK, Cytokine-induced killer cells; TCM, Traditional Chinese Medicine.

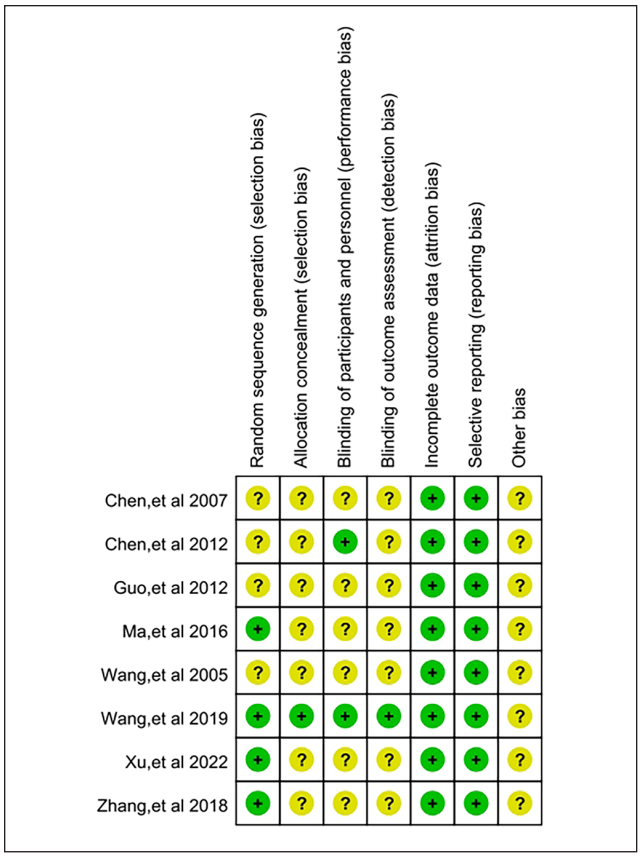

Figure 2. Risk of bias graph of the included studies.

events during treatment were unlikely to be related or unrelated to A. membranaceus polysaccharide injection treatment. One study[24] reported that no serious liver or kidney impairment and no adverse reactions such as allergy were found in either group during the drug administration. Other studies did not mention any uncomfortable symptoms in patients.

Publication Bias Assessment

Egger's test indicated that there was no publication bias ($P = .52$).

GRADE Evidence Quality Assessment

In this study, the quality of evidence was evaluated using the GRADE system, and the quality of CRF was assessed as "low" and the QoL was assessed as "very low," as detailed in Table 2.

Discussion

The evidence of this systematic review showed that A. membranaceus or A. membranaceus extracts could alleviate fatigue and improve the QoL of CRF patients with mild adverse effects.

CRF is one of the most common (70%-80%) symptoms in cancer patients throughout the course of their disease, with the majority (approximately 60%) of CRF occurring during anti-tumor treatment, and is an important factor in preventing cancer patients from actively receiving treatment and affecting their QoL.[27] Some studies[28] reported that CRF is associated with the nutritional status of patients, and in a review study of nutritional interventions for the treatment of CRF, it was clearly stated that A. membranaceus is effective as a herbal dietary supplement in alleviating CRF.[29] Pharmacological trial studies had also confirmed[30] that active compounds such as quercetin and kaempferol in A. membranaceus may have positive effects on the treatment of CRF through targets such as AKT1 and TP53, as well as IL-17, TNF, toll-like receptors and HIF-1 signaling pathways.

In this review, it was found that aside from intravenous injection, 2 other studies[22,26] used A. membranaceus injection for Zusanli acupoint (ST36), which also exerted good effects. Acupoint injection is a treatment method developed on the basis of acupuncture therapy in Chinese medicine and closure therapy in modern medicine, based on the meridian theory and the principle of drug therapy[22]. Acupuncture can regulate the level of lymphocytes, maintain the homeostasis of T-cell subsets and improve the immune function of the body.[31] The ST36 is a joint point of the Foot Yangming Stomach meridian, which has the effect of strengthening the spleen, harmonizing the Stomach, supporting righteousness and dispelling the evil, and is an important point for supplementing the deficiency and generating vital energy, which meets the needs for CRF tonicity. The ST36 enhances the body's specific and non-specific immune functions.[26] Therefore, the injection of A. membranaceus injection at the ST36 combines the combined effects of acupoints, meridians and drugs, which can effectively relieve the fatigue symptoms of cancer patients.

There was a large heterogeneity among studies in the effect of A. membranaceus on the QoL of patients with CRF ($I^2 = 82\%$, 62%). Removing the literature one by one for their inclusion in the analysis revealed that the heterogeneity decreased from 62% to 0% after removing the article by the "Wang, et al." study.[24] The source of heterogeneity may be related to the small size of included studies, inconsistent clinical characteristics of the study population, inconsistent interventions, and differences in study quality, but as only 3 studies were included, further subgroup analysis and Meta-response regression analysis could not yet be performed.

Limitations of this study, firstly, although authoritative databases and clinical guidelines on cancer treatment were searched both at home and abroad, the number of studies that met the inclusion criteria after rigorous screening was only 8, and the number of participants included was only

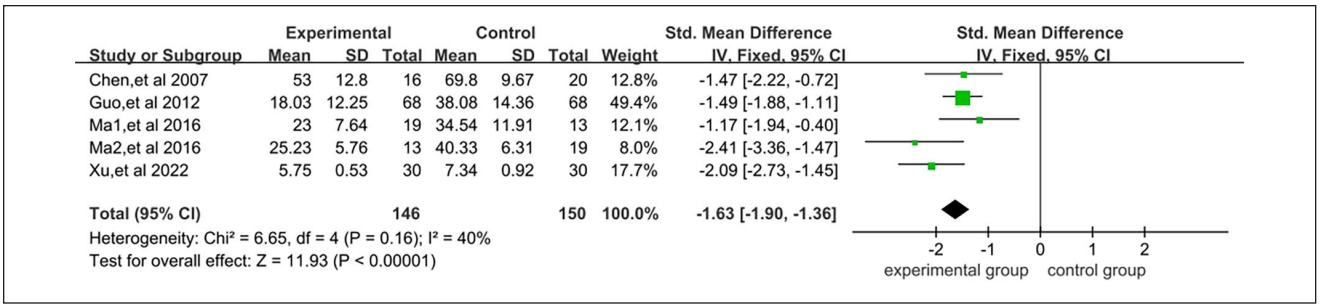

Figure 3. Meta analysis of continuous variables of the influence of A. membranaceus on CRF.

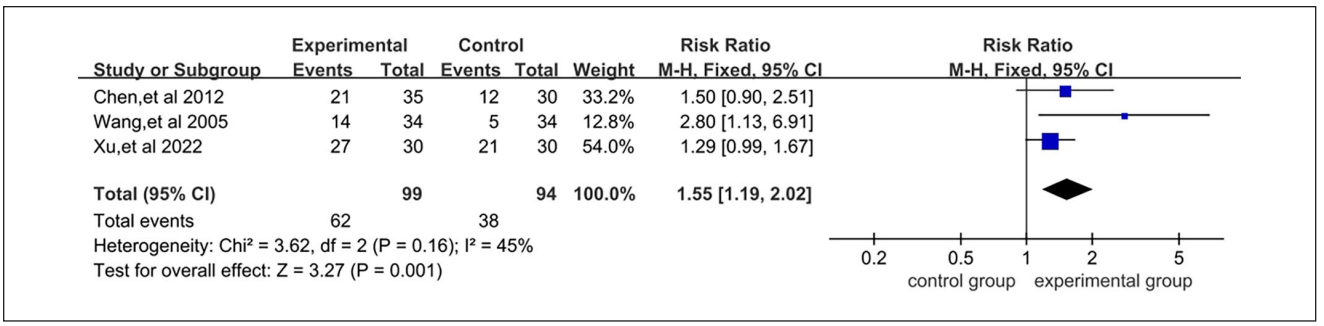

Figure 4. Meta analysis of dichotomous variables of the influence of A. membranaceus CRF.

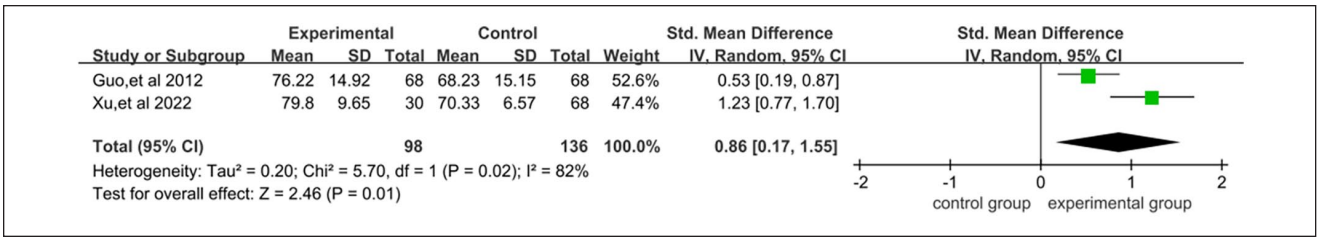

Figure 5. Meta-analysis of continuous variables of the influence of A. membranaceus on patients QoL.

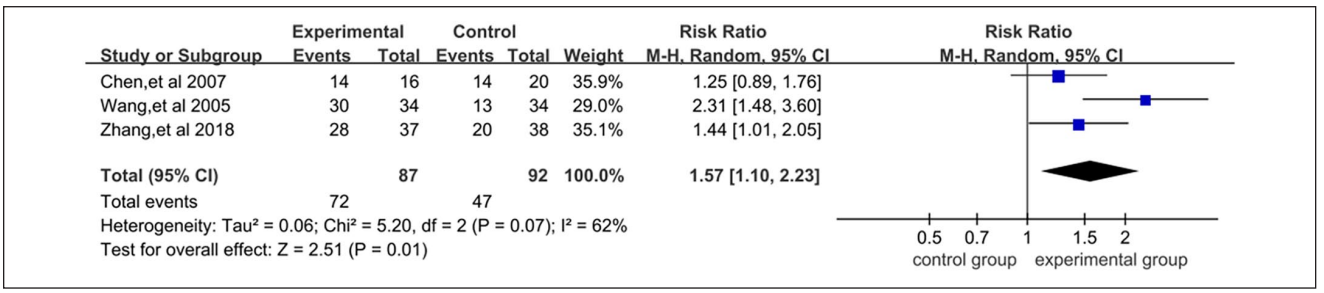

Figure 6. Meta-analysis of dichotomous variables of the influence of A. membranaceus on patients' QoL.

804, which is a small sample size. Due to the small amount of literature included, data from the included studies was merged based on the outcome indicators, and the number of studies available for data merging for each outcome indicator was small, and could not yet be considered sufficient evidence to conclude that A. membranaceus adjuvant therapy is effective for CRF patients and their QoL. Among the 8 included studies, only 1 study was conducted on non-Chinese patients, and there may also be regional ethnic limitations in the evidence. Second, although some of the included

Table 2. GRADE Evidence Profile in the Meta-Analysis.

Certainly assessment no. of patients certainty											
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental group	Control group	Relative (95%CI)	Absolute(95%CI)	
Fatigue 4	Randomized	Serious[a]	Not serious	Not serious	Serious[c]	None	127	137	—	SMD 1.63 lower (1.9 lower to 1.36 lower)	⊕⊕◯◯ Low
Fatigue 3	Randomized	Serious[a]	Not serious	Not serious	Serious[c]	None	62/99 (62.6%)	38/94(40.4%)	RR 1.55 (1.19-2.02)	222 more per 1000 (from 77 more to 412 more)	⊕⊕◯◯ Low
QoL 2	Randomized	Serious[a]	Serious[b]	Not serious	Serious[c]	None	98	98	—	SMD 0.86 higher(0. 17 higher to 1.55 higher)	⊕◯◯◯ Very low
QoL 3	Randomized	Serious[a]	Serious[b]	Not serious	Serious[c]	None	72/87 (82.8%)	47/92(51. 1%)	RR 1.57 (1.10-2.23)	291 more per 1000 (from 51 more to 628 more)	⊕◯◯◯ Very low

Abbreviations: CI, Confidence interval; SMD, Standardized mean difference; RR, relative risk.
Support for judgment:
a Most studies lack blinding and allocation concealment.
bConsiderable heterogeneity.
cSample sizes is <400.

studies provided information on random sequence generation, the methods of allocation concealment and blinding were not reported in detail, thus leading to a potential risk of selection bias and detection bias. Third, the included patients had different tumor types, tumor stages and treatment modalities. For intervention, the lack of uniformity in the pathways of action may have increased the heterogeneity of the treatment regimens. There were different types and doses of A. membranaceus preparations used. Additionally, different types of assessment scales were used among the studies. All of these have caused the heterogeneity of this systematic review to increase. Fourth, only one of the included studies showed follow-up of patients, and the remaining 7 studies were limited to observations of short-term efficacy, with a lack of follow-up period for patients, which has an impact on the quality of evidence for the results. And last, the current level of all available evidence using the scoring system was "low" or "very low," which weakens the impact, reliability, and applicability of the evidence.

The outlook and significance for the future are, firstly, to further clarify the efficacy of A. membranaceus on CRF and to develop a more rigorous design protocol. For sample size, doing randomization and blinding, enhanced homogeneity of interventions, and additional placebo controls should be considered. A variety of factors such as appearance, color, odor and container should be taken into account when designing the placebo to be consistent with that used in the treatment group as much as possible to improve blinding, so that high-quality evidence of A. membranaceus alleviating CRF can be obtained. Through more quality research to supplement the data, meta-analysis and subgroup analysis of the data could increase the persuasiveness of the study's conclusions. Second, although this study found that A. membranaceus can be effective by acupuncture point injection and intravenous infusion, in the future, research could consider applying A. membranaceus or A. membranaceus extract granules for brewed administration to make their application more convenient; Third, this systematic review found that the current clinical use of A. membranaceus preparations for CRF are A. membranaceus injection and A. membranaceus polysaccharide injection. A. membranaceus injection contains many components of A. membranaceus, while the main component in A. membranaceus polysaccharide injection is A. membranaceus polysaccharide, which is only one of the many components of A. membranaceus. In future trials, A.s membranaceus preparations with different main components of action could be compared in groups to better define the components of A. membranaceus that are most effective in intervening in CRF, to guide formulation formation. Fourth, although different doses of A. membranaceus polysaccharide injection had been studied for the efficacy of CRF, only 2 groups of doses of A. membranaceus polysaccharide injection (250 mg / 500 mg) were included, and these studies still cannot make a uniform standard for the doses of A. membranaceus and its extracts. Different doses of A. membranaceus could be selected in future studies to further determine the most appropriate dose. Fifth, the intervention duration proposed in this included study was relatively short (10 days-4 weeks) and a longer appropriate intervention duration and follow up may need to be considered in future clinical trial studies to determining the optimal duration of A. membranaceus' effectiveness.

Conclusion

In conclusion, this systematic review of A. membranaceus helps to alleviate fatigue and improve the QoL in CRF patients with few adverse effects and is safe to be recommended in clinical practice. However, the evidence is not yet adequate to provide strong support for the use of A. membranaceus in the management of cancer-related fatigue. Higher quality RCTs are warranted. It is hoped that more rigorously designed and multi-centered randomized controlled trials will be conducted to further validate to facilitate the promotion of the medicinal and food-derived A. membranaceus in clinical CRF patients.

List of Abbreviations

GRADE: Grading of Recommendation, Assessment, Development and Evaluation; CRF: cancer-related fatigue; QoL: quality of life; NCCN: National Comprehensive Cancer Network; SIO: Society of Integrative Oncology; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; RCTs: andomised controlled clinical trials; PRISMA: preferred reporting items for systematic reviews and meta-analyses; CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CNKI: China National Knowledge Infrastructure; VIP: China Science and Technology Journal Database; CBM: Chinese Biomedical Literature Database; SIGN: Scottish Intercollegiate Guidelines Network; WHO: the World Health Organization; ICD-10: 10th revision of the International Classification of Diseases; RR: relative risk; SMD: standardized mean difference; CI: confidence intervals; ST36: Zusanli acupoint; BFI-T: Brief Fatigue Inventory-Taiwan version; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer; PFS: Piper Fatigue Scale; KPS: Karnofsky Performance Scale; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer 30-item core instrument and 13-item lung cancer module; VAS: Visual Analogue Scale.

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Authors' Contributions

Study concept and design:Liu Yang; Xia Sheng. Acquisition of data: Liu Yang; Xia Sheng; Bichun Huang.

Analysis and interpretation of data: Liu Yang; Xia Sheng; Bichun Huang; Guijiao Lin; Yajiao Wang. Drafting of the manuscript: Liu Yang; Xia Sheng; Bichun Huang. Critical revision of the manuscript for important intellectual content: Liu Yang; Xia Sheng; Bichun Huang; Guijiao Lin; Yajiao Wang; Xinlei Wu; RuJia Lin.

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