

A REVIEW ON MUSHROOM: A CANCER ANTIDOTE

¹Rosalin Nath, ²Kakali Bandyopadhyay, ³Dolanchapa Sikdar and ⁴Arnab Saha

¹Assistant Professor, ²Associate Professor, ³Assistant Professor, ⁴Student
Department of Food Technology
Guru Nanak Institute of Technology, Panihati, Kolkata, India.

ABSTRACT: Cancer is the leading cause of death worldwide. The current anti-cancer drugs have numerous side effects. In a search for less toxic and effective treatment of cancer some prized mushrooms have been found to have validated anti-cancer properties. Numerous attempts have been made to assess their benefits for commercial purposes and cancer therapy. Certain bioactive molecules including polysaccharides, proteins, glycosides, alkaloids, volatile oils, tocopherols, phenolics, flavonoids, carotenoids, ascorbic acid enzymes, and organic acids which are also anti-tumour agents have been identified from various mushrooms. The anti-cancer potential of mushrooms lies in lentinan, krestin, hispolon, lectin, calcaelin, illudin S, psilocybin, Hericium polysaccharide A & B (HPA & HPB), ganoderic acid, schizophyllan, laccase, etc. Psilocybin mushrooms are used in folk medicine though it's not considered edible. Over 50 mushroom species have been found to yield immunoceuticals with anti-cancer properties for animals including six for human cancers. PSP (Polysaccharide-peptide) over the last 5 year tests have significantly improved quality of life with substantial pain relief besides enhancing immune status in most patients with cancers of stomach, oesophagus, lung, ovary, and cervix. PSK (Polysaccharid-K) and PSP boosted immune cell production, ameliorated chemotherapy symptoms, and enhanced tumours infiltration by dendritic and cytotoxic T-cells. These chemicals have extremely low side-effects, improve the quality of life, and highly compatible with chemo therapy and hence, well suited for cancer management regimens. So here in this review paper, anti-cancer drugs produced by edible & wild both mushrooms & their activity to prevent & cure cancer has been discussed briefly.

Keywords: Anti-cancer Drugs, Folk medicine, Immunoceuticals, cytotoxic T-cells, bioactive molecules.

1. INTRODUCTION

Recently it has been found that there are so many mushroom species which contains hundreds of novel constituents with great biological properties. Our ancestors have used mushrooms as medicine for thousands of years. The Greek physician Hippocrates, circa 450 BCE, classified the Amadou mushroom (*Fomes fomentarius*) as a potent anti-inflammatory and for cauterizing wounds. The alchemist Tao Hongjing, from the 5th century, described several medicinal mushrooms, including Ling zhi (*Ganoderma lucidum*) and Zhu ling (*Dendropolyporus umbellatus*), some in use reportedly by Shennong many centuries before. Ötzi, the Ice Man, who lived nearly 5300 years ago, carried Amadou and a birch polypore tethered in a pouch to help him survive in the Alps of northern Italy. Of late, mushrooms have emerged as wonderful source of nutraceuticals, anti-oxidants, anticancer, prebiotic, immune-modulating, anti-inflammatory, cardiovascular, anti-microbial, and anti-diabetic ^{[1][2][3]}.

Cancer is one of the most major causes of death world-wide. There are so many anti-cancer drugs and treatments are available in the markets which are not target specific and it poses several side-effects and complications like Fatigue, Early menopause, Heart problems, Kidney and urinary problems, Nerve problems etc. In this context, there is some supreme mushroom with their anti-cancer properties which is used as extracts in commercial preparation during numerous clinical trials to know the benefits of these medicinal mushrooms compounds & it gives satisfactory results against cancer cell. Recently, many research claimed that mushrooms contain huge number of bioactive molecules including anti-tumours agents. Including bioactive molecules such as polysaccharides, proteins, fats, ash, glycosides, alkaloids, volatile oils, tocopherols, phenolics, flavonoids, carotenoids, ascorbic acid, it has some active components which is responsible for bestowing anti-cancer potential are lentinan, krestin, hispolon, lectin, calcaelin, illudin S, psilocybin, Hericium polysaccharide A and B (HPA and HPB), ganoderic acid, schizophyllan, laccase, etc. Mushrooms are very effective in preventing breast and prostate cancer due to presence of Beta-glucans and conjugated Linoleic acid. Mushrooms contain natural insulin and enzymes which help in breaking down of sugar or starch in food, thus being an ideal low-energy diet for diabetics. Mushrooms are a rich source of calcium, which helps to absorb vitamin D in bones & teeth. Ergothioneine, is a powerful antioxidant present in various mushrooms which provides a great protection from free radicals as well as boosting immune system. Some scientific research claims that, there is some mushroom which shows synergistic effect in combination with commercial anticancer drugs. The purpose of the present review is to summarize the available information, and to tell that we have scope the exploration with mushrooms in food technology area also.

1.1 ANTI-CANCER AGENTS:

1.1.1 Maitake D-Fraction:

Maitake D-Fraction is a mixed β -D glucan fraction prepared from the maitake mushroom (*Grifola frondosa*) and is orally bioavailable.^[4] Maitake D-Fraction contains mainly β -D-glucan material with 1-6 main chains and 1-4 branching, and the more common 1-3 main chains and 1-6 branchings. Maitake D-Fraction has been used in a few exploratory studies in cancer patients.^{[6][7]} In 1994, a group from China published in abstract form their findings from a pilot study on 63 cancer patients. They reported the total effective rate against solid tumors at higher than 95 percent, and the effective rate against leukemia higher than 90 percent. Unfortunately, the concentration of the extract used was not disclosed.^[5]

1.1.2 Proteoglycans from *Coriolus versicolor*:

The mushroom-derived “polysaccharide-peptides,” are polypeptide chains or small proteins to which polysaccharide β -D-glucan chains are very stably attached. *Coriolus versicolor* is a mushroom which grows on tree trunks and belongs to the more-advanced Basidiomycetes class. In Japan around 1965 a chemical engineer investigated *Coriolus versicolor* for its anticancer constituents after observing his neighbor’s life-threatening cancer was cured after taking Yun Zhi. This led to the discovery of PSK (Polysaccharide-K).^[8]

1.1.3 PSK or Polysaccharide-K:

PSK is prepared from strain CM-101 of *Coriolus versicolor* by water extraction and salting out. It is approximately 62% polysaccharide and 38% protein, although the content of both may vary. The glucan portion of PSK consists of a β 1-4 main chain and β 1-3 side chains, with β 1-6 side chains that bond to a polypeptide moiety through O-or N-glycosidic bonds. While PSK is not a cure-all for cancers, it can improve five-year survival in some indications by as much as double, and perhaps extend survival to as much as 15 years.^{[9][10][12]} In some patient subsets, such as HLA B40-positive breast cancer, or in the presence of risk factors such as impaired immunity or high ACT or SA, PSK can be especially life-saving. PSK also helps conserve immune status in the face of toxic challenge by conventional treatments.^[8]

1.1.4 PSP or Polysaccharide-P :

PSP or Polysaccharide-P is prepared from cultured mycelium of the COV-1 strain of *Coriolus versicolor*. PSP may contain mainly four discrete molecules, which are likely to be true proteoglycans. Clinical research with PSP has taken a fast track since it was isolated in 1983.^[13] With Phase I, II, and III human trials now completed, PSP has been proven to be non-toxic with marked immune potentiation capacity sufficient to improve survival rate and quality of life in cancer patients.^{[14][15]} The Phase I trial provided PSP at doses up to 6 grams per day for one month to 16 healthy persons and five breast cancer patients.^{[14][16]} Appetite increased in a majority of the subjects, and in this and other preliminary trials no evidence was found for serious adverse effects.^[17]

1.2 CHEMICALS & NUTRITIONAL ASPECTS OF MUSHROOM:

Some mushrooms are indicated for energy restricted diets due to the low concentration of fat and energy, as well as the high concentration of dietary fibres and proteins. They also contain nutrients like phosphorus and iron and vitamins of group B especially thiamine, riboflavin, pyridoxine, pantothenic acid, nicotinic acid, folate, and cobalamin, as well as other vitamins including biotin and tocopherols^[18]. The vitamin B12 content found in mushrooms is the same one found in fish, red meat, and liver, suggesting the same bioavailability, which represents an important source for vegan diets.^[19] Mushrooms also exhibit ergosterol which can be converted to vitamin D2 when exposed to UV light. In animal experiments using ergocalciferol-enriched mushroom powder, an increase in hydroxyvitamin D and bone mineralization was observed.^{[20][21]} Selenium content in mushrooms varies according to the form of cultivation, soil selenium content, and latitude. Selenium is an essential micronutrient that plays a key role in cell cycle and apoptosis. Marginal selenium deficiency may contribute to the reduction of immune function in some types of cancer.^{[22][23]} Not only that, L-ergothioneine is found which is an unusual amino acid in mushrooms that has antioxidant properties as a free radical blocker with the ability to protect cells from oxidative stress. It may serve as a final defense against oxidation in cells. Also, some studies says that ergothioneine should be considered as a longevity vitamin based on triage theory.^[24]

1.3 HEALTH APPLICATION COMPOUNDS & EFFECTS:

Mushrooms are considered as functional foods due to the presence of bioactive compounds and as a source of drug and nutraceuticals development [25]. From a nutritional perspective and due to the high protein value and fibre content, cultivation of mushrooms has also been considered as an alternative to the source of proteins in countries with high level of malnutrition. [26] Aside from this, edible mushrooms have been reported as having an antitumor potential and anti-angiogenesis properties [27][28][29][30]. Fibers such as β -glucans, heteroglycans, lectin, and proteoglycans act as immune modulators [31][32]. Mushroom cell wall contains no starch polysaccharide components classified as dietary fiber, which depends on their morphological form and species. Among the bioactive components are fungal β -glucans, a type of high molecular weight polysaccharides; examples include lentinan, grifolan, and GL-1. There are also several other active compounds: proteoglycans (maitake D fraction) and polysaccharide peptides (e.g., PSP, PSK); glycans (ganoderans), lectins, triterpenes, and triterpenoids (ganoderic acids); and protein bound polysaccharides, lignins, purines, and polyphenols, especially flavonoids [32] [33]. The Maitake D fraction from *G. frondosa* has strong anticancer properties in breast cancer cells, by exerting proapoptotic effects and reducing tumor cell viability [34].

1.4 CLINICAL STUDIES WITH HUMANS:

The world cancer report states that cancer rates will go up to about 50% of the world population by 2030 thus increasing the demand after chemotherapy. Traditionally chemotherapy is the best method known for cancer treatment but it has got several side effects. An increase in the consumption of vegetables reduces the risk of epithelial cancer. Clinical trials has proved anticancer properties to be present in medicinal mushrooms which go pretty well with human observational qualities as is described above Table. A first epidemiological and observational report associating mushroom intake and epithelial ovarian cancer was conducted in China. During approximately 6 years, 500 patients diagnosed with epithelial ovarian cancer and 500 controls were accompanied [35]. Patients with ovarian cancer consumed less mushrooms than control patients. Study show that an increased intake of mushroom reduces the risk of epithelial ovarian cancer and the inverse association occurs for gastric and breast cancer. Another study conducted in Asian and European countries shows that increased consumption of edible mushrooms reduces the risk of breast cancer. Oyster mushrooms have also been clinically proved to be effective in opposing several diseases including cancer. Japanese people have traditionally depended upon oyster mushrooms for their anticancer and hypertension prevention properties. Thus oral intake of mushroom clearly reduces the risk of cancer thereby requiring an increase in the quantity of mushrooms in our daily diet. Mushrooms however serve in an indispensable way and their effectiveness is more failed when combined with chemotherapy surgery and radiotherapy. Lentinan is a neutral polysaccharide of high molecular weight extracted from fruiting body reported to produce antitumor activity and immune regulatory effects and approved as an anticancer drug in Japan [36]. *Ganoderma lucidum* (*G. lucidum*) is a type of mushroom believed to extend life and promote health and its popularity as an alternative medicine has been increasing in cancer therapies. *G. lucidum* contains polysaccharide and triterpene substances widely studied in traditional Chinese medicine and recommended by physicians. As a result, a systematic review evaluates the clinical effects of *G. lucidum* on long-term survival, tumour response, host immune functions, and quality of life in cancer patients, as well as adverse events associated with its use. The study concluded that incorporation of *G. lucidum* treatment can improve tumour response of lung cancer to conventional therapy and may enhance immunity by stimulating T-lymphocyte proliferation, suggesting that it is a promising adjunct to counter the unwanted common immunosuppressive effect of many chemotherapeutic drugs [37].

Mushroom	Type of study	No. of patients	Type of cancer	Extracts/ active principle	Findings	Ref.
<i>Agaricus bisporus</i>	Observational study	500 participants	Ovarian	Polysaccharides	Moderate inverse association between habitual mushroom intake and epithelial ovarian cancer	[54]
<i>Agaricus bisporus/ Amauroderm a rude</i>	Meta-analyses, observational studies	6890 women	Breast	Daily intake – 1 g/d in pre/postmenopausal women	Mushroom consumption associated to lower risk of breast cancer.	[55]
<i>Ganoderma lucidum</i>	Randomized, clinical tr	373 adults	Various types	Spore vs. mycelium	Improve tumor response of lung Cancer to conventional therapy. Enhance immunity. Promising adjunct treatment in immunosuppressive effects of Chemotherapy. Qol relatively Improved.	[56]
<i>Lentinula edodes</i>	Open pilot study	10 participants	Various types	L. edodes mycelia	Combine treatment of LEM and immunotherapy might improve QOL and immune function.	[57]
<i>Pleurotus cornucopiae Oyster</i>	Double-blind, placebo controlled study	20 participants	Various types	Oyster extract	Potentiate immune system, may prevent cancer and other diseases	[49]
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Table: Human clinical studies' Summary

1.5 ANTI-CANCERS USES OF MUSHROOM OF DIFFERENT SPECIES

1.5.1 Genus *Agaricus*:

In this genus both edible and poisonous species both are included, with possibly over 300 members worldwide. The genus includes the common button mushroom (*Agaricus bisporus*) and the field mushroom (*Agaricus campestris*) are mainly cultivated mushroom.^{[38][39]} *Agaricus bisporus* lectin (ABL) and *Agaricus polytricha* protein (APP) are stable immune stimulants, for health food and pharmaceutical utilization^[40]. In vitro, *A. bisporus* extract can suppress aromatase activity and prevent breast-cancer cell proliferation. The broth fraction of *A. blazei*, when examined on the growth of human prostate cancer inhibited cell proliferation in both androgen-dependent and androgen-independent prostate cancer cell lines. The broth of *A. blazei* induced lactate dehydrogenase leakage in three cancer cell lines, whereas the activities of caspase 3 and the DNA fragmentation were enhanced the most in androgen-independent PC3 cells.^[41] Adams et al. (2008) evaluated the effects of *A. bisporus* extract in vivo and its major component, conjugated linoleic acid on prostate cancer cell lines in vitro, respectively. DU145 and PC3 prostate tumor size and tumor cell proliferation were decreased in nude mice treated with mushroom extract. Microarray analysis of tumors identified significant changes in gene expression in the mushroom-fed mice as compared to controls. The conjugated linoleic acid inhibited proliferation in the prostate cancer cell lines in vitro.^[42]

1.5.2 Genus *Ganoderma*:

Ganoderma, commonly known as Lingzhi or Reishi, also called mushroom of immortality, belonging to family Ganodermataceae has been traditionally administered throughout Asia for centuries as a cancer treatment. *Ganoderma lucidum* exhibits anti-cancer effect alone or in combination with chemotherapy and radiotherapy.^[43]

The effects of ethanol extracts of *G. lucidum* on the growth of human gastric carcinoma (AGS) cell line were investigated which showed decrease in their viability. The treatment induced the expression of proteins such as death receptor 5 and tumor necrosis factor-related apoptosis-inducing ligand, which further triggered the activation of caspase-8 and the cleavage of Bid.^[44] Chen and Zhong (2011) reported the inhibition of tumor invasion and metastasis by ganoderic acid T, a lanostane triterpenoid *G. lucidum*.^[45] Ganoderic acid T promoted cell aggregation, inhibited cell adhesion, and suppressed cell migration with a dose-dependent manner in human colon tumor cell lines of HCT-116 p53+/+ and p53-/. GA-Me was found to possess remarkable cytotoxicity on human colon carcinoma (HCT-116) cells in a dose-dependent manner.^[46] Zhou et al. (2011) suggested that GA-Me may be a novel promising agent for the treatment of human colon carcinoma cells by mitochondrial pathway manipulation.^[47] Hsu et al. (2008) studied the anti-tumor effects of *Ganoderma tsugae* extracts on colorectal adenocarcinoma cell proliferation. Tumorigenesis study in nude mice revealed the extracts caused tumor shrinkage. In vitro and in vivo experiments showed that colorectal adenocarcinoma cells are inhibited by induction of G2/M cell cycle arrest.^[48]

1.5.3 Genus *Antrodia*:

Antrodia (camphor tree mushroom) is a genus of mushrooms in the family Fomitopsidaceae. These mushrooms are highly valued in Taiwan. The fermented culture broth of *Antrodia camphorata* has been shown to promote cell cycle arrest and apoptosis of human estrogen-non-responsive breast cancer (MDA-MB-231) cells. Yang et al. (2011) demonstrated that non-cytotoxic concentrations (20–80 µg/mL) of *A. camphorata* markedly inhibit the invasion/migration of highly metastatic MDA-MB-231 cells through suppression of the MAPK signaling pathway.^[48] It is mainly used to treat diarrhoea, abdominal pain, itchy skin, hypertension, inflammation etc.. Some studies show that this mushroom can increase the immune strength of humans. Researchers have also shown that *Antrodia cinnamomea* has antioxidant properties and can reduce oxidative damage caused by free radicals. In fact, recent research claimed as a promising

chemotherapeutic drug for cancer and may even be used in the future for chemoprevention, which uses natural agents to prevent the initiation or spread of symptoms caused by carcinogenesis.

There are some other mushrooms which are also used as a cancer drugs such as:

Coriolus versicolor, *Hericium erinaceus*, *Cordyceps militaris*, *Xerocomus badius*, *Calvatia utriformis*, *Flammulina velutipes*, *Suillus placidus*, *Inocybe umbrinella*, *Inonotus obliquus*, *Funlia trogii*, *Albatrellus confluens*, *Lactarius flavidulus*, *Coprinus comatus* etc.



Fig: Some medicinal mushroom with cancer properties [26]

2. CONCLUSION

Mushroom is the source of anti-cancer substances so that many studies claim that it is more convenient than other treatments. So several companies are started to prepare anti-cancer drugs from mushroom extracts using state-of-the-art technology and their products are gradually being recognized worldwide. Zhejiang Fangge Pharmaceutical & Healthcare Products Co. Ltd., a large pharmaceutical company in China sells mushroom extracts for cancer patients. There are so many companies who exports polysaccharide produces from mushroom such as *G. frondosa*, *L. edodes*, *G. lucidum*, *A. blazei*, *Cordyceps sinensis* and *H. erinaceus*. FineCo Ltd. in Korea develops effective drugs, including anti-cancer formulations from medicinal mushrooms. Its products are now sold in Japan, Hong Kong, Australia, America & so many countries. Aloha medicinal Inc. in USA develops an array of medicinal mushroom products including the cancer-inhibiting *Ganoderma* capsules. In near future, more companies are expected to join the flourishing market of cancer therapeutic manufacture from mushrooms.

Not only commercially, even if we gain proper knowledge about mushrooms and cultivate them for conjunction then and we will be benefited not only by the cancer preventing substance in them but also our body will get a bulk quantity of nutritional agents which would greatly reduce malnutrition. Besides mushroom is such a substance which cannot be cultivated artificially or by means of any chemical manure or fertilizer does reducing the risk of side effects of chemical manure which is a great concern these days.

And as a food technologist I feel that it instead of consuming mushroom directly we can try to extract the anti-cancer compounds in mushroom and try to incorporate them in the day to day food products we take in which will greatly bring down the number of cancer patients and also bring down the graph of malnutrition in the world. I feel so because studies reveal that direct consumption of mushroom is not as effective as the components that the mushrooms hold does taking in the components rather than the mushroom as a whole is more effective.

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