

Effect of anti-cancerous compounds on cancer cells extracted from edible mushrooms: A review

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Abstract

Mushrooms have been an invaluable ingredient in terms of food and medicine to humanity since time immemorial. Mushrooms have been shown to be possessing properties such as anti-tumor, antiproliferative, antioxidant, immunomodulatory, anti-diabetic. Traditional Czech republic medicine involved using *Piptoporus betulinus* in curing colorectal cancer; similarly, fruiting bodies of *Inonotus obliquus* were employed in Folk medicine in eastern Europe since the 16th century. The oriental practice of utilizing mushrooms has witnessed an overwhelming attentiveness from the global research fraternity in exploring its wonder substances. Cancer is one of the key problems faced by researchers in finding an efficient medicine without inducing severe health complications. Mushrooms contain a plethora of bioactive compounds involved in tumor inhibition, such as hispolon, lentinan, gannoderic acid, illudin-s, and many more. The current article briefly describes various edible mushrooms with anti-tumorigenic compounds and their effect on the cancer cells of various means.

Key Words: Edible Mushrooms, anti-cancerous, bioactive compounds, therapeutic, β -glucan.

1. Introduction

Mushroom has been considered gourmet cuisine across the planet since ancient times for its distinctive taste and flavor. In some traditions, mushroom consumption is linked to disease treatment, prevention, and surviving longevity. Among 14,000 mushroom species, 50 to 200 species have medicinal properties. Despite their long-term use in oriental medicine, their effects in promoting health are proven by contemporary based studies only. Few studies suggest that *Agaricus*, *Polyozellus*, *Coprinus*, *Amauroderma*, *Grifola*, *Pleurotus*, *Phellinus*, *Lentinula*, and *Ganoderma* helps in enhancing inflammatory responses and immune system (Figueiredo & Régis, 2017) (Patel & Goyal, 2012). *Boletus edulis*, commonly known as Penny Bun, is among the species of edible mushrooms used to observe anti-tumor activity in the middle of the 20th century.

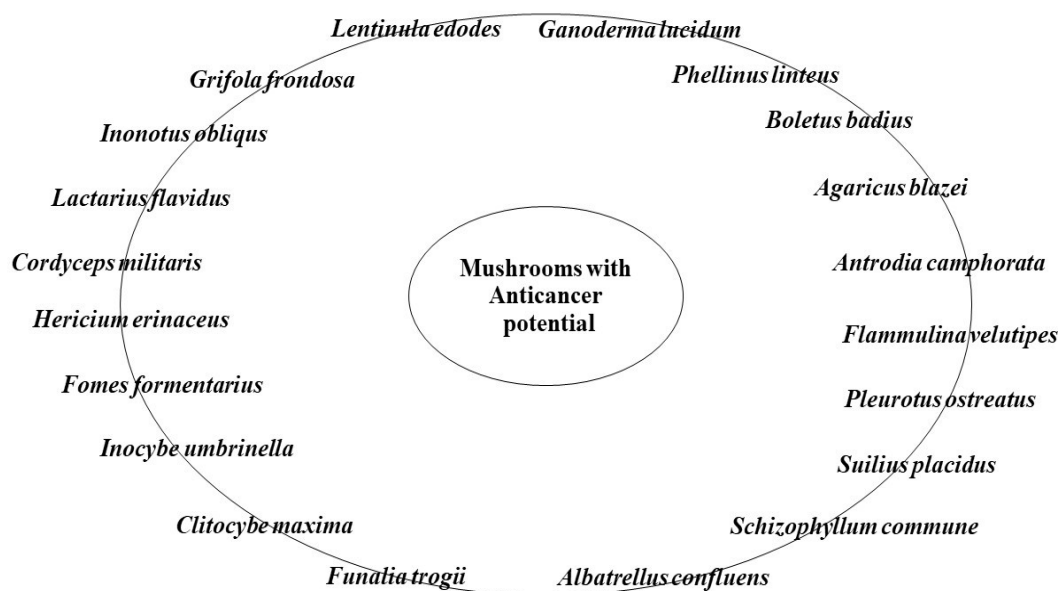


Figure 1: Medicinal mushrooms with anti-cancerous properties

Cancers are the leading cause of death worldwide, next to cardiovascular diseases, and the existing treatment methods are associated with various side effects. Conventional therapies

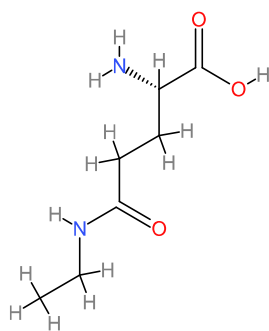
such as chemotherapy, surgery, and radiational therapy are very complex and related to various complications in clinical management, such as a decrease in the absorption of nutrients and minimized calory intake, which jeopardize the well-being of cancer patients. The urgency of finding an alternative approach has increased because the existing drugs are not target-specific and pose some complications. Mushrooms have attracted and caused immense interest with their wide range of biologically active compounds.

Scientific communities have started focusing on employing the compounds extracted, especially from edible mushrooms, which can be an important element in fighting against cancer. Edible mushrooms have also been used in adjuvant to complement chemotherapy; this helps overcome the complications such as anemia, nausea, lowered resistance, and bone marrow suppression. The current article reviews the importance of anti-cancerous compounds from edible mushrooms and their anti-tumorigenic activity.

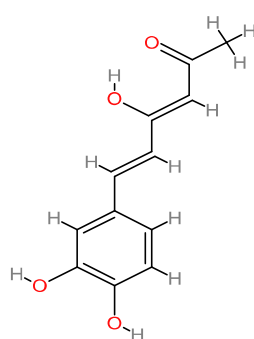
2. Anti-cancerous compounds of mushroom origin

Mushrooms are micro-sized factories of a plethora of bioactive compounds such as alkaloids, ascorbic acid enzymes, carotenoids, fats, folates, glycosides, organic acids, phenolics, proteins, polysaccharides, tocopherols. There are certain types of specific compounds in mushrooms that are effective in showing potential anti-cancer properties. The compounds conferring the properties are calcelin, hispolon, lectin, lentinan, krestin, *Hericium* polysaccharide A, illudin S, ganoderic acid, schizophyllan, psilocybin, laccase, and many more. Among these substances, polysaccharides are showing to be promising. β -glucan, the most versatile polysaccharide because of its broad-spectrum biological activity. The compound generally consists of a glucose backbone with β -(1 \rightarrow 3) and often with β -(1 \rightarrow 6) glucose residues (Chen & Seviour, 2007). The host immune system hinders their mechanism of action because they get recognized as non-self-molecules. Another molecule named hispolon, a polyphenol

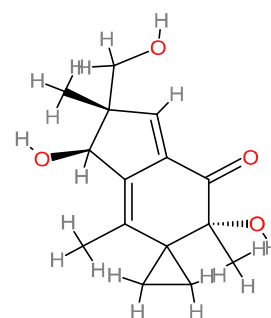
compound, has neutralized chemotherapy and antineoplastic activities (Patel & Goyal, 2012). Other compounds include maitake D-fraction (a proteoglycan derivative), polysaccharide peptides like PSP, PSK, triterpenoids, triterpenes. In vitro, in vivo, and clinical trials have shown the binding property of lectins to the membrane carbohydrates of mutant cells, thereby decreasing tumor growth. Lectins from the species such as *A.bisporus* and *G.froncosa* expressed anti-proliferative and anti-tumorigenic potential (Figueiredo & Régis, 2017). (S. T. Chang & Miles, 1989) In vitro experiments showed that 90 µg/ml of *A.bisporus* lectin extract could become potent antiproliferative agents.



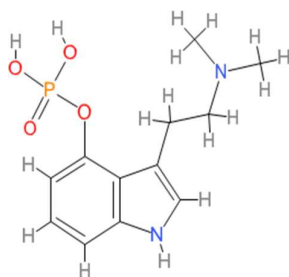
Structure 1: Theanine



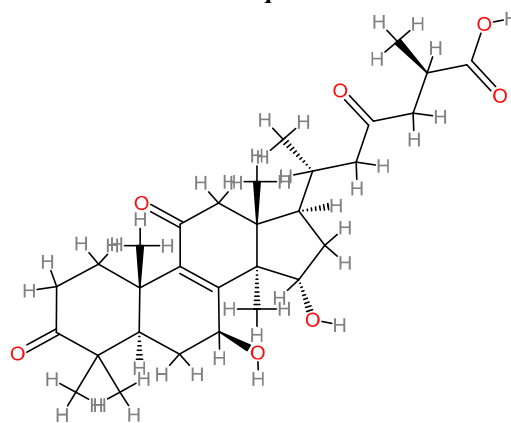
Structure 2: Hispolon



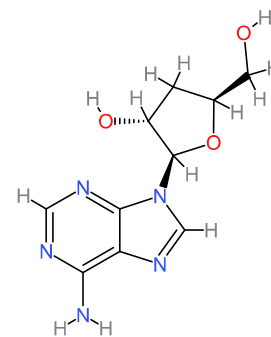
Structure 3: Illudin-S



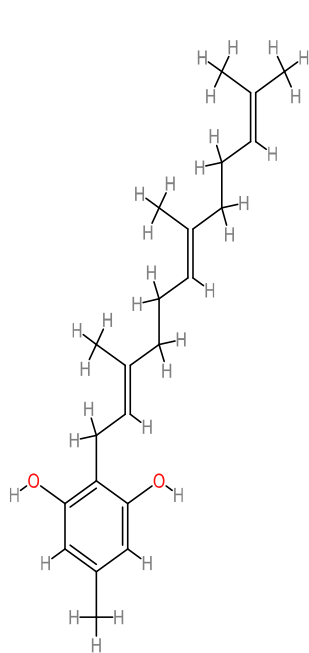
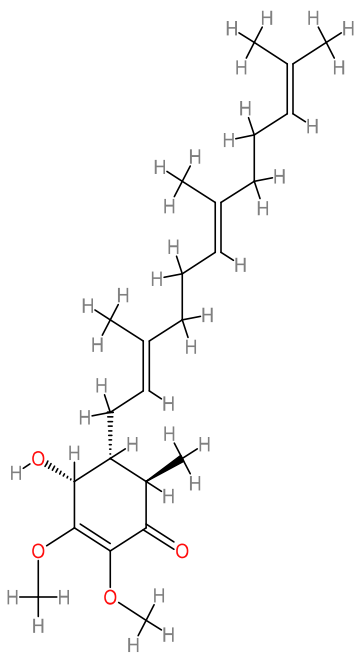
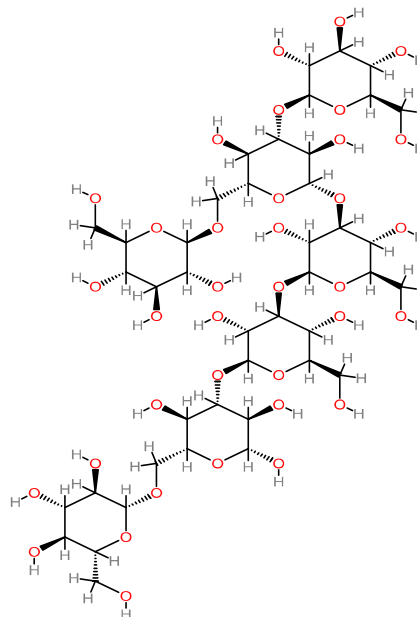
Structure 4: Psilocybin



Structure 5: Gannoderric acid



Structure 6: Cordycepin

*Structure 7: Grifolin**Structure 8: Antroquinonol**Structure 9: Lentinan*

3. Chemical and nutritional profile of edible mushrooms

Mushrooms are well known for being part of an energy-restricted diet since they have low concentrations of energy and fat, despite having high quantities of proteins and dietary fibers. Mushrooms could serve all the essential amino acids as per the dietary intake of humans. They also possess other nutrients like vitamins of the B group, vitamin E, and minerals like iron, phosphate, and selenium in minor amounts (Shang et al., 2006). Among the vitamins group, vitamin B12 stands out to be the predominant one and is found in red meat, fish, and the liver in terms of bioavailability, indicating an important ingredient of the vegan diet (Barros et al., 2008). Mushrooms are also known to be the source of ergosterol, which can synthesize vitamin D2 after exposure to UV light. Besides, mushrooms are the source of one of the unusual amino acids called L-ergothioneine, which has shown antioxidant properties (Figueiredo & Régis, 2017).

4. Edible mushrooms with anti-cancerous compounds and their effects on tumor cells

4.1. Genus *Agaricus*

Agaricus subrufescens (syn. *Agaricus blazei*), commonly known as almond mushrooms, are common species of the genus *Agaricus* used to prevent cancer. (Delmanto et al., 2001) induced clastogenicity in mice using cyclophosphamide and have observed the evidence proving extracts of *Agaricus blazei* Murrill with anti-carcinogenic, immunomodulatory, and antimutagenic properties. The extracts of *A.blazei* Murrill are rich in β -glucan, which is a key anti-cancerous compound in mushrooms. Broth fraction of *A.blazei* has shown the antiproliferative effect of human prostate cell lines of both androgen-independent and androgen-dependent. The contents in the broth fraction had caused leakage of Lactate dehydrogenase from cancer cell lines. Further, the DNA fragmentation and activities of caspases were enhanced in androgen-independent PC3 cells. The fractions elevated and enhanced the protein expression of genes involved in apoptosis. Mice with severe combined immunodeficiency (SCID) were supplemented orally with *A.blazei* (high concentrations of β -glucan) and shown significant suppression of tumor growth with minimal side effects (Yu et al., 2009). Agaritine, a hydrazine-derivative obtained from a hot-water extract of *A.blazei* Murrill shown promising effects on human leukemic monocyte lymphoma cells. Agaritine induced annexin V expression, DNA fragmentation, and cytochrome c release. Cells after treatment with agaritine shown an increase in their caspase 3,8 and 9 activities; thereby, apoptosis is induced easily in tumor cells. Extracts of *A.blazei* showing anti-leukemic effects were studied using tritiated thymidine cancer assays in vitro. The potent extracts were further investigated in human promyelocytic leukemia cells (Akiyama et al., 2011).

Studies including ELISA and DNA fragmentation assays showed that the fraction played a key role in inducing apoptosis of NB-4 cells (C.-F. Kim et al., 2009). Other species of the *Agaricus* genus were also found to exhibit anti-tumorigenic properties. *Agaricus polytricha* protein (APP) and *Agaricus bisporus* lectin are strong immunogenic stimulants used as pharmaceuticals and health foods. In vitro studies suggests that the extract of *A.bisporus* decreased the aromatic activity, thereby preventing breast cancer cell growth (H.-H. Chang et al., 2007). The major component of *A.bisporus* is conjugated linolenic acid, and it is tested for its efficiency on prostate cancer cells both in vivo and in vivo and showed a decrease in proliferation rate after treatment with mushroom extract (Adams et al., 2008) (Patel & Goyal, 2012).

4.2. Genus *Phellinus*

The genus *Phellinus* belongs to the family of Hymenochaetaceae. One of the important species in the genus *Phellinus* exhibiting anti-tumorigenic compounds is *Phellinus linteus*. *P.linteus* extract possesses a substance called β -glycan (1 \rightarrow 3), which has shown to be a potent immunomodulator with anti-metastasizing and antimutagenic properties (Baker et al., 2008). The extract plays a vital role in cancer prevention by inducing glutathione S-transferase and NAD(P)H: quinone oxidoreductase activities. Hispolon, a polyphenolic compound isolated from *P.linteus*, has played a vital role in inducing apoptosis in bladder and breast cancer cells (Lu et al., 2009). (G. Li et al., 2004) (S.-H. Kim et al., 2004) stated that *P.linteus* contains a protein-bound polysaccharide that ceases the G2/M phase and induces apoptosis in human colon cancer cells. Methanolic extract of *P.linteus* and its fractions, including ethyl acetate, n-butanol, methylene chloride, are potent with their anti-angiogenic effects observed with the inhibition of human umbilical vein endothelial cells proliferation, assembly into capillary-like structures, and in vivo angiogenesis (Y. S. Lee et al., 2010). (Huang et al., 2011) demonstrated the anti-cancer effects of *P.linteus* mycelial

cultures and depicted its mechanism. The mice were transplanted with human hepatoma (Hep3) cells and administered the mycelial culture extract for 8 weeks. A remarkable decrease in tumor growth and size was observed with an increase in T-cell population, phagocytic ability, and NK cell activity, increasing the secretion of IL-12, TNF- α , and IFN- γ . Further, this increased the macrophages and dendritic cells in the spleen and increased CD4⁺ cells. (Y.-G. Li et al., 2011) extracted and purified a heavily glycosylated protein, proteoglycan, from *P.linteus* and tested its possible anti-cancer effects on tumors and their mechanism. Assays suggested the antiproliferative effect of proteoglycans on human colon adenocarcinoma (HT-29), human hepatocellular liver carcinoma (HepG2), human breast adenocarcinoma (MCF-7), and human lung cancer (NCIH-460) cells. Mice bearing HT-29 cells were administered with 100 mg/kg of proteoglycan and observed a significant increase in the size of the thymus and spleen, the levels of IgA and plasmatic immunoglobulin receptor pIgR. ELISA studies showed a noteworthy reduction in protein kinase B, epidermal growth factor receptor, plasmatic prostaglandin E2 (PGE2), Reg IV (regenerating islet-derived protein 4) protein numbers. The proteoglycan helps as an immunopotentiator by defending T-cells from PGE2 attack and improving IgA secretion.

(Song et al., 2008) elucidated the anti-tumorigenic effects of *Phellinus igniarius*. The ethanolic extract of *P.igniarius* was made from its fruiting body and studied for its antiproliferative and antimetastatic properties. Rat heart vascular endothelial cells (RHE) and human hepatocarcinoma (SK-Hep-1) cells were administered with the extract dose-dependent. Proliferation was inhibited at IC₅₀ values of 103 and 72 μ g/mL for RHE cells and SK-Hep-1 cells, respectively. The extract at a 25 or 50 μ g/mL concentration combined with 5-fluorouracil or oxaliplatin showed synergistic decreased the proliferation of SK-Hep-1 cells. These pieces of evidence have proven the potential that ethanol extracts of *P.igniarius* can be used as an adjuvant for chemotherapy.

4.3. Genus *Pleurotus*

Pleurotus ostreatus extract rich in aqueous polysaccharide compound called pleura and evaluated for its proapoptotic and antiproliferative effects on HT-29 colon cancer cells (Lavi et al., 2006). Another novel water-soluble polysaccharide (POPS-1) was extracted from *P. ostreatus* fruiting bodies by Sepharose CL-6B gel filtration chromatography and DEAE-cellulose ion-exchange chromatography. Assays such as cytotoxicity assays suggested higher anti-tumor activity of POPS-1 against HeLa tumor cells and lower anti-tumor activity against human embryo kidney 293T cells in a dose-dependent manner but significantly higher than the anti-cancer drug 5-fluorouracil in vitro. This resulted in considering POPS-1 as a potent anti-tumorigenic agent with low toxicity (Tong et al., 2009).

(Wong et al., 2007) extracted and purified water-soluble polysaccharides from the mycelium and fruiting bodies of a novel edible mushroom *Pleurotus tuber-regium*. The extract obtained from the fruiting body expressed higher cytotoxicity (IC₅₀ of 25 µg/mL) and showed a productive antiproliferative effect (200 µg/mL) against HL-60 cells. Either of the extracts caused a notable increase in the ratio of Bax/Bcl-2 and could induce apoptosis in HL-60 cells. Flow cytometric and western blot analysis revealed that mycelium extract ceased the G2/M phase in HL-60 cells by reducing the expression of Cdk1 proteins. The fruiting body extract ceased the S phase of the HL-60 cells with a rise in cyclin E expression and depletion of Cdk2 proteins.

(Y. R. Li et al., 2008) extracted and purified a homodimeric lectin (32.4 kDa) from *Pleurotus citrinopileatus* fresh fruiting bodies. The lectins had shown 80% of inhibition against mice with sarcoma 180 when the mice were administered at 5 mg/kg for 20 days intraperitoneally.

4.4. *Hericium erinaceus*

Hericium erinaceus, commonly called Lions mane, has increased the attention of researchers with its immunomodulatory and anti-tumor effects. (J. S. Lee & Hong, 2010) elucidated the anti-tumorigenic activity of *H.erinaceus*. The extract of *H.erinaceus* increases the sensitivity of the cell towards doxorubicin (Dox)-mediated apoptosis by reducing the expression of c-FLIP protein via activation of JNK and accumulation of intracellular Dox.

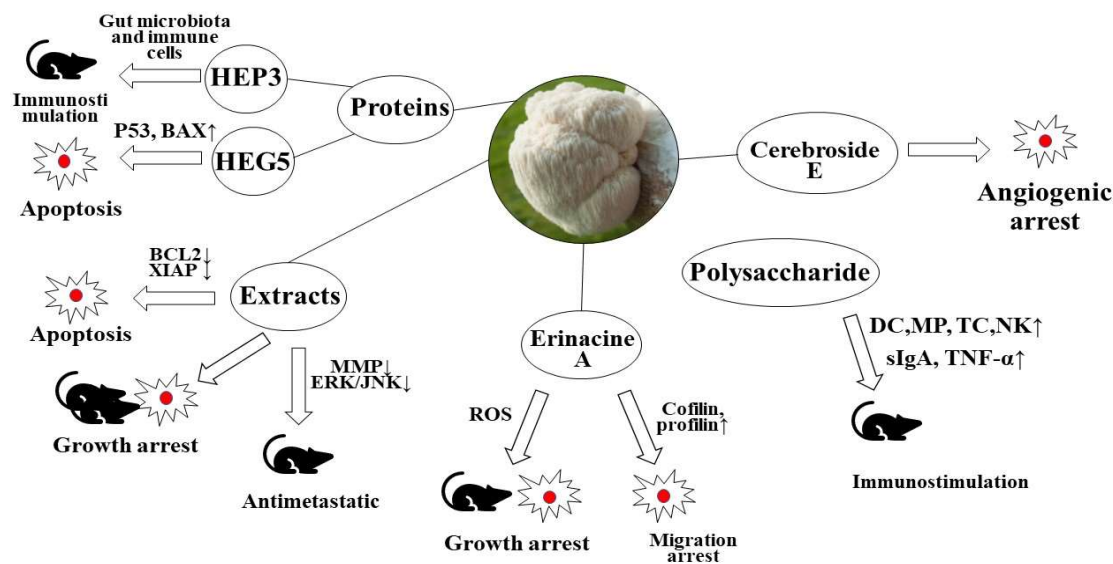


Figure 2: The anti-cancer properties of *Hericium erinaceus*

(S. P. Kim et al., 2011) demonstrated the effects of the extract in Balb/c mice transplanted with CT-26 colon cancer cells. Hot-water acquired by microwaving and boiling is rich in β -glucan showed a remarkable decrease in tumor weights 41 and 38%, respectively, when the extract was injected daily for two weeks. Tumor regressions were accompanied by an increase in tumor necrosis factors and natural killer cells. Significant reduction in expression of pro-angiogenic factors such as cyclooxygenase (COX-2), vascular

endothelial growth factor (VEGF), and 5-lipoxygenase (5-LOX) by tumor genes was observed. Following the reduction of 5-LOX and COX-2, inhibition of neo-angiogenesis was also noticed inside the tumors. The important events in reducing tumor size are macrophages' activation, triggering NK activity, and inhibition of angiogenesis.

4.5. *Flammulina velutipes*

Flammulina velutipes belongs to the family of Physalacriaceae, which is commonly known as velvet shank, velvet foot, winter mushroom, seafood mushroom, and many more. *F.velutipes* consists of a fungal immunomodulating protein (FIP-fve) is a potent activator of T-lymphocytes. FIP-fve had shown an anti-tumor effect when mice with hepatoma were orally administered with it (H.-H. Chang et al., 2010). Flammulin is an anti-tumor compound extracted and purified from fruiting bodies of *F.velutipes*. Another stable compound extracted from the fruiting body of this species is hemagglutinin which has shown to be antiproliferative against leukemia L1210 cells (Ng et al., 2006). Hot-water extracts of *F.velutipes* were shown to be potent anti-breast-cancer compounds. The estrogen receptors of breast cancer cells such as ER-(MDA-MB-231) and ER+ (MCF-7) were significantly inhibited. Further, the extract also played a vital role in inducing rapid apoptosis on various cancer types (Gu & Leonard, 2006).

4.6. *Lentinula edodes*

Lentinula edodes, commonly known as Shiitake mushrooms, possess a compound of lentinan origin with anti-cancer effects that could suppress the proliferation of leukemic cells. Ethanolic extract of the mushroom notably reduced the proliferation of CH72 tumor cells, but it could not generate a proliferative response of the non-tumorigenic keratinocytes (C50). Cell cycle analytical assays suggested that *L.edodes* extract caused the arrest of the transient G₁ phase (Gu & Belury, 2005) (Patel & Goyal, 2012).

4.7. *Grifola frondosa*

Grifola frondosa, commonly known as Maitake or dancing mushrooms, is an important mushroom species in showing anti-cancer effects. The extract of *G. frondosa* is abundant in β -glucan and was found to be working synergistically along with cisplatin, besides increasing its efficacy (Masuda et al., 2009). Mycelia of *G. frondosa* consists of a water-insoluble sulfated polysaccharide (S-GAP-P). Investigations have revealed that S-GAP-P worked effectively as an anti-tumorigenic agent against human gastric carcinoma (SGC-7901) alone and combined with 5-fluorouracil. S-GAP-P alone inhibited the growth of SGC-7901 and induced apoptosis in a dose-dependent manner. Significant tumor growth inhibition was observed when 5-FU of 1 $\mu\text{g/mL}$ and S-GAP-P of 10-50 $\mu\text{g/mL}$ were combined against SGC-7901 tumor cells. The evidence suggests that S-GAP-P can induce apoptosis and remarkably enhance the efficacy of 5-FU (Shi et al., 2007). A novel peptide-polysaccharide GFPPS1b was extracted and purified from the mycelia of *G. frondosa*. The extract of GFPPS1b expressed anti-proliferation and anti-tumor activities against human gastric adenocarcinoma (SGC-7901). The cells had undergone apoptosis followed by the events such as chromatin condensation, loss of villus, the emergence of apoptotic bodies. Data from annexin V-PI assay and flow cytometric analysis showed that GFPPS1b arrested the G₂/M phase of SGC-7901 cells (Cui et al., 2007).

4.8. *Calvatia utriformis*

Handkea utriformis or *Calvatia utriformis*, which belongs to the Lycoperdaceae family, commonly called puffball mushroom, has potent anti-oncogenic properties. A ubiquitin-like peptide extracted from the fruiting bodies of *C. utriformis* had shown excessive antiproliferative effect against breast cancer cells. (Ng et al., 2003) identified and purified a novel protein called calcaelin from *Calvatia caelata*, a potent ribosome inactivator with

anti-mitogenic and translation-inhibiting activities. A reduction in the viability of the breast cancer cells when treated with calcaelin (Patel & Goyal, 2012).

4.9. Genus *Clitocybe*

The genus *Clitocybe* belongs to the family of Tricholmataceae have shown anti-tumorigenic properties. *Clitocybe nebularis* consists of a ricin B-like lectin superfamily, an immunomodulatory protein (CNL) with antiproliferative properties. The lectin gets elicited in response to the carbohydrate receptors present over the surface of human leukemic T cells. CNL protein also has a vital application in treating hematopoietic malignancies (Pohleven et al., 2009). *Clitocybe maximus* possess an enzyme called laccase, exhibiting antiproliferative properties against MCF-7 and Hep G2 tumor cells (G.-Q. Zhang et al., 2010). The ethanolic extract of *Clitocybe alexandri* has a potent substance inhibiting the growth of colon, lung, breast, and gastric cell lines (Vaz et al., 2010). Human lung cancer cells (NCI-H460) have shown much sensitivity towards the ethanolic extract. The extract caused the cessation of the S-phase of the cell cycle, increased the levels of p53 and percentage of apoptotic cells. Synergistic use of the extract and cinnamic acid was the most successful combination in inhibiting tumor growth.

4.10. *Boletus badius*

Boletus badius or *Xerocomus badius* is a mushroom species extensively produced using submerged fermentation, consists of an anti-tumor agent called Theanine (γ -glutamyl ethyl amide) (J. Li et al., 2008). L-theanine is an analog of L-glutamate, and L-glutamine can work efficiently in combination with other anti-cancerous drugs such as cisplatin, doxorubicin, anthracyclines, irinotecan (Patel & Goyal, 2012). With the demonstration of fewer experiments, L-theanine has modulated effect on anti-cancer drugs with minimal health complications in cancer chemotherapy.

4.11. *Coprinus comatus*

Coprinus comatus, commonly known as shaggy ink cap mushroom, belongs to the family of Agaricomycetidae was tested for its anti-oncogenic properties. The ethyl acetate extract targeted the I α B α phosphorylation when the mushroom extract of IC₅₀ value 32 μ g/mL was administered. The effect of ethyl acetate was compared simultaneously with the effect of a known NF- κ B pathway inhibitor, curcumin. Besides, the ethyl acetate extract slowed down the IKK complex activity by 90% compared to the untreated sample. The results demonstrated that the extract could effectively treat malignant estrogen-independent breast cancer (Asatiani et al., 2011). (Zaidman et al., 2008) elucidated the effect of ethyl acetate and ethanol extract on prostate cancer cell growth (LNCaP). The extract was found to inhibit the cell viability of dihydrotestosterone-induced tumor growth, thereby arresting the G₁ phase. These pieces of evidence suggested the possible mechanism of action could be via androgen receptor or non-androgen receptor-mediated.

4.12. Genus *Russula*

Russula cyanoxantha produces a bioactive steroid called Ergosta-4,6,8(14),22-tetraen-3-one (ergone) has shown antiproliferative and cytotoxic activities against HepG2 cells. (Zhao et al., 2011) revealed the molecular mechanisms of the cytotoxic activity of ergone. Typical markers of apoptosis were observed when HepG2 cells were treated with ergone: a) nuclear fragmentation, b) G₂/M cell cycle arrest, c) phosphatidyl-serine exposure, d) chromatin condensation. Furthermore, other apoptotic events such as downregulation of Bcl-2 and up-regulation of Bax; PARP-cleavage; activation of 3,8,9 caspases were observed. These results further increased the attention of using medicinal mushrooms in cancer therapy. *Russula lepida* possesses a compound of lectin derivative shown antiproliferative activity against MCF-7 cells and HepG2 cells with an IC₅₀ value of 0.9

μM and $1.6 \mu\text{M}$, respectively. The lectin of 5.0 mg/kg was injected intraperitoneal daily for 20 days, shown up reductions of 67.6% in the weights of S-180 tumors (G. Zhang et al., 2010).

4.13. *Lactarius flavidulus*

Lactarius flavidulus, widely known as Japanese mushrooms, has anti-oncogenic properties, especially in its mycelial culture. The mushroom consists of a polysaccharide that inhibited the growth of white mice bearing sarcoma 180 by 100% when the extract was administered 300 mg/kg intraperitoneally. (Wu et al., 2011) extracted a dimeric lectin (29.8 kDa) from the fruit bodies of *L. flavidulus*. The lectin extract reduced the proliferation rate of L1210 cells and HepG2 cells with an IC_{50} of $6.81 \mu\text{M}$ and $8.90 \mu\text{M}$, respectively (Patel & Goyal, 2012).

4.14. *Schizophyllum commune*.

Schizophyllum commune belongs to the family of Schizophyllaceae, and it is commonly known as split-gill mushroom. It consists of a water-soluble, non-ionic homopolysaccharide called Schizophyllan with linear chain including $\beta\text{-D-(1-6)}$ -glucopyranosyl groups and $\beta\text{-D-(1-3)}$ - glucopyranosyl groups. Schizophyllan is a potent antineoplastic and immunomodulatory agent and has grabbed the pharmaceutical industry's attention recently (Kumari et al., 2008).

4.15. *Cordyceps militaris*

Cordyceps militaris belongs to the family of Cordycipitaceae contains a bioactive compound called CMP18. (Rao et al., 2010) extracted and purified CMP18 witnessed the inhibition of $\text{TNF-}\alpha$, nitric oxide secretion from $\text{INF-}\gamma$ /LPS-stimulated macrophages. It has shown a significant antiproliferative effect on the colon (205), prostate (PC-3), hepatoma

(HepG2) cancer cells. (Kim et al., 2010) elucidated the effect of a polysaccharide from *C.militaris* called Cordlan on dendritic cell maturation. Cordlan stimulates the phenotypic maturation of dendritic cells confirmed with the elevation of CD86, CD40, CD80, MHC-I, MHC-II molecules. Besides, cordlan enhanced the phosphorylation of p38, JNK, ERK, and nuclear translocation of NF- κ B p65/50, which were observed as vital molecules downstream of TLR-4. The important barrier in the success of cancer immunotherapy is the defect of inducing dendritic cell maturation in tumor cell microenvironments. *C.militaris* extract elevated the levels of IL-18 transcription by enhancing the activity of the P1 promoter region in mice liver and brain, thereby stimulating the INF- γ secretion in leukemic mouse monocyte cell line (C. S. Kim et al., 2008). NCI-H406 cell-transplanted nude mice were administered aqueous extract for 4 weeks. There was a significant reduction in tumor size, and the extract prolonged the lifespan of mice, indicating the anti-cancer effects of *C.militaris* in nude mice (Park et al., 2009). Cordycepin, an adenosine nucleoside derivative from *C.militaris*, effectively inhibited the growth of human leukemic cells in a dose-dependent manner by stimulating apoptosis. The stimulation was associated with activation of caspases, mitochondrial dysfunction, cleavage of polymerase protein, and production of reactive oxygen species. Cordycepin initiates apoptosis through a signaling cascade pathway along with ROS-mediated caspase pathway (Jeong et al., 2011).

5. Conclusion and Future perspectives

Mushrooms are a few things set to create a revolution in their usage, research, and therapeutic agent for various cancers. Mycologists across the globe firmly trust that mushrooms could be a breakthrough in curing various forms of cancers. Over the past 50 years, the interest in focusing on medicinal mushrooms increased exponentially. Many areas of the mushrooms as a useful source for producing beneficial products are neglected.

One such area is their oncogenic properties. 80% of fungal species have not been analyzed for their anti-tumor and antibiotic activity. Primarily, a tumor has many vulnerable spots and can be focused at various levels, viz., regulation of apoptosis, angiogenesis, tumor-specific proliferation signaling, metastasis, and modulation of the immune system. The eccentricity of the mushroom is a mass producer of various kinds of compounds and can be potentially used for cancer treatment either in a synergistic way or in combination with existing cancer drugs minimizing the harmful side effects. So, mushrooms can be the next biggest thing in oncology with their ubiquity in nature and abundance in producing a plethora of bioactive compounds. The use of mushroom extract as a sole therapeutic agent is also a key area to focus on and research.

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