




Review

# The Promising Role of Mushrooms as a Therapeutic Adjuvant of Conventional Cancer Therapies

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**Abstract:** Complementary and alternative medicine (CAM) has been fronted as an alternative due to its potential for holistic treatment. Many CAMs are plant-derived, including algae and mushrooms that have been used widely in many parts of the world, where they are regarded as biological response modifiers. The purpose of this article was to review the role of mushrooms as an adjuvant in conventional therapies, to reveal the therapeutic substances of mushrooms as an adjuvant in conventional therapies, to bring together the available scientific data on the medical effects of mushrooms in oncology, and verify its efficacy and safety. A literature search was conducted in September 2021 on the MEDLINE-PubMed and Cochrane databases to identify relevant randomized controlled trials or clinical trials studies addressing the use of whole mushroom formulations as complementary therapy during conventional cancer treatment.: The findings from the present study suggest that mushrooms may act as a potentiator of host defense mechanisms and decrease adverse events for patients with cancer undergoing conventional therapies. New protocols to conduct clinical trials are needed to elucidate the possible active mechanisms and clinical benefits of these fungi in various types of cancer.

**Keywords:** adjuvant; cancer; conventional therapy; mushroom



**Citation:** Plácido, A.I.; Roque, F.; Morgado, M. The Promising Role of Mushrooms as a Therapeutic Adjuvant of Conventional Cancer Therapies. *Biologics* **2022**, *2*, 58–68. <https://doi.org/10.3390/biologics2010005>

Academic Editor: João C Fernandes

Received: 8 January 2022

Accepted: 27 January 2022

Published: 29 January 2022

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## 1. Introduction

Cancer incidence and mortality are increasing worldwide. According to the World Health Organization (WHO), cancer is a leading cause of death [1,2]. Conventional therapies such as chemotherapy, radiotherapy, and immunotherapy are associated with secondary side effects including gastrointestinal symptoms or immunosuppression that compromise the quality of life of patients [3,4]. In this context, complementary alternative medicine (CAM) has gained consensus opinions as an alternative and/or complementary treatment [5,6]. Many CAMs take advantage of the ability of mushrooms to act as biological modifiers [3].

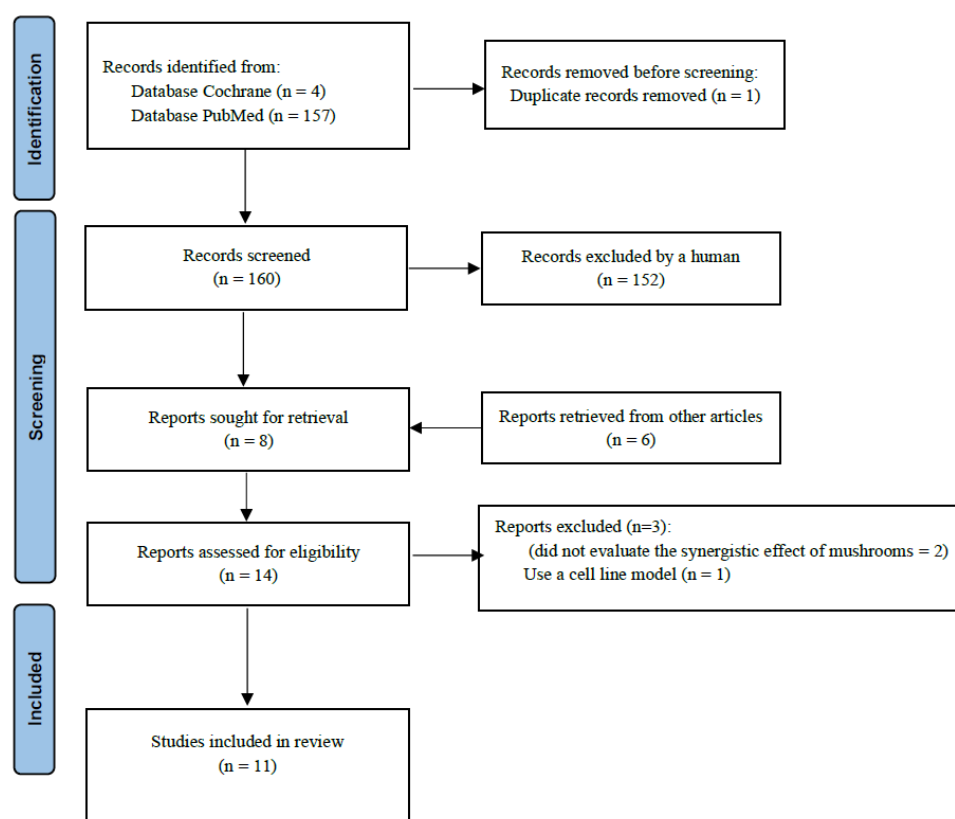
In vitro studies demonstrated that compounds isolated from mushrooms can modulate several biochemical pathways, including antioxidant [7], anti-inflammatory [8], and antimicrobial responses [9]. Mushroom bioactive compounds have also been associated with the modulation of apoptosis, cell proliferation, and angiogenesis [10].

The promising effects of mushrooms have been demonstrated on mushroom isolated compounds, and the role of the entire mushroom substances has been underestimated. Considering that it has been suggested that all active compounds of mushrooms can act

synergistically in cancer cell signaling pathways [11] and that mushroom active compounds combined with conventional therapies [11] can improve the outcome of and tolerance to invasive treatments [12–14], this work aims to provide an overview of the role of mushrooms as an adjuvant in conventional therapies, that emerged in clinical studies.

## 2. Results

The search of the databases yielded 161 citations (Figure 1). After screening titles and abstracts, seven articles potentially met the inclusion criteria and were fully screened. From the full screening analyses six new articles were retrieved. Within the 13 articles that potentially met the inclusion criteria, 3 were excluded because they did not evaluate the synergistic effect of mushrooms ( $n = 2$ ) or were performed in a cell line model ( $n = 1$ ). Eleven articles [5,15–24] fully satisfied the inclusion criteria and were included in this review.



**Figure 1.** PRISMA diagram of the literature selection in this narrative review.

### 2.1. Characteristics of the Included Studies

A description of the characteristics of the included studies is presented in Table 1. Among the included studies, four were conducted in Japan [18,19,21,23], two in Brazil [20,22], one in Singapore [15], one in Taiwan [16], one in China [5], one in South Korea [24] and one in Norway [17].

Regarding the study design, five articles were clinical trials [15–17,20,24], open label trials ( $n = 2$ ) [18,19], single-group open studies ( $n = 2$ ) [21,23] or randomized controlled trials [5,22].

**Table 1.** Characteristics of the included studies.

Author (Year)	Country	Species Name	Type of Study	Sample Size	Cancer Type	Conventional Therapy (CT)	Treatment (T)	Duration of Treatment	Outcomes Measures	Significant Findings
Chay et al. (2017) [15]	Singapore	<i>Coriolus versicolor</i>	Clinical trial	CT: 6 T: 9	Advanced hepatocellular carcinoma	Placebo	Standard continuous daily dose of 2.4 g	CT: 1.5 cycles (5.9 weeks) T: 3 cycles (12.1 weeks)	Primary outcomes: median time to progression. Secondary outcomes: response rates, toxicity, quality of life, progression-free survival, and overall survival.	Better social and emotional functioning scores. Better appetite. Less pain symptoms.
Tsai et al. (2016) [16]	Taiwan	<i>Antrodia cinnamomea</i> (AC)	Randomized clinical trial	CT: 20 T: 17	Advanced or recurrent, untreated, stage III–IV adenocarcinomas	Chemotherapy + placebo	Chemotherapy + <i>A. cinnamomea</i> (orally, 20 mL twice daily)	30 days	Primary outcomes: 6-month overall survival. Secondary outcomes: disease control rate, quality of life, adverse event, and biochemical features.	Improvements in quality of sleep.
Tangen et al. (2015) [17]	Norway	82.4% of <i>Agaricus blazei</i> Murill, 14.7% of <i>Hericium erinaceus</i> , and 2.9% of <i>Grifola frondosa</i> (AndoSan)	Randomized clinical trial	CT: 21 T: 19	Multiple myeloma	Chemotherapy with autologous stem cell support + placebo	Chemotherapy with autologous stem cell support + AndoSan (60 mL daily orally)	7 weeks	Primary outcomes: serum levels of cytokines, chemokines, and growth factors; expression levels of genes involved in immune activation by whole genome assay; stem cell harvest product of several mononuclear cell subsets associated with the immune system. Primary outcomes: overall survival, quality of life.	Increase in serum levels of IL-1, IL-5 and IL-7. Increased expression of immunoglobulin genes, killer immunoglobulin receptor genes and HLA genes.
Nagashima et al. (2013) [18]	Japan	<i>Lentinula edodes</i> (LEM)	Open-label trial with a single group	10	Breast cancer	Chemotherapy alone (3 weeks)	LEM (1800 mg/day) + chemotherapy (3 weeks)	6 weeks (3 weeks each)	Primary outcomes: quality of life and immune function.	Not achieved.
Suzuki et al. (2013) [19]	Japan	<i>Lentinula edodes</i> (LEM)	Single-arm, open-label study	20	Breast cancer	Hormone therapy (4 weeks)	Hormone therapy + LEM (oral ingestion at 1800 mg daily) (8 weeks)	12 weeks	Primary outcomes: quality of life and peripheral blood cytokine production levels.	Not achieved.
Valadares et al. (2013) [20]	Brazil	<i>Agaricus sylvaticus</i>	Randomized clinical trial	CT: 23 T: 23	Breast cancer	Chemotherapy + placebo	Chemotherapy + <i>A. sylvaticus</i> (2.1 g, in two daily administrations)	3–6 months (21 days cycles)	Primary outcomes: adverse events.	Improved nutritional status and reduced abnormal bowel functions, nausea, vomiting, and anorexia.

Table 1. Cont.

Author (Year)	Country	Species Name	Type of Study	Sample Size	Cancer Type	Conventional Therapy (CT)	Treatment (T)	Duration of Treatment	Outcomes Measures	Significant Findings
Zhao et al. (2012) [5]	China	<i>Ganoderma lucidum</i>	Randomized controlled trial	CT: 23 T: 25	Breast cancer	Placebo	Spore powder of <i>G. lucidum</i> (1000 mg 3 times a day)	4 weeks	Primary outcomes: functional assessment of cancer therapy-fatigue (FACT-F), hospital anxiety and depression scale (HADS), EORTC quality-of-life questionnaires (QLQ-C30). Secondary outcomes: TNF- $\alpha$ , IL-6, and liver-kidney function.	Beneficial effects on cancer-related fatigue and quality of life in breast cancer patients undergoing endocrine therapy.
Okuno and Uno (2011) [21]	Japan	<i>Lentinula edodes</i> (LEM)	Single-group open study	8	Gastric and colorectal cancer	Chemotherapy alone (4 weeks)	Chemotherapy + LEM (1800 mg/day) (4 weeks)	8 weeks (4 weeks each)	Primary outcomes: adverse events and IFN- $\gamma$ production by CD4 <sup>+</sup> T, CD8 <sup>+</sup> T and CD56 <sup>+</sup> NK/NKT cells.	Decrease in the incidence of adverse effects.
Valadares et al. (2011) [22]	Brazil	<i>Agaricus sylvaticus</i>	Randomized controlled trial	CT: 23 T: 23	Breast cancer	Chemotherapy + placebo	Chemotherapy + <i>A. sylvaticus</i> (2.1 g/day)	6 months	Primary outcomes: hematological and immunological parameters.	Increase of hematocrit, red blood count, MCHC, leukocytes, monocytes, and total lymphocyte count.
Yamaguchi et al. (2011) [23]	Japan	<i>Lentinula edodes</i> (LEM)	Single-group open study	7	Breast (3 patients), gastrointestinal (2 patients) or to prevent recurrence of gastrointestinal cancer (2 patients)	Chemotherapy	Chemotherapy + LEM (1800 mg/day for four weeks)	8 weeks	Primary outcomes: safety, quality of life and immune response.	Increase in LAK cell activity and NK cell activity and a decrease in IAP levels.
Ahn et al. (2004) [24]	South Korea	<i>Agaricus blazei Murill Kyowa</i> (ABMK)	Randomized clinical trial	CT: 61 T: 39	Gynecological cancer (cervical, ovarian and endometrial)	Chemotherapy + placebo	Chemotherapy + ABMK (daily oral consumption)	3 weeks for at least three cycles	Primary outcomes: activities of NK and LAK cells and the counts of white blood cells, lymphocytes, monocytes, CD3 $\beta$ , CD4 $\beta$ , CD8 $\beta$ , CD48 $\beta$ , and CD56 $\beta$ cells.	ABMK treatment might be beneficial for gynecological cancer patients undergoing chemotherapy.

ABMK—*Agaricus blazei Murill Kyowa*; CT—conventional therapy; HLA—human leukocyte antigen; IAP—immunosuppressive acidic protein; IFN—interferon; LAK—lymphokine-activated killer; LEM—*Lentinula edodes* mycelia extract; MCHC—mean corpuscular hemoglobin concentration; NK—natural killer; T—treatment.

The participants of the included studies had breast cancer [5,18–20,22,23], hepatocellular carcinoma [15], advanced or recurrent, untreated, stage III-IV adenocarcinomas [16], multiple myeloma [17], gastric and colorectal cancer [21,23], and gynecological cancer [24]. The species of mushrooms used in the different studies were *Lentinula eododes* [18,19,21,23], *Agaricus sylvaticus* [20,22], *Agaricus blazei* [17,24], *Coriolus versicolor* [15], *Antrodia cinnamomea* [16], and *Ganoderma lucidum* [5]. All mushrooms were administered orally. The dosage used varied according to mushroom species administered. In all studies that used *Lentinula eododes* the dosage administered was 1800 mg/per day [18,19,21,23]. The *Agaricus sylvaticus* was administered with a dosage of 2.1 g/per day [20,22].

## 2.2. Quality of Included Studies

The quality assessment result of each study is reported in Tables 2 and 3. Only two studies fulfilled more than 80% of the exploratory questions [17,20] (Tables 2 and 3). Seven studies pointed out potential sources of bias [5,15–18,21,23]. The main limitations were related to the low sample size, lack of similarity of participants at baseline that could affect outcomes, and the lack of blindness to the participants' exposures.

**Table 2.** Quality Assessment of Controlled Intervention Studies through National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool.

Quality Assessment of Controlled Intervention Studies				
No	Question	Number of Studies (n = 7)		
		Yes	No	Other (CD, NA, NR)
1	Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	7	0	0
2	Was the method of randomization adequate (i.e., use of randomly generated assignment)?	2	0	5
3	Was the treatment allocation concealed (so that assignments could not be predicted)?	2	0	5
4	Were study participants and providers blinded to treatment group assignment?	4	0	3
5	Were the people assessing the outcomes blinded to the participants' group assignments?	4	0	3
6	Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	1	3	3
7	Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	6	1	0
8	Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	6	1	0
9	Was there high adherence to the intervention protocols for each treatment group?	7	0	0
10	Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	6	1	0
11	Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	7	0	0
12	Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	1	6	0
13	Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	2	0	5
14	Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	1	0	6

**Table 3.** Quality Assessment of Before–After (Pre–Post) Studies with No Control Group Studies through National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool.

Quality Assessment Tool for Before–After (Pre–Post) Studies with No Control Group				
No	Question	Number of Studies (n = 4)		
		Yes	No	Other (CD, NA, NR)
1	Was the study question or objective clearly stated?	3	1	0
2	Were eligibility /selection criteria for the study population prespecified and clearly described?	4	0	0
3	Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	0	4	0
4	Were all eligible participants that met the prespecified entry criteria enrolled?	4	0	0
5	Was the sample size sufficiently large to provide confidence in the findings?	0	4	0
6	Was the test/service/intervention clearly described and delivered consistently across the study population?	4	0	0
7	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	4	0	0
8	Were the people assessing the outcomes blinded to the participants' exposures/interventions?	0	0	4
9	Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	4	0	0
10	Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	4	0	0
11	Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	0	0	4
12	If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis consider the use of individual-level data to determine effects at the group level?	0	0	4

### 2.3. Adverse Effects Associated with Mushroom Compounds Use as an Adjuvant on Conventional Cancer Therapies

The role of active substances of mushrooms in the attenuation of adverse events of conventional cancer therapies remains unclear. In breast cancer patients it was observed that the oral administration of *Lentinula edodes* mycelia extract [18,19] did not worsen or ameliorated the adverse events induced by the cancer conventional therapy. In addition, in breast cancer patients undergoing chemotherapy, Valadares et al. observed that the combined use of *Agaricus sylvaticus* extract and conventional therapy ameliorated the appetite and gastrointestinal symptoms such as diarrhea, constipation, nausea, and vomiting [20]. Similar results were observed by Chay et al. in a trial performed in patients with advanced hepatocellular cancer. According to this study, patients supplemented with *Coriolus versicolor* during chemotherapy had a decreased loss of appetite and pain when compared to the placebo group. Moreover, patients in the treatment group had lower average symptom scores for nausea, vomiting, pain, insomnia, constipation, and diarrhea [15].

The combined use of *Agaricus blazei* Murill *Kyowa* mushroom extracts in patients undergoing chemotherapy also decreased chemotherapy side effects such as loss of appetite and alopecia [24].

The use of *Antrodia cinnamomea* extracts as a chemotherapy adjuvant in patients with adenocarcinoma demonstrated that although gastrointestinal symptoms were more frequent, the intensity was lower compared to the untreated group [16].

Finally, in a preliminary study without a control group, Okuno et al. observed that during the first course of chemotherapy (without administration of *Lentinula edodes* mycelia extract) gastrointestinal cancer patients suffered from nausea and abdominal symptoms, and these adverse effects were not observed in the second course of chemotherapy (using *Lentinula edodes* mycelia extract combined with chemotherapy) [21].

#### 2.4. Hematological Parameters Associated with Mushroom Compounds/Extracts Use as an Adjuvant in Conventional Cancer Therapies

According to our knowledge, the synergistic effects of mushrooms and cancer therapies in hematological parameters remains poorly described. In patients with breast cancer and advanced gastrointestinal cancer, no changes in hematological parameters were observed before and after the use of *Lentinula edodes* mycelia extracts [18,21]. Additionally, in breast cancer patients undergoing chemotherapy, Valadares et al. observed an increase in red blood cell count, hematocrit averages and corpuscular hemoglobin concentration [22]. In a study involving adenocarcinoma patients, it was observed that the synergistic effect of chemotherapy and *Antrodia cinnamomea* extracts caused a decrease in the number of platelets [16].

#### 2.5. Immunological Parameters Associated with Mushroom Compounds/Extracts Use as an Adjuvant in Conventional Cancer Therapies

In breast cancer patients under chemotherapy, it was observed, through the evaluation of the ratio of IFN $\gamma$ /IL-10, that the administration of *Lentinula edodes* mycelia extracts can improve immune function [19] and prevent the reduction of natural killer (NK) cells activity [20]. Using a similar extract in advanced gastrointestinal cancer patients undergoing chemotherapy, Okuno et al [21] observed that the production of IFN- $\gamma$  by CD4<sup>+</sup> T, CD8<sup>+</sup> T and CD56<sup>+</sup> tend to increase.

According to Ahn et al., extracts of *Agaricus blazei* Murill can improve the activity of NK cells in gynecological cancer patients undergoing chemotherapy [24]. A clinical trial suggested that *Coriolus versicolor* extracts lead to a decrease in interleukin (IL) 17F and monocyte chemoattractant protein-1 (MCP-1) levels and to an increase in prolactin and TNF-related apoptosis-inducing ligand (TRAIL) R1 levels in patients with hepatocellular carcinoma [15].

#### 2.6. Quality of Life Associated with Mushroom Compounds/Extracts Use as an Adjuvant in Conventional Cancer Therapies

Chay et al. evaluated the quality of life of patients with advanced hepatocellular carcinoma using the FACT HEP and EORTC QLQ-C30 questionnaires and concluded that the use of *Coriolus versicolor* extracts as an adjuvant in conventional therapy improved the quality of life of cancer patients. Patients treated with *Coriolus versicolor* experienced better physical, emotional, cognitive, and social functioning compared to the untreated group. The treated group patients also reported less pain compared to the untreated group [15]. After the application of an EORTC QLQ-30 modified questionnaire to cancer patients undergoing chemotherapy, Anh et al. observed that the use of *Agaricus blazei* Murill *Kyowa* extracts improved physical and mental conditions, in particular appetite, alopecia, nausea/vomiting, emotional conditions, and general body strength [24]. Suzuki et al. reported that the use of *Lentinula edodes* mycelia extract as adjuvant significantly increased QOL and vitality of breast cancer patients undergoing postoperative hormone therapy, between week 4 to week 8 of treatment [19]. In a study of patients with advanced adenocarcinoma cancer, Tsai et al. observed that only sleep was significantly improved with *Antrodia Cinnamomea* treatment combined with chemotherapy [16]. Zhao et al. observed that in breast cancer patients undergoing endocrine therapy, the subscales on the EORTC QLQ-C30 physical function, and global quality of life were improved for weeks after the treatment, in comparison to the untreated group. Fatigue, loss of appetite, and anxiety were also significantly improved in patients treated with the mushroom extracts in comparison to the control group [5].

### 3. Discussion

Despite the low quality of the included studies, the results of the present study suggest that mushrooms may have a synergistic effect on cancer patients undergoing conventional therapies, through improved quality of life and increased immune response.

Adverse effects of conventional cancer therapy are one of the most important issues faced by cancer patients during their illness and significantly compromise their quality of life [25]. The majority of included studies that assessed quality of life (6/8) concluded that the use of mushroom treatments in combination with conventional therapies improves patients' quality of life, through improved physical [5,15], emotional [5,15], and cognitive, function [5,15,23], and quality of sleep [5,16]. Decreased quality of sleep is frequently reported by cancer patients and contributes to an increased risk of depression [26–28]. One study reported that the nutritional status of patients was improved by treatment with *Agaricus sylvaticus* combined with chemotherapy [20]. Moreover, the consumption of *Agraus brazei* and *Coriolus versicolor* extracts combined with chemotherapy decreased vomiting and diarrhea in patients with gynecological [24] or hepatocellular cancer [15], respectively. Regarding adverse effects, although the majority of studies reported that the use of mushrooms can reduce the adverse effects of conventional therapy, only one study [15] out of a total of five studies [5,15,16,20,23] that assessed adverse effects achieved significant values.

The immunomodulatory effects of medicinal mushrooms are well reported by in vitro studies and can potentially be used to minimize chemotherapeutic myelosuppression [29,30].

The included studies suggest that mushrooms can increase NK cells [23,24]. This observation was previously described in a Cochrane systematic review [31].

Cancer therapies can lead to leucopenia, granulocytopenia, thrombocytopenia, and anemia [32]. The included studies observed that the combined treatment of mushrooms and conventional therapies increased leukocytes, lymphocytes, and neutrophils [22,23].

The data obtained in this review suggest that mushroom products can enhance patients' tolerance to chemo and radiotherapy and reduce their toxicity and damaging side effects. Although the cell signaling pathway remains to be elucidated, in vitro studies suggested that mushrooms act as modulators of biochemical pathways associated with cell proliferation and transcription. The aberrant activation of this pathway was associated with the survival of cancer cells and resistance to chemotherapy and radiotherapy [33]. In future studies, new protocols to conduct clinical trials are needed to elucidate the possible active mechanisms and clinical benefits of these mushrooms in various types of cancer. Further investigations to evaluate the effects of mushroom treatments combined with conventional therapies in larger populations of cancer patients with a sample size large enough to detect clinical differences are needed to clarify whether mushrooms may play a role in the treatment of cancer.

The present study is not without some limitations. The search strategy was limited to the two main health research databases, and articles written in English, Spanish, and Portuguese. The included studies were heterogeneous in terms of population and sample size. As this review included studies regardless of the analysis of quality assessment and outcomes, bias may have been generated. Bias can be attributed to lack of randomization and concealment of interventions, sample size, and lack of similarity of participants at baseline which could affect outcomes, compromising possible scaling-up or extrapolation of interventions.

#### 4. Materials and Methods

A literature search was conducted in September 2021 on the MEDLINE-PubMed and Cochrane database.

The search strategy was designed to identify relevant randomized controlled trials or clinical trials studies addressing the use of whole mushroom formulations as complementary therapy during conventional cancer treatment. Only articles written in English, Spanish, and Portuguese were included.



#### 4.1. Outcome Measures

Our primary outcome measure was the impact of mushroom adjuvant therapy on cancer patients undergoing a conventional therapy through the analysis of adverse effects, hematological and immunological parameters, and improvement of quality of life.

#### 4.2. Data Extraction

Two researchers screened all titles and abstracts retrieved from the databases according to the inclusion criteria. To evaluate the eligibility of full-text articles, two researchers independently screened the full text of the articles. All discrepancies were resolved through discussion with the help of a third researcher.

Two researchers independently extracted data from the included studies. The data extracted from each article includes authors, publication year, study design, country, sample size, type of cancer, mushroom species name, outcome measures, and main results.

#### 4.3. Quality Assessment

Two researchers independently evaluated the quality and susceptibility to the bias of the included studies using the “Quality Assessment of Controlled Intervention Studies” or “Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group” tools (from the National Heart, Lung and Blood Institute), depending on the study design. All discrepancies were resolved through the discussion of a third or fourth researcher.

### 5. Conclusions

This study provides valuable data regarding the use of mushrooms as part of adjuvant therapy against many cancers; however, most of the included studies presented limitations that restrain the extrapolation of results to cancer pharmacotherapy. In order to obtain knowledge about the medicinal properties of mushrooms, studies designed with the aim of obtaining better evidence (existence of a control group and minimizing the risk of bias) are necessary, in order to clarify the beneficial effects of different species of mushrooms on different types of cancer.

**Author Contributions:** Conceptualization, A.I.P., M.M. and F.R.; methodology, A.I.P., M.M. and F.R.; validation, A.I.P., M.M. and F.R.; investigation, A.I.P., M.M. and F.R.; resources, F.R.; data curation, A.I.P. and M.M.; writing—original draft preparation, A.I.P. and M.M.; writing—review and editing, M.M. and F.R.; supervision, F.R. and M.M.; project administration, F.R.; funding acquisition, A.I.P. and F.R. All authors have read and agreed to the published version of the manuscript.

**Funding:** Participation of Ana I Plácido in this work was funded by the Grant CENTRO-04-3559-FSE-000162, financed by the Operational Programme from the budget of the Central Region of Portugal, within the European Social Fund (ESF) component.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** The authors would also like to thank the researchers Daniela Azevedo and Daniela Rodrigues, from the Polytechnic Institute of Guarda, for their collaboration in the collection of some data.

**Conflicts of Interest:** The authors declare no conflict of interest.

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