# The Role of Medicinal Mushrooms in Brain Cancer Therapies: Review

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**ABSTRACT:** Medicinal mushrooms are considered an unlimited source of polysaccharides (mainly β-glucans) and polysaccharide-protein complexes and possess various immunological and anticancer properties. In addition, their use in integrative medicine leads to a clear reduction of side effects in patients undergoing chemotherapy or radiotherapy. The literature reports a number of beneficial effects of using mushrooms as health supplements in patients affected by high-grade glioma. The effects of medicinal mushrooms on side effects in patients with brain cancer and a case study report are also described in this review.

**KEY WORDS:** integrative therapies, brain cancer, glioblastoma, medicinal mushrooms, mycotherapeutic support

**ABBREVIATIONS: CAM**, complementary and alternative medicine; **CMV**, human cytomegalovirus; **CNS**, central nervous system; **CT**, computed tomography; **GBM**, glioblastoma multiforme; **GL-PS**, *Ganoderma lucidum* polysaccharide; **HPA**, hypothalamic pituitary adrenal; **IDH**, isocitrate dehydrogenase; **IL**, interleukin; **INF**, interferon; **iNOS**, inducible nitric oxide synthase; **NGF**, nerve growth factor; **NO**, nitric oxide; **TNF**, tumor necrosis factor; **VR**, vanilloid receptor

## I. INTRODUCTION

The incidence of central nervous system (CNS) cancers compared to other cancer types is low (< 6 cases per 100,000 inhabitants/year).[1] Because of their infrequency, many of these cancers fall within the RARECARE definition of cancers. The cancers are represented by gliomas (astrocytomas, glioblastomas, oligodendrogliomas, ependymomas), medulloblastomas, meningiomas, and other rarer cancers (hemangioblastomas, germinomas, neuronal cancers, choroid plexus carcinomas, and embryonal cancers). Among the primary cancers of the CNS, glioblastoma is the most frequent malignant cancer in adults.[2] In addition, the brain is a target organ of metastatic cells that originate from cancers in other organs such as the breast, skin, and lung.[3] Standard treatment consists of surgery followed by radiotherapy and chemotherapy and, more recently, the use of the NovoTTF-100A "helmet," which produces electric fields that interfere with the cellular replication of the cancer.[4]

Many authors consider it appropriate to develop innovative therapeutic strategies combined with non-conventional medicines in the treatment of brain cancer.[5] More than 30% of patients affected by primary brain cancer utilize complementary and alternative medicine (CAM).[6] In a clinical trial, 76% of patients analyzed utilized a complementary and integrative health modality including vitamin consumption, massage, spiritual healing, prayer, and meditation.[7] In addition, music and relaxation therapy, acupuncture, and hypnotherapy are helpful in reducing anxiety, pain, and nausea.[8] Recent studies in mice and humans demonstrated that brain cancer can be slowed down by metabolic management with calorie restriction and a ketogenic diet.[9] Modulated electrohyperthermia in integrative therapy may have a role in the treatment of

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relapsed glioblastoma and astrocytoma.[10] Many drugs and substances reported in the literature as anticancer agents are used in brain cancer treatment, including mushroom extracts, a relatively new supplementation for the fight against brain cancers.[11] On the basis of information reported in the literature and some unpublished data, this review aims to contribute to knowledge on the use of medicinal mushrooms in the prevention and treatment of brain cancer.

## II. MATERIALS AND METHODS

For this review, an extensive body of literature was consulted mainly oriented on *in vitro* and *in vivo* tests in laboratory animals but also on patients suffering from various forms of brain cancers. For the case study report, reference was made to the medical records of the Santa Chiara Hospital of Pisa and to the mycotherapeutic applications in oncology that derive from the practice within the same hospital and in the outpatient clinic of two of the authors (FB, MGF).

## III. RESULTS

### A. Analysis of Literature Data

Higher Basidiomycetes and Ascomycetes mushrooms have a wide spectrum of pharmacological properties such as antiallergic, antibacterial, antidepressive, antidiabetic, antifungal, antihyperlipidemic, anti-inflammatory, antioxidative, antiviral, cytotoxic, hepatoprotective, hypotensive, immunomodulatory, nephroprotective, neuroprotective, and osteoprotective activities.[12] In addition, their use in integrative medicine leads to a clear reduction of side effects in patients undergoing chemotherapy or radiotherapy.[13] The literature reports *in vitro* and *in vivo* experiments on the use of medicinal mushrooms against brain cancer. The bioactive extract, maitake D-fraction from *Grifola frondosa* (Dicks.) Gray, is recognized for its immunomodulatory and anticancer properties. Its major effects include amelioration of immunologic and hematologic parameters, inhibition or regression of cancer cell growth, and improvement of quality of life in patients with cancer.[14] Maitake D-fraction combined with maitake powder is effective against brain cancer and shows a synergistic effect with chemotherapy in human and animal tests. In particular, in the treatment of patients affected by astrocytoma, pain was reduced and various side effects such as appetite loss, vomiting, nausea, hair loss, and leukopenia were ameliorated.[15] The anticancer action and immune system influence of polysaccharides extracted from *Ganoderma lucidum* (Curtis) P. Karst. (GL-PS) was demonstrated in glioma-bearing rats, in which GL-PS inhibited glioma growth and increased rat survival. GL-PS increases the concentration of serum interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (INF)-γ and improves the cytotoxic activity of natural killer cells and T cells; GL-PS also stimulates the functional maturation of dendritic cells and plays a role in inhibiting cancer growth, thus prolonging survival time in glioma-bearing rats.[16] The recurring presence of human cytomegalovirus (CMV) proteins and nucleic acids in brain cancers in both adults (glioblastoma) and children (medulloblastoma) has been recorded.[17] The assumption of *G. lucidum* extracts as immune boosters can help to keep CMV under control. Such activity was also demonstrated for polysaccharide-K (polysaccharide-Kureha), also known as krestin, and polysaccharopeptide from *Trametes versicolor* (L.) Lloyd, which have an antiviral effect on human immunodeficiency virus and CMV *in vitro*.[18] Extracts of *Albatrellus ovinus* (Schaeff.) Kotl. & Pouzar containing the sesquiterpenoid Scutigeral have shown pain-relieving properties. Szallasi et al.[19] have shown that oral intake of this compound generates affinity with the D1 dopamine receptors of the brain by targeting vanilloid receptors (VRs; e.g., VR1). Albaconol, another compound isolated from *A. confluens* (Alb. & Schwein.) Kotl. & Pouzar, is also recognized as an antagonist to the VR1 receptor.[20,21] The role of VRs in the etiology of

neurogenic inflammation and pain transduction has been demonstrated but the results of clinical studies in humans are still awaited.

Cordycepin, or 3′-deoxyadenosine, is a derivative of the nucleoside adenosine, isolated from *Cordyceps militaris* (L.) Fr. (Ascomycetes) widely used as an anticancer treatment.[22] Cordycepin is metabolized rapidly *in vivo* and nanoencapsulation is a promising method to improve its bioavailability. Zhao et al.[23] demonstrated that micelles containing cordycepin and phycocyanin–dextran complex have a comparable or even stronger inhibitory effect against C6 brain cancer cells than do free cordycepin and free phycocyanin, without side effects. In addition, cordycepin inhibited migration of human glioblastoma cells by affecting lysosomal degradation and protein phosphatase activation.[24]

Chaicharoenaudomrung et al.[25] found that cordycepin inhibited brain cancer cell growth and induced apoptosis in a dose-dependent manner in both SH-SY5Y and U-251 cell lines. Failure of dendritic cell maturation in cancer microenvironments is an important immunological problem restraining the efficacy of cancer immunotherapy. In experiments carried out on mouse brain, *C. militaris* extracts expressively induced the IL-18 transcription level via enhancing the P1 promoter region and activating IFN-γ.[26]

Betulinic acid, a triterpenoid with antiretroviral, antimalarial, and anti-inflammatory properties that is isolated from *Betula pubescens* Ehrh. and other plants, was also found in *Inonotus obliquus* (Fr.) Pilát (chaga mushroom), a parasitic species that grows mainly on birch and has long been used as a functional food and traditional Chinese herb. The efficacy of betulinic acid against neuroblastoma, medulloblastoma, and malignant head cancer cells has been tested *in vitro*.[27,28] Inhibitory effects of a polysaccharide extract from *I. obliquus* against primary cancer cells cultured from patients affected by medulloblastoma and glioblastoma were reported by Fulda et al.[29] and Ning et al.[30]

Extracts of *Tropicoporus linteus* (Berk. & M.A. Curtis) L.W. Zhou & Y.C. Dai (=*Phellinus linteus*) induce apoptosis through oxidative stress by stimulating Csp-3 and Csp-9 in prostate cancer metastasized to the brain (DU-145) and brain cancer in human primary glioblastoma cell lines (U-87).[31]

Experimental studies suggest that schizophyllan (sonifilan), a neutral extracellular polysaccharide produced by *Schizophyllum commune* Fr., can inhibit the growth of rat CNS-1 glioma cells, while polyphenols and polysaccharides from mushroom extracts show *in vitro* cytotoxic effects on brain astrocytoma cancer cells.[32] Nanoparticles (25.49 nm in diameter) capable of crossing the blood-brain barrier and entrapping CpG ODN 1826 were prepared by using schizophyllan to demonstrate efficacy on rat glioblastoma cells.[33] Rat glioblastoma (C6) cells assessed for intracellular oxidative burst and cytokine levels pre- and postincubation with nanoparticles revealed noticeable elevation in expression of intracellular IFN-γ and reactive oxygen species as well as IL-1β post-treatment. Nitric oxide (NO) is a molecule that plays an important role in glioblastoma multiforme (GBM) pathophysiology. NO is involved in stimulation of apoptosis, radiosensitization, and chemosensitization of cancers.[34] The cancer necrosis factor (TNF-α) is able to stimulate NO production in HSV-tk transduced 9L glioblastoma cell lines, mediated by upregulation of inducible nitric oxide synthase (iNOS) transcript and iNOS protein. A liquid extract of *Marasmius oreades* (Bolton) Fr., able to inhibit iNOS expression in MCF-7 cells, demonstrated its ability to affect TNF-α–induced iNOS expression in HSV-tk transduced 9L cell lines.[35]

Beneficial effects of using mushrooms as health supplements were reported in patients affected by high-grade glioma. Mulpur et al.[36] analyzed the relationship of complementary therapy usage with mortality in patients with GBM. Structured interviews to obtain information on use of CAM were carried out with 470 patients for 6 weeks following GBM diagnosis. These experimental analyses showed a reduction of mortality in patients affected by GBM by using multivitamins (including medicinal mushrooms) or omega-3 fatty acids.

Edible mushrooms contain compounds that exhibit positive effects on brain cells both *in vitro* and *in vivo*. In a study by Wong et al.,[37] hot water extract of *Hericium erinaceus* (Bull.: Fr.) Pers. mycelium and basidioma was tested on the NG108-15 neuroblastoma glioma hybrid cell line. In this experiment, the

mushroom extract induced neurite outgrowth. Ethanol extract of *H. erinaceus* also promotes neurite outgrowth of rat pheochromocytoma (PC12) cells, enhances nerve growth factor (NGF) mRNA expression, and increases NGF secretion from 1321N1 human astrocytoma cells.

The cytotoxicity and antioxidative capacity of several medicinal mushroom preparations (Lentifom, Super Polyporin, Agarikon, Agarikon Plus, Agarikon1, and Mykoprotect1) was tested on brain astrocytoma cancer cells (CCTG-1).[38] These mushroom preparations contain medicinal mushroom extracts from *Lentinus edodes*, *G. frondosa*, *G. lucidum*, *Pleurotus ostreatus* (Jacq.) P. Kumm., *Agaricus blazei* Murrill, and *Tricholoma matsutake* (S. Ito & S. Imai) Singer. Lentifom and Super Polyporin show a strong cytotoxic effect on human astrocytoma cells. In particular, astrocytoma cells were susceptible to Lentifom at the therapeutic dose through mitochondrial activity deprivation and were sensitive to Super Polyporin and Lentifom, which inhibited their growth by 30%.

## B. Effects of Mushrooms on Side Effects in Patients with Brain Cancer

Side effects of drugs most commonly used in the treatment of brain cancers such as temozolomide and nitrosoureas are diarrhea, reduced resistance to infection, anemia, nausea, vomiting, constipation, hair loss, dizziness, difficulty breathing, allergic reactions, and infertility. Medicinal mushrooms are effective in the prevention of immune diseases, particularly in immunodepressed patients undergoing different chemotherapy and radiotherapy treatments.

Schmiegelow et al.[39] carried out a study of children affected by brain cancer and demonstrated that radiation and chemotherapy negatively impacted hypothalamic pituitary adrenal (HPA) axis function. Another study highlighted that reduced cortisol output and disturbances in HPA axis function correlate with the peptide hormone corticotropin-releasing factor involved in the stress response.[40] The bioactive components that contribute to the antifatigue effects of mushrooms such as *G. lucidum*, *Ophiocordyceps sinensis*, *L. edodes*, *A. bisporus* (J.E. Lange) Imbach, and *P. ostreatus* include polysaccharides, peptides, adenosines, nucleosides, polyphenols, flavonoids, and triterpenoids.[41,42] These mushrooms can mitigate fatigue by acting on sites of the muscular, cardiovascular, body antioxidant, hormone, and immune systems. Few studies have been carried out on this topic and most have been conducted on animal models, so further research is needed for better understanding of the mechanism of the antifatigue function of edible and medicinal mushrooms.

Soups made with vegetables such as cooked asparagus tips, beets, carrots, peeled zucchini, mushrooms, and celery are effective in reducing intestinal motility and diarrhea in patients affected by brain cancers.[43] Ahmed and Aslam[44] tested the effect of *G. lucidum* extracts on the hematological parameters of Wistar rats. A significant increase in hemoglobin level, platelet count, and leukocyte count was observed at doses of 150 and 300 mg/kg body weight administered orally compared to the control group. *T. versicolor* and *L. edodes* are effective in inducing resistance to infection.[45] Daily intake of *G. lucidum* extracts is effective for nausea and vomiting. SunRecome, a mixture of extracts and spores of *G. lucidum* that is very popular in China, is suitable for alleviation of cisplatin-induced nausea and vomiting. In rats, there is a reaction to cisplatin with increased consumption of kaolin. This increase is a consequence of intraperitoneal injection of cisplatin and is evident in the following hours. Administration of 1.3 and 10 mg/kg of *G. lucidum* causes a decrease in kaolin and food intake by rats.[46] The use of *Auricularia auricula-judae* (Bull.) Quél. extracts in patients suffering from constipation following treatments with temozolomide and nitrosoureas significantly improved the number of bowel movements, sense of incomplete evacuation, and stool consistency.[47] In a nonrandomized clinical trial with the maitake D-fraction carried out in Japan on 165 patients with stage III–IV cancer aged between 25 and 65 years, various chemotherapy side effects (e.g., loss of appetite, vomiting, nausea, hair loss, and leukopenia) were strongly reduced in 90% of patients. Pain reduction was also found in 83% of patients.[48]

## C. Case Study Report

In this review, we report on the use of medicinal mushrooms in a patient with a grade IV primitive glioblastoma. This 61-year-old female patient had regular living habits and no previous notable pathologies. In September 2018, the patient reported episodes of mental confusion, later accompanied by visual and speech disorders, for which she was admitted to the Santa Chiara Hospital Emergency Room in Pisa, Italy. The patient underwent computed tomography (CT) and magnetic resonance imaging examinations that showed a left mesial occipitotemporal intraparenchymal neoformation associated with perilateral edema with a compatible framework for high-grade glial series lesions. For the extent of the lesion, the patient was judged inoperable and a stereotactic biopsy of the lesion was performed. Subsequently, a grade IV primitive glioblastoma was diagnosed with the following molecular profile: absence of methylation analysis of isocitrate dehydrogenase IDH1 and IDH2 gene mutations, absence of detectable alterations, and absence of codelection1p-19q. On November 29, 2018, the patient began concomitant radiochemotherapy treatment. Thirty sessions of radiotherapy (200 cGy per fraction, five fractions per week for a total dose of 60 Gy) and chemotherapy with temozolomide (dose of 75 mg/m$^2$ orally per day for 42 days) were scheduled. Cortisone therapy with high-dose dexamethasone (16 mg/day) was also administered. At the request of family members and in agreement with oncologists, traditional therapies were combined with an integrated complementary therapy with a low-carbohydrate isoprotein nutritional intake and a mycotherapeutic support based on *G. lucidum*, *A. blazei*, *Polyporus umbellatus*, and *G. frondosa* to reduce side effects particularly related to chemotherapy, radiotherapy, and cortisone therapy. The daily integrated therapy consisted of 2 g of *G. lucidum*, 1 g of *A. blazei*, 1 g of *G. frondosa*, and 1.5 g of *P. umbellatus* at breakfast. The patient was administered 1 g of *G. lucidum*, 500 mg of *A. blazei*, 500 mg of *G. frondosa*, and 500 mg of *P. umbellatus* before dinner. Medicinal mushroom capsules, containing the mushroom extract in the form of dry powder, were administered orally. The extract is of US origin and is encapsulated and distributed by an Italian company.

After approximately 2 weeks, a marked improvement in clinical symptomatology was noted, including a considerable reduction in cerebral edema. The cortisone therapy was reduced to one-third of the initial dose, most likely due to the synergistic effect of the mycotherapy.

The CT scan after 2 months (Fig. 1) confirmed the reduction of the mass effect and the re-expansion of the III ventricle, with less deviation of the structures of the median line to the right (3 mm vs. 10

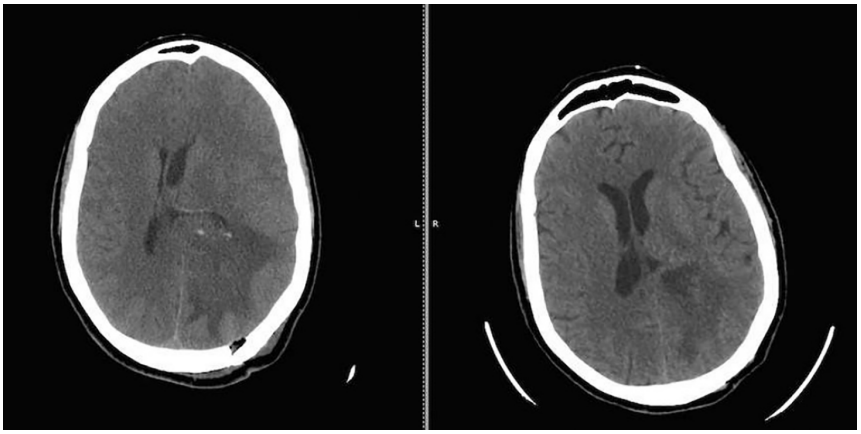

**FIG. 1:** Reduction of peripheral edema to the known intra-axial medial occipitotemporal lesion (left), with reduced signs of mass effect with less deviation of the structures of the median line (right) (maximum approximately 3 mm, ex 10 mm) and re-expansion of the middle cell of the lateral right ventricle. Daily integrated therapy comprised 3 g of *Ganoderma lucidum*, 1.5 g of *Agaricus blazei*, 1.5 g of *Grifola frondosa*, and 2 g of *Polyporus umbellatus*.

mm). In particular, compared to the previous Tc effectuated in October 2018, a significant reduction of peripheral edema to the known intra-axial medial occipitotemporal lesion with reduced signs of mass effect with less deviation of the structures of the median line (maximum approximately 3 mm, ex 10 mm) and re-expansion of the middle cell of the lateral right ventricle was appreciated in December 2018. Reduction of the mass effect was also evident at the mid-brain level. The hydrocephalus of the ipsilateral temporal horn remained unchanged. The solid component of the expanding cortico-subcortical occipito-temporal lesion appeared increased by dimensions with increased density due to a likely increase in the cellular component.

## IV. DISCUSSION

Medicinal mushrooms, which have long been used in Eastern countries, are gradually gaining a foothold in Europe thanks to scientific research highlighting their bioactive compound content and applications in integrated medicine. Some medicinal mushroom extracts have shown effectiveness in laboratory tests and on animal models, although clinical trials are still infrequent.[49] Medicinal mushrooms are effective on various types of cancer and side effects of chemotherapy treatments. In the case of brain cancers such as glioblastoma, medulloblastoma, and astrocytoma, the literature reports beneficial effects of fungal compounds in *in vitro* and *in vivo* experiments. In many cases, the mechanism by which the polysaccharides of medicinal fungi act as immunomodulators and anticancer agents on the brain glioma is still unclear. The evidence base for the use of fungi in integrated oncology has increased in recent years. Further effort is needed to purify and analyze the individual constituents of fungi to understand their effects on apoptosis, cell cycle inhibition, and immune modulation. The most recent studies show how the polysaccharides of *G. lucidum* can promote functional maturation of dendritic cells and inhibit growth of glioma in rats. A better understanding of how medicinal mushrooms act at various levels on cancers necessarily passes from a close link between the results of scientific research and traditional oncology in order to identify the most appropriate treatment for each individual, prevent side effects and complications, and increase patient survival.

The results of the case study reported here are especially encouraging for the improvement of quality of life in patients with brain cancer. These findings could provide new insights into the possible therapeutic uses of medicinal mushrooms and useful suggestions for the preparation of drugs and nutraceuticals for the fight against brain cancer. For integrated therapies to be truly effective, greater collaboration between oncologists and doctors using mycotherapy is needed.[50]

The recent establishment of the Italian Society of Medicinal Mushrooms can provide an umbrella under which to harmonize all actions in the field of mycotherapy in Italy that are currently unclear and also very expensive for patients who want to approach this type of integrated medicine.

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