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Mushrooms as therapeutic agents

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Abstract: Mushrooms have been known for their nutritional and culinary values and used as medicines and tonics by humans for ages. In modern terms, they can be considered as functional foods which can provide health benefits beyond the traditional nutrients. There are monographs that cover the medicinal and healing properties of some individual traditional mushrooms. There has been a recent upsurge of interest in mushrooms not only as a health food which is rich in protein but also as a source of biologically active compounds of medicinal value which include complementary medicine/dietary supplements for anticancer, antiviral, hepatoprotective, immunopotentiating and hypocholesterolemic agents. However the mechanisms of the various health benefits of mushrooms to humans still require intensive investigation, especially given the emergence of new evidence of their health benefits. In the present paper the medicinal potential of mushrooms is being discussed.

Review

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Introduction

It has been more than two decades since the concept of "functional foods" was first introduced as a factor in the analysis of foods after nutrients (Sadler & Saltmarsh, 1998). Consumers are now deeply interested in food bioactives that provide beneficial effects to humans in terms of health promotion and disease risk reduction. Detailed information about food bioactives is required in order to obtain appropriate functional food products. Therefore US, European Union and Asian countries like Japan, South Korea etc have drafted and revised various regulatory guidelines on functional foods and their health claims (Hasler, 1996).

One of the most prominent functional foods for human is mushrooms. They have been collected and cultivated for hundred of years in Asian countries, like China and Japan (Zhanga et al., 2007). They have a long history of use for their health promotion benefits (Zaidman et al., 2005). In recent years reports on the chemistry, and the nutritional and functional properties of mushroom have been overwhelming and more than 300 articles related to mushrooms have been published in the last two decades.

Mushrooms being neither plant nor animal have been placed in a kingdom, called Myceteae (Miles & Chang, 1997). The word mushroom may mean different things to different people and countries. In a broad sense "mushroom is a macro fungus with a distinctive fruiting body, which can be either epigeous or hypogeous and large enough to be seen with naked eye and to be picked by hand" (Chang & Miles, 1992). Thus, Mushrooms can be Ascomycetes that can grow underground and have a non-fleshy texture and need not be edible.

Edible mushrooms have been widely utilized as human foods for centuries and have been appreciated for texture and flavor as well as some medicinal and tonic attributes (Manzi et al., 2001). However, the awareness of mushrooms as a healthy food and as an important source of biological active substances with medicinal value has only recently emerged (Cheung et al., 2003). Mushrooms are considered as healthy food because they are low in calories and fat but rich in proteins and dietary fibers (Manzi et al., 1999). The mushroom protein contains all the nine essential amino acids required by humans. In addition to their good protein content, mushrooms are a relatively good source of the nutrients like phosphorus, iron and vitamins, including thiamine, riboflavin, ascorbic acid, ergo sterol, and niacin (Barros et al., 2008).

Nutritional composition of mushrooms

The evaluation of nutrient composition includes the determination of proteins, carbohydrates, and vitamins. The nutrient composition may be called as neutraceuticals if it provides medical or health benefits like the prevention and treatment of disease. Neutraceuticals may range from isolated nutrients and dietary supplements to genetically engineered foods, herbal products and processed products such as cereals, soups and beverages. The most common nutrients of mushrooms are as follows:

Proteins and amino acids

The crude protein content of edible mushrooms is usually high, but varies greatly and is affected by factors such as species and stage of development (Longvah & Deosthale, 1998). The crude protein content of some common edible mushrooms varies from approx. 10.0-40% w/w (Barros et al., 2008; Longvah & Deosthale, 1998; Diez & Alvarez, 2001). The essential amino acid content (g/100 g protein) of mushrooms ranges from approx. 34 to 47%. The essential amino acid profiles of mushrooms reveal that the proteins are deficient in sulfur-containing amino acids, including methionine and cysteine. However, these edible mushrooms are comparatively rich in threonine and valine. It has been reported that lysine, leucine, isoleucine, and tryptophan are the limiting amino acids in some edible mushroom proteins (Barros et al., 2008; Diez & Alvarez, 2001; Cheung, 1997). The free amino acid level in mushrooms is low, ranging from 7.14 to 12.3 mg/g in dry edible mushrooms and contribute to the main flavor properties of mushrooms (Sugahara et al., 1975; Maga, 1981).

Vitamins

Cultivated mushrooms are a good source of several vitamins, such as riboflavin, niacin, and folates, with concentrations that vary within the range of 1.8-5.1, 31-65, and 0.30-0.64 mg/100 g dry weight (DW), respectively, depending on the species. The vitamin B2 content in mushrooms is higher than that generally found in vegetables, and in some varieties even have a level as that found in egg and cheese (Mattila et al., 2001). Mushrooms contain moderately high amounts of folates at concentrations that are of the same magnitude as is generally found in vegetables. Furthermore, the bioavailability of folates is as good as that for folic acids (Clifford et al., 1991) with a content of 300-1412 μg/100 g. In addition to riboflavin, niacin and folates, cultivated mushrooms also contain small amounts of vitamin C and vitamin B1 and traces of vitamins B12 and D2 (Mattila et al., 2001).

Carbohydrates

The carbohydrate content of edible mushrooms varies with species and ranges from 35 to 70% DW (Mau et al., 2001; Mau et al., 2001). Edible mushrooms are believed to contain a high level of oligosaccharides and only a low level of total soluble sugars (Bano & Rajarathnam, 1988).

Fatty acids

The fatty acid level in mushrooms is generally low, around 2-8% of distilled water. The level of polyunsaturated fatty acids as compared to saturated fatty acids is quite high, constituting more than 75% of total fatty acids, of which oleic and lenoleic acids are the most significant (Ribeiroa et al., 2009), while palmitic acid is the main saturated fatty acid.

Therapeutic potential of mushrooms

The major attribute of mushrooms is their medicinal properties which have been the main focus of researchers around the world. The momentous pharmacological and physiological properties of mushrooms are immune enhancement, maintenance of homeostasis and regulation of biorhythm, cure & prevention of various diseases and improvement from life threatening diseases such as cancer, stroke and heart diseases. The various activities of mushrooms have been studied which includes hypotensive and renal effects (Ribeiroa et al., 2009), immuno-modulatory and antitumor activities of polysaccharide–protein complex (PSPC) from mycelial cultures (Yip et al., 1987) immuno-modulatory and antitumor activities of lectins from edible mushrooms (Wang et al., 1995) and various other medicinal effects of most commonly studied *G. lucidum* (Wang et al., 1996; Chang et al., 1993).

The present paper gives an overview about the present knowledge about the pharmacological potential of mushrooms. A brief description of the chemical constituents and potential effects of mushrooms have been given in Table 1.

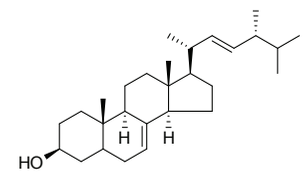
Health benefits of mushrooms

Due to the greater attention being paid to the potential health benefits of mushrooms to humans has resulted in many scientific publications, to the extent that there is now a database of scientific evidence about the specific health effects of mushrooms and their bioactive molecules. These include:

Table 1. The reported biological activity of mushrooms & active constituents.

Biological name of mushroom	Active principle/constituents/extracts	Activity reported
Auricularia auricula-judae (Bull.) J.Schrot.	Methanolic extracts, dietary fiber	Antioxidant (Yip et al., 1987), Hypocholesterolemic (Cheung, 1996)
Agrocybe cylindracea (DC.) Maire	β-Glucans	Antioxidant (Chang, 1993), Hypoglycemic (Kiho et al., 2000)
Agrocybe aegerita	Water and methanolic extracts, total phenolic content	Antioxidant (Mau et al., 2001), Hypocholesterolemic (Ng, 2005)
Agaricus bisporus (J.E.Lange) Imbach	Fibers, lectins	Hypocholesterolemic (Fukushima et al., 2000 & 2001), Hypoglycemic (Ahmad et al., 1984)
Agaricus campestris L.	Lectins	Hypoglycemic (Ahmad et al., 1984)
Astralagalus campertris	Non-lectin-type component	Hypoglycemic (Gray & Flatt, 1998)
Boletus edulis Bull.	Extracts of fruiting bodies	Antitumor (Lucas et al., 1957)
Calvatia gigantean (Batsch ex Pers.) Lloyd	Calvacin	Antitumor (Lucas et al., 1958)
Collybia maculate (Alb. & Schwein.) P. Kumm.	Purine derivatives	Antiviral activity (Leonhardt et al., 1987)
Eurotium chevalieri Mangin	Flavoglaucin	Antioxidant (Mau et al., 2002)
Flammulina velutipes (Curtis) Singer	Fibers, ethanolic extracts	Antioxidant (Wang et al., 1995 & 1996), Hypocholesterolemic (Fukushima et al., 2000 & 2001), Antiallergic (Sano et al., 2002)
Grifola frondosa (Dicks.) Gray	MD-fraction, ergosterol (**1**)	Antioxidant (Wang et al., 1995 & 1996), hypotensive, Hypoglycemic (Horio et al., 2001), Immunotherapy (Hazama et al., 1995), Anti-inflammatory activity (Zhang et al., 2002)
Ganoderma lucidum (Curtis) P. Karst	Ganoderan A and B, glucans, Triterpenes (ganoderiol F (**2**), ganodermanontriol (**3**), ganoderic acids (**4**) A, B, D, F, G, H, Z), ganosporeric acid A, ganopoly, the polysaccharide-containing preparation	Hypoglycemic (Hikino et al., 1985), antioxidant and antitumor (Thekkuttuparambil et al., 2007), antiviral (HIV-1) (El-Mekkawy et al., 1998), Antiallergic (Kohda et al., 1985; Tasaka et al., 1988), Anti-inflammatory (Koyama et al., 1997), antihepatotoxic (Hirotani et al., 1986; Chen & Yu, 1993, inhibit the biosynthesis of cholesterol (Komoda et al., 1989), antioxidative and free radical scavenging effects (Lin, 2004)
Ganoderma pfeifferi Bres.	Sesquiterpenoid hydroquinones, ganodermadiol (**5**), lucidadiol (**6**) and applanoxidic acid G (**7**)	Antimicrobial (Mothana et al., 2000), Antiviral (Mothana et al., 2003)
Ganoderma annulare (Pers.) Bres.	Applanoxidic acid A (**8**)	Antifungal (Smania et al., 2003)
Ganoderma applanatum (Pers.) Pat.	Steroids like 5α-ergosta- 7,22-dien-3β-ol or 5,8-epidioxy-5α,8α-ergosta-6,22-dien-3β-ol	Antimicrobial (Smania et al., 1999), Analgesic (Melzig et al., 1996)
Hericium erinaceus (Bull.) Pers.	Phenol-analogous compounds (hericenons C, D, E, F, G, H)	Antioxidant (Wang et al., 1995 & 1996), ameliorative effect in Alzheimer's dementia (Mizuno, 1999)
Hypsizigus marmoreus	Ethanolic extracts	Antioxidant (Chang, 2004), Antiallergic (Sano et al., 2002)
Hericium coralloides (Scop.) Pers.	Erinacin E (**9**)	Antinociceptive (Saito et al., 1998)
Inonotus obliquus Linn.	Fruiting bodies	Used as a folk medicine for cancer and stomach diseases (Molitoris, 1994)
Inonotus hispidus (Bull.) P. Karst.	Hispolon (**10**) and hispidin (**11**), phenolic compounds	Antiallergic (Ali et al., 1996), Antiviral activity (Awadh et al., 2003)
Kuehneromyces mutabilis (Schaeff.) Singer & A. H. Sm.	Mycelial extracts	Antiviral activity (Mentel et al., 1994)
Lentinula edodes (Berk.) Pegler	Methanolic and water extracts, eritadenine (**12**), lentinan, oxalic acid, ethanolic mycelial extracts	Antioxidant (Wang et al., 1995 & 1996), Hypocholesterolemic (Lee et al., 2007; Cheung, 2001), Immunotherapy (Hazama et al., 1995), Antimicrobial (Bender et al., 2003), antiprotozoal (Badalyan, 2004)

Laricifomes officinalis (Vill.) Kotl. & Pouzar	Dehydrotrametenolic acid (**13**)	Hypoglycemic (Sato et al., 2002)
Laetiporus sulphureus (Bull.) Murrill	Dehydrotrametenolic acid	Hypoglycemic (Sato et al., 2002)
Lenzites betulina (L.) Fr.	Betulinan A (**14**)	Inhibition of lipid peroxidation (Lee et al., 1996)
Pleurotus ostreatus (Jacq. ex Fr.) P. Kumm.	Water and 30% ethanolic extract	Antioxidant (Wang et al., 1995 & 1996), Hypocholesterolemic (Bobek et al., 1991 & 1993)
Pleurotus tuberregium (Rumph. ex Fr.) Singer	Crude methanolic and water extracts	Antioxidant
Pleurotus cornucopiae Singer	Dietary fiber	Hypocholesterolemic (Ryong et al., 1989)
Pleurotus pulmonaris (Fr.) Quel.	Methanolic extract	Antioxidant and antitumor (Thekkuttuparambil et al., 2007), Anti-inflammatory (Jose et al., 2002)
Pholiota nameko (T. Ito) S. Ito & S. Imai	Ethanolic extracts	Antiallergic (Sano et al., 2002)
Pleurotus eryngii (DC.) Quel.	Ethanolic extracts	Antiallergic (Sano et al., 2002)
Phellinus linteus	Ethanolic extracts and a proteoglycan	Anti-inflammatory activity (Kim et al., 2003 & 2004)
Polyporus umbellatus	5α,8α-epidioxy-ergosta-6,22-dien-3-ol	Potentiators of ADP-induced platelet aggregation (Lu et al., 1985)
Schizophyllum commune Fries	Schizophyllan	Immunotherapy (Hazama et al., 1995)
Scutiger ovinus	Scutigeral (**15**)	Pain killer (Szallasi et al., 1999)
Scutiger confluens	Albaconol (**16**)	Antagonist at the VR1 receptor (Liu, 2002)
Tremella fuciformis Berk.	Acidic polysaccharide from the fruiting bodies	Hypoglycemic (Kiho et al., 1994)
Trametes versicolor (L.:Fr.) Quel.	Coriolan, a β-glucan–protein complex	Hypoglycemic (Hikino et al., 1985), Immunotherapy (Hazama et al., 1995)
Tricholoma populinum	Whole mushrooms	Antiallergic (Kreisel et al., 1990)
Volvariella volvacea (Bulliard ex Fries) Singer	Methanolic and water extracts, exopolysaccharides	Antioxidant, Hypocholesterolemic (Cheung, 1996)
Wolfiporia cocos (F.A. Wolf)	Dehydrotrametenolic acid	Hypoglycemic (Sato et al., 2002)



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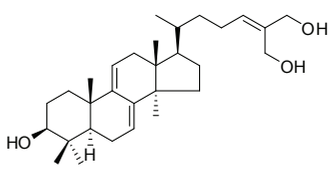

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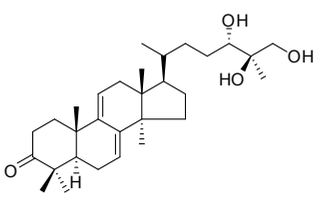

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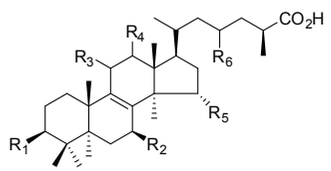
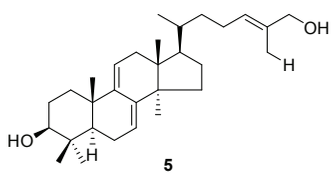


4a Ganoderic acid A: R_1=R_3=R_6=O; R_2=R_5=OH; R_4=H
4b Ganoderic acid B: R_1=R_3=R_6=R_5=O; R_2=OH; R_4=H
4c Ganoderic acid D: R_1=R_3=R_6=R_5=O; R_2=R_4=OH
4d Ganoderic acid F: R_1=R_2=R_3=R_6=R_5=O; R_4=OH
4e Ganoderic acid G: R_1=R_2=R_4=OH; R_3=R_5=R_6=O
4f Ganoderic acid H: R_1=OH; R_2=R_5=R_3=R_6=O; R_4=OAc
4g Ganoderic acid Z: R_1=OH; R_2=R_3=R_4=R_5=R_6=H
4h Ganosporeric acid A: R_1=R_2=R_3=R_4=R_5=R_6=H



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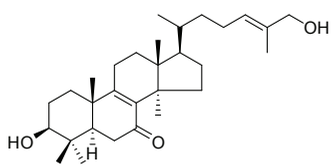

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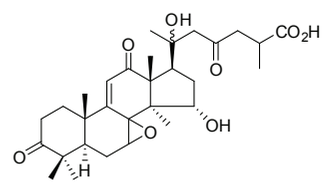

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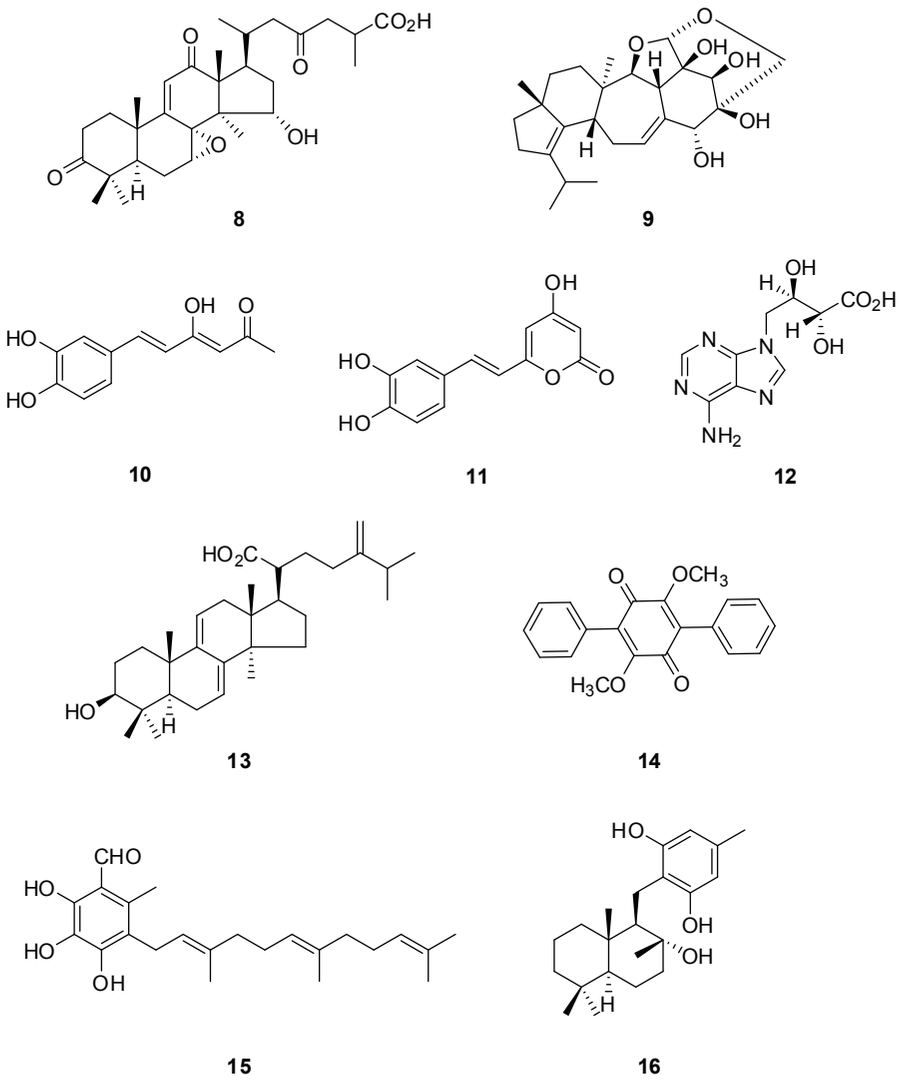

Mushrooms as antioxidants

Many studies have concluded that edible mushrooms possess potent antioxidants. In a research conducted in Japan, it was found that the crude ethanol extract of 150 mushrooms shows the antioxidant activity using the peroxide value in the methyl linoleate system (Chang & Miles, 2004). A study of methanolic extracts from black, red and snow ear mushrooms found that they had an inhibitory effect on lipid peroxidation, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging and hydroxyl radical scavenging and a strong reducing power and ability to chelate ferrous ions (Kasuga et al., 1993). Similar studies on other mushrooms, including *D. indusiata, G. frondosa, H. erinaceus, T. giganteum, F. velutipes, L. edodes, P. cystidiosus*, and *P. ostreatus,* showed that these mushrooms also possess the aforementioned antioxidant properties (Mau et al., 2001; Yang et al., 2002).

Similar antioxidant properties have also been reported for other edible mushrooms, including *Agrocybe cylindracea* (Mau et al., 2002) and *H. marmoreus*, both of which belong to the Tricholomataceae family (Tsai et al., 2006). Potent antioxidant activity was also found in crude methanolic and aqueous extracts of the common Chinese edible mushrooms *L. edodes* (shiitake mushroom), *Pleurotus tuber-regium* and *V. volvacea* (straw mushroom) and a lesser known edible mushroom, *A. aegerita*, belonging to the family Bolbitiaceae, was evaluated by the β-carotene bleaching method, DPPH radical scavenging activity and erythrocyte hemolysis assay (Lee et al., 2007). Fractionation of the crude methanolic and aqueous extracts of *L. edodes*, *P. tuber-regium* and *V. volvacea* further indicated that the dichloromethane and ethyl acetate fractions of these mushrooms have the strongest antioxidant activity and have the lowest median effective

concentration (EC50) values (Cheung, 2001).

The antioxidant activity and antioxidant compounds in seven wild edible mushrooms (Lo & Cheung, 2005) were determined, including phenolics, β-tocopherol and β-carotene in methanolic extracts, and their *in vitro* antioxidant systems, including their reducing power, free-radical scavenging, superoxide anion radical scavenging, total antioxidant activity, and metal-chelating activities. Phenolics with antioxidant ability have also been found in other mushroom species. Flavoglaucin, which is a phenolic compound isolated from the mycelial mat of *Eurotium chevalieri*, is an excellent antioxidant in vegetable oil at a concentration of 0.05% (Elmastas et al., 2007). In most of these studies a positive correlation was found between the total phenolic content in the mushroom extracts and their antioxidative properties, which confirms that edible mushrooms have a potential as natural antioxidants due to the ability of their phenolics to inhibit lipid oxidation.

Mushrooms as hypocholesterolemic agents

Cardiovascular disease is associated with atherosclerosis, LDL oxidation, and hypercholesterolemia, and thus the regulation of the cholesterol level is important for the prevention and treatment of this disease. Edible mushrooms are an ideal food for the dietetic prevention of atherosclerosis due to their high fiber and low fat content. Indeed, the inclusion of edible mushrooms in a natural hypocholesterolemic and antisclerotic diet is often prescribed in Oriental medicine (Ishikawa et al., 1984). Initial research on the cholesterol-lowering effects of mushrooms was conducted in Japan in the 1960s, and it was demonstrated that when rats were fed with a high-fat and high-cholesterol diet supplemented with 5% water of the fruiting bodies of *L. edodes* for ten weeks, the plasma cholesterol levels of the animals decreased significantly (Sun et al., 1984). The adenosine derivative lentinacin or lentysine (currently known as eritadenine [2(*R*), 3(*R*)-dihydroxy-4-(9-adenyl)-butyric acid] (**12**) was subsequently isolated and identified to be one of the active hypocholesterolemic components in the shiitake mushroom (Kaneda & Tokuda, 1966).

Eritadenine has also been found to reduce the serum cholesterol level in mice by the acceleration of the excretion of ingested cholesterol and its metabolic decomposition (Tokita et al., 1972). Eritadenine affects the metabolism not only of cholesterol but also of phospholipids and fatty acids in rats (Suzuki & Ohshima, 1976; Sugiyama et al., 1995). The dietary supplementation of eritadenine may therefore decrease phosphatidylcholine biosynthesis by altering the phosphatidylethanolamine concentration (Shimada et al., 2003). Similar to soybean protein, eritadenine lowers cholesterol by decreasing the ratio of phosphatidylcholine (PC) to phosphatidylethanolamine (PE) in liver microsomes and altering the composition of PC (Sun et al., 1984). Eritadenine can also suppress the metabolism of lipids (linoleic acid) by suppressing 1, 6-desaturase activity. Several other studies on *Lentinula* extracts have shown them to cause a significant decrease in serum cholesterol in young women and people older than 60 years of age in Japan (Tokita et al., 1972).

Recently, it has been reported that eritadenine may elicit its effect by the suppression of the hyperhomocysteinic effect of guanidinoacetic acid, which leads to the decreased production of homocysteine and increased cystathionine formation (Suzuki & Ohshima, 1976). In addition to eritadenine, nucleic acid compounds extracted from *L. edodes* were found to be inhibitors of platelet agglutination (Sugiyama et al., 1995). Lovastatin and its analogues are powerful inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase and as such are well-known cholesterol-lowering agents (Shimada et al., 2003). It has also been found that the addition of 2 and 4% of *P. ostreatus* to a hyperlipidemic diet can prevent the accumulation of cholesterol and triacylglyceride in both the sera and livers of rats with exogenous, endogenous, or genetically induced hyperlipidemia (Bobek et al., 1991; Bobek et al., 1993). A reduction of the serum cholesterol level of up to 80% was also observed from the feeding of the whole mushroom, water and 30% ethanol extract of *P. ostreatus* to rats. In another study, dietary fiber extracted from *P. cornucopiae* had a marked antiatherosclerotic effect *in vitro*, and patients with coronary disease showed a decreased atherogenic activity (20-40%) in their sera after the consumption of this mushroom, which confirms that it has a natural cholesterol-lowering agent that is responsible for this hypocholesterolemic effect (Ryong et al., 1989). Addition of 1-5% of oyster mushroom to a hyperlipidemic diet efficiently prevents the accumulation of LDL cholesterol and triacylglyceride in both the blood and liver of rats with hyperlipidemia (Bobek et al., 1998) and also reduces cholesterol biosynthesis by suppressing the activity of hepatic HMG-CoA reductase (Bobek et al., 1995) and accelerated cholesterol catabolism by up-regulating hepatic cholesterol 7β-hydroxylase (Bobek et al., 1994). It has been suggested that the fruiting bodies of oyster mushrooms could be recommended for consumption as a natural cholesterol-lowering agent in the human diet (Cimerman, 1999).

In addition to lovastatin and eritadenine, dietary fibers (nonstarch polysaccharides, mainly β-glucans) has also been suggested to be an important hypocholesterolemic component in mushrooms, and dietary fiber isolated from

Auricularia auricula-judae (Jew's ear) and *Tremella fuciformis* (white jelly-leaf) can significantly decrease the serum total cholesterol (TC) and LDL cholesterol levels (Cheung, 1996). Furthermore, exopolysaccharides produced by the submerged fermentation of the mycelium of *V. volvacea* can reduce the levels of serum TC, LDL cholesterol, and liver TC in alimentarially induced hypercholesterolemic rats (Cheung 1996). Fibers from *F. velutipes* (enokitake mushroom) and *A. bisporus* (button mushroom) can dramatically enhance the hepatic LDL receptor messenger RNA (mRNA), causing the diminution of the serum TC (Fukushima et al., 2000; Fukushima et al., 2001).

Mushroom like *A. auricula-judae*, display anticoagulation, antiaggregatory activity in the blood platelets of mice and rats, thus serving to lower their total cholesterol, total triacylglyceride, and lipid levels (Chen, 1989; Sheng & Chen, 1990). *G. frondosa*, reduced blood pressure in rats without changing the plasma high-density lipoprotein (HDL) level or serum cholesterol level (Mizuno, 1995). Various studies have shown that *Lentinula* mushrooms can lower both the blood pressure and the free cholesterol level in plasma and can accelerate the accumulation of lipids in the liver by removing them from circulation (Kabir & Kimura, 1989). It has also been reported that dried *A. aegerita* can significantly reduce the serum TC, triacylglyceride, atherogenic index, hepatic TC, and total triacylglyceride levels in rats fed a semisynthetic high-cholesterol diet compared with the control group (Yeung & Cheung, 2002). The hypocholesterolemic effect of *A. aegerita* has been suggested to be linked with its antioxidant activity (Ng, 2005).

Mushrooms as hypoglycemic agents

An extensive search for traditional plant treatments for diabetes has concluded that recognized edible mushrooms are an ideal food for the dietetic prevention of hyperglycemia because of their high dietary fiber and protein and low fat content (Alarcon-Aguilara et al., 1998). Many studies have been conducted on the hypoglycemic activity of whole mushrooms and their fruiting bodies (Horio et al., 2001) and on mushroom bioactive components, including polysaccharides (Kiho et al., 1994; Kiho et al., 1994; Kiho et al., 2002; Kiho et al., 2000; Kiho et al., 1995) and lectins (Ewart et al., 1975) isolated from the fruiting bodies. Moreover, endo and exopolymers produced in submerged mycelial cultures have also been found to have a hypoglycemic effect (Kim et al., 2001; Kim et al., 1997). The most common animal models used for the study of the hypoglycemic effects of mushrooms are rats and mice with insulin-dependent diabetes mellitus (IDDM) induced by streptozotocin (STZ) and genetically diabetic mice with non-insulin-dependent diabetes mellitus (NIDDM) (Beattie et al., 1980; Swanston-Flatt et al., 1989). The administration of *G. frondosa* to IDDM STZ diabetic albino Wistar rats at 20% dry weight in a semipurified diet for 100 days resulted in an increase in insulin excretion and a decrease in the blood glucose level in the animals. It has also been demonstrated that *G. frondosa* has an antidiabetic effect in NIDDM KK-Ay mice, which is produced by reducing the blood glucose level (Kurushima et al., 2000; Kubo et al., 1994; Kubo & Nanba, 1997). The β-glucans isolated from *A. cylindracea* showed remarkable hypoglycemic activity in both normal and STZ-induced diabetic mice when administered intraperitoneally. The antidiabetic activity of *Tremella aurantia* may also be mediated by an increase in the activities of glucokinase, hexokinase, and glucose-6-phosphate dehydrogenase and a decrease in the activity of glucose-6-phosphatase in normal and IDDM diabetic mouse livers after intraperitoneal administration (Kiho et al., 2000). Another acidic polysaccharide from the fruiting bodies of *T. fuciformis* was found to be effective in STZ-induced diabetic mice when administered orally (Kiho et al., 1994).

Lectins isolated from mushrooms (*Agaricus campestris* and *A. bisporus*) have been shown to enhance insulin release in isolated Langerhans rat islets (Ahmad et al., 1984). The presence of a non-lectin-type component in *A. campertris* that displays insulin-releasing and insulin-like activity has also been reported (Gray& Flatt, 1998). Guanidine, which is a known hypoglycemic substance related to the biguanide class of oral antidiabetic drugs, has been found in edible mushrooms (Windholz, 1983), but the detailed principles of these active components in mushrooms remain to be elucidated.

Ganoderan A and B, glucans from *G. lucidum* fruiting bodies (Hikino, 1985), coriolan, a β-glucan-protein complex obtained from submerged grown *T. versicolor* biomass exhibited hypoglycemic effects in several test systems and ameliorated the symptoms of diabetes. Seventy-one patients with confirmed type II diabetes were treated with polysaccharide fractions from *G. lucidum* (Ganopoly, 1800 mg three times daily for twelve weeks). The mean post-prandial glucose values had decreased to 11.8 mmol in the Ganopoly group (Gao et al., 2004). Preparations from the traditional Chinese drug Cordyceps (consisting of fungi parasitic in insects) and from fermented mycelia meliorate diabetes in a diabetic animal model using streptozotocin-induced rats after *p.o*. application (Hsu & Lo, 2002).

Dehydrotrametenolic acid (**13**), found in several polypores including *Wolfiporia cocos, Laricifomes officinalis* and *Laetiporus sulphureus* Murrill, acts as an insulin sensitizer in glucose tolerance tests and reduces hyperglycemia in mice with noninsulin-dependent diabetes

(Sato et al., 2002).

Mushrooms as antitumor agents

The mushroom *Cordyceps militaris* has been used for a long time in eastern Asia as a nutraceutical and in traditional Chinese medicine as a treatment for cancer patients. CMP exerted strong antifungal effect against the growth of the fungus *Fusarium oxysporum*, and exhibited cytotoxicity against human breast and bladder cancer cells. 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.

In one study, it was found that *Ganoderma lucidum, Phellinus rimosus, Pleurotus florida* and *Pleurotus pulmonaris* possessed profound antioxidant and antitumor activities (Thekkuttuparambil et al., 2007). The antitumor activity of the higher Basidiomycetes extracts of fruiting bodies of *Boletus edulis* and other Homobasidiomycetes were tested against the Sarcoma 180 line in mice (Lucas et al., 1957) and were found to have significant activity. In the 1960s, calvacin was the most commonly cited natural product isolated from the medicinal mushroom and was broadly used in many laboratories as an antitumor agent. Calvacin was isolated from the giant puffball (*Calvatia gigantean*) (Lucas et al., 1958) and it was found effective against many experimental tumors, including Sarcoma 180, mammary adenocarcinoma 755, leukemia L-1210, and HeLa cell lines. There are approximately 650 species of higher Basidiomycetes that have been found to possess antitumor activity (Wasser, 2002; Mizuno , 1995).

In Eastern Europe, the fruiting bodies of *I. obliquus* have been used as a folk medicine for cancer and stomach diseases since the 16th or 17th century (Molitoris, 1994). Antitumor effects of several extracts and isolated compounds from mushrooms have been demonstrated in tumor cell systems and in animal assays (Kahlos et al., 1987; Burczyk et al., 1996). Searching for new antitumor and other medicinal substances from mushrooms and studying the medicinal value of these mushrooms has become a matter of great significance.

Mushrooms as immunomodulators

So called 'immunomodulators' (biological response modifier, immunopotentiators and immunostimulants) are the most important medicinal mushroom drugs used especially in Japan, China, Korea and other East Asian countries today. Some polysaccharides or polysaccharide–protein complexes from mushrooms are able to stimulate the non-specific immune system and to exert antitumor activity through the stimulation of the host's defence mechanism (Chihara et al., 1969; Mizuno, 1999; Wasser & Weis, 1999; Reshetnikov et al., 2001). These drugs activate effector cells like macrophages, T lymphocytes and NK cells to secrete cytokines like TNF-a, IFN-g, IL-1b, etc., which are antiproliferative and induce apoptosis and differentiation in tumor cells (Wasser & Weis, 1999; Reshetnikov et al., 2001). There is evidence that β-d-glucans induce a biological response by binding to membrane complement receptor type 3 (CR3, alphaMb2 integrin or CD11b/CD18) on immune effector cells. The ligand-receptor complex can be internalized. The intercellular events that occur after glucan-receptor binding have not been fully determined till now (Zhou & Gao, 2002). In one experimental approach it was shown that schizophyllan produced by *S. commune* was able to bind the mRNA poly (A) tail (Karinaga et al., 2004).

Lentinan from *L. edodes*, schizophyllan from *S. commune*, MD-fraction from *G. frondosa* and compounds from *T. versicolor* (PSK and PSP) are in clinical use (*i.e.* 0.5-1.0 mg lentinan per day, intravenous), 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 (parenteral) 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). In a randomized multicentric study with 89 stomach cancer patients, the median survival time in the immunochemotherapy group (chemotherapy and lentinan 2 mg per week, intravenous) was 189 days and in the control group (only chemotherapy) 109 days (Ochiai et al., 1992). In another study of patients with advanced colorectal cancer, the median survival time was 200 days in the lentinan-treated group (2 mg per week, 23 patients) and 94 days in the control group (Taguchi et al., 1982). In a controlled randomized study, 130 patients were treated with schizophyllan (intramuscular 40 mg per week, totally 1134 mg) after surgical removal of the whole tumor tissue additionally to application of mitomycin and futraful. The schizophyllan treatment started at day 14 after operation. The median survival time after five years was 72.2% in the schizophyllan group and 61.9% in the control group (134 patients, chemotherapy only). Schizophyllan had no effect

on the survival time when the tumor tissue could not be removed totally (Fujimoto et al., 1991). The immunostimulating effect of lentinan was also investigated in patients with AIDS. In a phase II study, 107 HIV positive patients were treated with didanosin (400 mg per day, *p.o*. 6 weeks). After that time, 88 patients got additionally 2 mg lentinan per week intravenous for 24-80 weeks, the patients of the control group got only didanosin. The combined treatment resulted in a significant increase of the number of CD4 β cells after 38 weeks in comparison to control group (Gordon et al., 1995).

In a non-random case series, a combination of MD-fraction and whole powder of *G. frondosa* was investigated to determine its effectiveness for 22 to 57 years old cancer patients in stages II-IV. Cancer regression or significant symptom improvement was observed in 58.3% of liver cancer patients, 68.8% of breast cancer patients and 62.5% of lung cancer patients. The trial found a <10-20% improvement for leukemia, stomach cancer and brain cancer patients (Kodama et al., 2002). The MD-fraction has been approved by the Food and Drug Administration (FDA) for an Investigational New Drug application to conduct a phase II pilot study on patients with advanced breast and prostate cancer (Konno et al., 2002).

Mushrooms as antimicrobial agents

Mushrooms need antibacterial and antifungal compounds to survive in their natural environment. Hence, they are rich sources of natural antibiotics. Many of the externalized secondary metabolites (extracellular secretions by the mycelium) are known to combat bacteria (Benedict & Brady, 1972; Kupra et al., 1979; Lindequist et al., 1990) and viruses (Eo et al., 1999). Several compounds extracted from mushroom revealed antifungal and antibacterial activity, namely against *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli* (Takazawa et al., 1982). European Ganoderma species *Ganoderma pfeifferi* inhibited the growth of methicillin-resistant *Staphylococcus aureus* and other bacteria by new sesquiterpenoid hydroquinones (Mothana et al., 2000). Besides, this it was found that whole extracts of this mushroom inhibit the growth of microorganisms responsible for skin problems (*Pityrosporum ovale, Staphylococcus epidermidis, Propionibacterium acnes*).

Applanoxidic acid A (**8**) isolated from *Ganoderma annulare*, shows weak antifungal activity against *Trichophyton mentagrophytes* (Smania et al., 2003). Steroids like 5α-ergosta- 7, 22-dien-3β-ol or 5,8-epidioxy-5α,8α-ergosta-6, 22-dien-3β-ol, isolated from *Ganoderma applanatum*, proved to be weakly active against a number of grampositive and gram-negative microorganisms (Smania et al., 1999). Oxalic acid is one agent responsible for the antimicrobial effect of *Lentinula edodes* (Berk.) against *S. aureus* and other bacteria (Bender et al., 2003). Ethanolic mycelial extracts from *L. edodes* possess antiprotozoal activity against *Paramecium caudatum* (Badalyan, 2004). Epicorazins used in some parts of Yemen for the treatment of 'nappy rash' of babies and in South Africa against sun burn belong to the group of epipolythiopiperazine-2,5-diones, an important class of biologically active fungal metabolites. Other antimicrobial compounds from the Aphyllophorales were summarized by (Zjawiony, 2004).

Mushrooms as antiviral agents

In contrast to bacterial infectious diseases, viral diseases cannot be treated by common antibiotics and specific drugs are urgently needed. Antiviral effects are described not only for whole extracts of mushrooms but also for isolated compounds. They may act directly by inhibition of viral enzymes, synthesis of viral nucleic acids or adsorption and uptake of viruses into mammalian cells. These direct antiviral effects are exhibited especially by smaller molecules. Indirect antiviral effects are the result of the immunostimulating activity of polysaccharides or other complex molecules (Brandt & Piraino, 2000). Small molecular compounds with antiviral activities, several triterpenes from *Ganoderma lucidum* (*i.e*. ganoderiol F (**2**), ganodermanontriol (**3**), ganoderic acid B (**4**)) are active as antiviral agents against human immunodeficiency virus type 1 (HIV-1) (El-Mekkawy et al., 1998). Ganodermadiol (**5**), lucidadiol (**6**) and applanoxidic acid G (**7**), isolated from G. pfeifferi, but also from other known *Ganoderma* species, possess *in vitro* antiviral activity against influenza virus type A (IC50 values in MDCK cells >0.22; 0.22 and 0.19 mmol, respectively). Further, ganodermadiol is active against herpes simplex virus type 1, causing lip exanthema and other symptoms (IC50 in Vero cells 0.068 mmol) (Mothana et al., 2003). *In vitro* antiviral activity against influenza viruses type A and B was demonstrated for mycelial extracts of *Kuehneromyces mutabilis* (Mentel et al., 1994), and two isolated phenolic compounds from *Inonotus hispidus* (Awadh et al., 2003) and ergosterol peroxide, present in several mushrooms (Lindequist et al., 1989). The antiviral activity of *Collybia maculata* (vesicular stomatitis viruses in BHK cells) is due to purine derivatives (Leonhardt et al., 1987).

Mushrooms as antiallergic agents

Although extracts of many mushrooms can

stimulate the immune system, while others suppress immune responses. This could be of interest, *e.g*. for the treatment of allergic diseases that are increasing worldwide. Ethanolic extracts of the edible Japanese basidiomycetes *H. marmoreus, F. velutipes, Pholiota nameko* and *Pleurotus eryngii* show significant antiallergic effects in mice (oxazolone-induced type IV allergy) also after *p.o.* application (Sano et al., 2002). Some compounds from *G. lucidum* (ganoderic acids C and D); inhibit the histamine release from rat mast cells (Kohda et al., 1985; Tasaka et al., 1988). Eating of *Tricholoma populinum* J. E. Lange led to the regression of severe allergic symptoms in a patient with thromboangitis obliterans and in another patient with urticaria (Kreisel et al., 1990). Hispolon (**10**) and hispidin (**11**), isolated from fruit bodies of *I. hispidus*, inhibit the chemiluminescence response of human mononuclear blood cells and the mitogeninduced proliferation of spleen lymphocytes of mice (Ali et al., 1996).

Mushrooms as anti-inflammatory agents

Ethanolic extracts and a proteoglycan from *P. linteus* show anti-inflammatory effect in the collagen-induced arthritis and in the croton oil-induced ear edema test in mice and antinociceptive effect in the writhing test (Kim et al., 2004; Kim et al., 2003). Other compounds effective in the writhing test are the ganoderic acids A, B, G and H, isolated from *G. lucidum*. These substances showed a stronger effect in this animal model than acetylsalicylic acid (Koyama et al., 1997). Methanolic extract of *Pleurotus pulmonarius* fruiting bodies (500 and 1000 mg/kg) reduced carrageenan-induced and formalin-induced paw edema in mice. The activity was comparable to the reference diclofenac (10 mg/kg). The IC50 value for hydroxyl-radical scavenging was 476 mg/mL and for lipid peroxidation inhibition 960 mg/ml (Jose et al., 2002). The edible mushroom *G. frondosa* contains ergosterol (**1**), ergosta-4-6-8(14), 22-tetraen-3-one and 1-oleoyl-2-linoleoyl-3-palmitoylglycerol, which inhibit cyclooxygenases I and II activity (Zhang et al., 2002).

Mushrooms as hepatoprotective agents

Ganoderic acids *R* and *S* and ganosporeric acid A from *G. lucidum* show in vitro antihepatotoxic activity in the galactosamine-induced cytotoxic test with primary cultured rat hepatocytes (Hirotani et al., 1986; Chen & Yu, 1993). *In vivo* study of two fractions of total triterpenoids extract of *G. lucidum* (75% ethanol) protected mice against hepatic necrosis induced by chloroform and D-galactosamine. The hepatoprotective effects were perhaps related to the ability to promote the activity of scavenging enzymes for hepatic free radicals in mice, and thus to raise the ability of antioxidation in mice (Wang et al., 2002).

Ganopoly, the polysaccharide-containing preparation of *G. lucidum*, was proven in a double-blind, randomized and multicentered study in patients with chronic hepatitis B (HBV DNA positive; application of Ganopoly for twelve weeks, then thirteen weeks followed up, 600 mg three times per day equal to 27 g fruiting body, *p.o.*). Within the six months study period, 33% (17/52) of treated patients had normal aminotransferase values and 13% (7/52) had cleared hepatitis B surface antigen from serum, whereas none of the controls had normal enzyme values (Gao et al., 2002).

Mushrooms as centrally acting agents

Apart from well investigated psychoactive mushrooms like *Amanita muscaria* or *Psilocybe* species some further mushroom extracts and compounds have been found with special central effects that could be of pharmacological interest. Phenol-analogous compounds (hericenons C, D, E, F, G, H) from *H. erinaceus* induce the synthesis of nerve growth factor and might have an ameliorative effect in Alzheimer's dementia (Mizuno, 1999). Erinacin E (**9**) from *Hericium coralloides* fermentation broth is a highly selective agonist at the kappa opiod receptor (IC50 of 0.8 mM, binding at the m opiod receptor with an I 50 of >200 mM). Such compounds may exhibit antinociceptive activity without side effects observed with m receptor agonists like morphine (Saito et al., 1998). Screening investigations of selected basidiomycetes indicate inhibitory effects of *P. betulinus, G. applanatum, H. annosum*, *Fomitopsis pinicola* and *Daedaleopsis confragosa* on neutral endopeptidase (enkephalinase) (IC50 values between 40 and 55 mg/mL). Selective inhibitors of this metalloendopeptidase could be useful in the treatment of pain with a spectrum of activity similar to that of opioids (Melzig et al., 1996). Scutigeral (**15**), isolated from fruiting bodies of *Scutiger ovinus* has affinity to the brain dopamine D1 receptors and may act as an orally active pain killer targeting vanilloid receptors (VR1) (Szallasi et al., 1999). Albaconol (**16**) from the fruiting bodies of *Scutiger confluens* is an antagonist at the VR1 receptor with an IC50 value of 5 mM (Liu, 2002).

Other activities

Some triterpenes from *G. lucidum* (ganoderic acid C and derivatives) are able to inhibit the biosynthesis of cholesterol (Komoda et al., 1989) as well. Other triterpenes of this fungus contribute to atherosclerosis

protection by inhibition of angiotensin converting enzyme (ganoderic acid F) (Morigiwa et al., 1986) or of platelet aggregation (ganoderic acid S) (Su et al., 1999). The antioxidative and free radical scavenging effects of polysaccharides and triterpenoids from *G. lucidum* were shown in different oxidative injury models including *tert*-butylhydroperoxide damaged mice peritoneal macrophages, alloxan-induced diabetes and experimental liver injury models. The inhibition of low density lypoproteins (LDL) oxidation by endothelial cells and of monocyte adhesion to endothelial cells has been demonstrated (Lin, 2004). The antilipidemic effect of *L. edodes* is caused by eritadenin, a nucleotide derivative (Tokuda et al., 1974). Betulinan A (**14**) from *Lenzites betulinus* is about four times more active as a radical scavenger than vitamin E in inhibition of lipid peroxidation (Lee et al., 1996). Ergosta-4-6-8(14), 22-tetraen-3-one, isolable from many mushrooms, has been shown to possess antialdosteronic diuretic properties (Yuan et al., 2004). Potentiators of ADP-induced platelet aggregation have been found in *Polyporus umbellatus* (5α, 8α-epidioxy-ergosta-6, 22-dien-3-ol (4)) and others (Lu et al., 1985).

Conclusion

The mushrooms may be used directly in the diet to promote health, taking advantage of the additive and synergistic effects of the bioactive compounds present in them. The potential therapeutic implications of mushrooms are enormous but, detailed mechanisms of the various health benefits of mushrooms to humans still require intensive investigation, especially with the emergence of new evidence of their health benefit effects. The exploration of newly cultivated mushrooms and isolation of their active ingredients with mechanism based potential therapeutic value remains a challenge and hence mushrooms will keep on to be the foremost spotlight of research in the upcoming prospect as well.

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