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ANTIOXIDANT AND ANTICANCER THERAPEUTIC POTENTIALITY OF MUSHROOMS: A REVIEW

Arvind K. Sharma [1], Madhu Gupta [2], Archana Shrivastav [2] and A.M. Jana*[4]

Department of Biotechnology, College of Life Sciences, CHRI Campus, Gwalior, Madhya Pradesh, India
Department of Botany, College of Life Sciences, CHRI Campus, Gwalior, Madhya Pradesh, India
Director, Cancer Hospital and Research Institute, Gwalior, Madhya Pradesh, India
Former HOD of Biotechnology, College of Life Sciences, CHRI Campus, Gwalior, Madhya Pradesh, India

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Correspondence to Author:

Dr. A.M. Jana

155/B Sharda Vihar, City Center, New high court road, Gwalior, Madhya Pradesh, India

E-mail: arrvindsharrma@yahoo.in

ABSTRACT: Cancer is a substantial world health threat, & a largest cause of death in peoples of various age groups and economic backgrounds. This dramatic increase in the global burden of cancer has spurred research and many pharmacological studies as an attempt to limit the progression of this disease. Painful, expensive chemotherapy by dietary supplements have come forth as a novel significant approach in ailment of cancer. Since ancient times mushrooms has been used a good resource of dietary supplement. Mushroom is attributed by many medicinal properties, due to presence of phytochemicals, antioxidant, anticancer, antiviral, antimicrobial, anti-diabetic, anti-inflammatory etc. bioactive compounds in fruiting bodies and cultured mycelium. Polysaccharides and antioxidant have been extensively studied biologically active compounds of mushroom for their cytotoxic as well as immunomodulation properties. In this review we will highlight the recent findings on anticancereous bioactive compounds of mushroom, their therapeutic potentials and mode of action and the need for further investigation in cancer management.

INTRODUCTION: Since ancient times mushroom has been traditionally used for its amazing edible and medicinal properties.

Presently more than 150,000 mushroom species has been estimated on the Earth until now, imaginably only 10% (approximately 15,000 named species) are identified in this discipline or go as high as 22, 000.

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As per *Dictionary of the Fungi* [1] total 97,330 discovered species of fungi slime molds, chromistan fungi, chytridiaceous fungi, lichen-forming fungi, yeasts and molds including mushroom producing filamentous fungi.

Mushrooms are the more conspicuous fungi due to its distinctive structure known as fruiting body which can be hypogeous or epigeous, large enough to be seen with the naked eye and to be picked by hand [2].

In worldwide, *Phellinus, Pleurotus, Agaricus, Ganoderma, Clitocybe, Antrodia, Trametes, Cordyceps, Xerocomus, Calvatia, Schizophyllum, Flammulina, Suillus, Inonotus, Inocybe, Funlia, Lactarius, Albatrellus, Russula,* and Fomes

mushrooms that have been collected, cultivated and used for hundreds of years, are being appraised as edible and medicinal supplements for humankind. Current studies have raised the consciousness about the mushroom as a magnificent resource of nutraceuticals, anti-oxidants, anticancer, prebiotic, immunomodulating, anti-inflammatory, cardio vascular, anti-microbial, and anti-diabetic is a milestone in clinical studies [3].

The present review are aimed to encourage mushrooms as new generation ‘‘biotherapeutics’’.

However, Mushrooms are prominent for humans still and are considered as one of the inquisitiveness of nature and many of them are extensively consumed for their specific flavor and aroma regarded as a gourmet cuisine. The remarkable features of fungi are very crucial and their therapeutic potentiality will be extremely important. Worldwide a number of extensive attempts have been made to explore the use of mushrooms and to investigate the importance of their metabolites for the treatment of a variety of human ailments [4].

The world’s number one mushroom *Ganoderma* has been considered as a sovereign of all medicinal mushrooms and it is followed by *Lentinula* and others including *Pleurotus*, the later renowned as oyster mushroom. Anti-tumor activity was shown by Nanba in *Pleurotus* mushroom [5]; since then a number of studies have indicated their medicinal potentialities and accordingly Chang and Buswell called them as ‘mushroom nutraceuticals; of late they have been included in the category of functional foods [6].

Fruiting bodies as well as active mycelia of *Pleurotus* species also possesses a number of therapeutic properties to combated cancer, high cholesterol level, high blood pressure, blood sugar etc in humans[7].The potent anti-cancer bioactive components in mushrooms are lentinan, krestin, hispolon, lectin, calcaelin, illudin S, psilocybin, Hericium polysaccharide A and B (HPA and HPB), ganoderic acid, schizophyllan, laccase, etc.Most excellent and thereuptically potent mushroom-derived metabolite is a β-glucans a versatile, broad spectrum polysaccharide with anti-tumor and immunomodulating properties is best known for their biological activities.

Methanolic extracts of *P. ostreatus var. florida* showed significant inhibition of mutagenicity elicited through mutagens requiring activation [8]. *P. ostreatus* extracts diminished pathological changes in dimethylhydrazine-induced colon cancer in rats as well as extracts of *P. cornucopiae* significantly reduced H_2O_2 induced DNA damage in Chinese hamster lung cells [9]. *P. ostreatus* extract reduced genotoxicity through suppression of *DNA* damage induced by different mutagens in the *Drosophila* DNA repair test [10].

A morbidity and mortality rate of ailing person is vastly reduced by the ingestion of anti-cancer drugs aimed at minimizing the risk of carcinogenesis. These agents also comprise of Cyclooxygenase inhibiting, non-steroid anti-inflammatory drugs (NSAID) such as aspirin, sulindac, piroxican and indomethacin. cyclooxygenase (COX) is an enzyme that catalyses the conversion of arachdonic acid to prostaglandin a proinflammatory substances which activates carcinogens to take up forms that damage the genetic material that can significantly promote the growth of tumor cells and suppress immune system [11].

The addiction of tobacco smoking, alcohol consumption, excess use of caffeine and other drugs, sunshine, infection from such oncogenic virus like cervical papillomaviruses, adenoviruses Karposis sarcoma (HSV) or exposure to asbestos are implicated as contributory agents of mammalian cancers. Nevertheless a large population of people is often exposed to these agents with only very small number of person affected which let us know that these may not really be the root cause of cancer.

Polysaccharides are the well identified and most effective mushroom derived substances with antitumor and immunomodulating properties. Indentification and isolation of bioactive agent polysaccharides specifically β-glucans,: krestin from cultured mycelia biomass of *Trametes versicolor* (Turkwey Tail), lentinan from fruiting bodies of *L. edodes*, and schizophyllan from the liquid cultured broth product of *Schizophyllum commune* (Split Gill) led to the development of first three major drugs were polysaccharides. Many new antitumor and immunomodulating polysaccharides have been recognized and put into practical use.

Antioxidant, Anticancer and immuno-modulating activity of polysaccharides from different mushroom genus: Recently, ethanolic extracts of various valuable and crucial mushrooms showed a significant antioxidant activity against both DPPH and ABTS radicals. Moreover, regarding bioactive metabolites,an another protein purified from *P. ostreatus* extract through Cibacron blue affinity has been shown to have potent antitumor activity against different tumors using mice model [12].

Yang *et al.* reported that antioxidants activity of *P. ostreatus* against free radicals depend upon the colour of fruiting bodies. In addition to polysaccharides pleuran, another compound known as phenols also possesses free radical scavenging activity that reduces inhibitory effects of mutagens and carcinogens [13]. On comparing the phenol content with mycelium and fermentation broth filtrate of *P. citrinopileatus,* fruiting bodies of *P. ostreatus* have higher phenol concentration [14].

Recently a study has been carried out on concentration of phenols against the developing stages of fruiting bodies, very astounding result was shown by Shaha *et al* that highest concentration of phenols was 2.79 mg/g during initial one day stage (immature bud stage) and phenolic concentration gradually decreased to 1.27 mg/g in subsequent stages of bud development, but upon maturity (four day stage), the total concentration of total phenol was again increased (2.08 mg/g)[15].Earlier Iwalokun *et al* has found the similar result, when they compare the *in vitro* antioxidant capacity of acetone extract, methanolic extract and petroleum ether extract. Methanolic extract of *P. eous* significantly enhanced the activity of antioxidant enzymes [16].

Genus *Pleurotus*: Lavi *et al* (2006) reported that a novel water-soluble polysaccharide (POPS-1) was extracted from the fruiting bodies *of P. ostreatus* by hot-water extraction, ethanol precipitation, and fractionation by DEAE-cellulose ion exchange and Sepharose CL-6B gel filtration chromatography, induces anti-cancer and pro-apoptotic effects on HT-29 colon cancer cells [17]. In a dose dependent *in vitro* study on HeLa tumor cell , POP-1showed significant higher anti-tumor activity against HeLa tumor cell and lower cytotoxicity to human embryo kidney 293T cells than anticancer drug 5-fluorouracil. The results suggest POPS-1 may be taken into account as a potential remedy for developing a novel low-toxicity anti-tumor agent [18]. Lectin a homodimeric 32.4 kDa extracted from fresh fruiting bodies of the mushroom *Pleurotus citrinopileatus* showed potent anti-tumor activity in mice bearing sarcoma 180.When extract administered intraperitoneally at 5 mg/kg daily for 20 days,and inhibited tumor enlargement to agreat extent (approximately 80%) [19].

During an *in vitro* study, the aquous extracts of polysaccharides from the fruiting body and mycelium of a novel edible mushroom *Pleurotus tuber-regium* exhibited strong cytotoxicity (approximate IC50 25 µg/mL) as well as effective anti-proliferative activities (200 µg/mL) against human acute promyelocytic leukemia cells (HL-60).

The polysaccharides induced the apoptosis with an increased ratio of Bax/Bcl-2 in human acute promyelocytic leukemia cells. Flow cytometry and western blot studies , furthermore demonstrated the polysaccharides extract from the mycelium decreased the expression of Cdk 1causedG2M arrest in the HL-60 cells, at the same time as fruiting body extract caused a depletion of Cdk2 and high cyclin E expression by arresting the HL-60 cells in phase [20].

Genus *Ganoderma*: World famous mushroom *Ganoderma* is commonly known as Lingzhi or Reishi.*Ganoderma*, a mushroom of immortality is belonging to family Ganodermataceae has now been globally cultivated for its miraculous healing properties. Anticancer effect of Ganoderma lucidum has been studied alone or in combination with chemothereupatic drugs as well as radio therapy effectively. Treatment of human gastric carcinoma (AGS) cell line with Ganoderma extract, induced the apoptosis through expression of proteins, specialized for signaling cascade of death receptor-mediated extrinsic, (death receptor 5 and necrosis factor), as well as mitochondria-mediated intrinsic, which activated caspase 8, 9 and 3, downregulation of IAP family proteins (XIAP and surviving), concomitant degradation of poly (ADP-ribose) polymerase and Cleavage of Bid, all events were associated with inactivation of the Akt signaling pathway [33].

TABLE 1: SHOWING THE ANTICANCER EFFECT OF MUSHROOMS WITH THEIR ACTIVE COMPONENT

Mushrooms figure with name	Active component	Effective against
 ***Agaricus sps***	Acid treated fraction	Meth-A-tumor model [21]
	Polysaccharide fraction	Sarcoma-180 [22]
	Hot water extract	Sarcoma-180 [22]
	Ergosterol	Tumor[23]
 ***Ganoderma sps***	Ganoderic acid	Growth of hepatoma cells *in vitro* [24]
	Ganopoly	Advanced cancer [25]
		Growth arrest of LNCaP prostate cancer cell line [26]
 ***Lentinus sps***	Lentinan	Sarcoma 180 [27]
	Lentinan	Stomach cancer, Colon cancer [28]
	Lentinan	K36 murine lymphoma[29]
	Crude extract	K36 murine lymphoma[29]
	Lentinan	Various colon carcinoma cell line[29]
		Sarcoma 180 [30,31]
 ***Pleurotus sp***	Hot water extract	Sarcoma 180[30,31]
	Hot water extract	Sarcoma 180[30,31]
	Methanol extract	Ehrllich ascites carcinoma[32]

Ganoderic acid T, a lanostane triterpenoid extracted from *Ganoderma lucidum*, found very effective against tumour growth and metastatis. A dose-mediated investigation in human colon tumor cell lines of HCT-116 suggested that Ganoderic acid T, possess remarkable cytotoxicity ,promoted cell aggregation, inhibited cell adhesion, and surpressed cell migration in human colon tumor cell lines of HCT-116.

In a time mediated treatment of human colon tumour cell lines (HCT - 116) with methyl extract of Ganoderma, induced the apoptosis by reducing mitochondrial transmembrane potential that released cytochrome C and raised capases 3 activity.

In addition to, dysfunction of mitochondria, methyl extract also increased the expression of anti tumor protein P – 53 and up regulation of proapoptotic protein, Bsx as well as no significant alteration in Bcl 2 expression, therefore the ratio of Bsx/Bcl was increased [34]. Zhou, *et al*. (2011) recommended GA-Me as suitable new potential agent for the treatment of human colon carcinoma cells by mitochondrial pathway manipulation [35]. Liu and Zhong (2010) comperativly studied the effects of a pair of positional isomer of ganoderic acids, ganoderic acid Mf (GA-Mf) and ganoderic acid S (GA-S)by stimulating HeLa cells apoptosis [36].

The results showed that both isomers (ganoderic acid Mf (GA-Mf) and ganoderic acid S (GA-S) inhibited the cell population growth on various human carcinoma cell lines by MTT assay significantly, whereas GA-Mf efficiently differentiated the normal cells before inducing apoptosis in cancer cells, was investigated through Flow cytometry results and cell cycle arresting phases demonstrated as compared with GA-S.

Moreover, HeLa cells demonstrated decline in the mitochondrial membrane potential resulted the release of cytochrome c from mitochondria into the cytosol, causing stimulation of caspase- 3 and caspase-9 activity was necessary to bring about apoptosis. The Bax/Bcl-2 ratio was also increased in GA-treated HeLa cells. An *in vitro* study on mouse lymphocytic leukemia cancer revealed that mainly LZ-D4, a native glycopepetide and sulphonated derivative purified from *G.lucidum* were effective against cancer [37].

G. lucidum biometabolites flavonoids, terpenoids, phenolics and alkaloids showed anti-human papillomavirus 16 (HPV 16) E6 oncoprotein activity.Dichloromethane extract from *G.lucidum* inhibited the HPV 16 E6 production in epidermoid cervical carcinoma (CaSki) cells [38]. Tumorigenic *in vitro* and *in vivo* study of colorectal adenocarcinoma cells in nude mice revealed that *Ganoderma tsugae* extracts inhibited the proliferation of colorectal adenocarcinoma cells, possibly due to down regulation of cyclin A and B1 and up regulation of p21 and p27 that caused arrest of G2/M cell cycle [39].

As a result, potentiality of *G. tsugae* extracts was not significant for physiological changes in animal models. Anti-telomerase, recombinant fungal immuno-modulatory protein, purified from *G. tsugae* (reFIP-gts) has anti-telomerase effects in human lung adenocarcinoma by decreased growth of (A549) cells undergo premature cellular senescence. Liao *et al* (2008) demonstrated that reFIP-gts-treated lung cancer cells undergo premature cellular senescence and are arrested at G1 phase. The reFIP-gts- treated A549 cells grew slowly and formed significantly fewer cell colonies [40].

Genus *Agaricus*: Delmanto *et al* 2001) studied immunomodulatory, anti-carcinogenic and anti-mutagenic effects of *Agaricus blazei* Murrill extracts on clastogenicity induced by cyclo-phosphamide (CP) in mice [41].

The broth fraction of *A. blazei* inhibited cell proliferation in both androgen-dependent and androgen-independent prostate cancer cell lines, in human prostate cancer. In three cancers cell lines, the broth of *A. blazei* bring about lactate dehydro-genase leakage, while on the contrary the caspase 3 activities and the DNA fragmentation were increased the most in androgen independent PC3 cells as well as the protein expressions of apoptosis- related molecules were raised in PC3 cells. As a consequences of orally supplemented mice with *A. blazei* (with the higher ratio of β-glucan) significantly suppressed tumor growth and decreased proliferating cell nuclear antigen-positive cells and reduced tumor microvessel density without any adverse effects in severe combined immunodeficient mice with PC3 tumor xenograft [42].

Akiyama *et al* (2011) Agaritine, a hydrazine-derivative from hot-water extract of *A. blazei* Murrill moderately induces DNA fragmentation, annexin V expression, and cytochrome c release as well as apoptosis in human leukemic monocyte lymphoma (U937) cells. Agaritine progressively increased Caspase- 3, 8, and 9 activities. In ailment of cancer *A. blazei* and various kind of anti-leukemic bioactive constituent have been extracted from it, has been used as an adjuvant in cancer chemotherapy. Evaluations of in vitro anti-leukemic effects of A. blazei were made through MTT and tritiated thymidine incorporation assays. The most potent extract was further investigated using human promyelocytic leukemia (NB-4) cells-bearing nude mice [43].

In a study on human leukemia NB-4 and K-562 cells,the extract of JAB80E70 revealed the significant tumor specific growth inhibitory effect. JAB80E70 extract induces the apoptosis in NB -4 cells,analysed through ELISA detection of DNA fragmentation an cell death [44].

Adams *et al*. (2008) evaluated the activities of *A. Bisporus* extracts *in vivo* mainly possesses a major component, conjugated linoleic acid with anticancer activity against prostate cancer cell lines. in vitro inhibitory effect of linoleic acid decreased DU145 and PC3 prostate tumor size and tumor cell proliferation in nude mice. In Microarray study of tumor, in a mushroom consuming mice as compared to control, identified significant alterations in gene expression [45].

Genus *Lentinula*: *Lentinula edodes* is an antiproliferative mushroom widely known as Shitake mushroom, produces lentinan, a polysaccharide, attributed with anti leukemia cancer effect. The ethanol extract of Shitake mushroom significantly inhibited the cell proliferation of CH72 cells by inducing transient arrest of G1 phase of cell cycle, while no alteration was reported in proliferative response of the non-tumorigenic keratinocyte (C50) cell line [46].

Current scenario and Future Perspectives: In the last few decades, large number of mushroom fungi has been progressively used as a source of medicinal compounds and therapeutic adjuvants or health food supplements. Recently, the anticancer and anti-proliferative activities of polysaccharides or polysaccharide-protein complexes derived from mushrooms have received much attention in cancer treatment. Recent investigation has revealed that dietary supplementation with medicinal fungi is capable of significantly improving the physiological condition and prognosis of cancer patients because of their effects on red blood cells and the immune system.

In vitro and clinical studies has indicated that mushrooms exhibit cancer-preventive and anticancer activity, which might be attributed to its antioxidative and radical-scavenging effects, inhibition of metabolic activation and enhancement of detoxification of carcinogens, direct cytotoxicity, antiproliferation, and modulation of signaling transduction molecules, induction of cell-cycle arrest and apoptosis, and enhancement of host immune function.

One of the main side effects of radiation and chemotherapy in the treatment of cancer patients is the development of leukopenia, which significantly increases the risk of infections. Hence, several recent studies have addressed the question of whether mushroom extracts or constituents can enhance hematopoiesis by exploring optimum dosing, efficacy and safety, alone or in combination with chemotherapy/radiotherapy, by which they might do so.

The present studies provide new insights into the possible therapeutic uses of mushrooms and helpful suggestions for the design of anti-tumor drugs from mushrooms in combating cancer.

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