Review Paper:

Dietary edible mushroom: A suitable candidate for cancer chemoprevention

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Abstract

Cancer is a prolific cause of death globally and has long lasting consequences in the entire life time of the patient. The existing anticancer medications available on the market are not pointedly designed, thereby raise countless side effects and troubles in the diagnosis and treatment of different cancer types, indicating the imminent need for more effective and harmless cancer prevention strategies. Natural dietary chemoprevention is a satisfactory anticancer approach with minimal ancillary consequences compared to conventional cancer therapies which already exist.

Since historical times, mushrooms have been regarded by the human race as a dietary miracle and traditional medication in oriental practice. This will be widely recognized as fungus and in the traditional Chinese system, it is presumably the most vital pharmaceutical cultivar. Various edible mushrooms are used to combat against variety of diseases. The well-known mushrooms accredited as successful preventive agent against cancer belong to the genus Ganoderma lucidum, Agaricus bisporus, Agaricus blazei, Pleurotus ostreatus, Tricholoma giganteum and *Calocybe indica. This review highlights the recent discoveries on mushroom's chemo preventive properties and outlines the features that warrant forthcoming research to determine their mechanism and implementation in humans as a chemo preventive cancer agent.*

Keywords: Cancer, chemoprevention, mushroom.

Introduction

Cancer is a biggest killer worldwide and according to statistics from the WHO, millions of people will die prematurely if the cancer is untreated, especially in low- and middle-income countries where resources are scarce or non-existent for preventing, diagnosing and treating cancer. The world's foremost obstacle is finding a solution for cancer[43].

Besides the side effects of conventional treatments such as nausea, bone marrow suppression, anemia and decreased resistance, cancers respond poorly to chemotherapy and radiotherapy suggesting that chemoprevention is a practically workable and optimistic technique. The main driving force behind such chemopreventive action is to curtail the development of free radicals and other species of reactive oxygen (ROS) likely to be involved in both carcinogenesis initiation and promotional actions. Chemoprevention via dietary constituents will play an emerging role and a new cancer control strategy by the use of fruits, vegetables or edible mushrooms[11].

Mushrooms have been labelled worldwide gourmet cuisine for their exquisite taste and delicate flavour since antiquity. There have been 1.5 million species of mushrooms in the world, about 82,000 are described. The known species belong to macrofungi among them 5000 are edible and 2000 are healthy.

Mushrooms can be extremely nutritious, poisonous or medicinal. Many mushroom species, whether edible or poisonous, contain bioactive compounds that are vital to human health. A number of wild edible mushrooms from western Bengal have been extensively researched and considered attractive for treating cancer. Fungi from the *basidiomycota* group are of great interest as they contain a large number of biologically active compounds[24] which have been demonstrated to activate or modulate the immune system, thereby inhibiting metastasis and growth of cancer cells.

It has been discovered recently that many species of mushrooms are miniature pharmaceutical factories that create hundreds of new constituents with remarkable biological properties[37]. Figure 1 shows medicinal properties of mushroom. Bioactive compounds of mushrooms include polysaccharides, proteins, fats, glycosides, alkaloids, phenolics, flavonoids, carotenoids, folates, ascorbic acid, enzymes and organic acids. However, recent reports provide credible evidence that medical mushroom could serve as chemopreventive agent.

Nowadays, considerable attention is focused on a distinct class of chemopreventive medicinal mushrooms including *Ganoderma lucidum*, *Agaricus bisporus, Agaricus blazei*, *Pleurotus ostreatus, Tricholoma giganteum* and *Calocybe indica.*

In this review, we summarize some of the best chemo preventive medicinal mushrooms, which have a strong anticancer property which are popularly used in Chinese medicine.

Conventional cancer treatments and its pitfalls

The famous German chemist Paul Ehrlich set about developing drugs for the treatment of infectious diseases in

the early 1900s[19]. He was the one who coined and described the word "chemotherapy" as the use of chemicals to treat disease[5].

In general, chemotherapy is a systemic treatment that uses chemical agents to destroy all dividing cells. Chemotherapeutic agents currently in use are cytotoxic and affect both normal and malignant cells. Current anti-cancer medications on the market are not targeted and have many side effects including bone marrow suppression, nausea and vomiting, epilation, renal, cardiac, neurotoxicity and problems in the clinical management of multiple cancer types[49].

Radiation therapy (also known as radiotherapy) is a major treatment for cancer that uses high radiation doses to kill cancer cells and reduce tumors which destroying their DNA slows their development. Cancer cells whose DNA is impaired, either stop dividing or die after repair when the damaged cells die the body breaks down and destroys them[4]. Radiation treatment does not instantly destroy the cancer cells. Treatment takes days or weeks before DNA is sufficiently weakened in cancer cells. Then, after radiation therapy stops, cancer cells continue to die for weeks or months. Not only does radiation kill or delay cancer cell growth, it may also have an effect on healthy cells nearby. Damage to healthy cells can cause side effects, which highlights the urgent need for new therapeutic approaches that are successful and less toxic. Figure 2 shows that drawback of chemotherapy and radiotherapy.

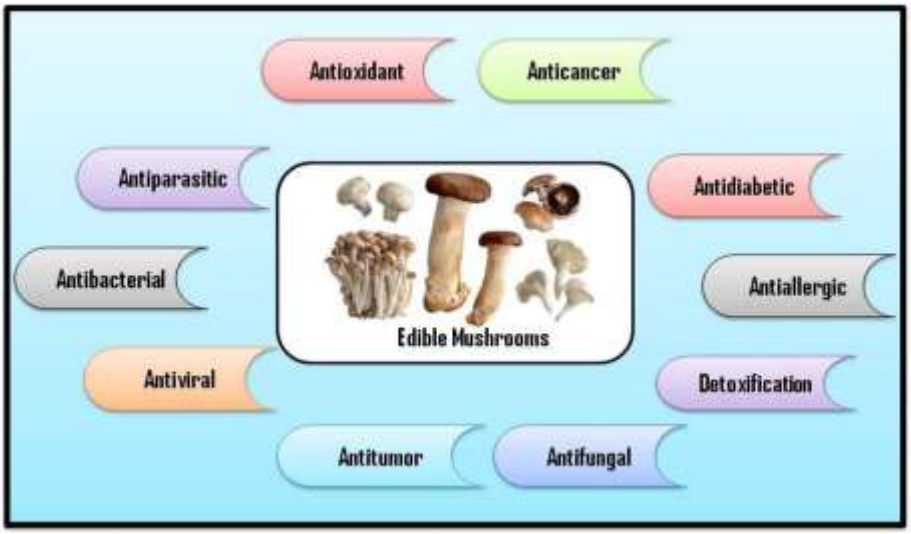

Figure 1: Medicinal properties of mushroom

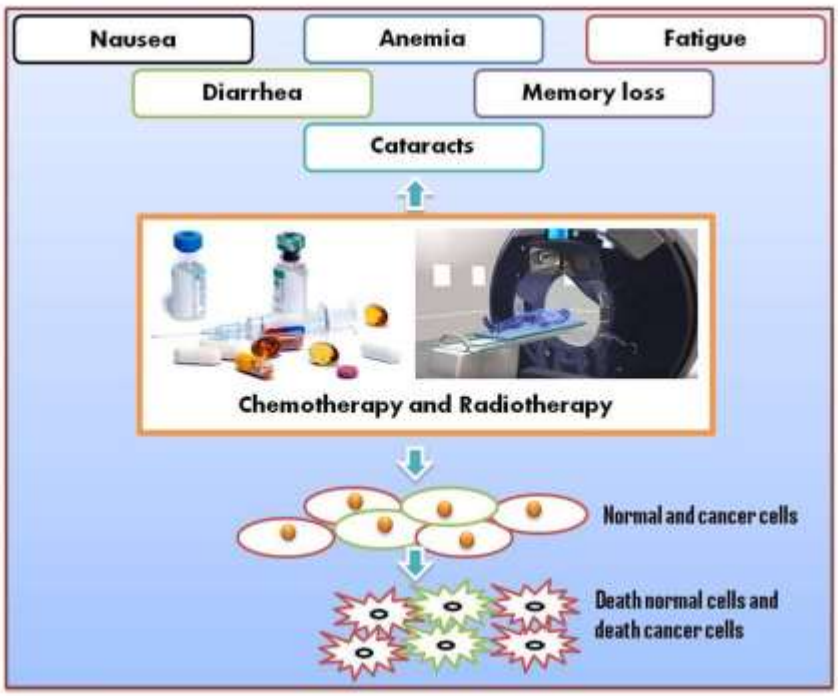

Figure 2: Drawback of chemotherapy and radiotherapy

Natural medicine-An innoxious approach: The medicinal use of substances of natural products obtained from natural sources such as plants, animals or micro-organisms is undoubtedly thousands of years preceding documented human history. Nature abounds with a rich potential medicinal tool heritage that has been used for successful and beneficial use against many human cancers, either as a method for prevention or as a medicinal weapon to destroy tumor cells. Many of these naturally existing nutritious dietary compounds have evolved to fight natural predators and also for self-defense[33,41]. In recent days, natural bioactive dietary compounds derived from edible mushrooms have attracted considerable attention in the fight against cancer.

Magical mushrooms – a therapeutic wonder

Most traditional culture around the world has long been known that decoctions of hot water from some fungi will have health-promoting benefits. Particularly, in China and Japan, many of these mushroom extracts have become important ingredients in traditional Chinese medicine (TCM) for many centuries over the past two millennia[48]. They have been used in both nutritional and herbal medicine applications. For example Chinese people have long believed that mushrooms not only taste good but also have a detoxification effect, cleaning and cleansing the body as well as wounds. From the nutritional point view, the Chinese believe that mushrooms are essential in cleansing the liver and kidney and are often included in the main daily meal[12].

Purified hot water extract made from cultivated fungal mycelium is used as an adjuvant treatment for cancer in Japan for its immune effects. Many edible mushrooms used in traditional folk medicine includes *Ganoderma lucidum*, *Agaricus bisporus*, *Agaricus blazei*, *Pleurotus ostreatus* and *Tricholoma giganteum*. Some major traditional uses of mushrooms against various scared diseases viz. pneumonia, respiratory problems, asthma, jaundice, pox, goiters, diabetes, cancer, aphrodisiac, invigorative, revitaliser, anti-aging, kidney stones and partial paralysis[27,35].

The eastern countries of Asia documented the traditional information on the utilization of cooked and therapeutic mushrooms which had been accepted from generation to generation but it was not so much in India[35]. In Eastern countries, medicinal mushroom extracts have been introduced into cancer therapy in combination with standard chemotherapy.

Phytoconstituents of therapeutic mushrooms: Mushroom has been described as a macro-fungal with a distinctive fruiting body that can be hypogenous or epigeous, large enough to be seen with the naked eye and picked by hand. It contains as high in proteins, minerals and low in lipids. Recorded literature suggests that mushrooms produce photo chemicals and other compounds such as phenolic compounds, alkaloids, saponins, flavonoids, tannins, sterols, triterpenes, coumarins and cyanogenic glycosides.[1,21,29]

Experimentally verified studies on medicinal mushrooms: Preclinical studies carried out in the past three decades have validated many of the traditional uses of mushrooms. Mirunalini et al[31,32] investigated that mushroom possesses antioxidants which are becoming increasingly popular and could bring diverse physiological benefits to the consumer such as protection against human diseases associated with oxidative stress like diabetes, infections (fungi, bacteria), immune system disorder and cancer.[1,14,16,20,31,32]

Compelling preclinical studies with both *in vitro* and *in vivo* systems have shown that mushroom possesses anticancer, chemo preventive, antiproliferative effects.[13,15,17] Here, an attempt is made to examine the role mushroom plays in cancer treatment and prevention. Table 1 shows the anticancer properties of mushroom.

Mushroom as a chemo preventive candidate: Cancer continues to be the world's largest cause of mortality. Today, chemoprevention is an extremely promising technique for cancer prevention, which is characterized by the use of natural substances to prevent cancer development or progression. Carcinogenesis is an extremely complex process, but the various stages are defined very broadly as initiation (days), promotion (several years) and progression (1-5 days). One or more stages of this multi-stage carcinogenesis cycle should be interfered with by a chemo preventive agent[40]. It must also be safe, nontoxic and effective when administered long-term[42].

Chemoprevention by dietary mushrooms has thus become an increasingly active area of research in the last few decades. Mushrooms have been used as essential food products and they also possess numerous therapeutic properties worldwide as they possess specific active constituents. The aqueous extract of mushroom provides significant prevention against mutagenicity[7].

***Ganoderma lucidum*:** In traditional Chinese medicine *Ganoderma lucidum* (Leyss. ex Fr.) Karst, also known as Lingzhi, has been used to improve health and longevity. Lingzhi has been used in the treatment of various diseases for thousands of years including neurasthenia, hypertension, hepatopathy and carcinoma. Currently, *G. Lucidamine* powder and water / ethanol extracts are used worldwide as dietary supplements[47].

Over the last few decades, inspections into the composition of *G. lucidum* have been modified that it contains a versatility of bioactive components like triterpenes, polysaccharides, nucleosides, steroids, fatty acids, alkaloids, proteins, peptides, amino acids and inorganic elements[51]. The anticancer and anti-metastatic properties of these mushrooms are thought to be derived from their diverse chemical constituents, although they consist primarily of two types of compounds: polysaccharides and triterpenes[9].

Table 1
Anticancer properties of mushroom

S.N.	Edible Mushrooms	Anticancer property
1.	 ***Ganoderma lucidum***	Lung cancer[34]
2.	 ***Agaricusbisporus***	Liver cancer, prostate cancer, Colon cancer, lung cancer and breast cancer[10,23,50]
3.	 ***Agaricus blazei***	Liver cancer[3,38]
4.	 ***Pleurotus ostreatus***	Colon cancer[25,26]
5.	 ***Tricholoma giganteum***	Stomach cancer[8]

6.	 ***Calocybe indica***	Lung cancer[36]

Polysaccharides are water soluble components in extract of *G. lucidam*. For the past 30 years, *G. Lucidum*has clearly demonstrated that polysaccharides have hypoglycemia, immuno-modulating, antitumor and anti-metastatic activity[28,52].

Many triterpenoid compounds such as ganoderic acids, ganolucidic acids, ganolactone, lucidenic acids, methyl lucidenate and hydroxylucidenic acid also present in the species *Ganoderma* have shown some therapeutic effects. In recent years, Nonaka et al[34] have been described that pre-feeding with the *G. Lucidum* antlered form (AF)-contains dietary could suppress lung metastasis in Cyclophosphamide (CY)-induced C57BL/6 mice injected in Lewis lung carcinoma (LLC). In particular, the number of nodules in the *G. lucidum* AF-fed group injected with LLC 7 days after CY administration was importantly lower in connection to the control group without *G. Lucidum*[34]. The mechanisms of action of *G. lucidum* include the generating of cell apoptosis, inhibition of cell proliferation and suppression of the motility of highly invasive breast and prostate cancer cells[44]. *G. Lucidum* in the form of a dietary supplement containing the main bioactive components can be helpful in preventing metastasis of cancer.

***Agaricus bisporus*:** *Agaricus bisporus* is commonly referred to as the common mushroom, button mushroom, white mushroom, table mushroom, portobello mushroom, cremini, crimini mushroom, Swiss brown mushroom, Roman brown mushroom, Italian brown mushroom, or cultivated mushroom. It is a strong source of trace elements such as selenium, sodium, potassium and phosphorus, linoleic acid conjugated with antioxidants. For humans and animals, selenium is an important trace element.

Clark et al[10] reported role of selenium in cancer chemoprevention. Mushrooms contain more selenium than other foods in the food group of fruits and vegetables and can be a vegetarian source of this essential mineral. Selenium has a potential role to play in cancer prevention by antioxidant defense and/or greater immune function. There is evidence from human studies that when administered at higher doses, selenium can reduce the occurrence of cancer.

Intervention studies have also demonstrated benefits with selenium in reducing cancer, especially in the liver, prostate, colon and lung, with the greatest benefits in those with the lowest selenium status[46].

A. bisporus can suppress aromatase and can thus reduce the levels of estrogen in the human body, which can also reduce the risk of breast cancer[40].It is well documented that fungi produce a wide and varied number of biologically active compounds that not only stimulate the immune system but also modulate different cellular responses by interfering with different signal transduction pathways, which specifically inhibit NF-κB DNA binding and have shown promising results in MCF-7 cells of human breast cancer.

It was found to be produced by *A.bisporus.* Several common and historically used medicinal mushrooms have also been investigated and have been confirmed to exhibit modulating properties of NF-κB. It has also been reported that *A.bisporus* produces substances which suppress the activity of aromatase[23]. Son et al[45] suggested that the water extract also induced macrophage activation, which resulted in the expression of the iNOS gene followed by the development of nitric oxide (NO) by activation of NF-κB.

***Agaricus blazei*:** *Agaricus blazei* (Ab) Murrill, a species native to Brazil where it is popularly known as ‘‘Cogumelo do Sol’’, has recently received attention in folk medicine due to its various medicinal property including cancer therapy. Since 1965, this species has been exported to Japan, where it is known as ‘‘Himematsutake’’ or ‘‘Kawariharatake’’. Various polysaccharides and protein-bound polysaccharides isolated from *Agaricus blazei*, mushroom mycelia and fruiting bodies have demonstrated anti-tumor activity in tumor-bearing mice through activation of specific and non-specific immune response. Recently, Pinheiro et al[38] demonstrated that the aqueous extract of this mushroom provides significant protection against mutagenicity induced both in vivo by cyclophosphamide (CPA) and in vitro by methyl methanesulfonate (MMS)[18,30].

In addition, 2-week treatment with this liquid preparation prior to the initiation of diethylnitrosamine (DEN) liver carcinogenesis in rats exerted a liver-protective effect as shown by decreased serum transaminase rates and regenerative cell proliferation and early liver pre-neoplasia growth 48 h after initiation[2].

Alternatively, when Ab's aqueous extract was administered for 6 weeks after DEN-initiation, it did not affect the production of putative preneoplastic hepatic alterations[3].Since this mushroom is also commonly eaten as a meal, the question was raised about the effects of mixing the mushroom in the diet on the cycle of liver carcinogenesis in rats. The DEN-partial hepatectomy (PH) model has proved to be a reliable bioassay for chemical hepatocarcinogen detection and assessment of the beneficial capacity of chemopreventive agents[38].

***Pleurotus ostreatus*:** Oyster fungus, *Pleurotus ostreatus* is an edible mushroom common in the world's hardwood forests. A number of sources showed this to be *P. Ostreatus* that has effects such as anticancer, antioxidant, hypocholesterolemic and antiatherogenic. Polysaccharides, primarily ß-1,3-D glucans, are the biologically active compounds responsible for anticancer and antioxidant activity isolated from *P. Ostreatus*[5,6,25]. Therefore, Jedinak et al[25,26] examinated the Chemopreventive effect of *P. ostreatus* on inflammation-associated colon carcinogenesis in the mouse model using 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP) and colitis-inducing agent dextran sulfate sodium salt (DSS) for the formation of colon duration, tumor occurrence, multiplicity, dysplasia, neoplasia and aberrant crypt foci (ACF).

In addition, immunohisto chemical expression of biomarkers involved in the progression of cancer (cycline D1 and Ki-67) and biomarkers involved in inflammation regulation (COX-2 and F4/80) were also assessed in colonic tissues[26]. These findings suggest that edible oyster mushroom can suppress associated colon carcinogenesis and may be relevant in clinical trials with humans.

Jedinak and Sliva[25] identified as the most active, *P. ostreatus* (*oyster* mushroom) that suppressed breast cancer proliferation (MCF-7, MDA-MB-231) and colon cancer (HT-29, HCT-116) cells, without affecting epithelial MCF10A and regular colon FHC cells. Flow cytometry showed that inhibition of *P. ostreatus* cell proliferation was associated with halting the cell cycle in MCF-7 and HT-29 cells at the G0/G1 level. Moreover, *P. ostreatus* induced the expression of the tumor suppressor p53 and the cycline-dependent kinase inhibitor p21(CIP1/WAF1), while MCF-7 cells inhibited the phosphorylation of Rb protein retinoblastoma.

Furthermore, *P. ostreatus* also up-regulated p21 expression and inhibited Rb phosphorylation in HT-29 cells, indicating that *P. ostreatus* suppresses breast and colon cancer cell proliferation through p53-dependent and p53-independent pathway. These results indicated that the edible oyster mushroom has potential therapeutic/preventive effects on breast and colon cancer[25].

***Tricholoma giganteum*:** *Tricholoma giganteum* of the Tricholomataceae family, a wild edible mushroom during the rainy season is most conspicuous in the tropical region. Because of their being a gastronomic and nutritional delicacy, they are robust in size and common among the people of these areas. Chatterjee et al[8] identified chemopreventive role of *Tricholoma giganteum* Fa fraction (80% ethanolic extract) against benzo[a]pyrene-induced forestomach cancer in Swiss albino mice. B[a]P-induced large numbers of tumors at forestomach also caused abnormal alterations in the activities of superoxide dismutase, catalase, glutathione S-transferase, reduced glutathione and lactate dehydrogenase. Fa fraction administration effectively suppressed forestomach cancer as revealed by the decrease in lipid peroxidation and all the above alterations were observed to return towards normal.

The preventive effect may probably occur by controlling the expression of certain essential cell cycle-related genes and apoptosis such as p53, p21, Bcl-2, Bcl-xl, Bax and cyclinD1. The treatment profoundly reverted back the histopathological changes observed in cancerous animals and thus further supports our findings. The present data suggests that the Fa fraction of *T. giganteum* might extend its chemo preventive potential by modulating lipid peroxidation, augmenting antioxidant defense system, inhibiting cell proliferation and inducing apoptosis[8].

***Calocybe Indica*:** *Calocybe indica*, a tropical edible mushroom, is ubiquitous as it has good healthy nutritive content and can be commercially harvested. *Calocybe indica's* strong antioxidant activity will be able to counteract diseases triggered by free radicals and the regular intake of *C. indica* will prevent diseases of oxidative stress[39]. The administration of C. Indica exhibits cytotoxic activity by altering the lipid peroxidation and reversing the histopathological changes in cancer-bearing mice.

Several evidences have shown that phytochemicals exist in *C. indica* can have a powerful activity against cancer. Hence, *C. indica* might have strengthened the anticancer status as an edible and potential (natural) anticancer agent[22].The IC50 value of the *C. indica* to A549 lung cancer cell line was expressed as 4.9 µg/ml. Apoptosis analysis of *C. indica* was indicated as 80.13% and maximum rate of inhibition (54%) was observed in S phase.Thereby *C. Indica* implies their therapeutic potential[36].

Conclusion

The centrality and influence of mushroom products in cancer treatment and prevention are evident and cannot be neglected. Therapeutic mushroom derivatives which conflate new generations of pharmacologically active compounds might probably help to resolve some of the flaws of both the existing arsenal of chemotherapy and radiotherapy and strengthen it against existing and future therapeutic threats which have inhibitory effects on cancer cell proliferation, thereby inducing antioxidant and detoxifying enzymes.

As centred upon the proverb "Prevention is better than cure", the edible mushrooms daily intake is much safer and cheaper than the cancer conventional treatments. A rising segment of today's pharmaceutical industry is shaped owing to a variety of useful bioactive compound medicinal mushrooms. Therefore, future perspective will be directed at figuring out the exact molecular mechanisms of different mushrooms in cancer therapy and also will encourage the consumption of mushrooms and other natural substances attributable for its holistic trust.

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