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Review article

Antineoplastic effect of mushrooms: a review

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Abstract

Global awareness of cancer is one of the largest causes of death in people of various ages and racial backgrounds has led to research and many clinical studies in an effort to limit the progression of this disease. Chemoprevention by dietary constituents has emerged as a novel approach to control cancer incidence. A variety of mushrooms have been used traditionally for the maintenance of health, and for prevention and treatment of diseases. This review highlights some of the recent works that express promising anti-tumor effects. Mushroom extracts may modulate the response of host immune system; in particular, various mushroom polysaccharides are likely to effect promotion and progression stages towards cancer. Other substances contained in mushrooms may be able to interfere with tumor initiation through a variety of mechanisms.

Keywords: Antiangiogenesis; anticancer; apoptosis; fungi; immunomodulators.
Abbreviations: AKT/PKB: Protein Kinase B; BRM: Biological Response Modifiers; ConA: Concanavalin A; FDA: Food and Drug Administration; MD: Maitake D-fraction; NK: Natural Killer; PHA: Phytohemagglutinin; PSK: Protein-bound polysaccharide Krestin; PSP: Polysaccharide peptides.

Introduction

For many years, humankind has benefited from green plants as a source of drugs and herbal remedies. Fungi, on the other hand, have not been considered in any significant way. However, this is changing very rapidly and fungi are expected as a major source of pharmaceuticals and medicinal food in the coming years. The platform for fungi as a source of pharmaceuticals and health food will be very important and their economic potential will be extremely important (Pan Ming Li, 1992). The ancient people of India, China, Iran and Seythian used mushrooms in their ritualistic performances (Lowy, 1971). The ancestors of Finno-Ugric were also familiar with the religious conception of mushrooms (Bongard-Levin, 1980). The Mexican Indians seem to regard the psychotropic plants as mediators with God. Nahuati dialect speaking people named mushrooms as 'teohanotactl', which means flesh of God. Classical religious scriptures like "Vedas" have mentioned their medicinal value. The Greeks regarded mushrooms as "Providing strength to soldiers in war". The Romans considered them as "Food of the Gods" and the Chinese treated them as the "Elixir of life" (Chang and Miles, 1989). Mushrooms are not a taxonomic group. According to Chang and Miles (1992), mushrooms are defined as "a macro fungi with a distinctive fruiting body which can be hypogeous or epigeous, large enough to be seen with the naked eye and to be picked by hand". There are approximately 14,000 described species of mushrooms. However, there is an estimated 1.5 million species of fungi, of which it is likely that there are approximately 140,000 species that qualify as mushrooms; suggesting that only 10% have been reported so far in science. Medicinal mushrooms have a long tradition in Asian countries, whereas their use in Western nations has only slightly increased during the last decade (Sharma, 2003). Mushrooms are nutritionally functional food and a source of physiologically beneficial and non-toxic medicines (Wasser and Weiss, 1999). They have been used in folk medicine throughout the world since ancient times. Attempts have been made in many parts of the world to explore the use of mushrooms and their metabolites for the treatment of a variety of human ailments (Jose and Janardhanan, 2000). A variety of mushrooms have been used traditionally for the maintenance of health and for prevention and treatment of diseases such as cancer, inflammation, viral diseases, hypercholesterolemia, blood platelet aggregation and hypertension (Breene, 1990; Jong et al., 1991; Chihara, 1992; Ooi and Liu, 1999; Wasser and Weiss, 1999; Biswas et al., 2010). In recent years the most significant effect of mushrooms and their metabolites which attracted the attention of scientists is their antineoplastic activity. Mushroom metabolites are usually used as adaptogens and immunostimulants and they are now considered one of the most useful antitumor agents for clinical uses (Jose and Janardhanan, 2000). The global awareness of cancer as the second largest cause of death in people of various ages and background has led to so much research effort and clinical studies in the fight against the disease (Daba and Ezeronye, 2003). The continuing magnitude of the cancer problem and the failure of conventional chemotherapy of the advanced invasive disease to effect the major reduction in the mortality rates for the common forms of epithelial malignancies such as carcinoma of lung, colon, breast, prostate, pancreas etc., indicate that new approaches to the control of cancer are critically needed. Even though great advances have been made in basic scientific knowledge relating to cancer as well as in the clinical treatment, death rates from some of the common cancers continue to rise (Sporn and Suh, 2002).

Furthermore, the misperception of cancer as a disease whose most fundamental characteristics is excessive cell proliferation has led to an over emphasis of testing and development of cytotoxic drugs that kill cancer cells. Unfortunately, most cytotoxic drugs used in cancer chemotherapy are also highly toxic to a wide spectrum of normal tissues, such as those found in gastrointestinal tract, bone marrow, heart, lungs, kidney and brain. Iatrogenic failure of these organs is a frequent cause of death from cancer (Sporn and Suh, 2002). As an alternative approach, we need to consider that cancer is ultimately the end stage of a chronic disease process characterized by abnormal cell and tissue differentiation. This process, which eventually leads to the outcome of invasive and metastatic cancer, is carcinogenesis. We need to focus more effort on control of carcinogenesis rather than attempting to cure the end stage disease (Sporn and Suh, 2002). In many cases, cancer is long drawn-out disease that emotionally drains both the patients and their family (Kim, 2004). Although enormous energy has been invested in treating existing cancer by chemotherapy, prevention of cancer is the preferred option. Empirical approaches to discover anticancer drugs and cancer treatments have made limited progress in the past several decades in finding a cure for cancer. New discoveries in molecular oncology along with rapid expansion of our knowledge concerning the processes that govern differentiation, apoptosis, immune surveillance, angiogenesis, metastasis, cell cycle, and signal transduction control have unveiled an abundance of specific molecular targets for cancer therapy, including a variety of small-molecule compounds that inhibit or stimulate these molecular targets (Zaidman et al., 2005). Because cancer cells develop when normal cells grow abnormally and become malignant, it may not be feasible for any drug to prevent carcinogenesis and inhibit the growth of cancer cells without injuring the normal cells of the host. Thus, attention has recently focused on the development of some kind of immunotherapy that would identify and eliminate cancer cells as foreign matter, as well as act on substances, such as immunopotentiators, immunoinitiators and biological response modifiers (BRM)-special biophylactics that would prevent carcinogenesis and carcinostasis (Mizuno, 1999). Mushroom extracts may modulate the response of the host immune system. In particular, various mushroom polysaccharides are likely to affect promotion and progression stages towards cancer. Other substances contained in mushrooms may be able to interfere with tumor initiation through a variety of mechanisms, e.g., by enhancing the host's antioxidant capacity or by upregulating phase I and phase II enzymes involved in the metabolic transformation and detoxification of mutagenic compounds (Lee and Nishikawa, 2003). Yet other mushroom constituents may inhibit promotion or progression to a cancer by exerting direct cytotoxic effects on tumor cells (Fujimiya et al., 1998), by interfering with tumor angiogenesis (Takaku et al., 2001), or by upregulating other non-immune tumor-suppressive mechanisms.

Anticancer activity of Mushrooms and their Constituents

The use of medicinal mushrooms in the fight against cancer is known in China, Korea, Japan, Russia, United States and Canada. Such mushrooms effective against cancers of the stomach, oesophagus, prostate and lung, belong to the family of Polyporaceae (Mizuno, 1999). In Russian medicine, an extract of Chaga (*Inotus obliquus*) is used as an antitumor medicine. A. Solzhenitsyn stated in the article entitled "Cancer of the White Birch" that a cancerous lesion was cured by application of Chaga, a mushroom that grows on the trunk of white birch (*Betula alba*) (Wasser and Weiss, 1999). Some species of edible higher Basidiomycetes have been reported to inhibit the growth of different kinds of tumors. Approximately 200 species of higher Basidiomycetes have been reported to exhibit antitumor activity (Lucas et al., 1957; Gregory et al., 1966; Ying et al., 1987; Yang and Jong, 1989; Mizuno, 1995 a, b, 1996). The search for new antitumor and other medicinal substances from the higher Basidiomycetes and the study of medicinal value of these edible mushrooms have become matters of great interest. Thus, some authors have combined the use of mushrooms both for nutritional and medicinal purposes (Ying et al., 1987; Pai et al., 1990; Mizuno et al., 1995; Wasser and Weiss, 1997 a, b; Miles and Chang, 1997). The antitumor activity of the higher Basidiomycetes has been first demonstrated by Lucas et al. (1957), employing extracts of fruiting bodies of *Boletus edulis*, another Homobasidiomycetes in tests against Sarcoma 180 cell line in mice. In the 1960s, calvacin was the most commonly cited natural product isolated from the medicinal mushroom, *Calvatia gigantea* and broadly used in many laboratories as an antitumor agent. It is interesting to note that calvacin emerges indirectly from the recorded ancient application and verification of folk medicine (Lucas et al., 1957, 1959). The chemical nature of calvacin reveals it as moderately heat-stable, nondiffusible, basic muco-protein. Calvacin has been tested against many experimental tumors, including Sarcoma 180, mammary adenocarcinoma 755, leukemia L-1210, and HeLa cell lines. Ikekawa and coworkers (1968, 1969) reported that hot water extracts obtained from the fruiting bodies of six edible wild higher Basidiomycetes namely, *Flammulina velutipes*, *Lentinus edodes*, *Pholiota nameko*, *Pleurotus ostreatus*, *Tricholoma matsutake* and *Pleurotus spodoleucus*, showed a marked host mediated antitumor activity against Sarcoma 180 in Swiss albino mice. In 1962, Yoshida and his collaborators isolated an agent from *Lampteromyces japonicus*, active against Ehrlich carcinoma of the mouse. Gregory and collaborators (1966) surveyed more than 7,000 cultures of higher Basidiomycetes for antitumor activity against three rodent tumor systems. 50 cultures representing 22 species produced in fermentation media, showed inhibitory effects against Sarcoma 180, mammary adenocarcinoma 755, and leukemia L-1210. Using standard methods of fractionation and purification of polysaccharides, Chihara and coworkers (1969, 1970 a, b) isolated a water soluble anti-tumor polysaccharide from the fruit bodies of *Lentinus edodes*, which was named "*Lentinan*" [β(1-3), β(1-6) glucan] after the generic name of this mushroom. The molecular formula of Lentinan is $(C_6H_{10}O_5)_n$; the mean molecular weight is about 1×10^5-5×10^5 Da, $[\alpha]_D$ + 20°-22° (NaOH). It has been confirmed to be a β-D-glucan, as shown by electrophoresis and ultracentrifugation, as well as by various techniques and instrumental analysis (Sasaki and Takatsuka, 1976). Chihara reported on the antitumor properties of *L. edodes*, and stated that lentinan "*was found to almost completely regress the solid type of tumors in synergic host-tumor system A*". The antitumor effect of lentinan was originally confirmed by using Sarcoma 180 transplanted in CD-1/ICS mice (Chihara et al., 1969). Lentinan is not only effective against allogenic tumors but also against various synergic and autochthonous tumors. It also prevents chemical and viral oncogenesis (Zakany et al., 1980). Antitumor activity of lentinan was found to be significantly higher than that of polysaccharides isolated from many other fungi, lichens and higher vascular plants. Since then, numerous researchers have isolated some essential substances from

mushrooms. They established that these are a type of β-D-glucan, a polysaccharide, yielding D-glucose only by acid hydrolysis. The basic β-D-glucan is a repeating structure with the D-glucose units joined together in linear chains by beta-bonds (β). These can extend from carbon 1 of one saccharide ring to carbon 3 of the next (β1-3), from carbon 1 to carbon 4 (β1-4) or from carbon 1 to carbon 6 (β1-6). Mostly there is a main chain which is either β1-3, β1-4 or mixed β1-3, β1-4 with β1-6 side chains. The study of their steric structures by NMR analyses and X-ray diffractions clarified that active β-D-glucan shows a triple-stranded right-winding helix structure (Bluhm and Sarco, 1977). Molecular weight, degree of branching, number of substituents, as well as ultrastructure, including the presence of single and triple helices, significantly affect the biological activities of β-glucans (Adachi et al., 2002). Higher anti-tumor activity seems to be correlated with higher molecular weight, lower level of branching and greater water solubility of β-glucans (Zjawiony, 2004). However, the high branched maitake D-fraction (MD-fraction) from *G. frondosa* (MW 1 000 000–1 200 000 dalton) exerts a high anti-tumor activity (Nanba et al., 1987; Kodama et al., 2003). The carcinostatic mechanism of β-D-glucan is somewhat different from that of conventional chemotherapeutics for cancers, because it belongs to the field of immunotherapeutics, which strives to inhibit or eliminate the growth of cancer cells by activating and reinforcing the immunological functions of the host. It indicates that antitumor polysaccharides to be positioned as a sort of BRM based on their action mechanism, with minimal adverse effects and drug-induced sufferings. In Japan, 3 polysaccharide carcinostatics are available. They are produced from 3 different mushrooms (fruit body of *Lentinus edodes*, mycelium of *Coriolus versicolor*, and a substance produced in medium for *Schizophyllum commune*) (Mizuno, 1999). Polysaccharides demonstrating remarkable antitumor activity *in vivo* have been isolated from various species of mushrooms belonging to Auriculariales, Tremellales, Polyporales, Gasteromycetideae and Agaricomycetideae through screening against Sarcoma 180 in mice, through intraperitoneal (i.p.) or oral (p.o.) methods of administration (Ikekawa et al., 1969; Mori et al., 1989; Mizuno et al., 1995a; Wasser and Weiss, 1997 a, b). Polysaccharides or polysaccharide-protein complexes from mushrooms are able to stimulate the non-specific immune system and exert anti-tumor activity through the stimulation of the host's defense mechanism (Chihara et al., 1969; Mizuno, 1999; Wasser and Weiss, 1999; Reshetnikov et al., 2001). The drugs activate effector cells like macrophages, T lymphocytes and NK cells to secrete cytokines like TNF-α, IFN-γ, IL-1β, etc., which are antiproliferative and induce apoptosis and differentiation in tumor cells (Lindequist et al., 2005). There is evidence that β-D-glucans induce a biological response by binding to membrane complement receptor type 3 (CR3, alphaMβ2 integrin or CD11b/CD18) on immune effector cells; and that the ligand–receptor complex may be internalized. The intercellular events that occur after glucan-receptor binding have not been fully determined until now (Zhou and Gao, 2002). A recent study has reported that schizophyllan produced by *S. commune* is able to bind the mRNA poly (A) tail (Karinaga et al., 2004). Schizophyllan consists of a main chain of (1->3)-linked β-D-glucopyranosyl units with β-D-glucopyranosyl branch units linked 1->6 at, on average, an interval of three main chain units, degree of branching (DB 0.33), and have average molecular weight of 450,000 (Sasaki and Takasuka, 1976). A single helical conformer of schizophyllan stimulated the synthesis of a variety of cytokines, including TNF-α, from differentiated U937 cells, THP-1 cells, or human PBMC (Hirata et al., 1998). Schizophyllan is also commercially available in Japan as the drug sonifilan, which is effectively used against cervical cancer. Polysaccharides from mushrooms acting as immunomodulators work mainly by increasing macrophage activity. Macrophages and other phagocytes can be regarded as the body's protective shield. Currently, it is known that many mushroom polysaccharides from *Tremella fusiformis, Schizophyllum commune, Dendropolyporus umbellatus, Grifola frondosa, Hericium erinaceus, Inonotus obliquus, Ganoderma lucidum, G. applanatum, Lentinus edodes, Flammulina velutipes* have shown the ability to stimulate macrophage activity and strengthen immune system (Wasser and Weiss, 1999). In addition to β-D-glucans, a number of high molecular weight antitumor components were isolated from medicinal mushrooms, including heteroglycans, chitinous substances, peptidoglycans, lectins, RNA components, dietary fiber, and/or indigestible polysaccharides (Wasser and Weiss, 1999). A number of low molecular weight organic substances, such as terpenoids, steroids, novel gamma-pyrones, and novel phenols, isolated from mushrooms and identified, were screened for growth inhibition of cultured cancer cells, such as those in carcinoma of the cervical canal (HeLa cells) and the liver (hepatoma cells) (Jong et al., 1991; Mizuno, 1995 a, b, 1996; Kawagishi, 1995). Some terpenoids and their derivatives from Polyporales and Ganodermatales mushrooms are cytotoxic. These compounds are candidates for antitumor agents; indeed, about 100 different triterpenoids has been reported from the fruiting bodies and mycelia of *Ganoderma lucidum* and *G. applanatum*. These include highly oxidized lanostanine type triterpenoids. X-ray analysis has confirmed that some of these compounds like ganoderic acids, ganolucidic acids, ganosporeric acids, etc. have a boat shaped ring in their structure. Triterpenoids such as ganoderic acids, isolated from submerged cultured mycelial mass have been reported to inhibit growth of hepatoma cells *in vitro* (Toth et al., 1983). Zaidman et al. (2007) has reported that *G. lucidum* downregulated cyclin D1 expression leading to dephosphorylation of pRb and growth arrest of LNCaP prostate cancer cell line. *Omphalatus olearius* and *Lampteromyces japonicus* produce the cytotoxic tricyclic sesquiterpene, illudin S (lamterol) (Konno, 1995), which demonstrates anticancer properties and inhibits cancer growth cells by unique mechanism. It is believed that illudin S undergoes activation by glutathione. The activated form is then capable of covalent binding to DNA. This halts DNA replication and leads to cell death. The lipid fraction of *A. blazei* was reported to contain a compound with antitumor activity, subsequently identified as ergosterol (Takaku et al., 2001). Ergosterol was even identified as one of the most active constituents in the lipid fraction of *Grifola frondosa*, which exhibited antioxidant activity and inhibited the cyclooxygenase enzymes, COX-1 and COX-2 (Zhang et al., 2002). Oxidative damage is strongly implicated in the development of many chronic diseases, including cancer. The inducible form of COX, COX-2, also appears to play an important role in certain cancers. Its inhibition can result in the inhibition of tumor development, and it appears to be beneficial even in some established tumors (Prescott and Fitzpatrick, 2000). Apart from these, recent literature reports

Table 1. Anticancer effect of mushrooms

Mushroom name	Active component	Effective against	Reference
Agaricus blazei	Acid treated fraction	Meth-A-tumor model	Fujimiya *et al.*, 1998
Agaricus blazei	Poysaccharide fraction	Sarcoma-180	Minato *et al.*, 1999
Agaricus blazei	Hot water extract	Sarcoma-180	Minato *et al.*, 1999
Agaricus blazei	Ergosterol	Tumor	Takaku et al., 2001
Agaricus sylvaticus		Colorectal cancer	Fortes et al., 2009
Boletus edulis	Extracts	Sarcoma 180	Lucas et al., 1957
Calvatia gigantea	Calvacin	Sarcoma 180, mammary adenocarcinoma 755, leukemia L-1210, and HeLa cell lines	Lucas et al., 1957, 1959
Coriolus versicolor	PSP	Non–small cell lung cancer	Tsang et al., 2003
Coriolus versicolor	Polysaccharide peptide (PSP)	Non small cell lung cancer	Tsang *et al.*, 2003
Flammulina velutipes	Hot water extract	Sarcoma 180	Ikekawa et al., 1968, 1969
Ganoderma lucidum	Ganoderic acid	Growth of hepatoma cells *in vitro*	Toth et al., 1983
Ganoderma lucidum	Ganopoly	Advanced cancer	Gao et al., 2002
Ganoderma lucidum		Growth arrest of LNCaP prostate cancer cell line	Zaidman et al., 2007
Grifola frondosa	Ergosterol	Tumor development in some established tumors	Prescott and Fitzpatrick, 2000
Grifola frondosa	MD- fraction	Breast, prostate, lung, liver and gastric cancer	Deng et al., 2009
Inotus obliquus	Extract	Tumor	Wasser and Weiss, 1999
Lampteromyces japonicus		Ehrlich carcinoma	Yoshida, 1962
Lampteromyces japonicas	Illudin S	Growth of Cancer cells	Konno, 1995
Lentinus edodes	Lentinan	Sarcoma 180	Chihara et al., 1969
Lentinus edodes	Lentinan	Stomach cancer, Colon cancer	Hazama et al., 1998
Lentinus edodes		Sarcoma 180	Ikekawa et al., 1968, 1969
Lentinus edodes	Lentinan	K36 murine lymphoma	Ng *et al.*, 2002
Lentinus edodes	Crude extract	K36 murine lymphoma	Ng *et al.*, 2002
Lentinus edodes	Lentinan	Various colon carcinoma cell line	Ng *et al.*, 2002
Lepista inversa	Methanol and crude extract	Lymphocytic leukemia	Bezivin *et al.*, 2003
Lepista inverse		Lewis lung cancer	Bezivin *et al.*, 2003
Lyophyllum decastes	Ethanol precipitate of hot water fraction	Sarcoma-180	Ukawa *et al.*, 2000
Lyophyllum decastes	Poysaccharide fraction	Sarcoma-180	Ukawa *et al.*, 2000
Phellinus linteus		Growth, angiogenesis and invasive behaviour of breast cancer cells	Sliva et al., 2008
Phillinus rimosus	Ethyl acetate, methanol and aqueous extracts	Ehrllich ascites carcinoma	Ajith *et al.*, 2003
Phillinus rimosus	Ethyl acetate, methanol and aqueous extracts	Dalton's lymphoma ascites	Ajith *et al.*, 2003
Omphalatus olearius	Illudin S)	Growth cells of cancer cells	Konno, 1995
Pholiota nameko	Hot water extract	Sarcoma 180	Ikekawa et al., 1968, 1969
Pleurotus ostreatus	Hot water extract	Sarcoma 180	Ikekawa et al., 1968, 1969
Pleurotus spodoleucus	Hot water extract	Sarcoma 180	Ikekawa et al., 1968, 1969
Pleurotus pulmonarius	Methanol extract	Ehrllich ascites carcinoma	Jose *et al.*, 2002
Schizophyllum commune	Schizophyllan	Cervical cancer	Okamura et al., 1986
Sparassis crispa	Several polysaccharide fractions	Sarcoma-180	Ohno *et al.*, 2000
Tricholoma matsutake	Hot water extract	Sarcoma 180	Ikekawa et al., 1968, 1969

Phellinus linteus to suppress growth, angiogenesis and invasive behaviour of breast cancer cells through the inhibition of serine-threonine kinase protein kinase B (PKB/AKT) signaling. It suppresses phosphorylation of AKT at Thr^{308} and Ser^{473} in breast cancer cells (Sliva et al., 2008). Upto date report on anticancer activity of different mushrooms were summarized in Table 1.

Human Clinical Trials

Lentinan from *L. edodes*, schizophyllan from *S. commune*, MD-fraction from *G. frondosa* and compounds from *T. versicolor* (protein-bound polysaccharide Krestin/PSK and polysaccharide peptides/PSP) are in clinical use, especially in Japan and China, for the adjuvant tumor therapy (immunotherapy) in addition to the major cancer therapies like surgical operation, radiotherapy and chemotherapy. Application of lentinan in addition to chemotherapy led to prolongation of survival time, restoration of immunological parameters and improvement of life quality in patients with stomach cancer, colon cancer and other carcinomas in comparison to patients who had chemotherapy alone (Hazama et al., 1995). A randomized, placebo-controlled, double-blind study was conducted with orally administered PSP isolated from *Coriolus versicolor* in 68 patients with advanced (stages III or IV) non–small cell lung cancer (Tsang et al., 2003). The patients received three capsules of 340 mg each (or placebo) three times daily for 4 weeks. Leukocyte and neutrophil counts rose significantly after PSP treatment, whereas they decreased in the control group. Total IgG and IgM levels were significantly increased in the PSP group but not in the placebo group, with the difference between the groups being statistically significant. There were, however, no complete or partial responses to PSP treatment. The number of patients that withdrew from the study, mostly due to significant deterioration, was significantly higher in the placebo group (n = 8) compared with the PSP group (n = 2), suggesting that ingestion of PSP was associated with a reduced rate of deterioration. A phase I/II study was conducted with Ganopoly (a crude polysaccharide fraction of *Ganoderma lucidum*, 600 mg given orally three times daily for a total dose of 1800 mg/day in patients with advanced cancer (Gao et al., 2002). No partial or complete responses occurred, but some patients reportedly experienced palliative effects. Immune parameters were assessed in 75 of the 143 patients originally enrolled and were found not to be affected by the mushroom fraction. In a subgroup of 32 patients with stable disease for 12 weeks, however, the lymphocyte mitogenic response to phytohemagglutinin (PHA) and concanavalin A (ConA) were significantly increased, as was the natural killer (NK) cell activity. In a case, series of eight patients with various cancers (mostly stage II, stage III, stage IV), who were given 100 mg of D-fraction, a polysaccharide isolated from *Grifola frondosa* (maitake), daily for up to 34 months, there was an, at times marked, increase in Natural-Killer (NK) activity (Kodama et al., 2002). The maitake D-fraction is a relatively new compound, and there are a number of clinical trials in breast, prostate, lung, liver and gastric cancers underway in the United States and Japan (Deng et al., 2009). Most of these are at an early clinical stage (phase I/II). In early 1998, for example, Maitake products received FDA (Food and Drug Administration, USA) approval for an investigational new drug application to conduct a phase II pilot study on the efficacy of a maitake D-fraction in treating advanced breast and prostate cancer patients (Zhuang and Wasser, 2004). Dietary supplementation with *Agaricus sylvaticus* produces benefits in hematological and immunological parameters and can reduce fasting glycemia levels in patients with colorectal cancer in the postoperative phase (Fortes et al., 2009). This reduction results in beneficial effects on the metabolism of carbohydrates in these patients. As for low molecular weight mushroom compounds, only a minute fraction of the many newly discovered compounds have proceeded to a higher level of clinical evaluation. To our knowledge, irofulven is the most extensively studied compound in this group. Irofulven (6-hydroxymethylacylfulvene) is a hemisynthetic analogue of the toxin illudin S (McMorris et al., 2001). Phase II clinical trials were performed in advanced melanoma (Pierson et al., 2002), advanced renal cell carcinoma (Berg et al., 2001), relapsed or refractory non-small cell lung cancer (Sherman et al., 2004), metastatic colorectal cancer (Nasta et al., 2003), and recurrent or persistent endometrial carcinoma (Schilder et al., 2004). Unfortunately, irofulven demonstrated minimal to no significant antitumor activity in these trials. Despite evidence of irofulven activity in pancreatic cancer, MGI PHARMA Inc., Minneapolis, Minnesota, USA (April 2002) stopped a phase III irofulven clinical trial for refractory pancreatic cancer, based on preliminary data analysis. There are still ongoing phase II clinical trials in ovarian, prostate, and hepatocellular cancers.

Conclusion

Hematological and immunological alterations are common in patients with malignant neoplasms. Scientific evidence has shown that dietary supplementation with medicinal fungi is capable of significantly improving the physiological condition and prognosis of patients with cancer because of their effects on red blood cells and the immune system (Fortes et al., 2006; Sullivan et al., 2006). Current research on the immune modulation exerted by mushrooms has gone beyond the mechanisms involved in their antitumor activities. One of the risks of radiation and chemotherapy in the treatment of cancer patients is the development of leukopenia, which substantially 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. Collectively, the literature published supports the concept that certain mushrooms and mushroom extracts may have potent antiangiogenesis, antipromotion, and antiprogression actions. The structures and bioactivities of numerous substances, including various polysaccharides and triterpenoids isolated from mushrooms have been identified. Accumulating evidence from *in vitro* and clinical studies has indicated that mushrooms exhibit cancer-preventive and anticancer activity, which might be ascribed 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. Prerequisition for a use as drug, nutraceutical or other purpose is the continuous production of mushrooms (fruiting bodies or mycelium) in high amounts and in a standardized quality. There is a need in the field for detailed information on the extraction procedure and, if at all-possible, a thorough analysis of the chemical composition of the extract under investigation. This would not only enhance reproducibility, but would eventually make it possible to correlate specific chemical constituents or combinations of

constituents with particular biological activities. Natural products have been major molecular structural resources for drug discovery. Antibiotics, penicillin, the analgesic and antipyretic drug aspirin, the anticancer drug taxol, the anti-malarial drug artemisinin, and the anti-Alzheimer's disease drug huperzine A are typical, successful examples. The reservoir of natural products contains an abundance of chemical novelty and diversity: about 40% of the chemical scaffolds of the published natural products are unique and have not been made by synthetic chemistry. Another advantage is their chiral center. Most natural products are chiral and occur as single enantiomers; and many modern drugs are chiral and have their biological activity associated with only one of the enantiomers. Therefore, using natural products as enantiomerically pure starting materials is a good solution to this problem. Today, it becomes increasingly difficult to synthesize or discover new and interesting lead compounds. However, with the aid of techniques like high-throughput screening assays, 3-D protein–ligand models, virtual screening, computer assisted rational drug design, and the expanding knowledge of the molecular basis of tumorigenesis and metastasis, it seems feasible to harness the natural pool and discover novel compounds that rationally target the abnormal molecular and biochemical signals leading to cancer. Thus, the immediate goal must be to identify the pharmaceutical activities of mushrooms and their constituents aimed at improving their potency, selectivity, bioavailability, as well as pharmacokinetics and pharmacodynamics, and explore their potential synergy with other pharmaceutical compounds available for combating cancer.

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