Figueiredo and Régis *Nutrire* (2017) 42:28
DOI 10.1186/s41110-017-0050-1

Nutrire

REVIEW Open Access

Medicinal mushrooms in adjuvant cancer therapies: an approach to anticancer effects and presumed mechanisms of action

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Abstract

Mushrooms have been used for centuries as a source of nourishment and sensory properties. Mushrooms are considered functional foods due to their bioactive compounds and a source of drug and nutraceutical development. More than 50 species present immunological potential that exhibit anticancer activity in vitro or in animal models, and some of them have been investigated in human cancers. Cancer is a major cause of death all over the world, promoting long lasting effects throughout the lifetime of the patient. Mushrooms are a source of ergothioneine, selenium, fiber, and several other vitamins and minerals. They have bioactive compounds used in cancer treatment due to their antitumor and anticarcinogenic effects. They contain β-glucans, β-proteoglycans, lectins, triterpenes, ergosterol, glutamine, and arginine. In the present study, we perform a literature review of studies that analyze positive impacts of mushroom compounds on cancer treatment due to their antitumor and anticarcinogenic effects and possible compatibility with chemotherapy management. The review indicates that a healthy diet with frequent consumption of mushrooms apparently reduces the risk of developing cancer. However, a clearer understanding of how mushrooms' bioactive principles may affect adjuvant treatments requires further research with long-term double-blind and placebo-controlled studies that evaluate a larger population in clinical trials by each type of cancer. Therefore, more robust statistical results are necessary to verify their efficacy and safety on cancer treatments.

Keywords: Medicinal mushrooms, Neoplasm, Cancer

Background

It is well established that the consumption of medicinal mushrooms has beneficial effects on human health due to its therapeutic properties. Mushrooms have been used as food for centuries, representing an important source of nourishment and their consumption in some cultures is associated with disease prevention, treatment, and longevity. Medicinal species have been used by oriental countries as popular medicine in disease treatments. Over the past 30 years, scientific and medical research in Japan, China, and Korea and recently in the USA have confirmed the properties and unique compounds extracted of mushrooms for prevention and treatment of cancer and other chronic diseases. There are approximately 10,000 species of fungi, of which 50 to 200 have medicinal properties. Distinct species contain fundamental chemical constituents and macro- and micronutrients. They are a rare source of ergothioneine, proteins, selenium, essential amino acids, vitamins, and fibers [1, 2]. Preliminary evidences suggest that mushrooms such as *Agaricus*, *Amauroderma*, *Coprinus*, *Ganoderma*, *Grifola*, *Lentinula*, *Phellinus*, *Pleurotus*, and *Polyozellus* genera may support healthy immune and inflammatory responses. Major bioactive mushrooms are β-glucans, β-proteoglycans, lectins, triterpenes, ergosterol, glutamine, and arginine [3, 4]. Some preclinical and clinical studies suggest impacts of mushrooms on cancer treatment due to their antitumor and anticarcinogenic effects [5].

Their consumption is associated with disease prevention, treatment, and longevity. Cancer is a leading cause of death all over the world, and according to the WHO reports, millions of people will die of cancer if the disease is untreated, especially in low- and middle-income

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countries, where resources available for prevention, diagnosis, and treatment of cancer are limited or nonexistent. Cancer as a chronic disease may cause death or promote long lasting effects throughout the lifetime of the patient. The major challenge faced by the entire world is to find a cure for cancer [6].

Conventional therapies used in cancer treatment are surgery, chemotherapy, and radiation therapy, depending on the type of cancer and the stage of tumors' development. Anticancer treatment is complex and causes several side effects in clinical management. Those side effects include reduced caloric intake and decreased absorption of nutrients that could jeopardize and reduce the quality of life of cancer patients [7]. Also, they result in damage and weakening of patient's natural immunological defenses [3, 5]. Some mushrooms' extract has shown promising effects on cancer therapies. The source of their biologically active compounds is due to their capacity to grow in the darkness and dampness in highly competitive environments. To protect themselves from the attack of other organisms, they developed natural protective substances. Several scientific studies have isolated substances from many mushrooms with potential benefits for humans [5].

Chemical and nutritional aspects of edible mushrooms

Certain types of mushrooms are indicated for energy-restricted diets due to the low concentration of fat and energy, as well as the high concentration of dietary fibers and proteins. Mushroom proteins possess nine amino acids required by dietary intake for humans. They also contain nutrients like phosphorus and iron and vitamins of group B especially thiamine, riboflavin, pyridoxine, pantothenic acid, nicotinic acid, folate, and cobalamin, as well as other vitamins including biotin and tocopherols [7]. The vitamin B12 content found in mushrooms is the same one found in fish, red meat, and liver, suggesting the same bioavailability, which represents an important source for vegan diets [8]. Mushrooms also exhibit ergosterol which can be converted to vitamin D2 when exposed to UV light. In animal experiments using ergocalciferol-enriched mushroom powder, an increase in hydroxyvitamin D and bone mineralization was observed [9, 10]. Selenium content in mushrooms varies according to the form of cultivation, soil selenium content, and latitude. Selenium is an essential micronutrient that plays a key role in cell cycle and apoptosis. Marginal selenium deficiency may contribute to the reduction of immune function in some types of cancer [10–12].

In addition, L-ergothioneine is an unusual amino acid found in mushrooms that has antioxidant properties as a free radical blocker with the ability to protect cells from oxidative stress. It may serve as a final defense against oxidation in cells where glutathione may have depleted suggesting an advantageous role for long-term human health. Also, it has been suggested that ergothioneine should be considered as a longevity vitamin based on triage theory because of its unique role in protecting mitochondria from oxidation [2, 13].

Health-application compounds and effects

Many foods have contributed to the decrease and prevention of diseases and have promoted health benefits, which in turn boosted the emergence of functional foods. Health authorities around the world consider the prevention and treatment of various chronic diseases using functional foods and nutraceutical products [13]. Literature suggests that consumption of certain mushroom species, as food, extracts, or intake of specific constituents, may reduce certain risks of diseases [14, 15]. Mushrooms are considered functional foods due to their bioactive compounds and a source of drug and nutraceutical development [16]. From a nutritional perspective and due to the high protein value and fiber content, cultivation of mushrooms has also been considered as an alternative to the supply of proteins in countries with high level of malnutrition [17]. Aside from this, edible mushrooms have been reported as having an antitumor potential [17–19] and anti-angiogenesis properties [20, 21].

Among the bioactive components are fungal β-glucans, a type of high molecular weight polysaccharides; examples include lentinan, grifolan, and GL-1. There are also several other active compounds: proteoglycans (maitake D-fraction) and polysaccharide peptides (e.g., PSP, PSK); glycans (ganoderans), lectins, triterpenes, and triterpenoids (ganoderic acids); and protein bound polysaccharides, lignins, purines, and polyphenols, especially flavonoids [5, 21, 22]. Compounds' benefits and possible mechanisms of action are described in Table 1. Polysaccharides are the best-known constituents derived from mushrooms with different chemical compounds. β-Glucan, a glucose polymer, is one of the most abundant forms of polysaccharides and derives from different sources. These glucose polymers are reported in studies with *Agaricus blazei*, *Agaricus bisporus*, *Phellinus linteus*, *Lentinula edodes*, *Coprinus comatus*, and *Grifola frondosa* and are considered the most powerful immune stimulant and antitumor constituent known [6, 21, 23].

Fibers such as β-glucans, heteroglycans, lectin, and proteoglycans act as immunomodulators [16, 21, 24]. Mushroom cell wall contains no starch polysaccharide components classified as dietary fiber, which depends on their morphological form and species. The composition of total dietary fiber in mushrooms is prevalently of insoluble dietary fiber and a low-level presence of soluble dietary fiber [25].

Lectins have the function of binding to membrane carbohydrates. Its generic therapeutic principle is to bind to

Table 1 Characteristics of studies in vivo and in vitro

Mushroom	Ref.	Research question	Methodology
Agaricus bisporus	[42]	Are white button mushrooms potential breast cancer chemopreventive agents?	Evaluation in vivo of the ability of mushroom extract to inhibit MCF-7aro-derived tumor growth in athymic mice. In vitro studies to determine the consequence of aromatase inhibition by mushroom extract.
		Sample	Findings
		Athymic nude mouse for in vivo, Chinese hamster ovary cells, MCF-7aro and MCF-10A cells.	Decreased both tumor cell proliferation and tumor weight with no effect on the rate of apoptosis. Prevent tumor growth through the inhibition of cancer cell proliferation and not through the promotion of apoptosis.
Mushroom	Ref.	Research question	Methodology
Agaricus bisporus	[20]	Does lectin from *A. bisporus* inhibit cell proliferation of some ocular and cancer cell lines?	Primary human RPE cells were isolated and grown in DMEM/F12 with or without the ABL (20 or 90 g/mL) for 3 days.
		Sample	Findings
		In vitro: human postmortem eyes	ABL may be a potent antiproliferative agent by preventing human RPE cells from entering the S phase of the cell cycle.
Mushroom	Ref.	Research question	Methodology
Agaricus blazei (Murill)	[29]	What are the effects of β-glucan extract from *A. blazei* on the expression of the ERCC5, CASP9, and CYPIAI genes and metabolic profile in HepG2 cells?	Cells were exposed to only benzo[a]pyrene (B[a]P), β-glucan, or a combination of B[a]P with β-glucan.
		Sample	Findings
		In vitro: human hepatocellular carcinoma (HepG2).	The results demonstrated that 50 mg/mL β-glucan significantly repressed the expression of the ERCC5 gene when compared with the untreated control cells in these conditions.
Mushroom	Ref.	Research question	Methodology
Agaricus blazei (Murill)	[30]	What are the effects of glucans from *A. blazei* encapsulated with n-3 polyunsaturated marine phospholipid liposomes and unencapsulated glucan on myeloma sp2 cell induced cancer in mice?	Orally administrated volumes of 5 mL per day per mouse for all groups.
		Sample	Findings
		In vivo: study with male BALB/c nu/nu mice. In vitro with Caco-2 cells.	Antitumor effect of β-glucan and/or marine phospholipid with the absence of side effects.
Mushroom	Ref.	Research question	Methodology
Agaricus blazei (Murill)	[31]	Does polysaccharide extract from *A. blazei* indicate potential antitumor agents or adjuvant in tumor treatment?	Matrigel invasion assay was applied to evaluate the effect of LMPAB on the migration of BEL-7402 hepatic cancer cells in vitro. In vivo, investigated in mouse B16 melanoma and a double-grafted SW180 tumor model.
		Sample	Findings
		In vivo: 72 mice in vitro: hepatic cells	Intratumoral treatment of LMPAB inhibited the growth of tumor. LMPAB displays anti-metastatic activities.
Mushroom	Ref.	Research question	Methodology
Coprinus comatus	[34]	Can *C. comatus* bioactive substances modulate the NF-κB pathway?	Hydrogen peroxide for activate (NF-κB) transcription factor. 76 μg/L on MCF7, IC50 32 μg/mL.

Table 1 Characteristics of studies in vivo and in vitro *(Continued)*

		Sample	Findings
		In vivo: human breast cell line MCF7.	*C. comatus* bioactive substances can modulate the NF-κB activation pathway.
Mushroom	Ref.	Research question	Methodology
Lentinula edodes	[21]	Does protein latcripin-1 from *L. edodes* induce apoptosis of human lung cancer cells A-549?	Latcripin-1 induced and expressed with pPIC9K in *Pichia pastoris* GS115.
		Sample	Findings
		In vitro: human lung cancer cells and *Pichia pastoris* yeast.	The protein can induce apoptosis in human lung cancer cells A549.
Mushroom	Ref.	Research question	Methodology
Lentinula edodes	[35]	Does the molecule Lactripin-13 domain from L. edodes induce apoptosis of A549 lung cancer cells?	Latcripin-13 expressed in *E. coli* Rosetta-gami (DE3) in the form of inclusion bodies.
		Sample	Findings
		In vitro: human lung cancer cells line A549.	The Latcripin-13 domain can induce apoptosis of A549 lung cancer cells.
Mushroom	Ref.	Research question	Methodology
Maitake (D fraction)	[27]	Does maitake (D fraction) extract induce apoptosis in breast cancer cells?	Cells treated with maitake (D fraction) extract at 18 mg = mL, 36 mg = mL, 91 mg = mL, 183 mg = mL, or 367 mg = mL or were left untreated (control) for 24 h.
		Sample	Findings
		In vitro: human breast cancer cells line MCF7.	Maitake D-fraction has anti-cancer properties with proapoptotic effects and reducing tumor cell viability.
Mushroom	Ref.	Research question	Methodology
Phellinus linteus	[36]	What are the effects of a *P. linteus* treatment in colon cancer growth, invasion and neoangiogenesis?	PL was examined in SW480 cells by evaluating cell proliferation, invasion, and matrix metallo-proteinase (MMP) activity. In vivo effect evaluated in an athymic nude mouse SW480 tumor engraft model.
		Sample	Findings
		In vitro: human colon cancer cells and HT1080 fibro-sarcoma. In vivo: 8 nude mice.	PL isolated from *P. linteus* causes a significant reduction in β-catenin protein levels and the downregulation of certain downstream genes in the Wnt/β-catenin pathway in SW480 colon cancer cells in vitro and in vivo.
Mushroom	Ref.	Research question	Methodology
Pleurotus eryngii	[24]	What are the effects of *P. eryngii* protein PEQP 2 on macrophage-mediated immune responses and tumor cells?	PEQP extract from dried fruiting bodies. In vitro antiproliferative activity evaluated in human cell lung cancer A549 (NSCLC), stomach adenocarcinoma BGC-823, hepatocellular carcinoma HepG2 and gastric carcinoma HGC-27 cell lines using conventional cancer drugs (paclitaxel, doxorubicin, and mitomycin C) as positive controls.
		Sample	Findings
		In vitro: human Chang liver cell line (Chang cells), non-small-cell lung cancer A549 (NSCLC), human stomach adenocarcinoma BGC-823, human liver hepatocellular carcinoma HepG2, human gastric carcinoma HGC-27 and murine macrophage RAW264.7 cell lines.	*P. eryngii* protein (especially PEQP 2) was not only toxic to tumor cells and less toxic to normal cells (Chang cells), but it also activated the macrophage-mediated immune responses.

Table 1 Characteristics of studies in vivo and in vitro *(Continued)*

Mushroom	Ref.	Research question	Methodology
Pleurotus ostreatus	[19]	What are the effects of *P. Ostreatus* against DMBA induced mammary cancer?	6 groups of 6 animals each received 25 mg of DMBA.
		Sample	Findings
		In vivo: 36 Sprague Dawley rats.	*P. ostreatus* ethanolix extract has a potent antioxidant capacity and offers protection against DMBA-induced mammary carcinogenesis.
Mushroom	Ref.	Research question	Methodology
Polyozellus multiplex	[38]	Can components of *P. multiplex* use as chemopreventor in cancer treatment?	*P. multiplex* extract. Viable cell number determined by the trypan blue dye exclusion method. Animals received 150 mg/kg of MNNG dissolved in 10% (DMSO).
		Sample	Findings
		In vitro: human promyelocytic leukemia cell line HL60, human histiocytic leukemia cell line U937, human colon cancer cell line HT-29, human hepatocellular cancer cell line HepG2 and human gastric cell line SNU668. In vivo: 20 Wistar rats species.	*P.multiplex* has inhibitory effects on proliferation of cancer cell lines induced antioxidative and detoxification enzymes, inhibited cell proliferation in rats. MTT revealed significant tumoristatic effects.

the membrane of the mutant cell or its receptors, causing apoptosis and, consequently, promoting the decrease of the tumor. They have been shown as a therapeutic agent with anticancer activities in vitro experiments, with animals, and in clinical trials [15, 18]. Some lectins from *A. bisporus* and *G. frondosa* display antiproliferative and antitumor potential. Cheung et al. [18] demonstrated in vitro that a 90 μg/ml dose of *A. bisporus* lectin extract may be a potent antiproliferative agent by preventing human postmortem eyes from entering the S phase of the cell cycle. Also, lectins work by stimulating immunological functions, phagocytic macrophage activity, and the enhancement of the functions of the reticuloendothelial system. Finally, they alleviate the undesired effects produced by chemotherapy and improve tumor infiltration by cytotoxic T cells. The maitake D fraction from *G. frondosa* has strong anticancer properties in breast cancer cells, by exerting proapoptotic effects and reducing tumor cell viability [26].

Experimental studies with mushrooms

Evidences indicate that fractions of mushrooms have a potential use in the treatment of varied types of cancer as described in Table 1.

Antiproliferative, antitumor, antioxidant anti-metastatic activities and apoptosis inducer activities of bioactive mushroom compounds have been related to a variety of studies summarized in Table 2. The lectin found in genus *A. bisporus* has been exhibited an antiproliferative action in ocular cancer [18].

Phytochemicals of *A. bisporus* extract inhibits aromatase at estrogen receptor in vivo in the MCF-7aro cell and in ovarian rats [27, 28]. Chen et al. [28] also described that in vivo mushroom extract decreased both tumor cell proliferation and tumor weight with effect on apoptosis rate. The interaction of linolenic acid and linolenic acid present in the *A. bisporus* extract is effective in inhibiting aromatase activity by modifying or mutating active cell sites. Experiments with hepatocellular carcinoma cells (HepG2) investigate the protector effect of β-glucan *A. bisporus* extract on the expression of ERCC5, CASP9, and CYP1A1 genes. Silva et al. [29] exposed HepG2 to benzo[a]pyrene (B[a]P), β-glucan, or a combination of (B[a]P) with β-glucan. Findings demonstrated that 50 m/l of β-glucan extract repressed significantly the expression of ERCC3 gene compared to untreated control cells. No change was found at the CASP9 transcript level. Nevertheless, the expression of CYP1A1 showed cell damage caused by (B[a]P), as an enzyme modulator of phase I (CYP1A1). Finally, results showed that β-glucan polysaccharide has a protective effect on the HepG2 cells suggesting that β-glucan modulates cellular metabolism.

Agaricus blazei Murill (ABM) is considered as functional food, and a natural therapy used mostly for prevention, and as adjuvant in cancer treatment. ABM extracts play a role in immune cell modulation that confirm its possible anticancer activity [5, 29]. Similarly, a study investigated the combination of the ABM extracted with marine phospholipids in comparison to ABM extract alone on myeloma sp2 tumor suppression when orally administrated. Results of the in vivo study showed that oral administration of ABM extract, directly or encapsulated liposomal form, suppressed myeloma in

Table 2 List of mushrooms per cancer type

Type of cancer	Mushroom recommended	Reference	Type of study	Strength of recommendations/ level of evidence[a]
Breast	*A. bisporus*	[42]	In vitro	D/5
	Coprinus comatus	[34]	In vivo	D/5
	Maitake (D fraction)	[27]	In vitro	D/5
	Pleurotus ostreatus	[19]	In vivo	D/5
Ocular	*A. bisporus*	[20]	In vitro	D/5
Hepatocellular carcinoma	*Polyozellus multiplex*	[15]	In vivo/in vitro	D/5
	Pleorutus Erybgii	[24]	In vitro	D/5
Myeloma	*A. blazei Murill*	[30]	In vivo/in vitro	D/5
Hepatic	*A. blazei Murill*	[31]	In vitro	D/5
	Polyozellus multiplex	[15]	In vitro	D/5
Lung	*Lentinula edodes*	[21]	In vitro	D/5
	Lentinula edodes	[35]	In vitro	D/5
Colon	*Phellinus linteus*	[36]	In vitro	D/5
	Polyozellus multiplex	[38]	In vitro	D/5
	Polyozellus multiplex	[38]	In vivo	D/5
Leukemia	*Polyozellus multiplex*	[38]	In vitro	D/5
Gastric carcinoma	*Polyozellus multiplex*	[38]	In vitro	D/5
	Pleurotus Eryngii	[24]	In vitro	D/5

Source: Created by the authors
[a]Strength of recommendations/level of evidence according to the Oxford Centre for Evidence-based Medicine

mice. Also, findings suggest that the antitumor effect of β-glucan and/or marine phospholipid occurred with the absence of weight loss, which might indirectly affect cancer [30].

Niu et al.'s [31] in vivo and in vitro assay has investigated antitumor agents and antiangiogenic effects of *A. blazei* low molecular weight polysaccharide extract (LMPAB). LMPAB inhibited tumor metastasis both in vitro in BEL-7402 hepatic cancer cells and in vivo in mouse B16 melanoma and a double-grafted SW180 tumor model. The experiment was shown to suppress crucial stimulator MMP-9 and at the same time to activate the suppressors as *nm*23-H1, which appear to be responsible for its anti-metastatic activities. These results suggest that the dual action of LMPAB may be a promising agent for prevention and treatment of tumor metastasis.

The factor NF-kB participates in the inflammatory response and plays a key role in regulating the immune infection response and in protecting cells from undergoing apoptosis in response to cell stress [32]. Due to its role in a wide variety of diseases, NF-κB has become a major target for drug development. Most chemopreventive agents appear to suppress the activation of NF-κB, through inhibition of NF-κB signaling pathway components. In general, these observations suggest that NF-κB is an ideal target for chemoprevention and chemosensitization [33]. *C. comatus* crude extracts have high antioxidant activity and modulate the NF-κB activation pathway. Experiments with *C. comatus* crude extract and in MCF7 breast cancer cell line showed that both extracts affected IκBα phosphorylation in a dose-dependent manner suggesting that *C. comatus* contains powerful components capable of inhibiting NF-κB function and a possible antitumor agent [34].

L. edodes C_{91-3} is a mycelia fermentation protein isolated from fungi of Basidiomycetes Umbelliferae [20]. Its extract contains a variety of proteins with significant effects on inducing cell apoptosis confirmed by in vivo and in vitro experiments. Liu et al. [21] induced and expressed the protein (Latcripin-1 gene) with *Pichia pastoris* expression system and incubated the human lung cancer cell A549. Results concluded that this protein can induce apoptosis in cell A549. *L. edodes* C_{91-3} was also tested in A549 cell line utilizing Latcripin-13 domain and expressed in *Escherichia coli* Rosetta-gami (DE3) in the form of inclusion bodies [35]. Similarly, cell apoptosis with Latcripin-13 was observed in A549 cells which could be used into the future development of new antitumor drugs.

Angiogenesis is the process where tumor cells stimulate the formation of new blood vessels needed to supply essential nutrients for their growth, transplantation, and metastasis. Previous studies with *Phellinus linteus* (PL) extract have demonstrated strong anti-angiogenic activity using embryo chorioallantoic membrane (CAM) [36]. In

another experiment, Song et al. [36] also utilized Pl extract to evaluate cell proliferation, invasion, matrix metalloproteinase activity, and the potential effect of PL on β-catenin protein level in SW480 colon cancer cells. The anti-angiogenic effects of PL were examined by assessing human umbilical vein endothelial cell (HUVEC) and capillary tube formation revealing a significant dose-dependent cytotoxic effect on the proliferation of HUVECs. In addition, the in vivo effects were evaluated into nude mice model resulting in the inhibition of β-catenin accumulation and the expression of its downstream genes. *P. linteus* extract was also tested by Tsuji et al. [37] to sensitize advanced prostate cancer cells in athymic nude mice.

Polyozellus multiplex components were tested in vitro for human gastric and other cancer cells. *P. multiplex* water fraction significantly increased glutathione S-transferase (GST) and superoxide dismutase activities, showing a tendency of increasing glutathione (GSH) levels, compared to the *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) alone group [38]. The results indicate that proliferation of distinct types of cancer cells can be significantly inhibited by the *P. multiplex* water fraction and might find application as a chemopreventor of stomach cancer also verified in *Pleurotus eryngii* extract [24].

Clinical studies with humans

According to the World Cancer Report, cancer rates are expected to grow about 50% to 15 million by 2020, which will lead to an increased need for chemotherapy. Even though chemotherapy is an essential component in traditional cancer treatment, it comes with a package of side effects. The report also says that a healthy diet with frequently consumption of some vegetables may reduce the risk of developing cancers of epithelial origin [39].

Besides several studies of cell cultures and animal model experiments, anticancer effects of medicinal mushrooms have been related to human observational studies and clinical trials as described in Table 3. A first epidemiological and observational report associating mushroom intake and epithelial ovarian cancer was conducted in China. During approximately 6 years, 500 patients diagnosed with epithelial ovarian cancer and 500 controls were accompanied [1]. Patients with ovarian cancer consumed less mushrooms (mean [SD] 28.48/37.45 g/day) than control patients (mean [SD] 30.75/41.85 g/day). Results suggest that mushroom intake at elevated levels is associated with a reduced risk of epithelial ovarian cancer [1]. Similarly, inverse association has been reported for gastric and breast cancers. Another observational study conducted in Asian and European countries was performed to clarify the evidence between associations of dietary mushroom intake with breast cancer risk and to quantify its dose dependency. Reports suggest that consuming elevated levels of edible mushrooms may be associated with lower risk of breast cancer. In a clinical study using *Pleurotus cornucopiae* better known as Oyster mushroom (Tamogitake), the effectiveness of extract with respect to immune potentiation for several diseases including cancer was verified. Oyster mushrooms have been traditionally consumed by Japanese people for their properties of preventing cancer and hypertension [40]. Results of observational studies have concluded that oral intake may contribute to cancer prevention, illustrating the importance of including mushrooms in a regular diet suggested by WHO [6, 37].

Table 3 Summary of human clinical studies

Mushroom	Type of study	No. of patients	Type of cancer	Extracts/compounds/ active principle	Findings	Ref.
Agaricus bisporus	Observational study	500 participants	Ovarian	Polysaccharides	Moderate inverse association between habitual mushroom intake and epithelial ovarian cancer	[1]
Agaricus bisporus/ Amauroderma rude	Meta-analyses, observational studies	6890 women	Breast	Daily intake – 1 g/d in pre/postmenopausal women	Mushroom consumption associated to lower risk of breast cancer.	[16]
Ganoderma lucidum	Randomized, clinical trial	373 adults	Various types	Spore vs mycelium	Improve tumor response of lung cancer to conventional therapy. Enhance immunity. Promising adjunct treatment in immunosuppressive effects of chemotherapy. QoI relatively improved.	[41]
Lentinula edodes	Open pilot study	10 participants	Various types	*L. edodes* mycelia	Combine treatment of LEM and immunotherapy might improve QOL and immune function.	[22]
Pleurotus cornucopiae Oyster	Double-blind, placebo controlled study	20 participants	Various Types	*Oyster extract*	Potentiate immune system, may prevent cancer and other diseases.	[19]

Regarding clinical trials, they are indispensable for every new drug development. They have shown that the active compounds from medicinal mushrooms work best when combined with surgery, chemotherapy, and radiotherapy. Adding medicinal mushroom drugs greatly improve the outcome and tolerance to invasive treatments [39].

Several oncology studies have been initiated to find alternative cancer medication in the last few decades. A Japanese study combined treatment with *Lentinula edodes* mycelia (LEM) and chemotherapy and reports improvements in QOL and immunological function in cancer patients. The mycelial extract of *L. edodes* is a hot-water extract obtained of after production of culture Shiitake mushroom mycelia. Lentinan is a neutral polysaccharide of high molecular weight extracted from fruiting body reported to produce antitumor activity and immunoregulatory effects and approved as an anticancer drug in Japan [22].

Ganoderma lucidum (*G. lucidum*) is a type of mushroom believed to extend life and promote health and its popularity as an alternative medicine has been increasing in cancer therapies. *G. lucidum* contains polysaccharide and triterpene substances widely studied in traditional Chinese medicine and recommended by physicians. As a result, a systematic review evaluates the clinical effects of *G. lucidum* on long-term survival, tumor response, host immune functions, and quality of life in cancer patients, as well as adverse events associated with its use. The study concluded that incorporation of *G. lucidum* treatment can improve tumor response of lung cancer to conventional therapy and may enhance immunity by stimulating T-lymphocyte proliferation, suggesting that it is a promising adjunct to counter the unwanted common immunosuppressive effect of many chemotherapeutic drugs [41]. As mentioned in WHO's report, new drugs not necessarily eradicate tumors but, when combined with other agents, may turn cases of fatal cancer into manageable chronic illness. Also, the study demonstrated relative improved quality of life in cancer patients treated with *G. lucidum* while no major toxicity was observed across the studies and was well tolerated by most of the participants.

Conclusions

The revised studies have showed that the mushrooms' active principles possess therapeutic properties that play a key role in alternative oncology treatments, in addition to their nutritional value. Medicinal mushrooms are composed of polysaccharides, protein complexes, β-glucan, and other constituents that are widely studied for application in several diseases such as cancer. Those outstanding constituents present antitumor, immunomodulating, antioxidant, and other properties extensively described by studies. This review highlights new approaches and beneficial results from medicinal mushrooms applied to cancer treatment that help thousands of patients to have a better quality of life. These new approaches and results are also emphasized by observational studies that show how a culture of mushroom consumption could prevent cancer.

However, we should not neglect the heterogeneous effects of different mushroom varieties in several species throughout the world that are not included in this review. The latest discoveries of bioactive components with application in human health may give an additional boost for mushroom consumption, improve dietary habits, and draw attention of societies and governments to change their priority from treatment and detection to prevention programs. In conclusion, the results of this review indicate the necessity of further researches with long-term double-blind and placebo-controlled studies that evaluate a larger population in clinical trials. It is important to verify different reactivity of bioactive principles in each type of cancer to assure the efficacy and safety of medicinal mushrooms with robust statistical results.

Abbreviations

A-549: Adenocarcinomic human alveolar basal epithelial cell; ABM: *Agaricus blazei* Murill; B[a]P: Benzo[a]pyrene; BEL-7402: Cellosaurus cell line; CAM: Chorioallantoic membrane; CASP9: Cysteine-aspartic acid protease 9; CYP1A1: Cytochrome P450 family 1 subfamily A member 1; DMBA: 7,12-Dimethylbenz(a)antheracene; DMEM/F12: Dulbecco's modified Eagle's medium; DMSO: Dimethylsulfoxide; ERCC5: Excision repair cross-complementing 5; GSH: Glutathione antioxidant; GST: Glutathione S-transferase; HepG2: Hepatocellular carcinoma cells; HUVEC: Human umbilical vein endothelial cell; IC50: Half maximal inhibitory concentration; IκBα: Inhibitor of kappa β; LEM: *Lentinula edodes* extract; LMPAB: Low molecular weight polysaccharide extract; MMP-9: Matrix metallopeptidase 9 [(human)]; MNNG: *N*-methyl-*N*-nitro-*N*-nitrosoguanidine; NF-kB: Nuclear factor kappa-light chain; NM23-H1: Nucleoside diphosphate kinase; PL: *Phellinus linteus* mushroom; SD: Standard deviation; UV: Ultraviolet; WHO: World Health Organization; Wnt/b: Signaling pathway

Acknowledgements

Not applicable.

Funding

None.

Availability of data and materials

This review was not sent to any other publication, and we agree that Nutrire will have all rights to publish it.

Authors' contributions

LF and WR performed the bibliographic research and writing. WR made the general supervision and text revision. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

This study does not require approval from the local ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 23 March 2017 Accepted: 13 August 2017
Published online: 05 November 2017

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