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Medicinal and nutraceutical genetic resources of mushrooms

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Abstract

Mushrooms are the fungi that have been used as food since time immemorial. Nutritionally they are a valuable source of health food, which is low in calories, and rich in carbohydrates, essential amino acids, fibre, important vitamins and minerals. Mushrooms have also been used in medicine for centuries in the Orient but their potential as health potentiators and elicitors of immune system is recent. In the last two decades there has been an upsurge on the use of mushrooms as nutraceuticals and many edible species have been thoroughly investigated and authenticated for medicinal use. The species that have been properly analysed for medicinal value are: *Ganoderma lucidum* (Reishi), *Lentinus edodes* (Shiitake), *Grifola frondosa* (Maitake), *Agaricus blazei* (Himematsutake), *Cordyceps militaris* (Caterpillar fungus), *Pleurotus ostreatus* (Oyster mushroom) and *Hericium erinaceous* (Lions mane). There are many more species of cultivated and wild edible and non-edible mushrooms that have been analysed for both their nutritional and nutraceutical components but to a lesser extent than those listed above. The active constituents found in mushrooms are polysaccharides, dietary fibres, oligosaccharides, triterpenoids, peptides and proteins, alcohols and phenols, and mineral elements such as zinc, copper, iodine, selenium and iron, vitamins, amino acids etc. These have been found to boost the immune system, have anti-cancerous properties, act as anti-hypercholesterolaemic and hepato-protective agents, show anti-HIV activity and anti-viral activity, and ameliorate the toxic effect of chemo- and radiotherapy. Many of the species are known to be aphrodisiacs. Many commercial products from these mushrooms are available in the market. Prominent among these are: Lentinan from *Lentinus edodes*, Concord Sunchih and Reishi Plus from *Ganoderma lucidum*, Grifon from *Grifola frondosa* and Didanosine from *Cordyceps militaris*. The nutraceuticals have been found to relieve the stress and pressure of modern society by stimulating both basic and secondary immune responses of the immune system. There are more than 5000 species of mushrooms recorded from all over the world out of which around 2000 are identified as edible. A large number of the species are yet to be analysed for their nutraceutical/medicinal potential.

Keywords: anti-cancerous agents; bioactive compounds; functional foods; immunomodulators; medicinal mushrooms; mushroom; nutraceutical mushrooms; nutraceuticals

Introduction

Mushrooms are a heterogenous group of fungi with members from both Ascomycotina and Basidiomycotina. Generally, agarics or fleshy species of the group of fungi are called mushrooms. Mushrooms are comprised of around 230 genera and 5000 species. Of these more than 2000 species are reported to be edible throughout the world and about 283 of these are reported to be available in India (Purkayastha and Chandra, 1985).

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Mushrooms have been devoured as health food by mankind since ancient times. Nutritionally, they comprise a valuable source of health food—low in calories and carbohydrates; rich in proteins, essential amino acids, fibres and important vitamins and minerals, including B vitamins, iron, potassium, selenium and zinc (Mattila *et al.*, 2001) (Table 1).

Many mushrooms have also been used in medicine for centuries; especially in Asian countries where a lot of work has been done on medicinal aspects of several edible mushrooms (Helpern and Miller, 2002). Most of the research has been cancer related, but studies conducted have shown that mushroom extracts also impart reduction of blood pressure and cholesterol concentration, enhancement of the immune system, anti-viral and anti-inflammatory properties, treatment of anaphylactic shock, anti-HIV properties and an increase of oxygen utilization and antioxidant properties (Chang and Miles, 1996).

Approximately 300 mushroom species are known to have medicinal or nutraceutical properties and another 1800 species have been identified with prospective medicinal properties. *Ganoderma lucidum* (Reishi), *Lentinus edodes* (Shiitake), *Hericium erinaceous* (Lion's mane), *Pleurotus ostreatus* (Oyster mushrooms) and *Grifola frondosa* (Maitake) are just a few of the cultivated mushrooms species that have been analysed for medicinal value or nutraceutical potential.

Nutraceuticals

Nutraceuticals (often referred as phytochemicals or functional foods) are natural, bioactive, chemical compounds that have health-promoting, disease-preventing or medicinal properties. The term 'nutraceutical' was coined in 1979 by Stephen De Felice, founder and chairman of the Foundation for Innovation in Medicine located in Cranford, NJ, USA. It was defined as 'a food or part of food, that provides medical or health benefits, including the prevention and treatment of disease' (Biesalski, 2001). The term 'mushroom nutraceuticals' has been coined by Chang and Buswell (1996) to describe those compounds that have considerable potential as dietary supplements and for use in the prevention and treatment of various human diseases without the troublesome side-effects that frequently accompany treatments involving synthetic drugs. As such, a mushroom nutraceutical is a refined/partially defined extractive from either mycelium or fruiting bodies, which is consumed in a capsule or tablet form as a dietary supplement (not as a regular food) with potential therapeutic applications.

Mushrooms as health potentiators

Mushrooms have been used as food and medicine since very early times (Zhuang and Mizuno, 1999). They are a typical source of physiologically active compounds that have been studied for the development of some natural medicines. The stress and pressure of modern society takes a toll on the immune system. Medicinal mushrooms support and enhance overall immune functions and can directly stimulate both basic and secondary immune responses of the immune systems. Most mushroom-derived preparations and substances find their use not as 'pharmaceuticals' (real medicines/chemical preparations), but as a novel class of 'nutraceuticals' (dietary supplements and medicinally active components).

A 'mushroom nutraceutical' is a refined/partially refined extract/dried biomass from either the mycelium of the fruiting body of a mushroom, which is consumed in the form of capsules/tablets/powder as a dietary supplement (not as a conventional food) or which has therapeutic application. Regular intake of nutraceuticals may enhance the immune response of the human body, thereby increasing resistance to diseases, and in some cases causing regression of a disease state. The use of medicinal mushrooms goes hand in hand with their artificial cultivation. Most of the compounds found in mushrooms are HDPs—host defence potentiators. Mushrooms have been known for their culinary properties for thousands of years.

In the Chinese System of Medicine medicinal properties of mushrooms have been recognized for many centuries. The mushrooms that have been exploited and investigated for their medicinal potential to a greater or lesser extent are: *Ganoderma lucidum*, *Lentinus*

Table 1. The proximate composition of common edible mushrooms under commercial cultivation (g/100 g fresh weight)

Mushroom species	Moisture	Protein	Fat	Carbohydrate	Fibre	Ash	Calorie
Agaricus bisporus	90.1	2.9	0.3	5.0	0.9	0.8	36
Pleurotus sajorcaju	90.2	2.5	0.2	5.2	1.3	0.6	35
Volvariella volvacea	90.1	2.1	1.0	4.7	1.1	1.0	36
Lentinus edodes	90.0	0.1	0.1	5.0	0.8	0.8	21

edodes, *Grifola frondosa*, *Agaricus blazei*, *A. bisporus*, *Cordyceps sinensis*, *Pleurotus* spp., *Tremella* sp., *Flammulina velutipes*, *Hericium erinaceous*, *Auricularia* sp., *Schizophyllum commune* and *Trametes versicolor* etc. (Fig. 1). Out of all of these some of the mushrooms have been intensively investigated. Their potential as health potentiators (HP) is discussed below.

Major medicinal mushrooms

Ganoderma lucidum (Leyss.) Karst

Ganoderma lucidum tops the list of such mushrooms. It is a polyporoid fungus commonly known as lacquered mushroom, royal gano, young ji or varnished conk. It is known by the name 'Reishi' by the Japanese and 'Lingzhi' by the Chinese. It is also called 'the mushroom of immortality'. It has long been heralded for its health-stimulating properties and illness remedies. It has been traditionally used in the treatment of cancer that has also been substantiated scientifically. It is rarely eaten as food because of its bitter taste (R. Chang, 1993).

Active constituents

Ganoderma lucidum contains a number of bioactive components; many of them are biological response modifiers, which activate the immune system for a multitude of defensive functions. The pharmacological activities have been ascribed mainly to the active components, namely polysaccharides, triterpenoids, amino acids, steroids, nucleotides and nucleosides, lectins, germanium and dietary fibres. These active agents are known to modulate the function of the immune system in humans (Chang and Miles, 1996).

Mechanism of action and clinical application

Meschino (2001) has classified the primary active agents in *G. lucidum* into three broad categories based on: (i) specific polysaccharides—which occur in the form of β-D-glucans bound to amino acids. These agents are known to possess immune-modulating and anti-cancer properties; (ii) triterpene compounds—known as ganoderic acids, which have been shown to lower blood pressure, reduce platelet stickiness and may decrease low-density lipoprotein-cholesterol, and (iii) other major active constituents—including sterols, coumarin and mannitol.

Polysaccharides

Around 50 types of polysaccharide have been isolated from the fruiting bodies of *Ganoderma lucidum* and related species (Jong and Birmingham, 1992; Su *et al.*, 1993, Lindequist, 1995). The various types of polysaccharide include neutral polysaccharides, acidic glucans, polyglucans (Mizuno *et al.*, 1984, 1992; Chang, 1993), proteoglycans—protein-bound heteroglycans (Mizuno *et al.*, 1992), arabinoxyloglycans—a highly branched heteroglycan (Miyanzaki and Nishijima, 1982), peptidoglycans: ganoderans A, B, C (Hikino *et al.*, 1986), β-D-glucans and Lucidon—protein-bound heteroglycans (Kim *et al.*, 1993). The methanolic extracts of *G. lucidum* and *G. tsugae* have been shown to possess antioxidant properties (Mau and Ma, 2002) whereas an amino-polysaccharide fraction (G009) isolated from *G. lucidum* is known to be an inhibitor of reactive oxygen species, that have been implicated in the pathophysiology of cancer.

Aqueous extracts of a *G. lucidum* polysaccharide (GL-P) named 'Ganoploy' has been shown to have immunomodulating effects. This activates macrophages, T-lymphocytes and natural killer cells (Gao, 2000), and enhances the immune response of the patients in advanced stages of cancer (Cassileth, 2000; Jacobson *et al.*, 2000). GLP (AI) peptide fraction shows high antitumour and anti-angiogenic activity when used in combination with cytotoxic anti-cancerous drugs (adriamycin, flurouracil, thioguanine, methotrexate etc.; Lee *et al.*, 1995). GL-P, especially the (β-1 → 3) configuration, possesses immunopotentiating properties, i.e. stimulation of T-cells (Nakashima *et al.*, 1979), activation of cytotoxic NK (natural killer) cells (Won *et al.*, 1989) and stimulation of cytokines. Crude *Ganoderma* extracts activate NK cells *in vitro*. Another *G. lucidum* polysaccharide (Gl-B7) decreases the production of oxygen-free radicals and antagonizes the respiratory burst induced by peripheral mononuclear antioxidant in murine peritoneal macrophages, thus playing an important role in anti-ageing (Li and Lie, 2000).

Triterpenoids

The fruiting bodies of *G. lucidum* are extremely bitter in taste due to highly oxidized lanostane triterpenoids (Lindequist, 1995). More than 100 types of oxygenated and pharmacologically active lanostane-type terpenes have been isolated from *G. lucidum* such as: lucidimol (A, B), lucidenic acid, ganodermanodiol, ganoderiol (A, B), ganosporaric acid, ganoderans (B, C), ganodermic acid, ganodercnic acid, ganolucidic acid, applanoxide acid, lucidones, ganoderals, ganoderols, cyclo octa sulphur and ganoderic acids etc. (Shiao *et al.*, 1994). *G. lucidum* has both hypotensive and hypertensive properties. The hypertensive properties are due to the presence of ganoderic acids: B, D, F, H, K, S and Y (Morigiwa *et al.*, 1986). It also contains other pharmacologically active substances, which reduce blood pressure, blood sugar, eliminate cholesterol and inhibit platelet aggregation (Liu, 1993; Zhu and Mori, 1993; Mizuno, 1995).

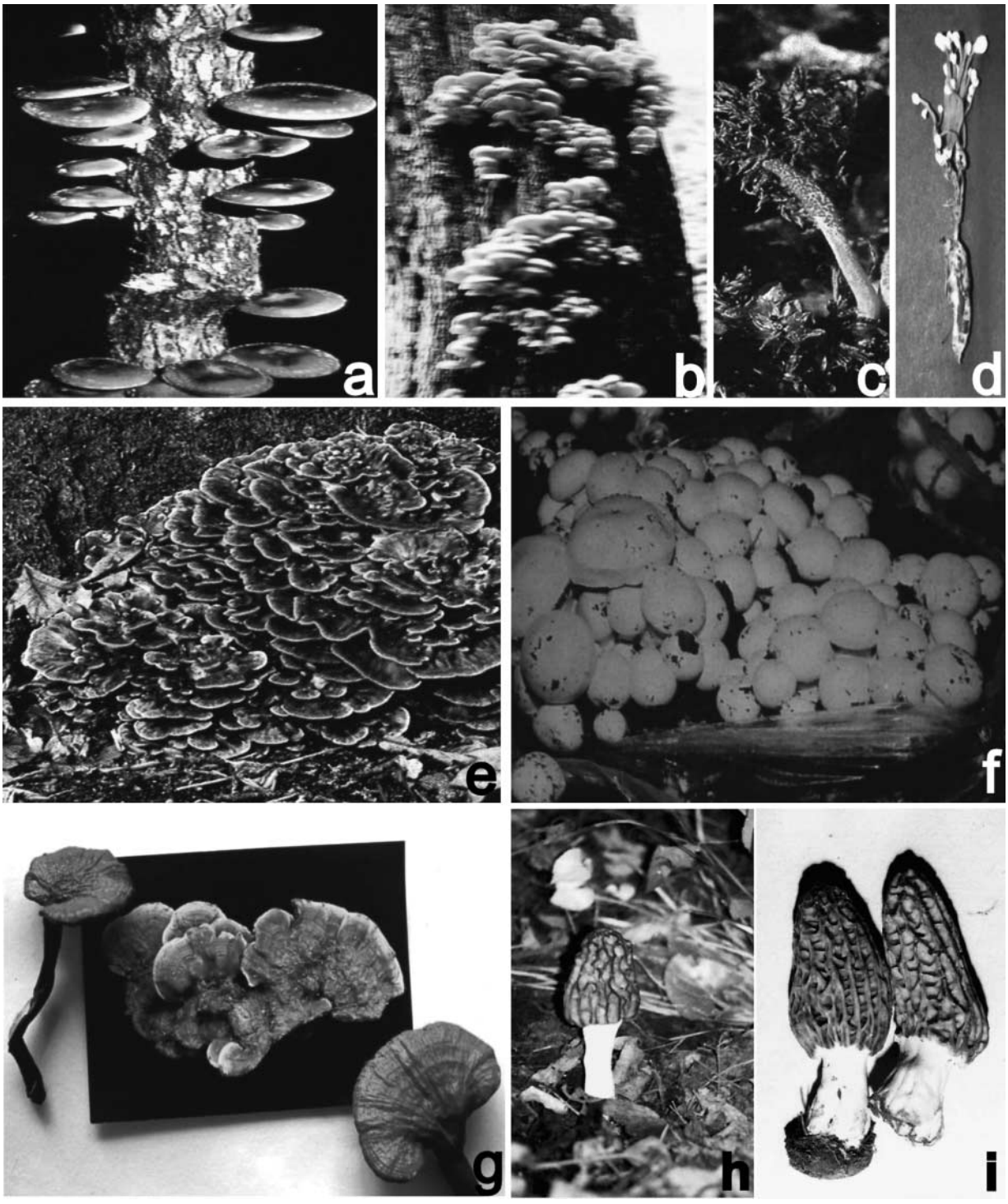

Fig. 1. Fruiting bodies of selected medicinal/nutraceutical mushrooms. (a) Mature fruiting bodies of *Lentinus edodes* on wood log. (b) Fruiting bodies of *Pleurotus ostreatus* growing on a decorticated tree trunk. (c, d) Fruiting body of *Cordyceps militaris*: (c) asexual stage; (d) sexual stage. (e) Mature tiered fructifications of *Grifola frondosa*. (f) Fructifications (buttons) of *Agaricus bisporus* under cultivation. (g) Fruiting bodies of *Ganoderma lucidum* collected from nature. (h, i) Mature fruiting bodies of *Morchella* species: (h) *M. angusticeps*; (i) *M. esculenta*.

Ganoderic acids R and S isolated from cultured mycelia of *G. lucidum* show strong anti-hepatotoxic activity in galactosamine-induced cytotoxic tests with primary cultured rat hepatocytes (Hirotani and Ito, 1986). Another hepatoprotective compound ganoderic acid A was isolated from the ester-soluble fraction of the spores of *G. lucidum* (Chen and Yu, 1993).

Triterpene acts on mammalian cell surfaces and morphologically alters the membrane, exhibiting a variety of responses such as platelet aggregation and disturbing the entry of virus into the cells (Wang *et al.*, 1991; Mayaux *et al.*, 1994).

Ling-Zhi-8

Ling-Zhi-8 (LZ-8), a potent biological responses modifier (BRM; a small immunomodulating protein, 12,420 Da, 110 amino acids), has been isolated from the mycelium of *G. lucidum*. It has been shown to possess a variety of health benefits and to promote T-cell functions and cytokine production (Kino *et al.*, 1989; Tanaka *et al.*, 1989). This protein imparts mitogenic activity *in vitro* and immunomodulating activity *in vivo*, thus regulating the immune response and inhibiting anaphylaxis (Kino *et al.*, 1989).

Nucleosides and nucleotides

G. lucidum has been reported to contain anti-platelet aggregation activity preventing thrombosis on account of the presence of adenosine and its derivatives such as 5′-deoxy-5′-methylsulphinyl adenosine, 5-G′MP and 5-X′MP-guanosine (Shimizu *et al.*, 1985; Kawagishi, 1995).

Organic germanium

This is another component isolated from *G. lucidum* which shows anti-tumour activity, relieving pain caused by cancer. It increases oxygen-carrying capacity of red blood corpuscles and enhances blood circulation (Sato and Iwaguchi, 1979; Quain and Zhang, 1993). Germanium also promotes the circulatory system as well as the metabolism of the body by providing more oxygen (Mizuno *et al.*, 1988).

Steroids

G. lucidum contains lipid-like substances called steroids, e.g. ergosterol and ganodesteron etc. These steroids show antioxidant and immunomodulatory activity.

Dietary fibres

They have carcinostatic activity and absorb the carcinogenic substances and prevent their absorption in intestine and then show laxative action, thus preventing cancer of the colon and rectus.

Lentinus edodes (Berk.) Sing.

Lentinus edodes, gilled mushroom (family: Tricholomataceae), is commonly known as 'Shiitake' or Japanese mushroom. In China it is called 'hsaing ku' or 'fragrant mushroom' and elsewhere as 'Black forest mushroom' The Shiitake is currently the second most widely cultivated mushroom in the world, serving both as an edible as well as for medicinal and health purposes.

Active constituents

Shiitake is known to contain proteins, lipids (primarily linoleic acid), carbohydrates, fibres, minerals, vitamins B1, B2 and C and ergosterol, the D provitamin, vitamin E and selenium. Shiitake is a rich source of D, C and A vitamins. It is also reported as a good source of antioxidants, such as vitamin E. Shiitake also contains a number of enzymes such as asparagine, pepsin and trypsin that help in digestion and treatment of childhood leukaemia. The mineral ions present in Shiitake are mainly zinc and selenium. The former aids in skin, nails and hair repair and also improves plasma testosterone level, while the latter acts as an antioxidant. Various components extracted are polysaccharides, eritadenine, chitin, enzymes, minerals, nucleic acids, amino acids, cortinelin and interferons etc.

Mechanism of action and clinical application

On account of its low calorific value, high fibre, proteins and microelement contents, *L. edodes* comprises most ideal diets designed to prevent cardiovascular diseases (Breen, 1990; Hobbs, 1995). Shiitake improves stamina and circulation, preserves health, cures colds, and lowers blood cholesterol level (Jong and Birmingham, 1993). Water extract of shiitake fruiting bodies has been found to inhibit transplanted tumours in mice (Ikewawa *et al.*, 1969).

Polysaccharides

The polysaccharides from *L. edodes* (Berk.) Sing. show anti-tumour and anti-viral activities (Mizuno, 1995). Chihara *et al.* (1970) isolated an anti-tumour polysaccharide from Shiitake and named it 'Lentinan'. It is described as a host-mediated anti-cancerous drug that has been put through numerous clinical studies in Japan (Ooi and Liv, 2000). Lentinan has been found to activate macrophages, T-lymphocytes and other immune effector cells that modulate the release of cytokines, which in turn account for its indirect anti-tumour and anti-microbial properties. Taguchi and Furue (1985) also reported significant improvement in survival of patients with advanced gastric cancer treated with Lentinan and chemotherapy compared with those treated with chemotherapy alone. Lentinan and sulphated Lentinan exhibit a potent anti-HIV

activity resulting in the inhibition of viral replication and cell fusion.

Another polysaccharide, 'KS-2' (α-mannan peptide) isolated from hot water extracts of cultured mycelium of *L. edodes*, suppresses Sarcoma-180 when administered both orally and intraperitoneally.

Glycoproteins in *L. edodes* mycelial extracts (LEM) have been shown to inhibit HIV infection *in vitro* and are also known to activate the host immune system (Mizuno, 1995). The mushroom extracts can also lower both blood pressure and free cholesterol in plasma as well as accelerate accumulation of lipids in liver by removing them from circulation (Kabir and Kumura, 1989). Lentinan and LEM give favourable results in treating chronic hepatitis and viral hepatitis B patients (Zhu, 1985; Amagnase, 1987).

Amino acids

Shiitake contains eight essential amino acids and is rich in lysine and leucine. An amino acid derivative 'Eritadenine' in Shiitake lowers blood serum cholesterol and lipid concentrations in rodents (Chihara *et al.*, 1969; Yamura and Cochran, 1976). It also accelerates the excretion of ingested cholesterol and its metabolic deposits, and in humans lowers the cholesterol levels (Susuki and Ohshima, 1974). Another amino acid derivative, thioproline, blocks the formation of carcinogenic *N*-nitroso compounds, and lenthionine, a sulphur-containing peptide, has anti-bacterial and anti-fungal activity (Hatavani, 2001).

Nucleic acids

Adenosine derivative from *L. edodes* have significant platelet agglutinating inhibitory effects (anti-thrombotic activity) (Hokama and Hokama, 1981). Cortinellin is a substance isolated from Shiitake which acts as broad-spectrum anti-bacterial agent. It kills a wide range of pathogenic bacteria.

Grifola frondosa (Dick.: Fr.) S. F. Gray

Grifola is a basidiomycete polyporoid fungus that is commonly known by the Japanese name 'Maitake' ('mai' meaning dance and 'take' means mushroom). It is a premier culinary and medicinal mushroom, though less well known than Shiitake and Reishi. During the past two decades, it has gained importance as a dietary supplement with significant health benefits.

Active constituents

The active constituents of Maitake are: polysaccharides (1,3- and 1,6-β-glucans, α-glucans), lipids (octadecanoic, octadecadienoic acid), phospholipids (phosphatidylethanolamine, phosphatidylecholine, phosphatidylinositol, phosphatidylserine, phosphatidic acid), sterols (ergosterol) and nucleotides etc.

Mechanism of action and clinical applications

Fruiting body and liquid-cultured mycelium of this mushroom have been reported to contain useful polysaccharides such as β-glucans (Mizuno *et al.*, 1986). The polysaccharides and polysaccharide protein complexes from this mushroom have been shown to have significant anti-cancerous activity (Ohno *et al.*, 1985; Hishida *et al.*, 1988; Kurashiga *et al.*, 1997). Glucans activate the macrophages and subsequently increase T-cell cascade, i.e. increase the body's immune defence mechanism (Yanaki *et al.*, 1983). β-Glucan fractions from the mushroom are now being used for prevention and treatment of flu and common infections, AIDS-HIV, diabetes mellitus, hypertension, and hypercholesterolaemic and urinary tract infections (Kabir and Kimura, 1989; Kabir *et al.*, 1989; Cichoke, 1994; Kubo *et al.*, 1994; Kubo and Nanba, 1997; Choi *et al.*, 2001; Smith *et al.*, 2002; Talpur *et al.*, 2002). The bioactive glucans have cytotoxic effects, presumably through oxidative stress on prostatic cancer cells *in vitro* leading to apoptosis. The high molecular weight polysaccharides obtained from Maitake are effective against non-insulin-dependent diabetes mellitus (NIDDM; Kubo *et al.*, 1994). The Maitake powder also has an anti-diabetic mechanism (Kubo and Nanba, 1996). Maitake extract exerts effects through its ability to activate various effector cells, such as macrophages, natural killer cells, interleukin-1 and suppressor ions, all of which show cancerous activity (Adachi *et al.*, 1987; Kubo *et al.*, 1994). Some extracts also show hypoglycaemic activity and have synergistic effects with other hypoglycaemic activities. Other fractions (D-GF-1, Grifon-7N) from Maitake exhibit immunological enhancement together with anti-HIV, anti-hypertension, anti-diabetic and anti-obesity properties (Adachi *et al.*, 1988; Kubo *et al.*, 1994; Mizuno, 1995; Kubo and Nanba, 1996; Jones, 1998; Borchers *et al.*, 1999). The lipid fraction of *G. frondosa* exhibits antioxidant activity. It inhibits the cyclo-oxygenase enzymes, COX-1 and COX-2. Ergosterol is identified as one of the active constituents. The inducible form of COX-1 and COX-2 appears to play an important role in cancers. Its inhibition can result in the inhibition of tumour development. Maitake also affects weight loss or weight gain (Ohtsuru, 1992). Yokota (1992) gave 30 patients powdered Maitake food supplement for two months with no change in their regular diet. All patients successfully lost 7–13 pounds.

Agaricus blazei Murill

Agaricus blazei Murill has become popular after its discovery in Brazil some 30 years ago. It is among the

most common popular mushrooms in Japan now called 'mushroom of sun', Him-matsutake, Royal Agaricus, God's mushroom. It is famous by the common name ABM (*Agaricus blazei* Murill) all over the world.

Active constituents

Polysaccharides, nucleic acids, neutral lipids, phospholipids and dietary fibres are major active constituents found in this species.

Mechanism of action and clinical applications

This species has been found to be the most effective against cancer compared to Shiitake, Maitake, Reishi and other medicinal mushrooms. *A. blazei* is effective against Ehlich's ascites carcinoma, sigmoid colon cancer, ovarian cancer, breast cancer, lung cancer and liver cancer as well as against solid cancer (Mizuno *et al.*, 1990). The pharmacologically active compounds of *A. blazei* are β-glucans: β-(1 → 3)-D-glucans, β-(1 → 4)-α-D-glucans and β-(1 → 6)-D-glucans. They specifically activate the immune system cells (such as macrophages, interferons, T-cells and natural killer cells) in order to prevent the multiplication, metastasis and recurrence of cancer cells. *A. blazei* is mainly used for its tumour-inhibiting effects (Fujimiya *et al.*, 1998). In addition to glucans, steroids, nucleic acids, lipids and lectins also have cancer inhibition properties, namely β- and protein glucans decrease and control cancerous cell proliferation; steroids, nucleic acids, lipids and lectins restrain cancerous cell multiplication; they reduce blood sugar, so are effective in fighting diabetes; and they lower cholesterol level and ease arterio-scleroses. *A. blazei* can also prevent or improve chronic fatigue syndrome and autoimmune conditions such as rheumatoid arthritis, diabetes and lupus. In addition, it reduces hair loss and can heal wounds and clear up skin problems. The lipid fraction of *A. blazei* contains a compound, ergosterol, with anti-tumour activity.

Agaricus bisporus (Lange) Imbach

A. bisporus, the most anciently used among the widely cultivated species of mushrooms, has not yet been thoroughly investigated for its nutraceutical aspects. Beelman *et al.* (2003) demonstrated that the nutritional value of *A. bisporus*, especially the brown strain, compares favourably with *L. edodes* and *Pleurotus* spp. in terms of fibre and solid content. However, *A. bisporus* is a significantly better source of riboflavin, important minerals potassium and selenium, and copper compared to synthetic sources of proteins and vitamins (niacin, thiamine and folate).

Active constituents

The active constituents are polysaccharides, oestrogens, agaritine, lectins, 1-octen-3-ol and 10-oxo-trans-8-decenoic acid (ODA), minerals especially selenium, B-complex vitamins, total dietary fibres and amino acids.

Mechanism of action and clinical applications

A. bisporus has hypocholestrolic compounds that are effective in reducing blood serum cholesterol levels (Tokita *et al.*, 1972; Suhadolnik, 1979). It is also known to be a good dietary source of B-complex vitamins, especially riboflavin, potassium, copper and selenium (USDA, 2001). The brown strains of *A. bisporus* are excellent for selenium (Spaulding and Beelman, 2003). Selenium is known to decrease the incidence of cancer (Clark *et al.*, 1996). Recent studies show that selenium-enriched *A. bisporus* significantly reduced the occurrence of 7,12-dimethyldibenz(A)anthracene-induced mammary epithelial cell DNA adducts (Spolar *et al.*, 1999).

A. bisporus in cold extracts has been found to act as a genoprotective agent, i.e. it neutralizes the genotoxic effect of reactive oxygen species. The genoprotective effect was associated with tyrosinase, the enzyme that catalyses the browning reaction (Beelman and Simons, 1996; Kukura *et al.*, 1998; Shi *et al.*, 2002). Extracts of *A. bisporus* suppress the aromatase activity (Gurbe *et al.*, 2001). Aromatase/oestrogen synthetases are known to play a dominant role in tumour proliferation in breast cancers in women.

1-Octen-3-ol is a valuable natural flavour substance widely used for food flavouring (Manley, 2000). ODA, a metabolite, is formed by *A. bisporus* concurrently with 1-octen-3-ol by the action of lipogenase and hydroperoxide lyase when tissues of fruiting bodies/mycelia are damaged/disrupted (Wurzenberger and Grosch, 1982; Schindler, 1989). It is a very important co-factor in the enzyme system of glutathione peroxidase that protects cell membrane lipids from the damaging effects of free radicals (Reilly, 1996). Lectins/agglutinins are the proteins showing anti-proliferating effects on human keratinocytes (Parslew *et al.*, 1999).

Cordyceps militaris (L.) Link

Cordyceps is an ascomycetous fungus belonging to the family Clavicipitaceae. The name *Cordyceps* comes from the Latin words: 'cords' and 'ceps' meaning club and head, respectively. In English it is called 'Caterpillar fungus'. In China it is called 'hia tsao tong tehong' and also 'winter worm, summer plant'.

Table 2. Supplementary mushroom species

Mushroom species	Active constituents	Medicinal value	Reference
Agrocybe aegerita	Polysaccharides (AG HN-1, AG NH-2)	Reduces glycaemia	Gunde-Cimerman, 1999
Armillriella mellea	Polysaccharide (AGM-1)	Decreases heart failure rate, reduces peripheral and coronary vascular resistance, increases cerebral blood flow	Chang and But, 1986
		Cerebral protective effects	Watanabe *et al*., 1990
		Increases coronary efficiency without affecting blood pressure	Zhang *et al*., 1985
		Pathogenic against bacteria, inhibits the growth of Gram-positive bacteria and yeasts	
Auricularia spp.	Polysaccharides (1,3-β-glucans)	Anti-tumour activity	Misaki and Kishida, 1995
		Lowers cholesterol, triglyceride, lipid levels	Chen, 1989; Sheng and Chen, 1990
		Anti-aggregatory activity of blood platelets, beneficial in coronary heart diseases, immune tonic	Wasser and Weis, 1999
Boletus edulis	Polysaccharides	Anti-tumour activity	Wasser and Weis, 1999
Calvatia gigantea	Polysaccharide (calvacin)	Anti-tumour activity	Wasser and Weis, 1999
Coriolus versicolor	Polysaccharides (PSK, PSP)	Prevents cancer of digestive system (stomach, oesophagus, colon)	Fukushima, 1989; Yang *et al*., 1992
		Elimination of immunosuppressive functions due to chemo- and radiotherapy	Chu *et al*., 2002
		Prophylaxis and treatment of cancer and infection	Mau and Ma, 2002
	Methanolic extracts	Antioxidants	
Dendropolyporus umblettus	Polysaccharide (β-glucans)	Hepatoprotective	Lin and Wu, 1988
		Anti-tumour	Ito *et al*., 1973
		Anti-tumour action *in vitro* against *Staphylococcus aureus*, *E. coli*	Chang and But, 1986
Flammulina veluptipes	Polysaccharide	Anti-cancerous	Ikekawa *et al*., 1968
	Flammulin	Anti-viral and stimulates immune system	Ying, 1987
		Pharmacological activities	Weil, 1987
	FVP (*Flammulina* polysaccharide)	Anti-tumour activity	Wasser and Weis, 1999
	Proteins (Fip-fve)	Immunomodulatory	Ikekawa, 1995
	Peptide glycans (EA6-PII, EA6)	Anti-tumour activity against Sarcoma-180, cancer of lungs, improves immunization by freezing	Wasser and Weis, 1999, Mizuno, 1999
	Prolamin (active sugar protein)	Anti-tumour	Ikekawa *et al*., 1985
	Proflamin (glycoprotein	Anti-tumour against allogenic and syngeneic tumour by oral administration	
Hericium erinaceous	Polysaccharide (β-D-glucans)	Anti-hypercholesterolaemic agent	Kiho *et al*., 2000
		Anti-tumour activity	Wasser and Weis, 1999
Lactarius vellereus	Sesquiterpenes (velleral isovelleral)	Anti-bacterial and anti-fungal	Wasser and Weis, 1999
Lampteromyces japonicus	Illudin S	Anti-cancerous properties and inhibits cancer growth	McMorris and Anchel, 1963, 1965
Mycena leaiana	Leaianafulvene (cyclohumulanoides)	Cytotoxic	Wasser and Weis, 1999; Kohno, 1985
Omphalotus olearius	Tricyclic sesquiterpene Illudin A, B, S	Cytotoxic	Wasser and Weis, 1999

Table 2. *Continued*

Mushroom species	Active constituents	Medicinal value	Reference
Phellinus linteus	Polysaccharides	Improves digestive system cancer	Mizuno, 1999
		Gives symptomatic responses and tumour responses in combination with chemotherapy	Mizuno, 2000
Pleurotus spp.	Plovastin/mevinolin (Lovastin) polysaccharide	Hypocholesteraemia, prevents cardiovascular disorders	Gunde-Cimerman and Cimerman, 1995; Mizuno, 1999
Schizophyllum commune	Polysaccharide (Schizophyllan, sonifillan, sizofiran, sizofllan)	Cytostatic	Wasser and Weis, 1999
		Increase survival of the patients with head and neck cancers	Kimura *et al.*, 1994
	Sulphated Schizophyllan	Anti-HIV activity	Ito and Sugawara, 1990
		Protection against *Staphylococcus* spp., *Pseudomonas*, *E. coli* etc. infection	Cochran, 1978
	Sulphated polysaccharide (SPG)	Treatment of chronic Hepatitis B, enhances immunological responsiveness to virus, production of interferons 'g'	Matsuyama *et al.*, 1992
Trametes versicolor	Polysaccharides (PSK, PSP)	Inhibits growth of *Candida albicans*	Sakagami *et al.*, 1991
		Treatment of colorectal, lung, breast and gastric cancer for stage IV	Kidds, 2000; Kibarara *et al.*, 1976; Sakagami and Takeda, 1993
		Increased delayed type of hypersensitivity on skin tests and enhances chemotactic migration of neutrophils	Kondo and Torisu, 1985; Yang *et al.*, 1993
		PSK in conjugation with chemotherapy is useful in breast cancer patients	Wasser and Weis, 1999
		Amelioration of toxic effects of chemo- and radiotherapy by PSP	Ikekawa *et al.*, 1985
		Anti-viral activity by inhibiting HIV replication	Ikekawa *et al.*, 1985
		Liver protective activities	Wasser and Weis, 1999
	Coreolan (β-glucan protein)	Shows activity against experimental diabetes in animals both *in vitro* and *in vivo*	
	Glycoprotein (PSK)	Activity against experimental hypertension and thrombosis inhibits blood platelet aggregation, anti-hyperlipidaemic, anti-arrhythmic	
	Coriolon	Decrease in LDL cholesterol in hyperlipidaemia (stage IIa) patients	
		Antibiotic inhibits Gram-positive and *Trichomonas vaginalis*	
Tremella spp.	Polysaccharide Tremellastin	BRMs, source of dietary fibres, prevents cardiovascular disorders, hypercholesterolaemic, hyperglycaemic, immune stimulatory	Wasser and Weis, 1999; Chen, 1989
	Tremella acidic polysaccharide (TAP)	Reduces glycaemia	Gunde-Cimerman, 1999
	Spore extract + polysaccharides	Anti-lipidaemic activity	Wasser and Weis, 1999
		Prolonged thrombus formation, reduces thrombus size, reduces blood platelet adherence	Sheng and Chen, 1990
Volvariella volvacea	Glycoproteins (Flip-vvo, VVG)	Cardio-protective, lowers blood pressure	Misaki and Kishida, 1995
Wolfiporia cocos	Polysaccharides (carboxymethyl pachymaran, β-glucans)	Immediate cure of chronical viral hepatitis in human clinical studies, useful in treatment of arrhythmia	Guo,1984; Ding, 1987; Kanayama *et al.*, 1983

Active constituents

Medicinal benefits of *Cordyceps* are not related to one species. Different species of *Cordyceps* are being used in health supplements and pharmaceutical drugs worldwide. It is highly valued in traditional Chinese medicine (TCM). Active constituents present are polysaccharides (cordycepic acid, cyclofurans, β-glucans, β-mannans, β-mannose polymers, complex polysaccharides), proteins, polyamines, nucleosides (adenosine, 2′3′-dideoxyadenosine, hydroxyethyladenosine, deoxyuridines, cordycepin, cordycepin triphosphates, cordycepin triphosphate, guanidine, deoxyguanindine), cordycepic acids, sterols and trace elements.

Mechanism of action and clinical applications

Cordyceps is a true promoter of overall health and homeostasis. In TCM *Cordyceps* has been used to treat a range of conditions, including respiration, pulmonary diseases, renal, liver, cardiovascular diseases, hyposexuality and hyperlipidaemia. *Cordyceps* is regularly used in all types of immune disorders as an adjunct to cancer therapy (Zhu *et al*., 1998). Usage increases both cellular ATP level (Guowei *et al*., 2001) and oxygen utilization (Jia-Shi-Zhu and James, 2004). Clinical studies have shown that the patients treated with *Cordyceps sinensis* reported significant clinical improvement in the areas of fatigue, cold intolerance, dizziness, tinnitus, hyposexuality and amnesia. *Cordyceps* is a potential source of anti-cancer drugs. It inhibits the growth and in some cases has been helpful in even dissolving certain types of tumour. The immune system of the body is also kept strong and vital (Nakamura *et al*., 2003).

Polysaccharides

In *Cordyceps*, the polysaccharides are perhaps the best known and understood of the medicinally active compounds (Ukai *et al*., 1983). A number of polysaccharides have been extracted as cordycepic acid and their pharmacological activity has been reported. These polysaccharides are effective in regulating the blood sugar (Kino *et al*., 1986), they also have anti-metastatic effect (Nakamura *et al*., 1999) and anti-tumour effect (Bok *et al*., 1999).

Polysaccharide fractions CI-P and CI-A, derived from *Cordyceps*, have been found to exhibit substantial antitumour activities in mice with Sarcoma-180. Another alkali-soluble polysaccharide, CI-6P, yields remarkable results against murine Sarcoma-180 when administered in doses of 10 mg/kg/day (Mizuno, 1999). Amongst the polysaccharides produced by *Cordyceps*, β-D-glucans have been shown to increase both innate and cell-mediated immune responses. They increase the production of cytokines, tumour necrosis factor α, interleukins, interferons and antibodies by the activated immune cells. This activation of immune response is generally triggered by polysaccharide binding to specific receptors on the surface of immune system cells called CR3 receptors (Shin *et al*., 2003). The cancer patients administered *Cordyceps* show high counts of white blood corpuscles and some reduction in tumour size (Zhu *et al*., 1998). *Cordyceps* and other fungal-derived polysaccharide immunomodulators such as polysaccharide-kresetin, polysaccharide-peptide, Lentinan etc., reduce the severity and duration of side-effects associated with chemo- and radiotherapy (Xu *et al*., 1988; Wang *et al*., 2001).

Nucleosides

Some altered nucleosides are found in *Cordyceps*, e.g. cordycepin (3′-deoxyadenosine). These compounds interrupt DNA replication, which is probably responsible for the mechanism of anti-viral effects (Liu and Zheng, 1993).

The presence of amino acids, vitamins, zinc and other trace elements found in *Cordyceps* are hypothesized to account for increased sperm survival rates, as demonstrated in clinical and periclinical studies (Guo, 1986). *Cordyceps* contains proteins, peptides, all essential amino acids and several polyamines (1,3-diaminopropane, cadaverine, spermidine, spermine, putrescine etc.); produces some potent antibiotics, immune stimulants and anti-tumour agents (Hobbs, 1986); and is also used for the treatment of respiratory diseases, renal dysfunction, hyperlipidaemia and hyperglycaemia (Zhu *et al*., 1998).

Cordyceps affects the maturing of leukaemia cells by exerting some influence over the differentiation mechanism that signals the body to direct immature cells for maturation (Chen *et al*., 1997). The fruiting bodies are also highly effective in treating cancers. They allow the host's immune system to effectively fight off the cancer invasion (Yoshida, 1989).

Cordyceps has kidney-enhancing potential on account of its ability to increase 17-hydroxy-corticosteroid and 17-ketosteroid levels. Some of the other sterols present are δ-3-ergosterol, ergosterol peroxide, 3-sistosterol, daucosterol and campesterol (Zhu *et al*., 1998). Zhang and Xia (1990) studied the inhibitory effects of *Cordyceps sinensis* on the immune response responsible for organ transplants and found that *C. sinensis* can prolong the survival of grafted heart without causing infection, and it does not exert a detrimental effect on vital organs.

There is a belief that the fruiting bodies help in the cure of impotence or act as an aphrodisiac in both men and women (Holliday *et al*., 2004).

Table 3. Marketed mushroom nutraceutical products

Product	Use
Ganoderma lucidum	
Concord Sunchih (1–2 caps twice a day to promote health; 3 caps three times a day during illness)	Treatment of Angina pectoris, chronic bronchitis, enhancement of immune system, prevents cardiovascular and hypercholesteraemia, promotes blood circulation and anti-platelet aggregation, liver protection, anti-microbial and anti-inflammatory
GLP (AI), GI	Increases life span of tumour implanted cells, blood vessel dilator and accelerates the blood circulation
Galopy (aqueous extract)	Immunomodulating effect
Rare Red Reishi™	Promotes good health and longevity
Lentinus edodes	
Lentinan	Anti-cancerous agent (especially gastric and colorectal carcinoma), stimulates the production of lymphocytes, natural killer cells, controls cancer and other infections
LEM and LAP	Anti-tumour activity in xenograft models
Grifola frondosa	
Grifon® (liquid extract) (5–6 drops three times a day for general health; 11–12 drops three times a day for therapeutic dose)	Taken orally and combines with chemotherapeutic agents against cancer, immunomodulators
Maitake Gold 404™ (caps 500 mg)	Inhibits metastasis especially hepatic metastasis
Agaricus blazei	
Capsules	Improves chronic fatigue syndrome and immunomodulators, reduces hair loss and can heal wounds and clear up skin problems
Cordyceps	
Didanosine (capsules, dried mycelium)	Treatment of AIDS
Pleurotus spp.	
Plovatin (mycelial extract)	Inhibits cholesterol metabolism in the body or cholesterol-lowering dietary supplement, prevents cardiovascular disorders such as arteriasclerosis
Tremella mesentrica	
Tremallastin (mycelial extract)	Biological response modifier, supports nervous, hormonal and immune systems of the body, prevents cardiovascular disorders
Reishi Plus (50% *G. lucidum* + 50% *L. edodes*, 200 caps/600 mg each)	Daily nutritional supplement adaptogen, good health vitality
Trimyco-Gen™ (33% *C. sinensis* + 33% *G. lucidum* + 33% *L. edodes*, 100 caps/600 mg each)	Immunomodulant, promotes good health and longevity
Mycoplex-7™ (14% *C. sinensis* + 14% *Tremella fuciformis* + 14% *A. blazei* + 14% *Coriolus versicolor* + 14% *Poria cocos* + 14% *S. commune* + 14% *Hericium erinaceous*)	Promotes good health vitality
Garden of Life (RM-120) (10 medicinal mushrooms + *Aloe vera* + *Uncaria tomentosa*)	Nourishes immune system (immunomodulatory), regulates the cholesterol level, anti-tumour activity, treatment of cardiovascular diseases, anti-viral and anti-bacterial, protects against harmful effects of radiations, anti-HIV factors

A concise account of the therapeutic potential of other mushroom species is briefly described in Tables 2 and 3.

Other important health mushrooms: *Morchella* Dill. ex Fr.

In India, in the Himalayan region, many species of mushrooms are collected and consumed from the wild, and morels (*Morchella* spp.) constitute the most important of them. This mushroom is collected from the wild and exported to many countries for its excellent culinary properties (Lakhanpal and Shad, 1986a, 1986b; Shad, 1989; Rana, 2002). Ethnic people also use it as a medicine for treatment of different ailments. Analysis shows that compared to other mushrooms, morels are the better source of carbohydrates, proteins, important minerals especially selenium, and germanium, important

vitamins, amino acids, nucleosides (adenosine) etc. (authors' unpublished results), and are therefore considered nutraceutically more important than other mushrooms.

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