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MUSHROOM EXTRACTS AND COMPOUNDS WITH SUPPRESSIVE ACTION ON BREAST CANCER

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Abstract:

Breast cancer is a major global health concern, and the limitations of conventional cancer therapies have increased interest in natural products as potential complementary therapeutic agents. Medicinal and edible mushrooms contain diverse bioactive compounds, including polysaccharides, β-glucans, proteins, lectins, triterpenoids, phenolic compounds, terpenes, steroids, and other secondary metabolites, which exhibit several biological activities relevant to cancer suppression. The reviewed literature indicates that mushroom extracts and their bioactive constituents can inhibit breast cancer-cell proliferation, induce cell-cycle arrest and apoptosis, and suppress tumor migration, invasion, angiogenesis, and metastasis. Ganoderma lucidum and other medicinal mushrooms have demonstrated promising effects through modulation of pathways involved in cancer-cell survival and progression, including PI3K/Akt, MAPK, NF-κB, and p53-related signaling. Mushroom-derived polysaccharides may additionally enhance antitumor immune responses by stimulating macrophages, natural killer cells, dendritic cells, and other immune components. Evidence also suggests that certain mushroom extracts can influence multidrug resistance by reducing P-glycoprotein-mediated drug efflux, potentially improving chemotherapy sensitivity. However, variations in mushroom species, extraction methods, cultivation conditions, compound composition, and experimental models remain important challenges. Overall, mushroom extracts and their bioactive compounds show promising multi-targeted potential for breast cancer suppression and as complementary agents to conventional treatment, although further standardized preclinical and clinical studies are required.

Keywords: *Medicinal Mushrooms, Mushroom Extracts, Breast Cancer, B-Glucans, Polysaccharides, Triterpenoids, Apoptosis, Immunomodulation, Metastasis, Multidrug Resistance PI3K/Akt, NF-κB.*

1. Introduction

Breast cancer is one of the most significant health challenges worldwide and represents a major cause of cancer-related morbidity and mortality. Despite considerable advances in early diagnosis, surgery, chemotherapy,

radiotherapy, hormonal therapy, targeted therapy, and immunotherapy, effective management of breast cancer remains challenging because of tumor heterogeneity, recurrence, metastasis, treatment-associated toxicity, and the development of therapeutic resistance. The search for safer and more effective complementary approaches has therefore increased interest in naturally occurring bioactive compounds. Among these, edible and medicinal mushrooms have attracted considerable scientific attention because they contain a broad spectrum of biologically active molecules with potential anticancer properties.

Mushrooms are considered an important source of nutraceutical and medicinal compounds, including polysaccharides, β-glucans, glycoproteins, proteins, lectins, triterpenoids, terpenes, phenolic compounds, steroids, ergosterol derivatives, fatty acids, and other secondary metabolites. These compounds exhibit diverse biological activities, including antioxidant, anti-inflammatory, immunomodulatory, cytotoxic, antiproliferative, antiangiogenic, and antimetastatic effects. Among them, polysaccharides, particularly α- and β-glucans, are extensively investigated because of their ability to stimulate immune responses and activate immune cells such as macrophages, natural killer (NK) cells, dendritic cells, T cells, and other components of the antitumor immune system.[1]

Among medicinal mushrooms, Ganoderma lucidum (Reishi) has received substantial attention for its potential activity against breast cancer. Its bioactive constituents include triterpenoids such as ganoderic acids and related compounds, as well as polysaccharides and β-glucans. These constituents have been associated with suppression of cancer-cell proliferation, induction of apoptosis, inhibition of invasion and metastasis, and modulation of immune responses. Studies involving breast cancer cell models have reported that G. lucidum triterpenes can induce apoptosis and cell-cycle arrest by decreasing proteins such as cyclin D1, Bcl-2, and Bcl-xL while increasing Bax and caspase-9. Extracts of G. lucidum have also demonstrated inhibitory effects on migration, invasion, and metastatic behavior in breast cancer models. Other medicinal mushrooms have also demonstrated promising effects. A mushroom blend containing Agaricus blazei, Cordyceps sinensis, Coriolus versicolor, Ganoderma lucidum, Grifola frondosa, and Polyporus umbellatus was reported to inhibit proliferation and cause G2/M cell-cycle arrest in highly invasive MDA-MB-231 breast cancer cells. The same preparation reduced cell adhesion, migration, and invasion and suppressed secretion of urokinase plasminogen activator (uPA), a factor associated with tumor invasion. These findings suggest that combinations of mushroom-derived compounds may exert complementary effects against different characteristics of breast cancer. [1]

Another important area is the ability of mushroom bioactives to influence multidrug resistance (MDR). Overexpression of ATP-binding cassette transporters, particularly P-glycoprotein (P-gp), can reduce the intracellular accumulation of chemotherapeutic agents and contribute to treatment failure. Studies summarized in the reviewed literature indicate that extracts of Fomes fomentarius and Tricholoma anatolicum can suppress P-gp-dependent drug efflux and restore sensitivity to certain chemotherapeutic drugs in multidrug-resistant MCF-7 breast cancer cells. Mushroom polysaccharides have also been associated with modulation of NF-κB and P-gp expression. In addition, β-glucans may enhance antitumor immune responses and have potential as immune adjuvants alongside immune checkpoint-based therapies.[1]

Overall, the available evidence indicates that mushroom extracts and their bioactive compounds possess multi-targeted anticancer potential and may suppress breast cancer through interconnected mechanisms involving proliferation, cell-cycle regulation, apoptosis, angiogenesis, metastasis, immune modulation, and drug resistance.

However, much of the available evidence remains based on in-vitro and experimental studies, while variations in mushroom species, cultivation conditions, extraction methods, chemical composition, dosage, and preparation can influence biological activity. Therefore, further mechanistic, pharmacological, and clinical investigations are required to establish standardized preparations and determine their efficacy and safety. A comprehensive review of mushroom extracts and their bioactive compounds may help clarify their potential role in suppressing breast cancer and their possible application as complementary agents alongside established cancer therapies.[1]

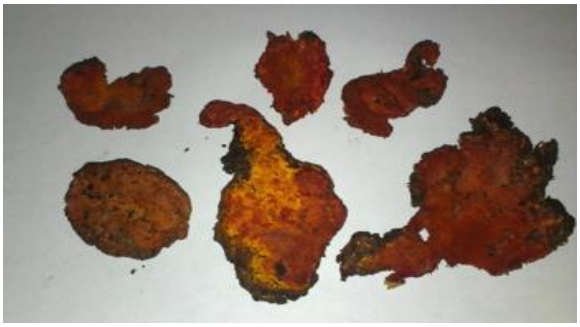
The anticancer potential of mushroom-derived compounds is not limited to immune stimulation. Evidence from experimental studies indicates that mushroom extracts and isolated bioactive compounds can directly interfere with important molecular processes involved in breast cancer development and progression. These mechanisms include inhibition of cancer-cell proliferation, induction of cell-cycle arrest, promotion of programmed cell death or apoptosis, suppression of angiogenesis, and inhibition of tumor-cell migration and invasion. Mushroom-derived compounds can influence several signaling pathways associated with cancer-cell survival and progression, including PI3K/Akt, MAPK, NF-κB, p53, and other regulatory pathways. Such multi-target activity is particularly important because breast cancer involves complex interactions between multiple molecular pathways rather than a single therapeutic target. [2]

In addition, the article provides insights into the anti-cancer properties of other mushrooms. Therefore, it has been shown that a combination of medicinal mushroom extracts (Agaricus blazei, Cordyceps sinensis, Coriolus versicolor, Ganoderma lucidum, Grifola frondosa, Polyporus umbellatus) is capable of inhibiting proliferation of human breast invasive carcinoma MDA-MB-231 cells with pronounced effect of G2/M cell cycle arrest. This combination was also shown to inhibit the adhesion, migration, and invasion of the cancer cells and reduce the secretion of urokinase plasminogen activator (uPA) by breast cancer cells, which is related to the invasiveness of the tumor cells. One of the promising approaches in the fight against cancer is the development of compounds derived from mushrooms, capable of overcoming MDR. Overexpression of the efflux pumps of ATP-binding cassette family, in particular P-glycoprotein, plays a crucial role in the mechanism of MDR. The review has analyzed the possibility of using the extracts of Fomes fomentarius and Tricholoma anatolicum to overcome MDR in MCF-7 cells resistant to doxorubicin. It has been shown that extracts of these mushrooms significantly inhibited P-glycoprotein activity, increasing the concentration of doxorubicin in tumor cells. It indicates the possibility of their use as adjuvants in cancer chemotherapy. Mushrooms polysaccharides were found to be able to regulate NF-κB and P-glycoprotein signaling pathways, inhibiting cell proliferation and invasion. Moreover, β-glucans derived from mushrooms have immune potentiating effect and can be used as adjuvants in immunotherapy, including immune checkpoint inhibitors. The review provides detailed information about anti-cancer properties of various medicinal mushrooms and their extracts and demonstrates great potential of these natural compounds in the treatment of breast cancer. However, it should be noted that the majority of the studies mentioned in the review are conducted in vitro experiments, which means that more preclinical and clinical trials are required to confirm the findings. In addition, the dosage and methods of preparation of extracts, as well as chemical composition of mushrooms depending on the season, growing conditions and other factors, are important issues. Thus, further pharmacological and clinical studies are required to establish optimal dosages and therapeutic schemes for the use of these preparations. The comprehensive study of mushrooms may allow to select substances that are capable of inhibiting the development of breast cancer at different stages and be used either independently or as adjuvants

in cancer treatment.Tumor cells usually bypass apoptosis through the regulation of pro- and anti-apoptotic gene expression. [3]

Agaricus bisporus

Cordyceps versicolor



Antrodia cinnamomea

Cordyceps sinensis

Cordyceps militaris

Pleurotus ostreatus

Lentinula edodes

Ganoderma lucidum

Figure 1: Edible /medicinal mushroom active in breast cancer [1]

2 Methods and Materials

2.1 Cell culture

HUVECs cells are obtained from Thermo Fisher Scientific (Waltham, MA, USA) then cultured in Medium 200 + Low serum growth supplement (LSGS), penicillin (100IU/ml) and Streptomycin (100µg/ml). The cells are cultured in flasks coated with Attachment factor protein with gelatine (all purchased from Thermo Fisher Scientific, Waltham, MA, USA). The human breast cancer cell line MCF-7was acquired from European Collection of Cell cultures (Lot 13K023; Salisbury, UK). The cells were cultured in the complete culture medium RPMI 1640; 2mM L-glutamine, 10% foetus bovine serum (FBS) heat-inactivated, streptomycin (100g/ml), penicillin (100 IU/ml) and non-essential amino acids (all purchases from Sigma-Aldrich, Darmstadt, Germany). All cell lines were incubated at 37C and humidified incubator with 5% CO2 in normal atmospheric pressure.[4]

2.2 preparation of the CV extract and LPS solution

Corrilous Versicolor extract was purchased in ready form in capsules from the commercial supplier Myco Medica Company (Police nad Metuj , Czech Republic) manufacturer claims that major components of soluble molecules comprise approximately 25% of that capsule weight. CV extract was then diluted in the appropriate culture media for all treatments to prepared solutions of 8 mg/ml and 4 mg/ml over 48hr under gentle agitation and in room temperature. Insoluble components were eliminated by 2000g centrifuge for 10 minutes and remaining solution (containing 2 mg/ml and 1 mg/ml) filter Sterilized by a 0.22 µm filter and thereafter it was diluted to working concentrations by respective culture media, Control media used to dilute the CV solution was accordingly defined, because used together with the cell medium for cell stimulation: Complete medium 200 to HUVECs and complete RPMI 1640 to MCF-7. LPS derived from Escherchiacoli 0111: B4, purchased from Sigma-Aldrich, Darmstadt, Germany) was prepared in PBS solution and further diluted by the adequate culture medium for cell stimulation up to working concentrations of 100ng/ml and 1 g/ml (HUVECs) and 2 and 20 g/ml (MCF-7).[4]

2.3 cell treatment

Cells were seeded in tissue culture plates in density adequate to requested essay. Two cell lines were pre-incubated over 24h after what cells were stimulated together with both, CV extract (50, 100, 200 and 300 µg/ml) and LPS (100 ng/ml and 1g/ml for HUVECs cells, and 2 and 20 g/ml for MCF-7). The LPS stimulation time and concentrations are chosen to be non-cytotoxic for the cell and at the same time effective to produce enormous amounts of cytokines. In separate experiments cells were treated with either CV extract or LPS solution. Control cells were incubated simply alone in complete growth medium.[4]

2.4 Cell viability

The MTT assay was used as cell viability test. This assay measures the reduction of the yellow tetrazolium salt MTT (3-4,5-Dimethylthiazolyl-2,5-Diphenyl Tetrazolium Bromide] ; Sigma Aldrich, Darmstadt, Germany) by the activity of the mitochondrial tetrazolium reductase on to the blue formazan product; this action demonstrates the normalcy function of the mitochondria, thus the metabolic activity. 0.5x104 cells was seeded in tissue culture plates and the cells was first pre-incubated for 24hours, following by incubation with the different concentrations of CV extract and LPS. Blank wells were prepared, in which cells were replaced by culture media added with mentioned concentrations of supplemented CV and/or LPS. Plates are incubated over 24 hours for HUVECs and 48 hours for MCF-7. Afterward each solution the formazan product was extracted by addition 100 µl 100% DMSO /well. The absorbances was read on spectrophotometer at 570 nm (reference 630nm); (Synergy HT Multi-Mode

Microplate Reader Bio Tek Instruments, Winooski, VT, USA). In every experiment control value measured using untreated cells was recognized as 100%[4]

2.5. Western blot analysis

Western blot was performed to assess expression of TLR4 and p-IB in HUVEC cells treated with CV extract (100g/mL) and/or LPS (100ng/mL) for 24h and MCF-7 cells treated with CV extract (100g/mL) and/or LPS (20g/mL) for 48h. At the end of stimulation, cells were rinsed with ice cold PBS and lysed in 70 L lysis buffer containing 4% SDS, 20% glycerol, 4% 2-mercaptoethanol, 0.004% bromophenol blue, 0.250M Tris HCl (pH 6.8), and 2mM EDTA. The protein concentration of these lysates was determined by Peirce BCA Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the kit manufacturer instruction. The lysates supplemented with sample buffer were separated by a 4–20% precast polyacrylamide gel and transferred onto nitrocellulose membranes. The membranes were then immunoblotted with mouse anti-TLR4 IgG (Santa Cruz Biotechnology, Dallas, TX, USA) and rabbit anti-phosphorylated-IB IgG (Ser32; Cell Signaling, Leiden, The Netherlands) or mouse anti-actin IgG (MP Biomedicals, Santa Ana, CA, USA). Finally, they were incubated with the respective anti-rabbit (Merck Millipore, Burlington, MA, USA) or anti-mouse IgG (Jackson, ImmunoResearch, Cambridge, UK) conjugated with peroxidase. Immunoreactive bands were visualizing by chemiluminescence using SuperSignal West Pico substrate (Thermo Fisher Scientific, Waltham, MA, USA) and quantifying by ImageJ software (National Institute of Mental Health, Bethesda, MD, USA). [4]

2.6. Statistical analysis

All values obtained were assessed by GraphPad Prism 7.0 software (GraphPad Software Inc., San Diego, CA, USA). A comparative assessment among various values was performed. All values obtained were express as means standard error of the mean (SEM). Data were assessed using analysis of variance followed by Bonferroni multiple comparisons test, with level of significance considered as $p < 0.05$.[4]

3. Bioactive compounds of medicinal mushrooms

The anticancer activity of mushroom is due to the participation of chemically diverse components in their structure. In the available literature, there is special importance put to polysaccharides and -glucans; triterpenoids; phenolic compounds; proteins and lectins, but their activities can be integrated, and whole extracts can exert an activity resulting from the synergism of the various participating compounds, rather than acting on a single active molecule. The bioactivity of mushroom can be related to various biologically active components, among them polysaccharides, which are the structural element of the cell wall of the fungal organism. Polysaccharides have been demonstrated to show antioxidant, anti-inflammatory, antitumor, antimicrobial, immunomodulatory, and antidiabetic activity. However, based on their structural characteristics, i.e. Percentage of branching, backbone, side chains or type of constituent sugar monomers, polysaccharides could interfere in varying degrees in the development and promotion of a broad array of cellular activities. -and -glucans are the most abundant class of polysaccharides, but other fractions like heteroglycans, peptidoglycans and polysaccharide-protein complexes exhibit some biological effects. Mushrooms have a high concentration of proteins with anticancer and cytotoxic activity. Some of them are known for their particularly marked immunomodulatory effect and are named "fungal immunomodulatory proteins" (FIPs), with different mechanisms of action. Other mushrooms proteins that play an important role in the treatment of cancerous diseases, include the lectins. These are proteins which specificallybind rever-si-bly to mono-andoligo-saccharides

with varying avidities and recogniz-es and bind to carbohydrate and proteoglycans present on the cell surface. Involved in most aspects of immunity such as cell mediate immune response, they are able to modulate the effects of im-munity through various mechanisms de-pend-ing on the nature of the lectin. They seem to have antitu-mor, im-mu-no-mo-du-la-to-ry, and anti-pro-li-fe-ra-tive effects. Other components involved in bioactivity are terpenes, quinones, triacylglycerols, isoflavones, catechols, steroids. Also, other active compounds are: pheno-lic compounds (natural antioxidants involved in oxy-gen scavenging, metal inacti-vation, scav-en-ging of free radicals, or peroxidases decomp.), laccases (type of co-pper con-taining oxidases) and fatty acids [1,5].

Table 1. Bioactive compounds of medicinal mushrooms [1]

Compound class	Representative examples	Relevance to breast cancer
Polysaccharides / β-glucans	Lentinan; D-fraction; α/β-glucans; ganode	Immune activation; apoptosis; modulation of proliferation and metastasis
Protein-bound polysaccharides	PSK; PSP	Immunomodulation; p53/Bcl-2-related effects; antitumor activity
Triterpenoids	Ganoderic acids; ganodermic alcohols	apoptosis; cell-cycle arrest; invasion/metastasis suppression
Cordyceps spp	Cordycepin, ergosterol and related metabolites	caspase activation; PI3K/Akt effects; EMT suppression; reduced migration/invasion
Agaricus spp	Extracts and metabolites	reclinical and supportive clinical evidence; immune and quality-of-life outcomes in selected

4. Major mushrooms and breast-cancer evidence

The supplied breast-cancer review highlights nine major edible and medicinal mushrooms that have been investigated for their potential anticancer properties. The available evidence comes from different types of studies, including laboratory experiments using cancer cell lines, animal models, and a limited number of clinical investigations. Together, these studies suggest that certain mushroom-derived compounds may influence several biological processes involved in breast-cancer development and progression.[1]

In addition to their medicinal importance, mushrooms have considerable economic value. Mushroom cultivation can provide farmers with an income-generating and commercially valuable agricultural activity. However, many growers struggle to obtain good profits because of inadequate marketing strategies. A common practice is to sell freshly harvested mushrooms directly to retailers or consumers, but this approach has several limitations. Mushroom production is often seasonal, and during periods of high production, particularly in North India during the winter season, the market can become saturated. This may force farmers to sell their produce at low prices, sometimes resulting in financial losses.[1]

Therefore, simply increasing mushroom production without addressing marketing challenges may not be sufficient. Better marketing approaches are needed to improve the profitability of mushroom cultivation. Fresh mushrooms can be marketed through different channels, while processing them into value-added products such as pickles, nuggets, and dried mushroom powder may provide additional opportunities. Such processed products can have a longer shelf life and may generate ho better returns for growers.[1]

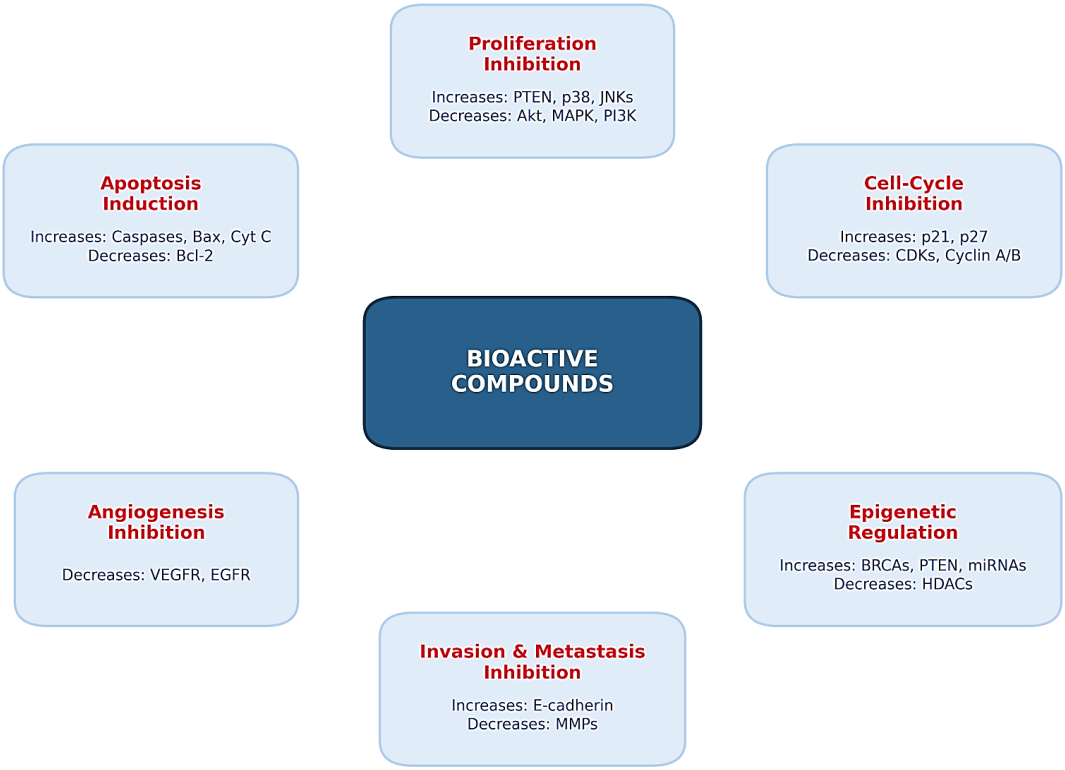


Figure 2: Bioactive compounds [1]

5. Molecular mechanisms of breast-cancer suppression

5.1 Cell-cycle arrest and inhibition of proliferation

Mushroom extracts and their bioactive fractions have been reported to interfere with the cell cycle, particularly at the G0/G1 and G2/M stages. These effects may involve changes in cyclins, cyclin-dependent kinases, and other proteins associated with cell proliferation. For example, a mushroom blend was reported to reduce the proliferation of invasive MDA-MB-231 breast-cancer cells and promote G2/M cell-cycle arrest.[6]

5.2 Apoptosis

Induction of apoptosis, or programmed cell death, is one of the mechanisms frequently reported in mushroom-based experimental studies. Compounds obtained from Ganoderma lucidum have been associated with reduced expression of proteins such as cyclin D1, Bcl-2, and Bcl-xL, together with increased Bax and caspase-9 activity. Ergosterol peroxide has also been linked with activation of caspase-3/7 and PARP cleavage. Similarly, compounds from Cordyceps species have been reported to influence Bax translocation, cytochrome-C release, and caspase activation.[6]

5.3 Migration, invasion, and metastasis

Several mushroom-derived compounds have demonstrated the ability to reduce cancer-cell migration and invasion in experimental models. These effects have been associated with changes in molecules such as MMP2, MMP9, uPA, epithelial–mesenchymal transition (EMT)-related factors, and other pro-invasive genes. Ganoderma lucidum has also been investigated for its possible role in limiting breast-cancer cells from developing metastatic behavior, including spread toward the lungs.[6]

5.4 Angiogenesis

Mushroom polysaccharides and extracts have shown antiangiogenic effects in experimental studies. Some findings suggest that these compounds may reduce the activity or expression of angiogenic mediators such as vascular endothelial growth factor (VEGF). However, evidence specifically connecting these effects to clinical breast-cancer treatment is still limited, and further research is required.[6]

5.5 Immune modulation

β-glucans present in mushrooms can interact with receptors on immune cells and may influence macrophages, dendritic cells, natural killer (NK) cells, and cytokine production. Because of these immunomodulatory properties, mushroom preparations have been investigated for their potential role as supportive or adjunctive components of cancer treatment. However, their clinical usefulness requires further validation.[6]

5.6 Oxidative stress and inflammatory signaling

Phenolic compounds and other mushroom-derived molecules may contribute to antioxidant activity and can also affect pathways involved in inflammation. Their effects on reactive oxygen species (ROS) and cellular antioxidant systems can vary depending on the particular compound, concentration, and experimental model. Therefore, mechanistic findings should be interpreted carefully rather than generalized to all mushroom species or preparations. [6]

6. Key signaling pathways

An extraction was done to obtain C.M.E from C. Mushrooms with 70% ethanol. MTT assay and Western blotting were used to determine the cytotoxic properties of C.M.E and protein expressions, respectively. In order to study the anti-cancer potential of C.M.E in vivo, C.M.E (2 g/kg) was given every other day orally for 30 consecutive days (15 dose). This experiment involved 4T1 tumor-bearing BALB/c mice and their tumor size was measured. C.M.E was fractionated using silica gel column chromatography. The 1H and 13C-NMR, and LC-MS results identified major constituents of C.M.E to be responsible for the cytotoxic nature of C.M.E. [5]

Table 2: Key cellular signaling pathways modulated by mushroom bioactive compounds

Pathway	Reported relationship to mushroom bioactive
PI3K/Akt/mTOR	Suppression of Akt phosphorylation and survival signaling; mushroom-derived
NF-κB	Inhibition linked to reduced proliferation/inflammatory signaling; polysaccharide and extracts are prominent ex
MAPK / ERK	β-glucans can activate MAPK in immune cell, while selected metabolites may modulate ERK-related tumor signaling.
p53	Associated with apoptosis and cell-cycle control; PSK and several mushroom preparations increase p53 response
Estrogen receptor signaling	G. lucidum has been reported to downregulate estrogen receptor-associated signaling in breast-cancer models.
Wnt/β-catenin	G. lucidum and other mushroom compounds have been associated with suppression of tumor growth/migration through.
EMT-related signaling	Cordyceps-associated effects include reduced TWIST1, SLUG, SNAIL1 and ZEB-related changes and altered E-cadherin

The data demonstrated that C.M.E inhibited the multiplication of 4T1 mouse breast cancer cells in a dose and time-dependent manner. Treatment with C.M.E increased LC3 expression and AMPK phosphorylation while decreased mTOR, S6, and S6K1 phosphorylation. These results were indicative that C.M.E mediated autophagic pathways by activating AMP Kind activating them TOR pathway. This was consistent with in vitro data because C.M.E markedly inhibited the growth of 4T1 tumor-bearing BALB/c mice. Furthermore, Inotodiol and trametenolic acid were found to be constituents responsible for inducing cytotoxic effect of C.M.E in breast cancer cells. Meanwhile, the combined extract containing Inotodiol and trametenolic acid shows its cytotoxicity against the three cancer cell types independently and had no interference with the cytotoxic effects of general drugs [7].

7.conceptual mechanistic flow

Mushroom extract / bioactive compound

↓

Molecular targets and receptors

PI3K/Akt • NF-κB • MAPK/ERK • p53 • ER • Wnt/β-catenin

↓

Cellular responses

Cell-cycle arrest • apoptosis • reduced proliferation • altered ROS/inflammation

↓

Tumor-behaviour effects

Reduced migration • invasion • angiogenic signaling • metastasis

↓

Immune effects

↓

Macrophage/NK/T-cell modulation • cytokine regulation

↓

Potential therapeutic outcome

Suppression of breast-cancer progression and possible enhancement of treatment response

8. Mushroom extracts and chemotherapy multidrug resistance

In terms of conventional chemo-therapy and mushroom extracts combinations and multidrug resistance, there has been recently interest. One breast cancer experiment indicates the Suillus collinitus methanolic extract with etoposide was effective to significantly increase growth inhibition compared with single treatment with either. Other studies indicate these mushroom extracts could also potentially affect P-glycoprotein-dependant drug efflux and alter chemotherapy sensitivity. [4]

This is relevant since P-gp, an ABC transporter, is involved in the reduced intracellular cancer chemotherapeutic drugs concentrations. The presented literature showed that several mushroom extracts can modulate P-gp-dependent resistance, including some studies on MDRA MCF-7 cells. However these studies should not be considered to provide definitive clinical benefits, and remain preliminary. [4]

Epidemiologic African-American female studies, immune response to chemotherapy agents or radiation, and the literature from Asian country of the value of polysaccharide immune therapy indicate that the functioning of the immune system play a role in the primary and secondary Prevention of breast cancer. Critical areas of research

on breast cancer immunotherapy include studies of Tc, alone and its polysaccharide peptide extract, Krestin (PSK). We are calling for 2 type of research studies on breast cancer immunotherapy. First is a clinical trial of Tc as a concurrent adjuvant therapy to conventional chemotherapy, radiotherapy, andHER2/new Ab (trastuzumab) and second, given the hypothesized role of Tc in secondary prevention and its wide usage of conventional medical practice in the country of origin is in patients after having received conventional therapy. [4]

9. Clinical evidence and patient related evidence

While the laboratory data seem promising, most of the data on clinical use are limited. One randomized controlled trial of Agaricus sylvaticus in stages II/III breast cancer demonstrated that extracts of A. Sylvaticus improved quality of life, gastrointestinal function, and several haemato logic markers in patients. A pilot trial on G. Lucidum in patients with breast cancer suggests a reduction of treatment-related symptoms including can cerrelated fatigue and enhancement of mental well-being under endocrine treatment, while a phase I/II trial on G. Frondosa in patients with postmenopausal breast cancer reported beneficial immunological activity. We cannot interpret most of these preliminary observations to establish efficacy; since there may be considerable methodological shortcomings (small sample sizes, short follow-up periods, and variable preparations). Breast cancers may also exist in different molecular subsets (based one strogen or progesterone status and HER-2 amplification), which are the underlying biology for many different clinical behaviour patterns, risks, and treatments. [9]

White Button / Cremini / Portobello (Agaricus bisporus) In population studies, consuming ~ 10-18 gm a day (less than ¼ cup) of fresh mushrooms showed 45 % reductions in overall cancer rates. The risk reduction being most closely associated with breast cancer. However, mushrooms must always be eaten cooked, or the agar tine a naturally occurring toxin contained in fresh mushrooms could pose a risk. Turkey Tail (Coriolus versicolor) This is one of the most well- studied mushrooms used for medicinal purposes. Its active component, Polysaccharide-K (PSK) is approved in Japan as an adjuvant therapeutic for patients on conventional cancer therapy to reduce survival rates and help restore the immune system. Shiitake (Lentinula edodes) Contains lentinan. Clinical studies showed a significant improvement in breast cancer patients undergoing conventional hormone or chemotherapy with the addition of shiitake mushroom extracts, specifically reducing pain and physical exhaustion. Maitake (Grifola frondosa) Preliminary laboratory research indicated that maitake extract reduces the viability of aggressive triple-negative breast cancer cells and could possibly enhance therapies like trastuzumab (Herceptin).[10]

10. Mechanisms of action at cellular level of mushroom extracts properties

CAFs elevate the levels of anti-apoptotic protein (e.g. Bcl-2) and decrease the level of caspase-3 that is a protein involved in apoptotic process. Tgf-1 secreted by CAFs is responsible for docetaxel resistance. The level of TGF-1 is decreased by MPSSS and this contributes to the prevention of docetaxel resistance in tumor. MPSSS acts through the TLR4 receptor on CAFs to inhibit the JAK2/STAT3 pathway, that is related with CAF activity and Tgf-1 secretion. The inhibition of this pathway in CAFs results in its deactivation and reversal of docetaxel resistance in prostate cancer cells [6]. Cen et al. Have demonstrate that the effectiveness of GAD on cisplatin sensitivity is achieved by inhibiting the extracellular signal regulated kinase (ERK1/2) signaling in the mitogen-activated protein kinase (MAPK) pathway. First, GAD stimulates the production of reactive oxygen species (ROS), that cause oxidative stress in cancer cell.[11]

ROS generation is closely associated with cisplatin sensitivity, because the chemotherapeutic drug exerts effects on cells in part through the accumulation of ROS. GAD potentiates the action by upregulating the generation of ROS inside tumor cell ROS generation then interferes with the activation ofERK1/2 in the MAPK pathway. It is widely acknowledged that the activation ofERK1/2 plays an important role in the resistance of cells to cisplatin and ThereforeERK1/2 activation is necessary for tumor cell to survival. However, GAD inhibitsERK1/2 signaling pathways thereby decreasing the ability of tumor cells to survive and resist is platin treatment. Consequently, GAD Cisplatin combination induces a serial of cellular events, including higher levels of intracellular ROS and suppression of ERK1/2 signaling pathways, resulting in increased sensitivity of tumor cell to cisplatin. These investigators verified this hypothesis by measuring reduced level of P-ERK induced in combination therapy group and this reduced level of P-ERK can be restore by N-acetylcysteine (ROS scavenger) TREATMENT. Finally, GAD can block the signaling pathways in the MAPK pathways by inhibitingERK1/2 activity, which regulates some of normal cellular processes including differentiation and programed death of cells. [11]

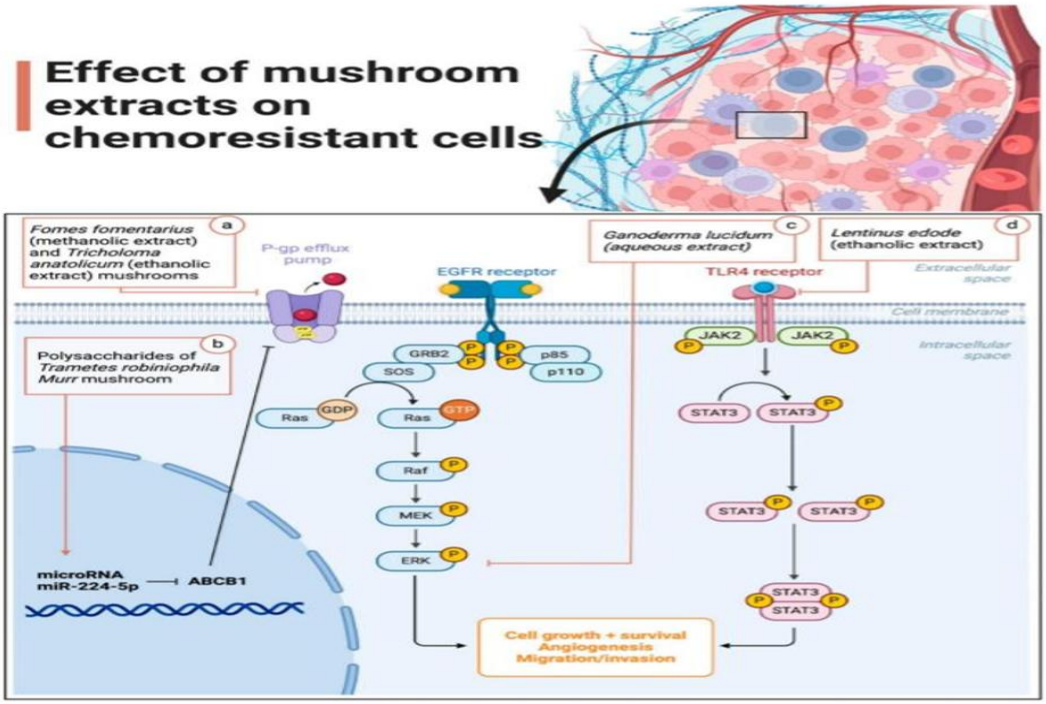


Figure 3: Effect of mushroom extract on chemo resistant cells [12]

The mechanism by which the Pleurotus pulmonarus extract improved the sensitivity of tumor xenotransplants to the use of the conventional chemo therapeutic drug treatment was not studied in the work by Xu etal. The cellular mechanisms by which mushroom extracts improved the therapeutic efficacy in chemo therapies in articles summarized in this review were Illustrated in the following figure [6]. Figure. 1 The mechanisms of anti-cancer efficacy of mushrooms on cellular level (a) Vincristine or paclitaxel-resistant breast cancer cells (MCF-7) inhibited by extract from Fomes fomentarius and Tricholoma anatolicum through the inhibition of P-gp protein. (b) Polysaccharides extracted from Trametes robiniophila Murr enhanced sensitivity of human hepatocellular carcinoma cells (HepG2 and Bel-7404), in nude mice in vivo (BALB/c), to oxaliplatin therapy through the up-regulation of microRNAs (miR-224-5p) that inhibit the expression of ABCB1 gene, then inhibites pression of P-gp

protein. (c) Ganoderic Acid D and ganoderma lucidum spore inhibit the activation of extracellular signal regulated kinase ERK1/2 in MAPK signaling pathway and improve sensitivity to cisplatin by increasing intracellular ROS levels of SKOV3 and SKOV3/DDP ovarian cancer cells. (d) Polysaccharides isolated from Lentinula edodes reverse docetaxel resistance of docetaxel resistant prostate cancer cell (PC3) induced by CAFs through regulation TGF-1 levels, an essential mediator for docetaxel resistance, by means of theTLR4 receptor on the CAF cell, which inhibit the JAK2/STAT3 signaling pathways associated with CAFs and its TGF-1 secretions. This can inactivate the CAF cells, thereby reversing docetaxel resistance in prostate cancer cell [11].

11. Conclusion

The evidence provided is in support of the premise that mushrooms and their bioactive constituents have significant pre-clinical potential to affect breast-cancer-related processes. With particular reference, polysaccharides and the immunomodulatory, -glucans are of significance as is triterpenoids, sterols and further metabolites for ability to affect apoptosis, cell-cycle, proliferation, migration and invasion directly. There is particularly strong evidence supporting mushrooms against breast-cancer primarily that against breast cancer cell lines (BC-cell lines) in terms of antiproliferation and effects on apoptosis and cell-cycle, supported by considerable evidence with particularly well supported evidence regarding Ganoderma lucidum and Trametes versicolor (previously Coriolus versicolor/C. Hirsutus) Grifola frondosa Lentinula edodes, Cordyceps Pleurotus. Some extracts show potential for drug-response modulations to compliment standard breast cancer therapies. the evidence and mechanistic data supporting medicinal mushroom use has predominantly been pre-clinical thus although significant this still requires translation into human trials where information is comparatively lacking to ensure clinical effectiveness is justified. Mushroom products should not be considered a substitution for any current or future standard therapy used in breast cancer treatment. Use needs to take the form of additional research candidates, requiring standardized preparations, more specific studies of mechanism, more suitably designed trials before the clinical effectiveness of medical mushroom products can be firmly established.

Both medicinal and edible mushrooms have surfaced as promising sources for bioactive compounds applicable in managing breast cancer therapy. Based on reviewed research, evidence indicating that mushroom-derived extracts, polysaccharides, triterpenoids and further compounds manifest direct effects to reduce breast cancer cell growth and migration and are associated with direct influence of tumor cell apoptosis and autophagy, to impact immunity and also signaling cascades (such as AMP-mTOR) further support use of certain mushrooms as adjuvant support in breast cancer studies. Trials involving several medicinal mushrooms; Ganoderma lucidum, Trametes versicolor, Chaga mushroom and some combinations of mushrooms indicate that there is significant potential in utilizing these for modulating factors important to breast cancer immunity and cell biology.

Information from preclinical studies suggest potential for these extracts to enhance standard cancer treatments or diminish any limiting side effects from the latter. Literature searches indicated that the findings regarding this use as generally proven that evidence relating to it increases each year while its use is more prominently supported from studies using vitro systems and animal models with comparatively less human studies. Despite positive scientific indications it is not reasonable to support these studies and assume that their findings translate directly to proven efficacy that medicinal mushroom products are effective replacements for standard breast cancer therapy. Further properly designed clinical trials are required for accurate therapeutic dose administration and security before pharmacodynamics interactions can be considered relevant to the general application, as well

as for monitoring the duration of the impact. Overall, medicinal mushrooms are beneficial sources of investigation with potential benefit to adjuvant and complementary approaches to breast cancer therapy.

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