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Medicinal Mushroom Supplements in Cancer: A Systematic Review of Clinical Studies

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Abstract

Purpose of Review Patients seek clinical guidance on mushroomsupplements that can be given alongside conventional treatments, but most research on such fungi has been preclinical. The current systematic review focused on clinical studies of mushrooms in cancer care conducted in the past 10 years. We searched Medline (Ovid), Embase (Ovid), Scopus (Wiley), and Cochrane Library to identify all mushroom studies conducted in humans published from January 2010 through December 2020. Two authors independently assessed papers for inclusion.

Recent Findings Of 136 clinical studies identified by screening 2349, 39 met inclusion criteria. The studies included 12 different mushroom preparations. A survival benefit was reported using Huaier granules (*Trametes robiniophila Murr*) in 2 hepatocellular carcinoma studies and 1 breast cancer study. A survival benefit was also found in 4 gastric cancer studies using polysaccharide-K (polysaccharide-Kureha; PSK) in the adjuvant setting. Eleven studies reported a positive immunological response. Quality-of-life (QoL) improvement and/or reduced symptom burden was reported in 14 studies using various mushroom supplements. Most studies reported adverse effects of grade 2 or lower, mainly nausea, vomiting, diarrhea, and muscle pain. Limitations included small sample size and not using randomized controlled trial design.

Summary Many of the reviewed studies were small and observational. Most showed favorable effects of mushroom supplements in reducing the toxicity of chemotherapy, improving QoL, favorable cytokine response, and possibly better clinical outcomes. Nevertheless, the evidence is inconclusive to recommend the routine use of mushrooms for cancer patients. More trials are needed to explore mushroom use during and after cancer treatment.

Keywords Medicinal mushrooms · Mushrooms in cancer · Integrative cancer therapies · Complementary and alternative therapies · Reishi · Turkey tail · PSK · Shitake · Maitake · Cordyceps

Abbreviations

AHCC	Active hexose correlated compound
CD	Cluster of differentiation
HCC	Hepatocellular carcinoma
IFN-γ	Interferon-gamma
IL-1Ra	Interleukin-1 receptor antagonist
ILs	Interleukins
MCS	Mental component summary
MHC	Major histocompatibility complex
NK	Natural killer
OS	Overall survival
PCS	Physical component summary
PD-L1	Programmed death ligand 1
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Prostate-specific antigen
PSK	Polysaccharide-Kureha
QoL	Quality-of-Life
RFS	Recurrence-free survival
SEs	Side effects
Th1/Th2	T helper 1/T helper 2

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TNF-α	Tumor necrosis factor-alpha
Tregs	Regulatory T cells
UFT	Tegafur/uracil

Introduction

Patients with cancer either use complementary treatment modalities or want to know more about them. Nearly 4 in 10 Americans believe that "alternative treatments" may cure cancer, according to the American Society of Clinical Oncology's second annual National Cancer Opinion Survey in 2018 [1]. Results from the 2012 National Health Interview Survey show that the most commonly used complementary health approaches among adults in the US included natural products (17.7%; defined as dietary supplements other than vitamins and minerals), followed by deep breathing (10.9%) and yoga, Tai Chi, or Qigong (10.1%) [2]. Natural products include various substances such as vitamins, minerals, probiotics, herbs, and extracts. Cancer patients and survivors use complementary and integrative medicine strategies to reduce the side effects (SEs) of conventional treatments, such as organ toxicity; improve their quality-of-life (QoL); protect and stimulate immunity; or prevent cancer progression or recurrence [3].

Mushrooms are rich in bioactive compounds such as beta-glucan, selenium, and multiple antioxidants that are thought to play a significant role in the prevention of chronic disease and possibly premature deaths [4••, 5, 6]. The use of edible mushrooms as a food source is well known in Asia, mostly Japan and China, and in recent years has expanded to other parts of the world. Current research suggest that high mushroom consumption is associated with lower risk of cancer, reduced all-cause mortality, and cause-specific mortality [4••, 5, 6]. Preclinical studies demonstrate that several medicinal mushroom supplements are anti-inflammatory and immune enhancing, leading to slower cancer progression, decreased probability of metastasis, and longer survival in animal models [7–10]. However, there may be a risk of serious adverse effects. For example, Agaricus mushroom supplements cause autoimmune liver injury through excessive immune stimulation [11]. Chaga mushrooms may cause oxalate nephropathy [12]. Additionally, supplements may negatively interact with cancer treatment, prescription medications, and other herbs/supplements [13•, 14]. Maitake (*Grifola frondosa*) mushrooms interact with warfarin and increase bleeding tendencies [15]. Furthermore, patients are not always familiar with dietary supplements' limited regulation in the United States under the Dietary Supplement Health and Education Act of 1994 [16]. Under this legislation, supplements are exempted from the typical degree of scrutiny that the Food and Drug Administration imposes on medications. This limited oversight may increase toxicity due to contamination and/or lack of control on the contents of the products, leading to excessive amounts of certain harmful ingredients. For instance, heavy metal and microbial contamination of supplements may pose a health risk for patients [17].

Patients usually use mushroom supplements to enhance their immune system's ability to fight against cancer. Mushrooms are approved for use in some countries and are often integrated with treatment protocols. For example, polysaccharide-K (polysaccharide-Kureha; PSK) is commonly used in Japan, whereas Reishi (*Ganoderma lucidum*) is used in China [18]. Torkelson et al. conducted a phase 1 clinical trial enrolling 9 patients using *Trametes versicolor* in the US population and deemed it safe and tolerable [19]. Conversely, mushroom supplements are immunomodulators that either stimulate or inhibit cancer patients' immunity and could lead to adverse events [20]. These conflicting results are challenging when patients seek clinical guidance. Despite the increasing interest and evidence, there is little training on herbs and supplements in medical education, creating communication strain for oncologists who seek to provide reliable information to their patients. One solution that addresses this gap in knowledge is the development of a new field of care called integrative oncology. This new field covers evidence-based knowledge of the use of natural products among others to optimize health and improve quality of life across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment [21]. In integrative oncology, there is emphasis on shared decision-making and improved communication between patients and their families and their health care providers [22, 23].

To date, few recent systematic reviews of clinical research have evaluated the role of commonly used mushroom supplements across different cancer types. Herein, we present the results of a systematic review of the literature of clinical studies published during the past 10 years that examined the use of mushroom supplements in cancer care. Understanding the recent literature on clinical studies using mushroom supplements for cancer care would help clinicians counsel cancer patients on the benefit-risk profile of mushroom supplements.

Methods

Study Overview and Selection Criteria

A qualified medical librarian conducted a systematic search of the literature through the following databases: Medline (Ovid), Embase (Ovid), Scopus (Wiley), and Cochrane Library. Queries for mushrooms and cancer were performed using both the natural language and controlled vocabulary

terms with the taxonomic, colloquial, and Chinese or other names of mushrooms (including but not limited to Reishi, Turkey Tail, Shiitake, Maitake, Lion's Mane, Chaga, and Huaier granule) and cancer. A complete list of the search queries for Medline can be found in Supplemental Table 1. The database search was performed on January 9 and 10, 2020, with a limit of 10 years before this date for study publication. An updated search was performed on October 29, 2020. After the exclusion of duplicates, we retrieved 2349 records. We chose the past decade (2010–2020) because many advances in cancer treatment (e.g., immunotherapy) have occurred, and previous mushroom studies might not have used the latest therapies. Furthermore, studies prior to 2010, mainly in Asian countries, have shown that certain medicinal mushrooms have a direct effect on improved quality of life and improved survival [24–27]. Our goal was to understand if there are more recent clinical studies in the past 10 years that would further the evidence to routinely integrate the use of medicinal mushrooms in cancer care globally.

We included the studies having the following inclusion criteria: (1) clinical trial or cohort study involving more than 10 patients, (2) English language, (3) the use of mushroom(s) as an intervention added to standard cancer therapy, (4) patients with a confirmed diagnosis of cancer, and (5) reporting cancer-related outcomes, such as survival, immune function, adverse events (AEs), and/or QoL. We excluded case reports or case series as well as studies containing mushrooms as one of several ingredients in a supplement. To expand our analysis, we included studies independently of the outcome measured if they met the inclusion criteria. We used the Cochrane risk of bias assessment tool to evaluate the methodological quality of the included studies. We summarized the study details in Table 1 and their bias risk in Table 2.

Data Extraction and Quality Assessment

Two authors (Narayanan, S and Nazar, F or Narayanan, S and Rozman, A) independently reviewed the titles and abstracts of the retrieved citations to identify relevant trials. We resolved the disagreements by discussion. For each of the articles in our final selection, we extracted the following data: general information (the year of publication, first author, and duration of the study), study design (prospective, retrospective, and clinical trial), population baseline characteristics (age, gender, cancer diagnosis, staging, performance status, and previous treatment), intervention (the type of mushroom, extraction technique, dose, duration of therapy, and sample size), outcomes, and the authors' conclusions. We also collected data on blinding, randomization, and dropout reporting in clinical trials. Because of the heterogeneity of interventions, outcomes, and cancer diagnoses studied, we presented the results in a descriptive fashion instead of combining them in a meta-analytic statistical approach.

Results

Study Selection

The study selection process was recorded in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1). Of 2349 unique studies screened, 2210 were excluded because they did not meet the inclusion criteria through abstract review. We selected the remaining 139 for a further in-depth review. The final selection included 39 articles: 15 randomized control trials (RCTs), 11 prospective, and 13 retrospective studies. Of 39 studies, only 1 was conducted in the US, with 9 conducted in China, 20 in Japan, 2 in Taiwan, 2 in Brazil, 2 in South Korea, and 1 trial each in Norway, Iraq, and Thailand (Table 1). Table 2 depicts the risk of bias ratings of the included studies. High or unclear risk of bias ratings was mainly due to lack of blinding and small sample size.

Mushroom Compounds, Cancer Diagnosis, Staging, and Performance Status

Eleven different types of mushroom extracts were included. The most frequently studied mushroom was PSK (Turkey tail, $N=10$); followed by *Lentinula edodes* mycelia extract (Shiitake, $N=8$); *Trametes robinophilia Murr.* (Huaier granules, $N=5$); active hexose correlated compound (AHCC, $N=5$), a proprietary extract of Shiitake mushroom (*Lentinula edodes*); and others. The most studied cancer types were gastric cancer ($N=11$), breast cancer ($N=8$), and prostate cancer ($N=5$), followed by other cancer types. Seven studies included patients with advanced cancer (stage ≥ 4 or unresectable tumor), whereas the rest had early-stage disease. Most studies did not report the patients' performance status before the intervention.

Survival Analysis, Disease Control, and Tumor Biomarkers

A combination of Huaier granules with conventional treatment in breast cancer patients showed a statistically significant improvement in DFS (disease-free survival), 112.61 months in Huaier group compared to 91.43 months for control (hazard ratio (HR), 2.97; $P<0.01$) [28]. In a randomized control trial (RCT) of 62 patients with HCC, Huaier granules in combination with standard-of-care treatment improved mid- to long-term overall survival (OS) [29]. A retrospective analysis of 36 hepatocellular carcinoma (HCC) patients showed an increase in both time to

Table 1 Study characteristics

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Breast cancer						
Ali N K M, Iraq, 2019[47]	Breast cancer stage II-IV	Ganoderma lucidum (G. lucidum) 1000 mg b.i.d. 12 weeks	Plasma cytokines/immune markers: IFN-γ, TNF-α, IL-8 adiponectin	40 (T 20)	Increased IFN-γ, decreased TNF-α, and IL-8 after treatment period	G. lucidum in patients treated with chemotherapy may improve their immune stimulatory, anti-inflammatory, and anti-metastatic effect
Hangai S, Japan, 2013[63]	Breast cancer stage I-IIIA	AHCC 1 g	AEs	41	Fewer neutrophil decrease decreased use of G-CSF	AHCC had potential to reduce neutropenia severity, neutrophil-related events, and use of G-CSF
Nagashima Y, Japan, 2013[50]	Breast cancer stage IIA-IIIA	LEM extract 1800 mg daily 3 weeks during second course of chemotherapy	QoL (QoL questionnaire for cancer patients treated with anti-cancer drugs). Immune markers	T 10	QoL total and physical subscale were maintained after concomitant LEM. Lymphokine-activated killer cell, NK cell activity, % of NK, and activated NK cells were maintained with concomitant LEM	Concomitant LEM with chemotherapy may maintain QoL and immune function
Nagashima Y, Japan, 2017[51]	Breast cancer stage I-III	LEM extract 1800 mg daily	IL-4, IFN-γ, Th1/Th2 balance, among others, QoL (FACT-BRM, FACT-G, PWB, FWB)	47 (T 23)	QoL scores decreased from baseline in placebo group, but not in LEM group. Increase in proportion of Tregs to peripheral blood CD4 + cells tended to be inhibited in LEM group compared with the placebo group	Oral LEM administered with anthracycline-based chemotherapy was useful in maintaining QoL and immune function
Suzuki N, Japan, 2013[48]	Breast cancer stage 0-II	LEM 1800 mg daily	QoL (NBS) IL-10 IFN-γ)	20	IFN-γ/IL-10 ratio and IFN-γ production increased with LEM use in a subgroup of patients with IFN- γ/IL-10 ratio 0.2 or less. Total QOL and vitality score increased	The concomitant use of LEM with postoperative adjuvant hormonal therapy improved QoL and immune function
Valadares F, Brazil, 2013 [67]	Breast cancer stage II-III	A. sylvaticus 2.1 g/day	Comparison of nutritional parameters. Aes	46	Reduced loss of appetite, diarrhea, constipation, nausea, and vomiting	A. sylvaticus improved nutritional status and reduced ADRs in bowel function, nausea, vomiting, anorexia, and fever in patients treated with chemotherapy
Zhang Y, China, 2018 [28]	Breast cancer, no distant metastasis	Huaier granules 20 g t.i.d. median 6 months	DFS: tumor markers and imaging	284 (T 140)	DFS 112.61 months in Huaier group compared to 91.43 months for control group, HR-2.97	Oral Huaier granules showed longer DFS
Gastrointestinal cancers						
Ahn M, Korea, 2013[39]	Locally advanced gastric cancer stage IB-IIIB	PSK 3 g/day	OS	82	With a median follow-up of 82 months, there were no significant differences in the 5-year DFS (73% vs. 55%, $P=0.358$) and OS (77% vs. 66%, $P=0.159$) between the 2 groups receiving iv vs. po chemoimmunotherapy with PSK (both groups received PSK)	OS of the group with UFT/PSK was at least non-inferior to that of the IV 5 fluorouracil and mitomycin C with PSK for locally advanced gastric cancer

Table 1 (continued)

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Akagi, J Japan, 2010[33]	Gastric cancer stage II-III	PSK 3 g/day	Immune parameters	31 (T10)	3-year OS was 62.2% in the PSK group and 12.5% in the control group ($P=0.038$) After operation, CD57 + T cells decreased significantly in the PSK group vs. the control group ($P=0.0486$) In the group treated with PSK plus UFT, 3-year survival of CD57-high patients was as great as that of CD57-low patients (66.7% and 51.4%, respectively; $P=0.67$)	PSK improves OS partly by inhibiting CD57 + T cells, a proven poor prognostic factor in advanced gastric cancer
Chen Q, China, 2018[31]	Early-stage hepatocellular carcinoma		RFS	1044 (T 686)	The Huaier and control groups had a mean RFS of 75.5 weeks and 68.5 weeks, respectively (HR = 0.67). The difference in the RFS rate between Huaier and control groups was 62.39% and 49.05% ($P=0.0001$)	Among patients who underwent curative resection for HCC, adjuvant therapy of 20 g oral Huaier t.i.d. significantly increased RFS and OS and reduced the rate of EHR
Fortes, C Brazil, 2010[62]	Colorectal cancer stages I-III	A. sylvaticus 30 mg/kg/day in 2 doses	QoL	56 (28)	Patients treated with a dietary supplement with A. sylvaticus fungus had increased adhesion to physical activity; improved disposition and good mood; reduced complaints of pains and alterations of sleep such as insomnia and restless sleep; presenting more appetite, reduced constipation, diarrhea, alternate diarrhea/constipation, flatulence, flatus retention, pyrosis, postprandial fullness, nausea, abdominal distention and abdominal pain	A. sylvaticus improved QoL of patients with colorectal cancer post-surgery
Fukuchi M Japan, 2016[35]	Gastric cancer stage II-III	PSK 3 g t.i.d	RFS	136	Among 13 clinicopathological factors, non-T4 stage (OR, 0.61; $P<0.01$), N0-1 (OR, 0.65; $P=0.03$) and number of treatment cycles ≥ 7 (OR, 0.37; $P<0.01$) were significant independent factors for better RFS	S-1 adjuvant chemotherapy combined with PSK may reduce recurrence by prolonging the treatment cycles in patients with advanced non-T4 or N0-1 gastric cancer
Higashi D, Japan, 2012[66]	Unresectable gastric cancer	LNT	OS Aes	39 (T 19)	No significant differences in OS AEs tended to occur less frequently in the group receiving LNT	LNT did not prolong OS. Duration of therapy was longer for patients taking LNT due to low frequency of AEs

Table 1 (continued)

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Hsu J, Taiwan, 2016[28]		PSK	Long-term outcome in patients who underwent radical surgery and received adjuvant immunochemotherapy (5-FU-based regimens plus PSK). Effects of PSK on host immune cells	918	PSK prolonged patient survival in stages IIIA and IIIB ($P=0.031$)	In gastric cancer patients undergoing radical surgery and receiving adjuvant chemotherapy for stages IIIA and IIIB disease, PSK provided substantial survival benefits, especially in PD-L1 (-) subpopulation
Ito G, Japan, 2012[18]	Gastric cancer stage II-III	PSK 3 g/day	Effectiveness of PSK as postoperative adjuvant immunochemistry according to MHC I	349 (T 124)	Expression-negative cases demonstrated 3-year RFS rates of 65% in the PSK group and 47% in the chemotherapy-only group. Therefore, the PSK group revealed a prolonged survival For the 82 expression-negative cases with pN2 or greater, the RFS rates were 68% in the PSK group and 28% in the chemotherapy-only group, representing a significant difference	Addition of PSK to chemotherapy improved the prognosis in patients who underwent curative resection for gastric cancer in patients, where primary lesion is negative for MHC class I expression and in patients with advanced lymph node metastasis
Lee S, Korea, 2018[42]	Pancreatic ductal adenocarcinoma (T1 to T4, N0)	Phellinus linteus (P. linteus) mycelium extract 1100 mg t.i.d	Adherence to adjuvant therapy completion of adjuvant therapy	217 (83)	P. linteus medication was the only significant predictor for completion of adjuvant treatment after curative resection ($P=0.039$). DFS and OS of the PL medication group were significantly higher than the no PL medication group ($P<0.05$)	P. linteus increased patients' adherence to postoperative adjuvant chemotherapy, with low toxicity of chemotherapy
Miyake Y, Japan, 2016[41]	Colorectal cancer stages IIB/III	PSK 3 g/day	DFS	357 (178)	The 3-year DFS rate was 82.3% in those receiving UFT/LV and 72.1% in those receiving UFT/PSK. The 3-year OS rate was 95.4% in those receiving UFT/LV and 90.7% in those receiving UFT/PSK	UFT/PSK was non-inferior to UFT/LV in stage IIB and III colorectal cancer patients
Namikawa T, Japan, 2015[37]	Advanced gastric cancer	PSK 3 g/day	OS	190	OS was significantly longer in patients treated with S-1 plus PSK than in those given S-1 alone (HR, 0.608; $P=0.041$)	Immunochemotherapy using PSK improved the OS of advanced gastric cancer patients
Qi J, China, 2020[32]	Gastric cancer stage IIB post-surgery	Huaier granules 20 g t.i.d	Anti-tumor role and mechanisms	126 (54)	DFS improved to 51.32 vs 44.19. OS improved to 56.81 vs. 51.32 months	Huaier granules combined with TS-1 ameliorated disease prognosis and induced apoptosis by regulating Livin expression
Tanaka H, Japan, 2012[34]		PSK	OS	254 (115)	In patients with early tumor recurrence, OS was significantly better in the PSK group ($P=0.023$). In patients with pN3 lymph node metastasis, median OS was better in the PSK group vs the control group ($P=0.032$)	Adjuvant immunochemotherapy with PSK increased OS in patients with pN3 and early tumor recurrence

Table 1 (continued)

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Wang J, China, 2012[56]	Esophageal cancer	LNT IV 1 mg	QoL IL-2 IL-6 IL-12 IL-4 IL-5 IL-10	50 (38)	Patients in the LNT/chemotherapy group exhibited significantly greater improvement in the general condition, the symptoms and signs, and the quality of life of the patients following the first and second course of treatment vs. the control group ($P<0.05$) After 2 courses of treatment, clinical efficacy was significantly greater in the LNT/chemotherapy group vs. the control group ($P<0.05$)	Addition of LNT to chemotherapy improved the general condition, symptoms and signs, QoL, and the immune function of esophageal cancer patients
Yamashita K, Japan, 2015[55]		PSK 3 g/day for 2 weeks	TGF-β	31 (17)	All the 6 elevated cases in the neoadjuvant PSK therapy group showed a significant reduction of plasma TGF β (from 21.6 to 4.5 ng/mL, on average), vs. the neoadjuvant PSK-free therapy group There was a significant reduction in the difference of plasma TGF-β between both groups ($P=0.019$)	PSK reduced the higher plasma levels of TGF-β
Yanagimoto H, Japan, 2016[43]	Pancreatic ductal adenocarcinoma	AHCC 6 g/day	Effect on chemotherapy-related AEs	75 (T 35)	The CRP elevation and albumin decline of the AHCC group were significantly suppressed vs. the control group during the gemcitabine administration ($P=0.0012$, $P=0.0007$). AHCC group was significantly suppressed vs. the control group during the gemcitabine administration ($P=0.0012$, $P=0.0007$). AHCC group had less frequent taste disorder caused by gemcitabine (17% vs. 56%, $P=0.0007$). Frequency of grade 3 on the mGPS during chemotherapy was found significantly less in the AHCC group (14%) vs. control group (53%; $P=0.0005$)	AHCC may reduce the chemotherapy-related AEs and may maintain the QoL of patients with pancreatic ductal adenocarcinoma during gemcitabine
Yoshino S, Japan, 2016[40]	Unresectable/recurrent gastric cancer	LNT	OS	309 (155)	The median OS was 13.8 and 9.9 months ($P=0.208$), the median TTF was 4.3 and 2.6 months ($P<0.001$), and the ORR was 22.3% and 18.7% for the S-1 and S-1 plus LNT groups, respectively	OS did not improve and TTF was significantly worse in the LNT group compared to S-1 alone

Table 1 (continued)

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Zhao G, China, 2017 [29]	Primary hepatic carcinoma	Huaier granules 20 g t.i.d	OS	62 (31)	6- and 12-month OS was 100% and 93.5% in Huaier granule-treated group and 90.3% and 80.6% in control group, respectively. The difference in OS at 12 months was significant ($P<0.05$). The number of TACE procedures was significantly lower in the Huaier granule-treated group (2.9 ± 8.7) than the control group (4.1 ± 7.3; $P<0.05$)	Combining TACE with Huaier granules improved the response of HCC patients and mid- to long-term OS
Zhou L, China, 2017[30]	Hepatocellular carcinoma SP liver transplantation		Recurrence time OS	36	The Huaier granules group had significantly longer recurrence times ($P=0.008$) and survival times ($P<0.0001$) (OS, 1-year: 100%, 3-year: 94.4%, 5-year: 77.8%; DFS, 1-year: 88.9%, 3-year: 55.6%, 5-year: 50.0%). Huaier granules group had significantly lower serum AFP levels (both $P<0.0001$) and percentage of FoxP3 + Tregs ($P<0.001$) during the first year. In the Huaier granule group, FoxP3 + /CD8 + Treg lymphocyte percentages decreased significantly following LT ($P<0.001$); however, CD8 + /CD3 + T cells significantly increased ($P<0.001$)	Early SRL-based therapy with thymalfasin and Huaier granules following LT in advanced HCC may improve QoL and delay tumor recurrence without increasing the rejection rate
Genitourinary Cancers						
Guo L, China, 2018[65]	Epithelial ovarian cancer with ascites	LNT (IV 1 mg each time, twice/week and three weeks for a cycle)	Effective rate (CR + PR) DCR (CR + PR + SD)	212 (T114)	The effective rate in paclitaxel + cisplatin group was 31.6% and DCR was 80.6% The effective rate in paclitaxel + cisplatin + LNT group was 50.9% and the DCR was 88.6%	LNT combined with chemotherapy could enhance the efficacy of chemotherapy and control of ascites
Ohno S, Japan, 2013[61]	Prostate, endometrial, and bladder cancers among others in complete clinical remission	AbM 1.8, 3.6, or 5.4 g/day	QoL (SF-8 quality instrument)	67	The results showed a significant improvement in QoL in both physical and mental components. QoL effects of AbM showed male patients improved physical components, while female patients improved only mental components QoL effects in the different age groups showed that ages ≤ 65 improved mental components, while ages ≥ 66 improved physical components	AbM showed significant improvement in QoL in both physical and mental components in SF-8 qualimetric analysis

Table 1 (continued)

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Ohno S, Japan, 2011[64]	Prostate and endometrial cancers		Safety	78	AEs were observed in 9 patients. Most were digestive in nature such as nausea and diarrhea, and one patient developed a liver dysfunction-related food allergy, drug lymphocyte product None of these AEs occurred in a dose-dependent manner	AbM did not cause problems within laboratory parameters at the doses tested over 6 months, supporting previous evidence that AbM is generally safe
Sadahiro S, Japan, 2010[54]	Rectal adenocarcinoma T3-4, N + M0	PSK	Immune response	30 (15)	Significant increase of NK cell count in the peripheral blood and cytotoxic T cell counts in the peritumoral and normal mucosa and a significant decrease of serum immunosuppressive acidic protein level were observed in the PSK group	A combination of PSK and preoperative CRT may improve the immune function
Tsai M, Taiwan, 2016[46]	Patients with advanced and/or metastatic adenocarcinoma	*A. cinnamomea* (20 ml twice daily) orally for 30 days	6-month OS	37	QoL assessments were similar in the two groups, except that the mushroom group showed significant improvements in quality of sleep ($P = 0.04$)	*A. cinnamomea* combined with chemotherapy did not improve the outcome of patients but lowered the platelet counts
Sumiyoshi Y, Japan, 2010[45]	Early-stage prostate cancer	AHCC 4.5 g/day	Decreased PSA level by 50% from baseline	74	In only 1 of 74 patients, the PSA value decreased by > 50%	AHCC did not reduce > 50% of PSA level
Twardowski, P, USA, 2015[57]	Biochemically recurrent prostate cancer	WBM 8, 12, 14 g/day	Feasibility	36	Biochemically recurrent prostate cancer	WBM treatment affects levels of PSA and controls the biology of biochemically recurrent prostate cancer by lowering immunosuppressive factors
Yoshimura K, Japan, 2010[44]	Prostate cancer B0-CII	AbM mushroom and G. lucidum	PSA levels in 6 months vs. baseline	51	No PR regarding PSA was observed	No significant anticancer effects were observed
Hematological Cancers						

Table 1 (continued)

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Tangen J, Norway, 2015[59]	Multiple myeloma	AbM	Immunomodulating and clinical effects of Andosan given as adjuvant therapy	40 (19)	In the leukapheresis product harvested after stem cell mobilization, increased percentages of Treg cells and plasmacytoid dendritic cells were found in patients receiving Andosan. Also, in this group, a significant increase of serum levels of IL-1ra, IL-5, and IL7 at the end of treatment was found. Whole genome microarray showed increased expression of immunoglobulin genes, killer immunoglobulin receptor genes, and HLA genes in the Agaricus group. Andosan displayed a concentration dependent antiproliferative effect on mouse myeloma cells in vitro There were no statistically significant differences in treatment response, OS, and time to new treatment	Andosan did not exhibit significant impact, although trends for a longer median time to next treatment and a shorter period of IV antibiotics were noted in the Agaricus-treated group
Lung cancer						
Wang X, China, 2020[57]	Non-small cell lung cancer	LNT	The immunomodulatory effects of LNT on aberrant T subsets and cytokine profile	73 (38)	Chemoimmunotherapy with LNT resulted in a significant increase of CD3 + CD56 + NKT cells (15.7 ± 3.1%) vs. 8.6 ± 1.4% of NKT cells in single chemotherapy group and upregulated CD3 + CD8 + and CD3 + CD4 + subsets as well, but caused the decrease of CD4 + CD25 + Tregs induction, accompanied by significant alleviation of IL-10 and TGF-β1 and elevation of IFN-γ, TNF-α, and IL-12 ($P < 0.05$)	LNT enhanced cellular immunity and inhibited the expansion of suppressive Tregs. There was a shift in inflammatory status from Th2 to Th1
Miscellaneous						
Ito T, Japan, 2014[60]	Ovarian cancer, pancreatic cancer, lung cancer, and colorectal cancer stages I-IV	AHCC	Evaluation of AEs with NCI-CTCAE v3.0	24	AHCC significantly decreased the levels of HHV-6 in saliva during chemotherapy and improved not only QoL scores in the EORTC QLQ-C30 questionnaire but also hematotoxicity and hepatotoxicity	AHCC significantly decreased the levels of HHV-6 in saliva during chemotherapy and improved both QoL scores in the EORTC QLQ-C30 questionnaire, hematotoxicity, and hepatotoxicity

Table 1 (continued)

Reference	Type of cancer	Mushroom (or extract) studied	Primary outcome/endpoint	Sample size *N* (T)*	Significant findings	Authors' conclusions
Suknikhom W, Thailand, 2017 [52]	Epithelial ovarian cancer or peritoneal cancer stage I-IV	AHCC 3 g/day	The ability of AHCC to improve immune response and decrease AEs	28	Changes in CD4 + and CD8 + T cell lymphocyte levels were not significantly different between AHCC and placebo group ($P = 0.61$ and $P = 0.19$ for CD4 + and CD8 + T cell lymphocytes, respectively).CD8 + levels were significantly higher in the AHCC group at the sixth cycle of chemotherapy ($P = 0.03$) There was no difference in bone marrow suppression and QoL between both groups Nausea and vomiting significantly decreased, but muscle pain significantly increased in the AHCC group	AHCC did not significantly affect changes in CD4 + /CD8 + T cell lymphocytes from baseline. AHCC-treated patients had a significantly higher rate of moderate to severe muscle pain and lower rate of mild to moderate nausea and vomiting

*T denotes number of patients treated in the mushroom group. Abbreviations and acronyms: *AbM*, *Agaricus blazei* Murrill; *A. cinnamomea*, *Antrodia cinnamomea*; *ADRs*, adverse drug reactions; *AEs*, adverse events; *AFP*, α-fetoprotein; *AHCC*, active hexose correlated compound; *A. sylvaticus*, *Agaricus sylvaticus*; *b.i.d.*, twice daily; *CD*, cluster of differentiation; *CR*, complete response; *CRP*, C-reactive protein; *CRT*, chemoradiotherapy; *DCR*, disease control rate; *DFS*, disease-free survival; *EHR*, extrahepatic recurrence; *EORTC QLQ-C30*, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; *ET*, endocrine therapy; *FACT-BRM*, Functional Assessment of Cancer Therapy for patients receiving biological response modifier; *FACT-F*, Functional Assessment of Cancer Therapy-Fatigue; *FEC75*, fluorouracil/epirubicin/cyclophosphamide; *FM*, 5-FU/MMC; *FoxP3*$^+$, forkhead box P3$^+$, *FWB*, functional well-being; *G-CSF*, granulocyte colony stimulating factor; *G. lucidum*, *Ganoderma lucidum*; *HADS*, Hospital Anxiety and Depression Scale; *HHV-6*, human herpesvirus 6; *HLA*, human leukocyte antigen; *IFN-γ*, interferon-gamma; *IL*, interleukin; *LEM*, *Lentinus edodes* mycelia; *LNT*, lentinan; *LT*, liver transplantation; *LV*, leucovorin; *MHC*, major histocompatibility complex; *HR*, hazard ratio; *mGPS*, modified Glasgow prognostic score; *NBS*, norm-based scoring, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30; *NCI-CTCAE*, National Cancer Institute-Common Terminology Criteria for Adverse Event; *OR*, odds ratio; *OS*, overall survival; *PD-L1*, programmed death ligand 1; *P. linteus*, *Phellinus linteus*; *P.O.*, oral; *PR*, partial response; *PSA*, prostate-specific antigen; *PSK*, polysaccharide-K; *PWB*, physical well-being; *QoL*, quality of life; *RFS*, recurrence-free survival; *SD*, stable disease; *SF-8*, short form-8; *SRL*, sirolimus; *TACE*, transarterial chemoembolization; *TGF-β*, transforming growth factor-beta; *Th1/Th2*, T helper 1/T helper 2; *t.i.d.*, 3 times daily; *TNF-a*, tumor necrosis factor-alpha; T_{regs}, regulatory T cells; *TS-1*, tegafur/gimeracil/oteracil; *TTF*, time to treatment failure; *UFT*, tegafur/uracil; *WBM*, white button mushroom

Table 2 Bias risk table

Randomized clinical trials						
	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Ahn M, Korea, 2013	Low	High	High	High	High	Low
Akagi J, Japan, 2010	Low	High	High	High	Low	Low
Chen Q, China, 2018	Low	Low	High	Low	Low	Low
Costa Fortes R, Brazil, 2010	Low	Unclear	Low	Low	Unclear	Low
Miyake Y, Japan, 2016	Low	High	High	High	Low	Low
Nagashima Y, Japan, 2017	Low	Low	Low	Low	Low	Low
Sadahiro S, Japan, 2010	Low	High	High	High	Low	Low
Suknikhom W, Thailand, 2017	Low	Low	Low	Low	Low	Low
Tangen J, Norway, 2015	Low	Low	Low	Low	Moderate	Low
Tsai M, Taiwan, 2016	Low	Unclear	Low	Low	Low	Low
Valadares F, Brazil, 2013	Low	Low	Low	Low	Low	Low
Yamashita K, Japan, 2015	Low	High	High	High	Low	Low
Yoshino S, Japan, 2016	Low	Unclear	High	High	Low	Low
Zhao G, China, 2017	Low	High	High	High	Low	Low
Zhao H, China, 2012	Low	Unclear	Unclear	Unclear	Low	Low
Prospective studies						
	Selection bias	Information bias	Attrition bias	Reporting bias		
Ali N K M, Iraq, 2019	Low	Low	Low	Low		
Ito T, Japan, 2014	High	Low	Low	Low		
Nagashima Y, Japan, 2013	Moderate	Low	Low	Low		
Ohno S, Japan, 2011	Low	Low	Low	Low		
Ohno S, Japan, 2013	Low	Moderate	Low	Low		
Sumiyoshi Y, Japan, 2010	Moderate	Moderate	Low	Low		
Suzuki N, Japan, 2013	Low	Low	Low	Low		
Twardowski P, USA, 2016	Low	Unclear	Low	Low		
Wang J, China, 2012	High	Moderate	Low	Low		
Yanagimoto, H, Japan, 2016	High	Low	Low	Low		
Yoshimura K, Japan, 2010	High	Low	Low	Low		
Retrospective studies						
	Selection bias	Information bias	Attrition bias	Reporting bias		
Fukuchi M, Japan, 2016	High	Low	NA	Low		
Guo L, China, 2018	Low	Low	NA	Low		
Hangai S, Japan, 2013	Low	Low	NA	Low		
Higashi D, Japan, 2012	High	High	NA	Moderate		
Hsu J, Taiwan, 2016	Low	Low	Low	Low		
Ito G, Japan, 2012	Low	Low	Low	Low		
Lee S, Korea, 2019	Low	Low	Moderate	Low		
Namikawa T, Japan, 2015	Low	Low	Low	Low		
Qi J China, 2020	Low	Low	Low	Low		
Tanaka H, Japan, 2012	Low	Moderate	NA	Low		
Wang X, China, 2020	High	Low	NA	Low		
Zhang Y, China, 2018	Low	Low	Low	Low		
Zhoul L, China, 2017	Low	Low	Low	Low		

Cochrane bias risk assessment tool was used to access bias risk for each study

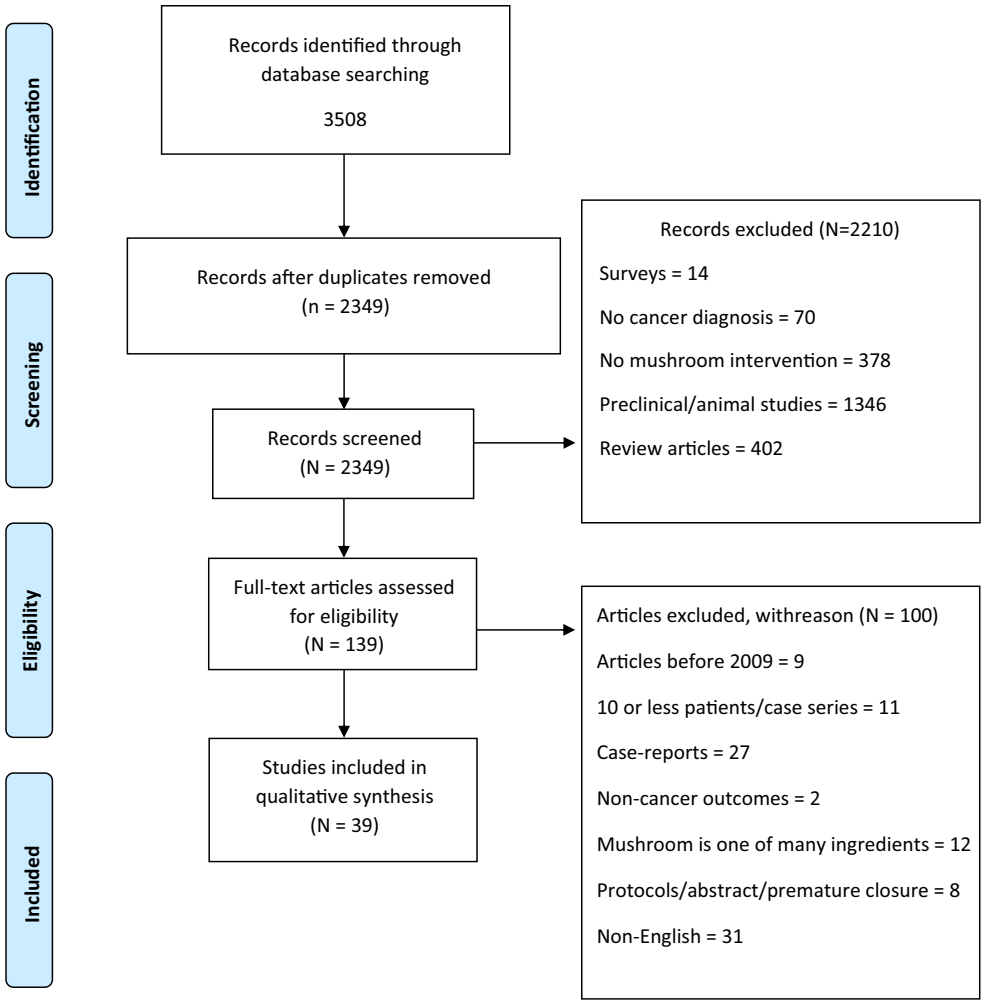

Fig. 1 PRISMA flow diagram

recurrence and OS with the use of Huaier granules [30]. Chen et al. performed a large multi-center RCT enrolling 1044 patients using Huaier granules as an adjuvant therapy for HCC after curative liver resection [31••]. This study reported a significant prolongation of mean recurrence-free survival (RFS), 75.5 weeks and 68.5 weeks for the Huaier ($n=686$) and control groups ($n=316$), respectively (HR, 0.67; 95% confidence interval (CI), 0.55–0.81). The same study also reported reduced extrahepatic recurrence (8.60% vs. 13.61%, $P=0.0149$) in the Huaier granule group vs. control group. Qi et al. in a retrospective study of stage 2b gastric cancer demonstrated an improvement in (DFS 51.32 vs. 44.19, $P=0.034$) and improved overall survival (56.81 vs. 51.32, $P=0.20$) with the use of Huaier granules in combination with chemotherapy [32].

PSK as an adjuvant with chemotherapy after curative gastric cancer resection increased the 3-year RFS, compared with chemotherapy only [18, 33]. This increase was seen in patients with major histocompatibility complex (MHC) class 1–negative primary lesions and those with more than 3 lymph node metastases. Tanaka et al. showed improved OS with PSK ($P=0.023$) in patients with early tumor recurrence and improved OS in patients with pN3 metastasis ($P=0.032$) [34]. PSK combined with chemotherapy increased the median number of cycles of chemotherapy (4.5 vs. 7.7) with better RFS in a retrospective study of gastric cancer patients [35]. PSK also improved 5-year OS (54.8% vs. 45.55; $P=0.031$) in stage IIIA/IIIB gastric cancer patients, especially in the programmed death ligand 1 (PD-L1)-negative subpopulation [36]. Additionally, PSK prolonged OS in patients with gastric cancer (HR, 0.608; 95% CI, 0.375–0.985; $P=0.041$) [37]. It is to be noted that in an RCT of 111 curatively resected gastric cancer patients showed a trend of slightly worse DFS and OS with PSK use, though the difference did not reach statistical significance and the trial closed prematurely and therefore excluded from our systematic review [38]. Ahn et al. used PSK as adjuvant in patients with locally advanced gastric cancer treated with

iv vs. po chemo-immunotherapy; therefore, the role of PSK in this study is inconclusive [39]. In a study of 309 unresectable gastric cancer patients using lentinan (LNT), OS did not improve, and time to treatment failure worsened 2.6 in the LNT group vs. 4.3 months with S1 alone ($P < 0.001$) [40]. A phase III trial in stage IIB, III colorectal cancer patients UFT (uracil and tegafur), and PSK adjuvant therapy was not non-inferior to UFT and leucovorin (LV) therapy with respect to the DFS (72.1 in PSK group vs. 82.3% in UFT/LV, − 9.06%, 90% confidence interval − 17.06 to − 1.06%) [41].

P. linteus along with adjuvant chemotherapy in pancreatic cancer patients led to the completion of chemotherapy in multivariable regression analysis (odds ratio, 2.14; $P = 0.039$) [42]. In this study, *P. linteus* potentially lowered the toxicity of chemotherapy, improving patients' adherence and ultimately DFS.

AHCC significantly reduced chemotherapy-related AEs in pancreatic cancer patients, compared with the control group (74% vs. 50%; $P = 0.003$) with similar response rates [43]. However, AHCC alone yielded no significant change in prostate-specific antigen (PSA) levels, and a combination of AbM-Reishi yielded no significant effect on PSA doubling time, in 2 prostate cancer studies [44, 45]. Tsai et al. did not find a survival improvement combining *A. cinnamomea* vs. placebo with chemotherapy among patients with advanced cancer in a randomized control study [46].

Immune Markers

The most commonly reported immune markers were interferon-gamma (IFN-γ, which stimulates the expression of tumor-suppressing factors), tumor necrosis factor-alpha (TNF-α), interleukins (ILs), T cells, natural killer (NK) cells, etc. Ali et al. reported higher IFN-γ levels after *G. lucidum* was given to breast cancer patients receiving chemotherapy [47]. Suzuki et al. found a significant increase in IFN-γ with *L. edodes* mycelia in a subgroup of 6 breast cancer patients with decreased immunity [48].

TNF-α is a proinflammatory cytokine involved in the growth, proliferation, and metastasis of breast cancer. *G. lucidum* reduced the levels of TNF-α in breast cancer patients undergoing chemotherapy or endocrine therapy [47, 49]. Moreover, *G. lucidum* decreased the levels IL-6 levels with linear correlation to cancer-related fatigue in breast cancer patients undergoing endocrine therapy [49].

AHCC did not significantly alter NK cell activity or levels of T helper 1/T helper 2 (Th1/Th2) cells in early-stage prostate cancer patients [45]. However, Nagashima et al. found that *L. edodes* mycelia with chemotherapy prevented decreased NK cell activity after the first week of chemotherapy in breast cancer patients [50]. A subsequent study from the same group did not replicate this finding [51] but found reduced $FoxP3^+/CD25^+$ regulatory T cells (T_{regs}) among the $CD4^+$ T cells in the *L. edodes* mycelia group compared with the placebo group. Such T_{reg} reduction was associated with reduced immunosuppression and increased tumor immunity. There were no significant changes in $CD4^+$ and $CD8^+$ lymphocytes with the use of AHCC vs. placebo in women with epithelial ovarian or peritoneal cancer [52].

PSK use in a post-surgical setting in patients with stage II/III gastric cancer lowered the number of $CD57^+$ T cells (16% vs. 28%; $P = 0.048$), compared with chemotherapy alone, at 3-month follow-up [33]. $CD57^+$ T cells suppress tumor immunity and are associated with poor prognosis in advanced gastric cancer [53]. PSK use in rectal cancer patients during preoperative chemoradiation before surgery increased NK cell counts in peripheral blood and also increased cytotoxic T cell counts in peri-tumoral and normal mucosa of surgically resected specimens [54]. PSK use as neoadjuvant therapy for 2 weeks preoperatively in patients with advanced gastric cancer reduced plasma levels of transforming growth factor-beta (TGF-β; 21.6 to 4.5 ng/mL, on average), which may antagonize immune evasion by cancer [55]. Lentinan administered with chemotherapy for esophageal cancer caused an increase in serum levels of IL-2, IL-6, and IL-12, and a decrease in IL-4, IL-5, and IL-10 to a greater extent compared to control group with no lentinan, which favor a better immune response [56]. Combining lentinan with chemotherapy in non-small cell lung cancer patients also increased $CD3^+/56^+$ NK T cells ($15.7 \pm 3.1\%$) compared with patients who did not receive lentinan ($8.6 \pm 1.4\%$) [57]. There was also a decrease in $CD4^+/25^+$ T_{reg} percentage, suggesting a shift from Th2 to Th1 status with lentinan use. Twardowski et al. detected high IL-15 levels in 3 patients with biochemically recurrent prostate cancer who had complete or partial response to white button mushroom powder [58]. IL-15 stimulates CD8 T cells, NK cells, and NK T cells.

Though most mushroom studies are conducted in solid tumor patients, Andosan, an AbM-based mushroom extract, when combined with autologous stem cell transplant and high-dose chemotherapy, significantly increased serum IL-1 receptor antagonist (IL-1Ra), IL-5, and IL-7 at the end of treatment in multiple myeloma patients [59]. Moreover, the harvested stem cells had increased T_{regs} and plasmacytoid dendritic cells in the mushroom group compared with the placebo group, suggesting positive and negative immunomodulatory effects.

Symptom Severity and QoL Assessment

Many of the studies assessed QoL and symptoms, yet there was considerable heterogeneity of the assessment tools used. All studies revealed that mushroom use improved at least 1 physical, psychological, or other QoL outcome. *G. lucidum* was associated with better physical well-being

and global QoL [49]. AHCC decreased both appetite loss and dyspnea symptoms [60], and AbM was associated with higher reports of physical component summary and mental component summary scores on SF-8 [61]. Studies using *L. edodes* mycelia showed that the mushroom-treated groups avoided lower QoL scores after second-line chemotherapy compared to controls [50], with higher scores on functional and physical domains in another study [36]. Lentinan-chemotherapy combination greatly improved QoL of esophageal cancer patients [56]. *L. edodes* mycelia use improved QoL in terms of symptoms and the function scale during the last 4 weeks of immunotherapy. AHCC and *A. cinnamomea* showed improvements in anxiety symptoms [45] and sleep quality, respectively [46]. *A. sylvaticus* supplementation in patients who had undergone resection of colorectal cancer reduced pain, insomnia, gastrointestinal symptoms, and improved mood, compared with placebo [62]. Patients who took Huaier granules felt less tense or irritable and had less difficulty remembering things or sleeping than did patients in the control group [28].

Adverse Events

Studies reported both the AEs of mushroom extracts themselves and/or the effect of mushrooms on adverse effects of chemotherapy. The studies that evaluated the AEs of mushroom extracts are AHCC [43, 45, 60, 63], *L. edodes* [48, 51], AbM [64], *A. cinnamomea* [46], and *G. lucidum* [49]. Grade 3 SEs related to mushroom extracts were observed for AbM (urticaria grade 3) [64] and *A. cinnamomea* (bleeding grade 3–4, lowered platelet count) [46]. The remaining reported SEs were grade 2 or lower.

Many reviewed studies showed reduction in chemotherapy-related AEs due to mushroom supplements. Patients with advanced cancer undergoing chemotherapy showed improvements in hematological toxicity and hepatotoxicity [60]. The concurrent use of AHCC during chemotherapy in breast cancer reduced neutropenia-related events, including a lower use of granulocyte colony-stimulating factor [63]. A lentinan-chemotherapy combination decreased the incidence of AEs in ovarian and gastric cancer [65, 66]. Women with breast cancer taking *Agaricus sylvaticus* demonstrated improved nutritional status and gastrointestinal parameters (i.e., nausea, vomiting, or anorexia) compared with those receiving placebo [67].

Discussion

This systematic review examined the evidence on the effects of mushroom supplements in cancer patients. Of 39 clinical trials extracted from the different databases that fit our inclusion criteria, 31 studies showed beneficial effects of the mushrooms, resulting in improved quality of life, reduced SE profiles of different chemotherapeutic drugs, improved anti-inflammatory and anti-metastatic effects, and improved DFS as well as OS in a few trials. Six of the 39 studies did not show any effect or advantage of adding medicinal mushrooms [39, 41, 44–46, 59]. Only 2 out of 39 studies revealed worsening outcomes and increased AEs due to mushroom supplements [40, 52]. We found significant heterogeneity among the reviewed studies in cancer diagnosis, cancer stage, types of mushrooms used, and outcome measures. Quantitative analysis of the study results was not feasible because of the heterogeneity of cancers and various outcome measures. Therefore, we found that the current evidence is insufficient to inform clinical decision-making on the use of mushrooms in cancer. Small sample size as well as lack of randomization and blinding were the main limitations of the reviewed studies, leading to a high risk of bias and precluding our ability to reach clear conclusions.

Mushrooms inhibited cancer cell lines in vitro and are considered a promising agent in cancer in vivo models [68–78]. However, the majority of the evidence is preclinical, compared to clinical studies in cancer patients in the last 10 years. Mushroom products may have AEs, including drug-supplement interactions, quality control issues, metabolic interactions, drug-drug interactions, organ toxicity, and tumor growth. Studies included in the current systematic review reported mostly lower grade SEs without major AEs. However, this should be interpreted with caution, as some studies were retrospective. There is a risk of interaction between supplements with other medications or cancer treatments, causing decreased efficacy or SEs [60–63]. This interaction risk was not explored in depth in the reviewed studies.

The safety and benefits of edible mushrooms are reflected in several systematic reviews and meta-analyses [5, 6]. In our review, mushroom extracts seemed to improve QoL outcomes and help decrease anticancer treatment-related toxicities, thus increasing treatment adherence and improving outcomes. Though numerous studies have shown favorable immune outcomes, a few studies showed immunosuppressive effects or mixed immune response [20, 59]. Therefore, the complex biological effects of mushrooms on the immune system in cancer are yet to be fully understood. Herein, mushroom supplements seemed to be well tolerated by most patients, without major AEs. However, large RCTs are needed to confirm the reported benefits and toxicities of mushrooms in combination with the standard of care in cancer.

There are several limitations to the current systematic review. Although the aim of the present systematic review was to include all relevant reports through an expansive list of keywords and multiple databases, there is still a possibility that we missed some studies. Particularly, we

omitted articles in languages other than English. Furthermore, small sample sizes as well as lack of randomization and allocation concealment in some of the included trials might have decreased the quality of evidence in the current review findings. Additionally, several studies were conducted in Asian countries, and it is unclear if the results are generalizable to other ethnic groups. We did not include a search of the Chinese knowledge databases, which would likely contain numerous studies using mushroom extracts and using traditional Chinese medicine with mushroom as 1 of the ingredients. We also did not include studies that measured outcomes that might affect cancer indirectly, such as improved metabolic effects associated with the use of mushroom supplements. We restricted the study period to 2010–2020, and this resulted in missing clinical trials published prior to 2010 or after 2020.

Despite these limitations, we believe the current systematic review provides cancer professionals a condensed source of information for clinicians to lead a discussion on the current clinical evidence of using mushrooms in cancer, their benefits, AEs, etc. [79]. In a survey of 61 clinicians and 529 patients in 2 oncology practices affiliated with 1 academic medical center, complementary and alternative medicine discussions in visits varied significantly by practice context, with the patient initiating most of the discussions [80]. However, such open discussions may help patients build trust in the physician–patient relationship and enable them to make an informed decision [22]. Furthermore, our systematic review might help inform the choice of mushroom supplements to study in different cancer types.

Conclusion

Most reviewed studies reported improved QoL and favorable immunological outcomes; however, evidence from this systematic review is insufficient to recommend the routine use of mushroom supplements in cancer patients. Huaier granules in HCC and PSK in gastric cancer seem to be the most studied mushroom extracts in the past 10 years for survival benefit and warrant further studies to confirm the results in other ethnic groups. We recommend open communication to discuss patients' priorities and goals as well as the available evidence on the benefits and risks of mushroom supplements. Further prospective trials, particularly high-quality RCTs, are required to investigate how to integrate mushroom supplements safely alongside conventional cancer treatment to improve patient outcomes. Furthermore, integration of natural products in oncology setting is feasible [81] and more research is needed to safely integrate mushroom supplements in cancer care.

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Data Availability Available in MD Anderson database.

Declarations

Conflict of Interest The authors declare no competing interest.

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Crawford K. National survey reveals surprising number of Americans believe alternative therapies can cure cancer. ASCO News Releases. 2018. https://www.asco.org/about-asco/press-center/news-releases/national-survey-reveals-surprising-number-americans-believe. Accessed August 24,2022.
2. Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002–2012. Natl Health Stat Report. 2015;79:1–16.
3. Mao JJ, Palmer SC, Straton JB, et al. Cancer survivors with unmet needs were more likely to use complementary and alternative medicine. J Cancer Surviv. 2008;2:116–24.
4.•• Ba DM, Ssentongo P, Beelman RB, Muscat J, Gao X, Richie JP. Higher mushroom consumption is associated with lower risk of cancer: a systematic review and meta-analysis of observational studies. Adv Nutr. 2021;12(5):1691–704. **This recent systematic review showed that higher dietary mushroom lowers the risk of cancer, especially breast cancer**.
5. Li J, Zou L, Chen W, et al. Dietary mushroom intake may reduce the risk of breast cancer: evidence from a meta-analysis of observational studies. PLoS One. 2014;9(4):e93437.
6. Lee DH, Yang M, Keum N, Giovannucci EL, Sun Q, Chavarro JE. Mushroom consumption and risk of total and site-specific cancer in two large U.S. prospective cohorts. Cancer Prev Res (Phila). 2019;12(8):517–26.
7. Barbieri A, Quagliariello V, Del Vecchio V, et al. Anticancer and anti-inflammatory properties of Ganoderma lucidum extract effects on melanoma and triple-negative breast cancer treatment. Nutrients. 2017;9:210.
8. Wang W, Wang X, Li C, et al. Huaier suppresses breast cancer progression via linc00339/miR-4656/CSNK2B signaling pathway. Front Oncol. 2019;9:1195.
9. Seo H, Song J, Kim M, Han DW, Park HJ, Song M. Cordyceps militaris grown on germinated soybean suppresses kras-driven colorectal cancer by inhibiting the RAS/ERK pathway. Nutrients. 2018;11:20.
10. Satria D, Amen Y, Niwa Y, Ashour A, Allam AE, Shimizu K. Lucidumol D, a new lanostane-type triterpene from

fruiting bodies of Reishi (Ganoderma lingzhi). Nat Prod Res. 2019;33:189–95.
11. Hisamochi A, Kage M, Arinaga T, et al. Drug-induced liver injury associated with Agaricus blazei Murill which is very similar to autoimmune hepatitis. Clin J Gastroenterol. 2013;6:139–44.
12. Kikuchi Y, Seta K, Ogawa Y, et al. Chaga mushroom-induced oxalate nephropathy. Clin Nephrol. 2014;81:440–4.
13.• Loquai C, Dechent D, Garzarolli M, et al. Risk of interactions between complementary and alternative medicine and medication for comorbidities in patients with melanoma. Med Oncol. 2016;33:52. **This study reported the elevated risk of interactions when natural products and supplements are used alongside conventional cancer treatment**.
14. Loquai C, Schmidtmann I, Garzarolli M, et al. Interactions from complementary and alternative medicine in patients with melanoma. Melanoma Res. 2017;27(3):238–42.
15. Hanselin MR, Vande Griend JP, Linnebur SA. INR elevation with maitake extract in combination with warfarin. Ann Pharmacother. 2010;44:223–4.
16. 103rd US Congress. Dietary Supplement Health and Education Act of 1994 (DSHEA). Public Law 103–417. 10–25–1994.
17. White CM. Dietary supplements pose real dangers to patients. Ann Pharmacother. 2020;54:815–9.
18. Ito G, Tanaka H, Ohira M, et al. Correlation between efficacy of PSK postoperative adjuvant immunochemotherapy for gastric cancer and expression of MHC class I. Exp Ther Med. 2012;3(6):925–30.
19. Torkelson CJ, Sweet E, Martzen MR, et al. Phase 1 clinical trial of Trametes versicolor in women with breast cancer. ISRN Oncol. 2012;2012:251632.
20. Deng G, Lin H, Seidman A, et al. A phase I/II trial of a polysaccharide extract from Grifola frondosa (Maitake mushroom) in breast cancer patients: immunological effects. J Cancer Res Clin Oncol. 2009;135:1215–21.
21 Witt CM, Balneaves LG, Cardoso MJ, et al. 2017 A comprehensive definition for integrative oncology. J Natl Cancer Inst Monogr. 2017;52:lgx012.
22. Frenkel M, Cohen L. Effective communication about the use of complementary and integrative medicine in cancer care. J Altern Complement Med. 2014;20(1):12–8.
23. Lee RT, Greenlee H. Don't ask, don't tell: it's time to talk about complementary, alternative, and integrative medicine with our patients. Cancer. 2020;126(13):2968–70.
24 Nakazato H, Koike A, Saji S, Ogawa N, Sakamoto J. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Study Group of Immunochemotherapy with PSK for Gastric Cancer. Lancet. 1994;343(8906):1122–6.
25. Oba K, Teramukai S, Kobayashi M, Matsui T, Kodera Y, Sakamoto J. Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curative resections of gastric cancer. Cancer Immunol Immunother. 2007;56(6):905–11.
26. Toge T, Yamaguchi Y. Protein-bound polysaccharide increases survival in resected gastric cancer cases stratified with a preoperative granulocyte and lymphocyte count. Oncol Rep. 2000;7(5):1157–61.
27. Yoshitani S, Takashima S. Efficacy of postoperative UFT (tegafur/uracil) plus PSK therapies in elderly patients with resected colorectal cancer. Cancer Biother Radiopharm. 2009;24(1):35–40.
28. Zhang Y, Wang X, Chen T. Efficacy of Huaier granule in patients with breast cancer. Clin Transl Oncol. 2019;21:588–95.
29. Zhao GS, Liu Y, Zhang Q, et al. Transarterial chemoembolization combined with Huaier granule for the treatment of primary hepatic carcinoma: safety and efficacy. Medicine (Baltimore). 2017;96:e7589.
30. Zhou L, Pan LC, Zheng YG, et al. Novel strategy of sirolimus plus thymalfasin and Huaier granule on tumor recurrence of hepatocellular carcinoma beyond the UCSF criteria following liver transplantation: a single center experience. Oncol Lett. 2018;16:4407–17.
31•• Chen Q, Chen XP. Adjuvant Huaier granule for hepatocellular carcinoma after curative resection: a phase IV, multicenter, randomized, and parallel-group controlled clinical trial. J Hepatol. 2017;66(suppl 1)S622. **This large multi-center randomised controlled clinical trial showed survival benefit of Huaier granule, a mushroom supplement, in hepatocellular cancer**.
32. Qi J, Xie FJ, Liu S, et al. Huaier granule combined with tegafur gimeracil oteracil potassium promotes stage IIb gastric cancer prognosis and induces gastric cancer cell apoptosis by regulating Livin. Biomed Res Int. 2020;2020:2403595.
33. Akagi J, Baba H. PSK may suppress CD57(+) T cells to improve survival of advanced gastric cancer patients. Int J Clin Oncol. 2010;15:145–52.
34. Tanaka H, Muguruma K, Ohira M, et al. Impact of adjuvant immunochemotherapy using protein-bound polysaccharide-K on overall survival of patients with gastric cancer. Anticancer Res. 2012;32:3427–33.
35. Fukuchi M, Mochiki E, Ishiguro T, et al. Improved efficacy by addition of protein-bound polysaccharide K to adjuvant chemotherapy for advanced gastric cancer. Anticancer Res. 2016;36:4237–41.
36. Hsu JT, Hsu CS, Le PH, et al. Immunochemotherapy benefits in gastric cancer patients stratified by programmed death-1 ligand-1. J Surg Res. 2017;211:30–8.
37. Namikawa T, Fukudome I, Ogawa M, et al. Clinical efficacy of protein-bound polysaccharide K in patients with gastric cancer undergoing chemotherapy with an oral fluoropyrimidine (S-1). Eur J Surg Oncol. 2015;41:795–800.
38. Okuno K, Aoyama T, Oba K, et al. Randomized phase III trial comparing surgery alone to UFT + PSK for stage II rectal cancer (JFMC38 trial). Cancer Chemother Pharmacol. 2018;81:65–71.
39. Ahn MS, Kang SY, Lee HW, et al. 5-Fluorouracil, mitomycin-c, and polysaccharide-k versus uracil-ftorafur and polysaccharide-K as adjuvant chemoimmunotherapy for patients with locally advanced gastric cancer with curative resection. Onkologie. 2013;36:421–6.
40. Yoshino S, Nishikawa K, Morita S, et al. Randomised phase III study of S-1 alone versus S-1 plus lentinan for unresectable or recurrent gastric cancer (JFMC36-0701). Eur J Cancer. 2016;65:164–71.
41. Miyake Y, Nishimura J, Kato T, et al. Phase III trial comparing UFT + PSK to UFT + LV in stage IIB, III colorectal cancer (MCSGO-CCTG). Surg Today. 2018;48:66–72.
42. Lee SH, Hwang HK, Kang CM, Lee WJ. Potential impact of Phellinus linteus on adherence to adjuvant treatment after curative resection of pancreatic ductal adenocarcinoma: outcomes of a propensity score-matched analysis. Integr Cancer Ther. 2019;18:1534735418816825.
43. Yanagimoto H, Satoi S, Yamamoto T, et al. Alleviating effect of active hexose correlated compound (AHCC) on chemotherapy-related adverse events in patients with unresectable pancreatic ductal adenocarcinoma. Nutr Cancer. 2016;68:234–40.
44. Yoshimura K, Kamoto T, Ogawa O, et al. Medical mushrooms used for biochemical failure after radical treatment for prostate cancer: an open-label study. Int J Urol. 2010;17:548–54.
45. Sumiyoshi Y, Hashine K, Kakehi Y, et al. Dietary administration of mushroom mycelium extracts in patients with early stage prostate cancers managed expectantly: a phase II study. Jpn J Clin Oncol. 2010;40:967–72.
46. Tsai MY, Hung YC, Chen YH, et al. A preliminary randomised controlled study of short-term Antrodia cinnamomea treatment

combined with chemotherapy for patients with advanced cancer. BMC Complement Altern Med. 2016;16:322.
47. Ali NKM, Saeed HA, Othman RT. Immunostimulatory and anti-inflammatory effect of Ganoderma lucidum on breast cancer patients. Asia Pacific J Cancer Biol. 2019;3:51–7.
48. Suzuki N, Takimoto Y, Suzuki R, et al. Efficacy of oral administration of Lentinula eododes mycelia extract for breast cancer patients undergoing postoperative hormone therapy. Asian Pac J Cancer Prev. 2013;14:3469–72.
49. Zhao H, Zhang Q, Zhao L, Huang X, Wang J, Kang X. Spore powder of Ganoderma lucidum improves cancer-related fatigue in breast cancer patients undergoing endocrine therapy: a pilot clinical trial. Evid Based Complement Alternat Med. 2012;2012:809614.
50. Nagashima Y, Maeda N, Yamamoto S, Yoshino S, Oka M. Evaluation of host quality of life and immune function in breast cancer patients treated with combination of adjuvant chemotherapy and oral administration of Lentinula edodes mycelia extract. Onco Targets Ther. 2013;6:853–9.
51. Nagashima Y, Yoshino S, Yamamoto S, et al. Lentinula edodes mycelia extract plus adjuvant chemotherapy for breast cancer patients: results of a randomized study on host quality of life and immune function improvement. Mol Clin Oncol. 2017;7:359–66.
52. Suknikhom W, Lertkhachonsuk R, Manchana T. The effects of active hexose correlated compound (AHCC) on levels of CD4+ and CD8+ in patients with epithelial ovarian cancer or peritoneal cancer receiving platinum based chemotherapy. Asian Pac J Cancer Prev. 2017;18:633–8.
53. Chochi K, Ichikura T, Majima T, et al. The increase of CD57+ T cells in the peripheral blood and their impaired immune functions in patients with advanced gastric cancer. Oncol Rep. 2003;10:1443–8.
54. Sadahiro S, Suzuki T, Maeda Y, et al. Effects of preoperative immunochemoradiotherapy and chemoradiotherapy on immune responses in patients with rectal adenocarcinoma. Anticancer Res. 2010;30:993–9.
55. Yamashita K, Sakuramoto S, Mieno H, et al. Preoperative administration of polysaccharide Kureha and reduced plasma transforming growth factor-β in patients with advanced gastric cancer: a randomized clinical trial. Mol Clin Oncol. 2015;3:471–8.
56. Wang JL, Bi Z, Zou JW, Gu XM. Combination therapy with lentinan improves outcomes in patients with esophageal carcinoma. Mol Med Rep. 2012;5:745–8.
57. Wang XE, Wang YH, Zhou Q, et al. Immunomodulatory effect of lentinan on aberrant T subsets and cytokines profile in non-small cell lung cancer patients. Pathol Oncol Res. 2020;26:499–505.
58. Twardowski P, Kanaya N, Frankel P, et al. A phase I trial of mushroom powder in patients with biochemically recurrent prostate cancer: roles of cytokines and myeloid-derived suppressor cells for Agaricus bisporus-induced prostate-specific antigen responses. Cancer. 2015;121:2942–50.
59. Tangen JM, Tierens A, Caers J, et al. Immunomodulatory effects of the Agaricus blazei Murrill-based mushroom extract AndoSan in patients with multiple myeloma undergoing high dose chemotherapy and autologous stem cell transplantation: a randomized, double blinded clinical study. Biomed Res Int. 2015;2015:718539.
60. Ito T, Urushima H, Sakaue M, et al. Reduction of adverse effects by a mushroom product, active hexose correlated compound (AHCC) in patients with advanced cancer during chemotherapy–the significance of the levels of HHV-6 DNA in saliva as a surrogate biomarker during chemotherapy. Nutr Cancer. 2014;66:377–82.
61. Ohno S, Sumiyoshi Y, Hashine K, Shirato A, Kyo S, Inoue M. Quality of life improvements among cancer patients in remission following the consumption of Agaricus blazei Murill mushroom extract. Complement Ther Med. 2013;21:460–7.
62. Costa Fortes R, LacorteRecôva V, Lima Melo A, CarvalhoGarbiNovaes MR. Life quality of postsurgical patients with colorectal cancer after supplemented diet with Agaricus sylvaticus fungus. Nutr Hosp. 2010;25:586–96.
63. Hangai S, Iwase S, Kawaguchi T, et al. Effect of active hexose-correlated compound in women receiving adjuvant chemotherapy for breast cancer: a retrospective study. J Altern Complement Med. 2013;19:905–10.
64. Ohno S, Sumiyoshi Y, Hashine K, Shirato A, Kyo S, Inoue M. Phase I clinical study of the dietary supplement, Agaricus blazei murill, in cancer patients in remission. Evid Based Complement Alternat Med. 2011;2011:192381.
65. Guo LY, Zhang SY, Chen C, Zeng HX, Li FY, Xu QX. Lentinan combined with cisplatin and paclitaxel in the treatment of patients with ovarian cancer with ascites. Eur J Gynaecol Oncol. 2018;39:615–20.
66. Higashi D, Seki K, Ishibashi Y, et al. The effect of lentinan combination therapy for unresectable advanced gastric cancer. Anticancer Res. 2012;32:2365–8.
67. Valadares F, GarbiNovaes MR, Cañete R. Effect of Agaricus sylvaticus supplementation on nutritional status and adverse events of chemotherapy of breast cancer: a randomized, placebo-controlled, double-blind clinical trial. Indian J Pharmacol. 2013;45:217–22.
68. Shreya S, Kumar DN, Mohapatra D, et al. Tracing the anticancer mechanism of Pleurotus osteratus by the integrative approach of network pharmacology and experimental studies. Appl Biochem Biotechnol. 2023;195(1):152–71.
69. Cheng S, Castillo V, Sliva D. CDC20 associated with cancer metastasis and novel mushroom-derived CDC20 inhibitors with antimetastatic activity. Int J Oncol. 2019;54(6):2250–6.
70. Chen S, Li X, Yong T, et al. Cytotoxic lanostane-type triterpenoids from the fruiting bodies of Ganoderma lucidum and their structure-activity relationships. Oncotarget. 2017;8(6):10071–84.
71. Chihara G, Hamuro J, Maeda Y, Arai Y, Fukuoka F. Fractionation and purification of the polysaccharides with marked antitumor activity, especially lentinan, from Lentinus edodes (Berk.) Sing. (an edible mushroom). Cancer Res. 1970;30(11):2776–81.
72. Deng S, Zhang G, Kuai J, et al. Lentinan inhibits tumor angiogenesis via interferon γ and in a T cell independent manner [published correction appears in J ExpClin Cancer Res. 2021 Nov 18;40(1):366]. J Exp Clin Cancer Res. 2018;37:260.
73. Du YC, Chang FR, Wu TY, et al. Antileukemia component, dehydroeburicoic acid from Antrodia camphorata induces DNA damage and apoptosis in vitro and in vivo models. Phytomedicine. 2012;19(8–9):788–96.
74. Fu J, Wei C, Cheng J, et al. Cordycepin inhibits breast cancer migration and invasion by targeting epithelial to mesenchymal transition-inducing transcription factors (EMT-TFs) [abstract]. Cancer Res. 2018;78(13_Supplement):2039.
75. Han CK, Chiang HC, Lin CY, et al. Comparison of immunomodulatory and anticancer activities in different strains of Tremella fuciformis Berk. Am J Chin Med. 2015;43:1637–55.
76. Hsu WH, Qiu WL, Tsao SM, et al. Effects of WSG, a polysaccharide from Ganoderma lucidum, on suppressing cell growth and mobility of lung cancer. Int J Biol Macromol. 2020;165(Pt A):1604–13.

77. Roda E, De Luca F, Di Iorio C, et al. Novel medicinal mushroom blend as a promising supplement in integrative oncology: a multi-tiered study using 4 T1 Triple-negative mouse breast cancer model. Int J Mol Sci. 2020;21:3479.
78. Winder M, Bulska-Będkowska W, Chudek J. The use of Hericium erinaceus and Trametes versicolor extracts in supportive treatment in oncology. Acta Pharm. 2021;71:1–16.
79. Sweet ES, Standish LJ, Goff BA, Andersen MR. Adverse events associated with complementary and alternative medicine use in ovarian cancer patients. Integr Cancer Ther. 2013;12(6):508–16.
80. Lee RT, Barbo A, Lopez G, et al. National survey of US oncologists' knowledge, attitudes, and practice patterns regarding herb and supplement use by patients with cancer. J Clin Oncol. 2014;32:4095–101.
81. Hou YN, Chimonas S, Gubili J, et al. Integrating herbal medicine into oncology care delivery: development, implementation, and evaluation of a novel program. Support Care Cancer. 2023;31(2):128.