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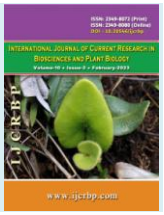

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Types of mushrooms and their bioactive constituents used in the treatment of cancer: A review

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Abstract

Mushrooms have been a culinary and folk medicine since ancient times. Recently overwhelming interest in pharmaceutical potential of mushrooms have been witnessed. One of the main reasons being the properties of mushroom such as immunomodulatory, anti-oxidant, anti-diabetic, anti-tumor, anti-cancer, anti-allergic, nephroprotective, and anti-microbial gents. The anti-cancer compounds present in medicinal mushrooms leads to apoptosis, and eventually inhibiting cancer cells proliferation. The review undertaken explores the types of medicinal mushrooms and active compounds where, clinical trials undertaken shows a good prospect in cancer treating properties such as anti-tumour potential and biological role. Study on the mechanism of compounds such as polysaccharides need to be carried out at an extensive level, additional clinical studies and further research should look at the preventive benefits of medicinal mushrooms in lowering the incidence of cancer by incorporating them into a healthy diet.

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Introduction

Originally used as food because of their distinct flavour, mushrooms were subsequently discovered to have medicinal benefits (Lucas, 1957). Since time memorial, mushrooms as a primary source of nutrients, full of vitamins, minerals such as selenium, ergothioneine, copper, potassium, beta-glucan, and antioxidants that promote and protect good health**.** Mycotherapy /Myotherapy is the practice of treating various illnesses and disorders by using extracts or chemicals from medicinal mushrooms which possess anti-carcinogens, chemicals extracted from mushrooms. Therefore, it is vital to grasp the underlying mechanisms of action of the anti-cancer chemicals, understanding the molecular pathways where underlying cancer formation and progression occurs as well as the molecular targets of mushroom-derived bioactive chemicals is crucial for improving the therapeutic success rates against cancer (Saroja, 2019). It is known that certain edible mushrooms are excellent providers of anti-cancer agents against many malignancies **(**Lucas, 1957). By reducing the negative effects of cancer treatment, such as nausea, bone marrow suppression, anaemia, and decreased resistance, mushrooms are known to support chemotherapy and radiation therapy. Genera *Phellinus, Pleurotus, Agaricus, Ganoderma, Clitocybe, Antrodia, Trametes, Cordyceps, Xerocomus, Schizophyllum, Flammulina, Suillus, Inonotus, Inocybe, Funlia, Lactarius, Albatrellus, Russula,* and *Fomes* are

responsible for the success against cancer claims (Seema Patel and Arun Goyal,2012). There are about 14,000 species of mushrooms out of which 700 species are reported to be medicinal in nature (Han et al., 1999).

Types of mushrooms used for cancer treatments

Several prized and edible mushrooms, including oyster, button, shiitake, etc., with potent anti-cancer effects and their active ingredients are being researched for anti-diabetic, anti-inflammatory, and anti-cancer properties, in the genera *Agaricus, Pleurotus, Flammulina, Ganoderma, Polyporus, Tricholoma, Lentinula,* and *Poria*, among others, have a great deal of potential for the treatment of cancer. *Reishi, cordyceps, Agaricus, maiitake, phellinus, trametes, shiitake, and hericum* are a few mushrooms that each have a unique anti-cancer effect on tumors. Shiitake mushrooms were shown to have an anti-cancer effect by the Chinese physician Wu RI, also known as Wu Shui, who lived during the "Ming Dynasty" (1368–1644 CE) (Saroja Preethy, 2019). The fact that both edible and medicinal mushrooms are used to cure a variety of infections in many cultures around the world highlights their significant contribution to human health and welfare and should not be disregarded (María et al., 2015). Various clinical trials were conducted to study the effectiveness of medicinal mushrooms. Lucas et al. (1957) used extracts of *Boletus edulis* and other mushrooms against Sarcoma-180 and also on HeLa cell lines, exhibiting considerable growth inhibition on these types of cancer. This was the first time that mushroom extract as anti-cancer activity had been demonstrated (John et al., 2022). Some of the most well-studied medicinal mushrooms have been proven to have anti-cancer effects which includes Shiitaki mushroom and Turkey tail. Though extensive research is needed these mushrooms could have effective supplementary therapy for cancer patients (Dan et al., 2023).

Clinical trials for various cancer treatments

Patients who underwent six cycles of chemotherapy with *Agaricus sylvaticus* experienced less loss of appetite over time, while those in the placebo group suffered from diarrhoea, vomiting, and nausea (Swapan Kumar Ghosh et at., 2018). *Agaricus blazei* Merrill significantly improved the immunological condition of multiple myeloma patients by preserving the population of white blood cells and immunoglobins and reducing infections (Wasser and Weis, 1999). Consuming *Agaricales* mushrooms and other therapeutic fungi as dietary supplements can assist breast cancer patients by having antiproliferative and immunomodulatory effects on tumour cells (Tangen et al., 2015). Comparing rats given oral doses of *Agaricus blazei* extract to water-treated controls, Takimoto found that rats receiving oral doses of *Agaricus blazei* extract displayed increased cytotoxic T lymphocyte development, increased levels of interferon-gamma, and an increase in natural killer cells. (Gennari et al., 2001). Consuming *Agaricus bisporus* with tea reduces breast cancer risk, and eating mushrooms has the opposite effect on breast cancer incidence in premenopausal women (Dolby, 1997). *Calocybe indica* known as, milky mushroom has ethanolic, methanolic, and aqueous extracts that have anti-cancer effects by inhibiting the growth of breast cancer (Shin et al., 2010). *Agaricus bisporus* extracts have been found to reduces oestrogen production by inhibiting the activity of aromatase, a key factor in postmenopausal breast cancer in women (Ghosh, 2015). *Phellinus linteus* extract has antimutagenic properties and can prevent cancer by activating glutathione S-transferase and NAD(P)H: quinone oxidoreductase. Hispolon, a phenolic substance isolated from this mushroom, may be able to cause breast and bladder cancer cells to undergo apoptosis (Maria et al., 2011).

Lentinula edodes without causing hematotoxicity or hepatotoxicity, dramatically increased cancer patients' quality of life scores and decreased herpes virus levels in their saliva during chemotherapy (Liu et al., 2009). *Lentinula edodes* benefits patients with advanced gastric cancer. Consumption of white buttom mushrooms seemed to be indirectly linked to the development of epithelial ovarian cancer in a case-control study with 500 ovarian cancer patients (Ito et al., 2014). Shiitake mushroom, *Lentinus edodes*, produces lentinan, a glucan. Lentinan's ability to inhibit the growth of both human and animal carcinomas has been extensively studied. It was initially discovered and investigated by Chihara et al., who found that it had stronger anti-cancer effects than other mushroom polysaccharides (Lee et al., 2015). *Lentinula edodes* has undergone multiple clinical trials in Japan, and several pharmaceutical companies now produce and market the medication. *Lentinula edodes* has been effective particularly with gastric and colorectal carcinomas (Chihara et al., 1970; Furue and Kitoh., 1981; Taguchi et al., 1985). *Lentinula edodes* along with chemotherapy by Yamaguchi et al. was found to be safe, improving the Quality of Life of patients with gastrointestinal and breast cancer (Taguchi

et al., 1985). However, research using *Lentinus edodes* extract by DeVere White et al., and Sumiyoshi *et al.*, failed to find any appreciable effects on prostate cancer (Yamaguchi et al., 2011; Sumiyoshi et al., 2010). Shiitake mushroom *Lentinula edodes* produced lentinan, a b-glucan known to inhibit leukaemia cells (DeVere White et al., 2002).

Agaricus bisporus extract can suppressed cell proliferation in breast cancer. The broth fraction of *Agaricus blazei* inhibited cell proliferation studied for the growth of human prostate cancer cell lines that were both androgen-dependent and androgen-independent. *Inonotus obliquus*, known as the chaga mushroom, has long been utilised in Russia and the majority of the Baltic States to treat a variety of malignancies. *Inonotus obliquus* hot-water and ethanol extract has the capacity to cause apoptosis in human colon cancer cells by preventing tissue damage brought by reactive oxygen species. Ethanolic extract of *Clitocybe alexandri*, Lung, breast, colon, and gastric cancer cell lines were found to be greatly inhibited in proliferation. The human lung cancer cells were significantly resistant to the ethanolic extract. Human oestrogen-non-responsive breast cancer cells have been reported to be more susceptible to cell cycle arrest and death when exposed to the fermented culture broth of *Antrodia camphorate* (Gu et al., 2005).

Agaricus blazeii caused improvements in body strength and mood indices when compared to controls. In addition, adverse symptoms such alopecia, emotional instability, and general weakness were less common in individuals who took mushrooms. At 3 and 6 weeks, the treated group's natural killer cell activity was much higher than that of the placebo group, with no discernible difference in white blood cells, monocytes, lymphocytes, T cells (Twardowski et al., 2015). Hsu et al. (2007) found that in human liver cancer cell line, an ethyl acetate extract from *Antrodia cinnamomea* fruiting bodies has anti-invasive properties (Ahn et al., 2004). The Korean wild mushroom *Polyozellus multiplex* in stomach increased expression of proteins, controls cell proliferation (Hsu et al., 2007). *Hericium erinaceus* known as Lions mane, received a lot of attention due to its anti-tumour and immunomodulatory effects. It was determined that the mechanism of tumour size reduction involves the induction of natural killer cells activity, activation of macrophages, and prevention of angiogenesis (Wang et al., 2004). *Ganoderma lucidum* may be used as an alternative adjuvant to traditional therapy because of its potential to improve tumour response and stimulate host immunity, according to a Cochrane evaluation (Hu et al., 2009).

Highly invasive human breast and prostate cancer cells may be susceptible to the effects of *Ganoderma lucidum*, which shows decrease cell motility, hinder cell proliferation, induce apoptosis, and suppress angiogenesis (Vaz et al., 2010; Srivani Sridhar, 2014). *In vitro* growth of colorectal cancer cells can also be inhibited by extracts of *G. lucidum* and *G. tsugae* (Stanley et al., 2005).The biological activities of *Ganoderma lucidum*, on the other hand, include activating T cells and inflammatory response, anti-cancer and immunomodulatory capabilities(Hu et al., 2002; Hsu et al., 2008; Chen et al., 2004).

Pleurotus tuber-regium and *Polyporus rhinoceros* Extracts have antitumor effects by enhancing lymphocyte and NK cell maturation, increasing macrophage proliferation, T helper cells etc. These effects are accompanied by an increase in spleen weight and size, which is attributed to the presence of more monocytes and granulocytes among other immune cells (Chien et al., 2004; Wang et al., 1997; Wong et al., 2011; Lai et al., 2005).

In cervical cancer patients (stage II or III, n = 228), Okamura et al (Zhang et al., 2004) investigated the effects of polysaccharides from *Schizophyllum commune* while tracking a number of variables, including tumour response, time to recurrence, survival, immunologic parameters, and side effects. It lengthened stage II patients' life times, though they were unable to detect any considerable change in the survival rate of patients with stage III cancer (Haradaet al., 2005). According to Eliza et al., (Gao et al., 2003) chemotherapy for breast, colorectal, and gastric cancer patients who received treatment with *C. versicolor* decreased 5-year mortality of cancer patients by up to 9% (Eliza et al., 2012) *Maitake* powder, 3 mg/kg twice daily for 12 weeks, on blood cancer patients was tested in a phase II trial and found to have positive immunomodulatory potential in myelodysplastic syndromes (MDS) (Yamaguchi et al., 2011).

Compounds observed in mushrooms

It has been shown that mushrooms contain substances that can hinder the growth of microorganisms, particularly secondary metabolites such as terpenes, quinolones, steroids, derivatives of benzoic acid, and

anthraquinones. Mushroom also make up significant amounts of primary metabolites such as oxalic acid, peptides, and proteins (Yamaguchi et al., 2011). It has been discovered that the immune adjuvant beta-glucan from medicinal mushrooms stimulates both innate and adaptive immune responses (Mwangi et al., 2022). The most significant anti-cancer components in mushrooms are fungus-derived-glucans, which include lentinan, grifolan, polysaccharide peptides, glycan, proteoglycans, triterpenes, triterpenoids, and flavonoids. Clinical investigations have demonstrated that the active ingredients or extracts from medicinal mushrooms are most effective when used in conjunction with radiotherapy, chemotherapy, and surgery. In fact, invasive treatments and tolerance are substantially improved when medicinal mushrooms are added to conventional treatments (Seema and Arun, 2012). Bioactive chemicals produced from mushrooms activate or regulate the immune system by influencing immune cell development, differentiation and proliferation and hence limiting cancer cell metastasis and growth (Park, 2022). The synergistic action is indicated by the activity observed with the combination of chemicals present in edible fungi (Pineda et al., 2020)

Compounds extracted for the treatment of cancer

Agaricus blazei polysaccharide extracts demonstrated potent *in vivo* and *in vitro* anti-cancer activity against various cancer cell lines, specifically lung and ovarian cancer (Park, 2022). A glucose polymer called b-glucan is found in therapeutic mushrooms. By the stimulation of natural killer cells, neutrophils, monocytes, macrophages, and T-cells, it demonstrates immunomodulatory effects as well as tumoricidal and antiproliferative properties in cancer patients. Inhibition of aromatase at the oestrogen receptor by an *Agaricus bisporus* extract *in vitro* cells, rat ovarian cells, and in vivo in rats. The extract reduced cell division. By changing or mutating the active sites, the linoleic and linolenic acid in the extract inhibited aromatase activity (Saroja Preethy, 2019). Mushroom have beneficial effects on immunological control and anti-cancer activities. By attaching to pathogen recognition receptors, chemicals produced from mushrooms stimulate immune cells to cause either cell-mediated or direct cytotoxicity in cancer cells (Maria et al., 2011). The proliferation of cytotoxic T cells and macrophages is increased by substances like lentinan, which also causes non-specific immunological reactions (Menezes, 2011). In *Phillinus linteus* proteoglycan showed Antiproliferative activity in humans significantly (Nowakowskiet al., 2021).

The most well-known and effective mushroom-derived compounds with anti-tumour and immunomodulating activities are polysaccharides (Park,2022). Instead of directly attacking cancer cells, the polysaccharides work to suppress tumour growth by triggering the immune system's NK, T, and other cells in the host (Wasser and Weis,1999). Mushroom polysaccharides are recognized as "biological response modifiers" substances that stimulate the immune system (Seema and Arun,2012). Mycomedicinals, or medicinal mushrooms, and products made from polysaccharides have been investigated as adjuvants and immune modulators in the treatment of cancer (Wasser,2002). Krestin, Lentinan, and Sonifilan are three polysaccharide-based carcinostatic. Immunotherapeutic drugs created from mushrooms. These are used to treat cancers of the digestive system, the lung, the breast, the stomach, and cervical cancer, respectively (Saroja,2014).

The polysaccharide known as schizophyllan obtained from *Schizophyllum commune* has demonstrated to improve overall survival in people with head and neck cancer (Srivani Sridhar,2014).The protein-bound polysaccharide from the turkey tail mushroom (*Trametes versicolor*) is effective in treating chronic hepatitis and hepatitis B, and prevention of liver cancer (Daba and Ezeronye, 2003; Kimura et al.,1994; Wang, 1989; Lin and Huang,1987).Polysaccharides from mushrooms have also been employed as immunoceuticals that work well for immunotherapy when ingested orally. Lentinan, Schizophyllan, Active Hexose Correlated Compounds, Maitake D-fraction, Polysaccharide-K, and Polysaccharide-P are six of these polysaccharides that have been studied in human cancers (Mizoguchi et al.,1987). Lentinan, Krestine, Hispolon, Lectin, Calcaelin, Illudin S, Psilocybin, Hericium Polysaccharide A and B, Ganoderic Acid, Schizophyllan, Laccase, etc. are the active ingredients in mushrooms that provide anti-cancer potential (Stamets,2000).*Coriolus versicolor* tested on human hepatoma cancer cell line, the polysaccharide showed to inhibit the multiplication of cancer cells both *in vitro* and *in vivo* **(**Chihara et al.,1970).Many polysaccharides and polysaccharide conjugates have been commercialized, enabling patients to take advantage of this anti-cancer therapy (Seema et al.,2012).By examining the effect of mushroom polysaccharides' inhibitory effect on the viability of two human

melanoma cancer cells, the anti-cancer activity of these compounds was investigated (Cai et al.,2010).By scavenging free radicals, bioactive substances found in medicinal mushrooms, including ascorbic acid, organic acids, flavonoids, polysaccharides, glycosides, phenols, and tocopherols, are essential in preventing the growth of malignant cells (Swapan et al.,2018; Ren et al.,2014).

The bioactive extract that has been extensively researched as a supplement to standard radiation and chemotherapy is *maitake* D-fraction. It serves as a biologic response modulator, enhancing and activating the immune system in a way that is T-cell reliant, which has an improved antitumor effect. Maitake works best against liver, breast, and prostate cancer (Kozarski et al.,2015). Purified bioactive compounds from *Cordyceps militaris* extracts were discovered by Rao *et al*. (2010). These compounds showed growth inhibition on nitric oxide, tumour necrosis factor-a, and interleukin-12 production from LPS/IFN-c-stimulated macrophages, as well as an anti-proliferation effect against human cancer cells, including prostate, colon and hepatoma cells (Loria Kohen et al.,2014).A ubiquitin-like peptide extracted from *C. utriformis* fruit-bodies had strong anti-proliferative activity against breast cancer cells (Srivani,2014).From *C. utriformis*, isolated calcaelin, a novel ribosome-inactivating protein with anti-mitogenic and translation-inhibitory properties where breast cancer cells' viability was decrease (Rao et al.,2010).Flammulin, an anti-tumour compound, was purified from the aqueous extract of *F. velutipes* fruit bodies. This mushroom's fruiting bodies contain a stable hemagglutinin that prevents the growth of leukaemia cells (Lam et al.,2001). *F. velutipes* water-based extracts were found to be effective anti-breast cancer treatments. Breast cancer cells extraordinarily quick apoptosis when exposed to the extract. The level of cytotoxicity on breast cancer cells was quite high, but after treatment, the breast cancer cells were suppressed by almost 99% (Ng et al.,2003). Aqueous *Funlia trogii* mycelia extract exhibits strong anti-tumour toxicity against a variety of tumour cell lines (Ng et al.,2006). According to research by Chen et al. (2011), the intracellular polysaccharide of *Fomes fomentarius* and the ethanol extract of mycelial biomass both have significant roles in the treatment of stomach cancer. Both extracts have a dose-dependent anti-proliferative impact on the human gastric cancer cell (Guet al.,2006).

The fermented culture broth of *Antrodia camphorata* has been shown to promote cell cycle arrest and apoptosis of human estrogen-non-responsive breast cancer (Rashid et al.,2011). In pancreatic cancer cells, antroquinonol, a ubiquinone derivative isolated from *A. camphorata*, caused a concentration-dependent inhibition of cell proliferation (Chen et al.,2011). Both *in vitro* and *in vivo*, the polysaccharides and triterpenoids from *Ganoderma lucidum* are powerful tumour growth inhibitors (Yang et al.,2011).Popular nutraceutical *Ganoderma lucidum* spores have been utilised to increase quality of life and lessen fatigue brought on by breast cancer (Yu et al.,2011).The neutral polysaccharide fraction of a hot-water extraction of the edible fungus *Pleurotus ostreatus* yielded an anti-cancer glucan (Minet al.,2000).Polysaccharide derived from *Tricholoma* species that contains proteins has also been discovered to have potent anti-tumour activity (Zhao et al.,2012).

In Japan and other Asian nations, trade name Krestin is frequently used for cancer immunotherapy. Its anti-cancer impact is thought to be derived from its immunomodulating activity on the tumour-bearing host (Yoshioka et al.,1985). Individuals with advanced hepatocellular carcinoma and liver dysfunction who received Coriolus versicolor treatment had longer median overall survival and longer median progression-free survival than those who received placebo (Wang et al.,1995).

The ability of mushrooms to stimulate the immune system response, where beta-glucan, a water-soluble polysaccharide, activates immune cells and proteins and macrophages, Thymus cells, natural killer cells, and cytokines that attack tumour cells, is a significant and frequently reported protective mechanism exerted by mushrooms against cancer (Iguchi et al.,2001). By enhancing immune surveillance against cancer by involving monocytes, macrophages, natural killer cells, and B cells, secrete antitumor related cytokines and activate immune organs, getting rid of cancers, and strengthening the weakened immune system, consumption of mushroom compounds initiates innate and adaptive immunity (Chaet at al.,2017; Vetvicka et al.,2008).

More than 50 different types of mushrooms have produced potential immunoceuticals that have anti-cancer and immunomodulatory effects both *in vitro* and *in vivo* as well as in human tumours. Lectins, polysaccharides, polysaccharide-peptides, polysaccharide-protein complexes like lentinan,

schizophyllan, polysaccharide-K, polysaccharide-P, active hexose correlated compounds (AHCC), and Maitake D fraction are among them. These compounds are produced by a variety of mushroom which includes *Trametes robiniophila* Murill, *Coriolus versicolor*, *Lentinus edodes*, *Grifola frondosa*, and *Flammulina velutipes*. Other sources of these compounds include *Ganoderma lucidum*, *G. tsugae*, *Schizophyllum commune*, *Sparassis crispa*, *Pleurotus tuberregium*, *Polyporus Rhinoceros* (Goodridgeet al., 2009).

Conclusions

The beneficial effects of medicinal mushrooms, such as reduction in the side effects of conventional medicines, as well as anti-cancer activity and immunomodulation, have only been shown in a few clinical investigations of a small number of mushrooms. As a result, additional clinical studies on mushrooms with anti-cancer potential are required. Future research should look at the preventive benefits of medicinal mushrooms in lowering the incidence of cancer by including them into a healthy diet and way of life (Swapan et al.,2018). Mushroom bioactive substances have become effective nutraceuticals with significant medical benefit Using mushroom extracts as nutritional supplements over time strengthens the immune system and has anti-tumour effects (Seema and Arun,2012). More scientists and businesses are anticipated to work together in the near future to extract, isolate, and purify natural products from mushrooms in order to assess their anti-cancer capabilities, formulate medications, and commercialize them (Srivani,2014).

A better understanding of the molecular principles driving mushroom action can hasten the commercial manufacture of medicines for cancer treatment (Kaushik,2015). Mycomedicinals rarely cause side effects, but should be used with caution in patients with leukemia and lymphoma, after a bone marrow transplant, and on immunosuppressants due to the immune modulation function of mushrooms. The molecular weight, degree of branching, and higher structure of certain mushroom polysaccharides determines their anti-cancer efficacy (Panda et al., 2022). Therefore, study on the mechanism of how polysaccharides fight tumour should be carried out at an extensive level. Beyond being a component of a healthy diet, further research is essential to support mushrooms' potential significance in the treatment of cancer. Since more people utilise mushrooms as a co-medication, there is a need to investigate the efficacy and safety of mushroom.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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