

Anti-Cancer Potential of Edible/Medicinal Mushrooms in Breast Cancer

Subjects: Anatomy & Morphology

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Edible/medicinal mushrooms have been traditionally used in Asian countries either in the cuisine or as dietary supplements and nutraceuticals. Among the different pharmacological activities reported (antibacterial, anti-inflammatory, antioxidative, antiviral, immunomodulating, antidiabetic, etc.), edible/medicinal mushrooms have been shown to exert in vitro and in vivo anticancer effects on several kinds of tumors, including breast cancer.

Keywords: breast cancer ; edible/medicinal mushrooms

1. Introduction

Breast cancer (BC) is among the major causes of cancer-related deaths worldwide, with 2.3 million new cases per year, according to the GLOBOCAN 2020 data ^[1]. Projections indicate that by 2030, the number of new cases diagnosed worldwide will reach 2.7 million, while the number of deaths will reach 0.9 million ^[2] (Global Cancer Observatory: Cancer Tomorrow, accessed on 29 April 2023. Available online: <https://gco.iarc.fr/tomorrow>). In addition, the incidence of breast cancer is expected to further increase, in particular in low- and medium-income countries, due to the effects of a westernized lifestyle, characterized by delayed pregnancies, reduced breastfeeding, low age at menarche, lack of physical activity, and poor diet ^[3].

In recent years, the impact of the adverse effects of conventional therapy, as well as the poor results obtained with conventional medicinal approaches, highlighted the need for alternative therapeutic strategies. Among the complementary and integrative approaches evaluated, the combination of conventional medicine and complementary activities, including the use of a wide range of products, such as herbs, vitamins, nutraceuticals, and probiotics, has shown promising results ^{[4][5][6]}. In this context, edible/medicinal mushrooms have emerged not only as sources of new nutraceuticals but also as a possible complementary and alternative medicine, showing interesting results as an adjuvant to conventional chemo- or radiation-therapy, enhancing their potency or reducing their side effects, thus improving the patient's quality of life ^{[7][8]}.

The antineoplastic effects of mushrooms have been mainly related to their ability to modulate the immune system, thanks to their content in glucans, sesquiterpenes, glycoproteins, or peptide/protein-bound polysaccharides ^{[7][9]}. Furthermore, minerals, amino acids, other organic compounds, and several vitamins (e.g., thiamin, riboflavin, ascorbic acid, and vitamin D) are contained in mushrooms and contribute to their overall health benefits ^[9]. Some of these natural mushroom compounds have demonstrated specific activity against signaling pathways that are aberrantly activated in cancer cells and have been shown to negatively modulate specific molecular targets involved in cell proliferation, survival, and angiogenesis ^{[10][11]}. The potential therapeutic effects of mushrooms have been investigated both at the preclinical and clinical levels.

2. Bioactive Compounds in Medicinal Mushrooms and Their Mechanisms of Action

Mushrooms' bioactivities have been related to several biologically active compounds, including polysaccharides, which are structural components of the fungal cell wall. Polysaccharides have been shown to exert antitumor, immunomodulatory, antioxidant, anti-inflammatory, antimicrobial, and antidiabetic activities ^{[12][13][14]}. However, specific chemical features, such as the weighted degree of branching, backbone linkage, side-chain units, and the type of constituent monosaccharides, can influence the type and modulation of these biological activities. α - and β -glucans are the most abundant polysaccharides, whereas other glycans, such as heteroglycans, peptidoglycans, and polysaccharide–protein complexes, are known to exert important biological activities ^{[12][15]}.

Mushrooms are rich in proteins that have cytotoxic and anticancer properties. Some of these are known for their characteristic and marked immunomodulatory effects. These proteins are indicated as fungal immunomodulatory proteins (FIPs), whose mechanisms of action can be diverse ^{[12][14]}. Proteins also include lectins, which bind reversibly to mono- and oligosaccharides with high specificity, recognizing and interacting with various carbohydrates and proteoglycans on the cell surface. They are involved in many biological activities, such as innate immunity and cell-to-cell interaction, and their immunomodulatory mechanism varies depending on the origin of each compound. They also have immunomodulatory, antitumor, and antiproliferative properties ^{[12][16]}.

Other compounds that play a pivotal role in the bioactivities of mushrooms are terpenes, quinones, triacylglycerols, isoflavones, catechols, and steroids. Other fungal metabolites showing interesting biological activities are phenolic compounds, antioxidants with different mechanisms of action (oxygen scavenging, metal inactivation, free radical inhibition, peroxidase decomposition), laccases (copper-containing oxidases), and fatty acids ^[17].

In the past, high molecular weight compounds (i.e., polysaccharides and glycoproteins) were believed to exert their antitumor activity through the immune response activation, while low molecular weight compounds were believed to directly regulate signal transduction pathways linked to cancer development, progression, and survival. However, evidence has been reported indicating a direct action of certain polysaccharides on tumor cells ^[7]. Mushroom-derived polysaccharides exhibit potent antitumor activity against several kinds of metastatic cells. Moreover, they show increased activity when used in conjunction with chemotherapy. Mechanistically, antitumor activity is facilitated through a thymus-dependent immune mechanism, which necessitates an intact T-cell component. Polysaccharide class components mainly trigger cytotoxic macrophages, natural killer cells, dendritic cells, monocytes, neutrophils, and chemical messengers that activate complementary and acute phase responses.

3. Edible/Medicinal Mushrooms in Breast Cancer

Several edible/medicinal mushrooms have been studied for their potential antineoplastic effects on breast cancer, which is still one of the main causes of death in the world. The inclusion of mushrooms in the diet has been shown to be protective against cancer ^[18]. Furthermore, dietary consumption of mushrooms has been associated with a diminished risk of BC ^{[19][20]}.

A summary of the principal bioactive components contained in *Agaricus bisporus* (J.E. Lange) Imbach, *Antrodia cinnamomea* T.T. Chang and W.N. Chou, *Cordyceps sinensis* (Berk.) Sacc. and *Cordyceps militaris* (L.) Fr., *Coriolus versicolor* (L.) Quél., *Ganoderma lucidum* (Curtis) P. Karst., *Grifola frondosa* (Dicks.) Gray, *Lentinula edodes* (Berk.) Plegrel, and *Pleurotus ostreatus* (Jacq.) P. Kumm., along with their possible anticancer mechanisms, is reported in **Table 1**, while **Figure 1** reports a simplified scheme of the mechanisms involved in the anticancer effects of the considered mushrooms on breast cancer.

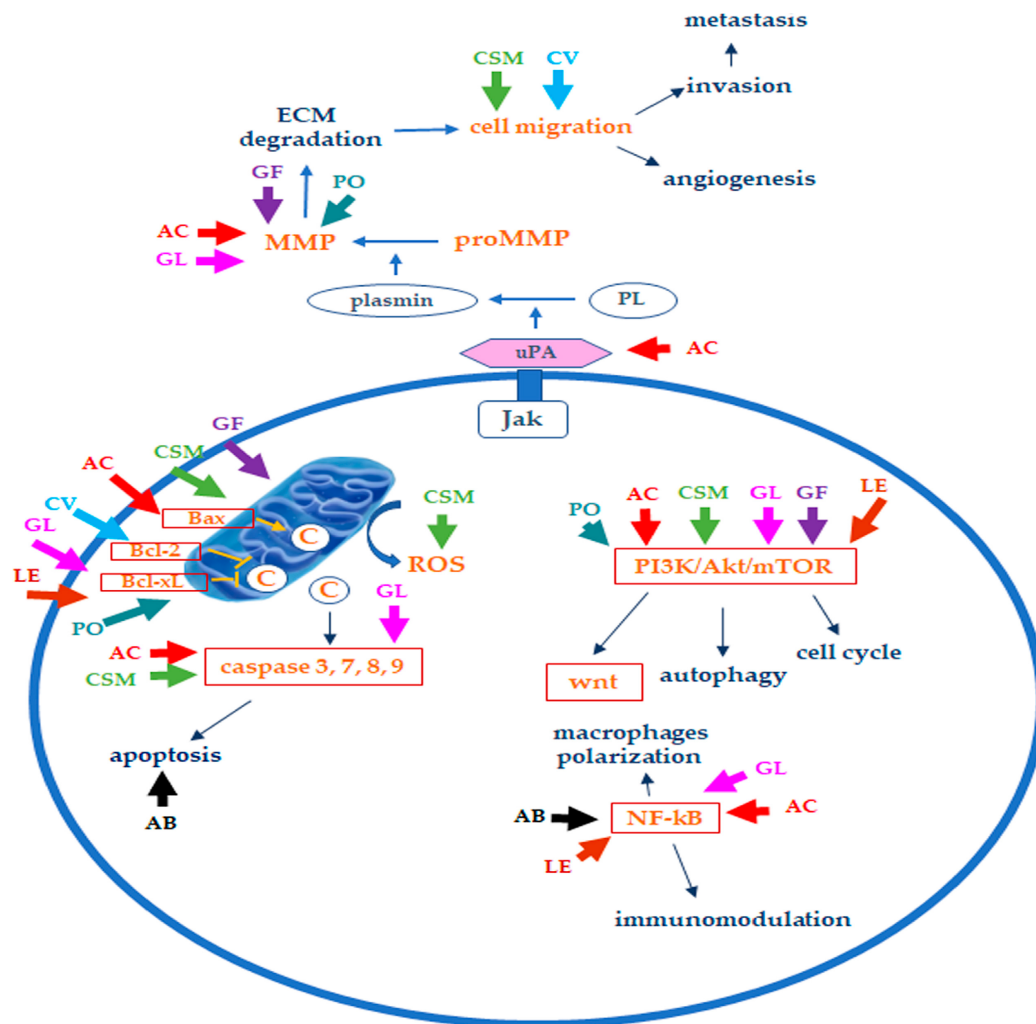


Figure 1. Simplified scheme of the mechanisms involved in the effects of the considered mushrooms on breast cancer (*Agaricus bisporus*, AB; *Antrodia cinnamomea*, AC; *Cordyceps sinensis* and *Cordyceps militaris*, CSM; *Coriolus versicolor*, CV; *Ganoderma lucidum*, GL; *Grifola frondosa*, GF; *Lentinula edodes*, LE; *Pleurotus ostreatus*, PO).

Table 1. Summary of the main bioactive constituents and of the in vitro and in vivo (in animal models) effects against breast cancer of the considered mushrooms and mechanisms involved in these effects.

Species	Main Bioactive Constituents	Mechanisms
<i>Agaricus bisporus</i>	Polysaccharides (ABP-1 and ABP-2 fractions), in particular, β -glucans (β -(1 $\rightarrow$ 6)-d-glucan, B16), lectins, amino acids, unsaturated fatty acids (linoleic and linolenic acids), vitamin B, vitamin C, sterols, phenolic and indole compounds, ergosterol, flavonoids, ergocalciferol, ergosterol	Inhibition of cell proliferation, suppression of tumor growth in nude mice xenografts; induction of macrophages polarization towards M1 phenotype and production of IL-6, IL-1 β , TNF- α , CoX-2; induction of nitric oxide, activation of NF- κ B and cell growth inhibition, probably due to the activity on macrophages; inhibition of proteins synthesis; lectins induce cytotoxicity, apoptosis, and immune system modulation [14][21][22][23][24][25]
<i>Antrodia cinnamomea</i>	Polysaccharides, terpenoids (ergostane, lanostane), lignans, glycoproteins, benzene derivatives, ubiquinone derivatives, maleic and succinic acids derivatives, Anticin A, Antrocin C, Antcin K, antcin C, antcin B	Induction of apoptosis, suppression of mRNA expression of S-phase kinase-associated protein 2 (skp2); decrease of urokinase plasminogen activator (uPA) activity, uPA receptor (uPAR), vascular endothelial growth factor (VEGF), and MMP-9 and MMP-2; inhibition of TGF- β 1-induced migration arrest epithelial to mesenchymal transition (EMT); suppression of the ERK1/2, p38, and JNK1/2 phosphorylation; inhibition of Akt/mTOR and NF- κ B pathways; apoptosis induction, cell cycle arrest, antimetastatic effect, dysfunction of mitochondrial caspase-3/-9 activation, cytochrome c release, degradation of PARP, and Bcl2/Bax dysregulation; HDAC inhibition, autophagy induction (LC3-II, p62, and FOX1 increase) [12][26][27][28][29][30][31][32][33]; proliferation inhibition related to the arrest of cells at the G1 phase and induction of autophagy; stress of the endoplasmic reticulum; reduction of tumor size [32]

Species	Main Bioactive Constituents	Mechanisms
<i>Cordyceps sinensis</i> and <i>Cordyceps militaris</i>	Cordycepin (3-deoxyadenosine), ergosterol, mannitol, modifies nucleosides	Induction of apoptosis by promoting expression and translocation of Bax to mitochondria and decreasing Bcl2 levels by releasing cytochrome C, activating p53, caspase-9, caspase 3, caspase-8; inhibition of cell growth, migration, and invasion, through reduction of the EMT (TWIST1, SLUG, SNAIL1, ZEB reduction, N-cadherin downregulation, E-cadherin upregulation); inhibition of migration; antiproliferative activity through induction of apoptotic cell death; LDH release, PARP increase, ROS production, inhibition of AKT activation and PI3K/Akt; increased level of Cu/Zn superoxide dismutase in cancer cells; induction of autophagy, DNA damage, and targeting of cancer stem cells ^{[28][34][35]} ; decrease in tumor weight and size; reduction of the number of metastasis; increase survival; increased expression levels of cleaved PARP, cleaved caspase-3, cleaved caspase-8, and Bax ^{[34][36][37]}
<i>Coriolus versicolor</i>	Protein-bound polysaccharides (polysaccharide peptide, PSP, and glycoprotein PSK, Krestin), terpenes, proteins, peptides, amino acids, purpurins	Suppression of cell proliferation through apoptotic cell death induction, upregulation of p53, and downregulation of Bcl-2; NK cell activation, p53, and Bcl-2 downregulation; inhibition of migration (MMP9 activity and protein levels downregulation); cytotoxicity via necroptosis activated through the TNF- α /TNFR1 pathway stimulation ^{[38][39][40]} ; suppression of cancer cell proliferation, reduction of tumor weight and antimetastatic effect, simultaneously protecting bones against breast cancer-induced osteolysis; migration and invasion inhibition; immunomodulatory (increase IL-2, 6, 12 TNF- α , INF- γ , histamine, prostaglandin E) and antimigratory effects ^{[33][41][42][43]}
<i>Ganoderma lucidum</i>	Polysaccharides (α -1,3, β -1,3 and β -1,6-D-glucans, ganoderan), triterpenes, ganoderic acids, ganodermic acid, ganodermic alcohols, lucidones, lucinedic acid, ergosterol, 5,6-dehydroergosterol, ergosterol peroxide, and palmitic acid	Inhibitory effect against Akt phosphorylation on Ser473 and downregulation of Akt expression, inhibition of NF- κ B, also related to estrogen receptors, cyclin D1, and subsequently cdk4 ^[33] ; suppression of adhesion, migration, and invasion of cancer cells, down-regulation of oncogene c-myc expression and secretion of uPA and inhibition of MMP2 and MMP9 ^{[44][45]} ; apoptosis induction through downregulation of cyclin F, Bcl-2, Bcl-xL and upregulation of Bax and caspase-9 levels ^{[46][47][48]} ; G1 phase arrest, apoptosis induction via caspase 3/7 activation, and PARP cleavage ^[49] ; inhibition of tumor growth and migration via inhibition of Wnt/ β -catenin signaling; suppression of cancer cell growth through apoptosis induction via mitochondria-mediated pathway; effects on protein expression of E-cadherin, mammalian target of rapamycin (mTOR), human eukaryotic translation initiation factor 4G (eIF4G), and p70 ribosomal protein S6 kinase (p70S6K) and activity of extracellular regulated kinase (ERK 1/2), reduction in tumor size and weight; downregulation of immune checkpoints; effects on cancer stem cells ^{[33][46][50][51][52][53]} ; reduction in incidence of mammary tumors ^[54]
<i>Grifola Frondosa</i>	β -glucans and α -glucan (D-fraction, X-fraction, Grifolan, MZ-fraction, and MT- α -glucan), proteins, carbohydrates, ergocalciferol, minerals	Apoptosis induction through the release of CytC from mitochondria, alterations in genes involved in cell proliferation and invasion; upregulation of E-cadherin protein levels, promotion of cell adhesion, downregulation of cell motility and MMP2 and MMP9; decrease in β -catenin levels; modulation of Bax/Bcl2 ratio, affecting the pro-survival pathways related to PI3K/Akt and ERK ^{[28][55]} ; immunomodulatory effects on macrophages, NK and T cells; decrease in metastasis; inhibition of carcinogenesis, angiogenesis, and cancer invasiveness; prolonged survival ^{[28][55]}
<i>Lentinula edodes</i>	β -glucans (lentinan), phenolic compounds, ergothioneine, sterols (ergosterol), eritadenine, peptides (lenthionine)	Induction of apoptosis associated with mitochondrial membrane potential decrease and decreased cdk4 and cyclin D1 resulting in cell cycle arrest; increased p21, p53, and Bax levels; inhibition of migration, autophagy induction ^{[33][56][57][58]} ; reduction in tumor growth through suppression of cell proliferation and apoptosis promotion; inhibition of multiple pathways (PI3K-Akt-mTOR, ERK, p53) ^[59]
<i>Pleurotus ostreatus</i>	α -glucans, β -glucans, lentinan, lipopolisaccharides, resveratrol, concavallin A, mevinolin, ergosterol	Cell growth inhibition related to cell cycle arrest at the G0/G1 phase, upregulation of the p21, p53, p27, and p19 genes and downregulation of E2f transcription factor 1, PCNA, CDK4, CDK6, and transcription factor DP-1; induction of oxidative stress and apoptotic cell death due to the upregulation of p53 and Bax, downregulation of Bcl2, and increase in caspase 3/7 activity; increased cytotoxic activity of natural killer cells; inhibition of angiogenesis and metastasis by the inhibition of MMP2 and MMP9 expression; downregulation of VEGF ^{[28][60][61]} ; decrease in tumor volume and increased body weight; decrease in tumor incidence, volume, and metastasis ^{[60][61][62]}

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