

Part I Shiitake

Chapter 1

What is Shiitake**NUTRITIONAL AND MEDICINAL VALUES OF SHIITAKE**Hyunjong Kwon (Miji)¹ and Christopher Hobbs²¹MushWorld, 150-5 Pyungchang, Jongro, Seoul, Korea (hjkwon@mushworld.com)²Institute for Natural Products Research, The U.S.

Shiitake has long been favored by Asian people as a gourmet and medicinal mushroom. They eat shiitake stir-fried, in soup and in decoction (Figs. 1). Today shiitake is found in markets throughout North America and Europe as well as Asia (Figs. 2, 3 and 4). It is the world's 2nd most commonly cultivated mushroom. Shiitake's popularity is ever increasing throughout Asia, North America, Europe and other parts of the world, partly because of its exotic flavor and partly because of its nutritional and various medicinal properties.

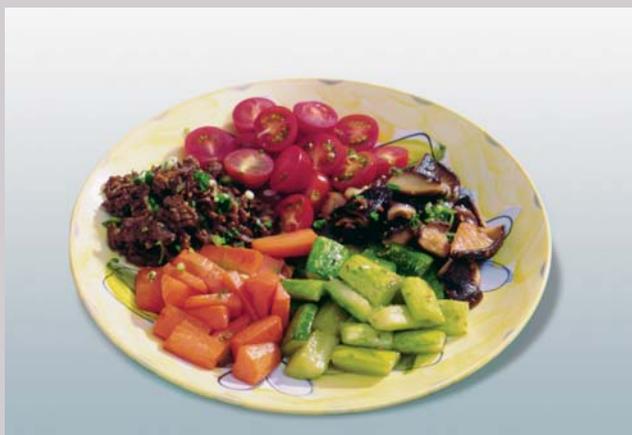


Figure 1. Asian cuisine with shiitake



Figure 2. Dried, sliced shiitake in U.S.A., Japan and Korea



Figure 3. Fresh shiitake in retail and wholesale markets



Figure 4. Leaflet about shiitake in a European country

Nutritional Health Benefits

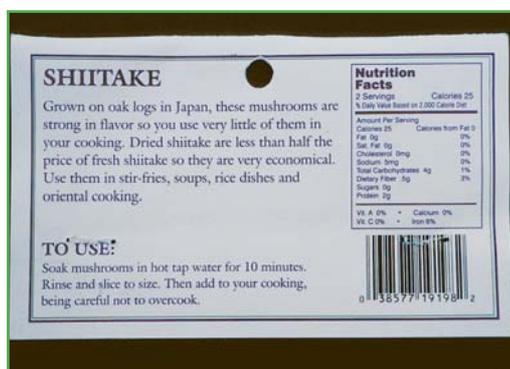


Figure 5. Nutrition facts on a package of dried shiitake

This delicate mushroom is also excellent in its nutritional value. It is a particularly good source of minerals and vitamins B₁ (thiamin), B₂ (riboflavin), B₃ (niacin) and D. It also contains all the essential amino acids and dietary fiber¹.

The caloric value of 100g of dried shiitake is higher than 100g of raw potatoes (80kcal) or beef loin (224kcal), but lower than that of whole wheat or brown rice (328-350kcal). The protein content of dried shiitake is comparable to that of chicken, pork and beef but the fat count is much lower and the dietary fiber count is considerably higher than those meats (Table 1). Shiitake contains almost all the essential amino acids, with lysine and arginine being particularly abundant (Liu and Bau, 1980), and methionine and phenylalanine less abundant (Lasota and Sylwestrzak, 1989). In laboratory analysis it was found that amino acids, protein, glycogen, lipids, ascorbic acid, and total ash contents increased as the fruiting body developed (Fasidi and Kadir, 1990). Based on these findings, it may be desirable to consume fully mature fruiting bodies for maximum nutritional value. The researchers generally found higher concentrations of nutrients in the cap than the stem of the fungus. Shiitake contains dietary fiber in the ratio of 6.7g per 100g of dried shiitake, which is a figure much higher than that for brown rice (0.2g), and sweet potatoes (0.9g). Dietary fiber prevents constipation, obesity, diabetes, hypertension, colon cancer and arteriosclerosis by lowering cholesterol level. In addition to dietary fiber, dried shiitake contains higher contents of potassium (K), iron (Fe), phosphorus (P) and vitamin B and D than most food sources. But it does not contain vitamins A and C (Table 1).

The high amount of ergosterol in fresh shiitake makes dried shiitake an important vitamin D source because ergosterol converts to vitamin D₂ in the presence of sunlight. Studies have shown that exposing shiitake to direct sunlight for 3 hours/day increases the vitamin D₂ content up to 5 times. Sunlight exposure also increases the free amino acid content which is about 2,180mg/dl in the dry fruiting bodies, and it makes them sweeter and less bitter (Kiribuchi, 1991).

Eating shiitake can prevent various vitamin B and D deficiencies including beri-beri² (thiamin); cheilosis³, glossitis⁴, corneal vascularization⁵, Seborrheic dermatitis⁶, nerve tissue damage (riboflavin); abnormal growth in infants and children (niacin); and rickets⁷ (vitamin D). Vitamin D boosts calcium absorption and thus plays an important role in bone formation.

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¹ dietary fiber: coarse, indigestible plant matter, consisting primarily of polysaccharides, that when eaten stimulates intestinal peristalsis

² beri-beri: disease involving swelling, tingling or burning sensation in the hands and feet, confusion, difficulty breathing (from fluid in the lungs), and uncontrolled eye movements

³ cheilosis: cracking at the corners of the mouth and inflammation of the mucous membranes in the mouth

⁴ glossitis: swollen and reddened tongue

⁵ corneal vascularization: reddening, burning, itching of the eyes and sensitivity to light

⁶ Seborrheic dermatitis: unusual dryness and greasy scaling of the skin

⁷ rickets: a childhood disorder involving softening and weakening of the bones

Table 1. Constituents of dried/fresh shiitake grown on different logs and other food sources (per 100g edible portion)

Food source	Energy (Kcal)	Moisture (%)	Protein (g)	Fat (g)	Ash (g)	Carbohydrates (mg)	
						Sugar	Fiber
Shiitake							
Dried / pitch pine	261	11.6	17.3	1.7	4.8	57.9	6.7
Dried / alder	277	11.0	14.2	2.7	2.8	62.5	6.5
Dried / Mongolian oak	277	8.9	17.1	2.5	3.7	60.8	7.0
Dried / oak	272	10.6	18.1	3.1	4.5	57.0	6.7
Fresh / oak	27	90.8	2.0	0.3	0.8	5.4	0.7
Other foods							
Whole wheat	328	11.8	12.0	2.9	1.8	69.0	2.5
Brown rice	350	11.6	7.6	2.1	1.6	74.4	2.7
Potato (raw)	66	81.4	2.8	∅*	1.1	14.4	0.2
Chicken (meat)	180	69.4	19.0	10.6	0.9	0.1	0
Pork (loin)	262	61.5	17.4	19.9	1.0	0.2	0
Beef (loin)	224	65.5	17.5	15.9	0.9	0.2	0

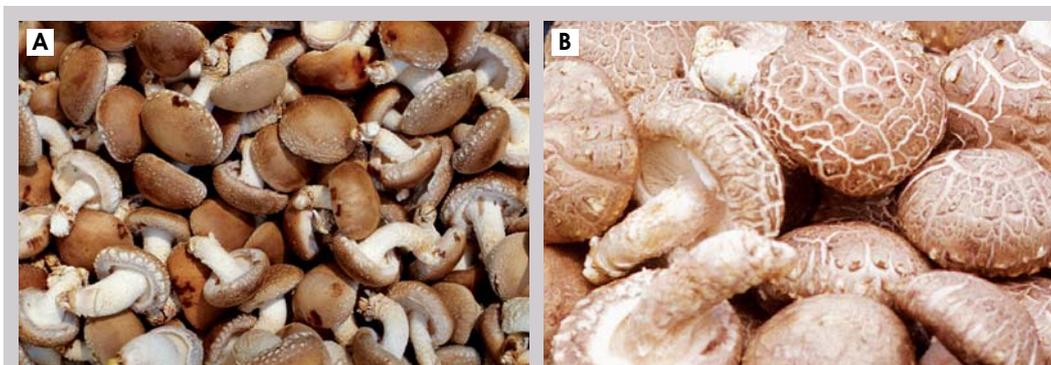
Food source	Minerals (mg)					Vitamins (mg)				
	Ca	P	Fe	Na	K	A***	B ₁	B ₂	B ₃	C
Shiitake										
Dried / pitch pine	20	206	3.6	**	-	0	0.66	1.61	7.7	0
Dried / alder	16	352	7.4	-	-	0	0.62	1.05	6.4	0
Dried / Mongolian oak	16	343	6.9	-	-	0	0.70	1.56	9.8	0
Dried / oak	19	268	3.3	25	2,140	0	0.48	1.57	19.0	0
Fresh / oak	6	28	0.6	5	180	0	0.08	0.23	4.0	∅
Other foods										
Whole wheat	71	390	3.2	3	380	0	0.34	0.11	5.0	0
Brown rice	6	279	0.7	79	326	0	0.23	0.008	3.6	0
Potato (raw)	4	63	0.6	3	485	0	0.11	0.06	1.0	36
Chicken (meat)	11	110	1.1	58	327	50	0.20	0.21	2.7	0
Pork (loin)	6	152	0.8	34	291	5	0.61	0.15	7.4	0
Beef (loin)	15	159	1.6	44	333	6	0.07	0.23	4.3	0

*∅: trace or nil

**.: not detected

***Unit: Vitamin A (RE)

Source: National Rural Living Science Institute, R.D.A. Korea, 2001

**Figure 6.** Fresh (A) and dried (B) shiitake

Medicinal Health Benefits



Figure 7. Shiitake (*Lentinula edodes*) fruiting body

Asian people have enjoyed shiitake fruiting bodies for ages as a folk or traditional medicine. Modern medicine has come up with more purified, concentrated shiitake derivatives. Among them, “lentinan” and “LEM” are the most frequently studied compounds. In the following sections, major published laboratory and clinical work available on the anti-tumor/ anti-viral/ anti-bacterial/ hepatoprotective effects, as well as cardiovascular effects will be reviewed.

Major active compounds isolated from *Lentinula edodes*

Lentinan

- a cell-wall constituent extracted from the fruiting bodies or mycelium of *L. edodes*
- a highly purified, high molecular weight polysaccharide (of about one million)
- containing only glucose molecules with mostly β - (1-3)-D-glucan linkages
- free of any nitrogen (and thus protein), phosphorus, sulfur, or any other atoms except carbon, oxygen, and hydrogen (Chihara, 1981)
- water-soluble, heat-stable, acid-stable, and alkali-labile (Aoki, 1984b)

LEM

- *Lentinula edodes* mycelium extract
- a preparation of the powdered mycelia extract of *L. edodes* harvested before the cap and stem grow
- containing a heteroglycan protein conjugate, that is, a protein-bound polysaccharide
- containing protein, sugars, mostly the pentoses, including xylose (a wood sugar) and arabinose (a pectin sugar), as well as glucose and smaller amounts of galactose, mannose, and fructose
- containing nucleic acid derivatives, vitamin B compounds, especially B₁ (thiamin) and B₂ (riboflavin); ergosterol; and eritadenine (Breene, 1990)
- also containing water-soluble lignins (Hanafusa *et al.*, 1990)

KS-2

- a polysaccharide containing α -linked mannose and a small amount of peptide
- Fuji *et al.* isolated

JLS

- a compound derived from the mycelium
- JLS-18, consisting of lignin, polysaccharides and proteins

Eritadenine

- a nucleic acid derivative

EPS and EPS4

- water soluble lignins

Anti-tumor effects

Most people who enjoy mushrooms, as well as health-care practitioners, seem to be quite interested in whether and what medicinal effects shiitake has in its whole, powder or extract form. Study results have shown that shiitake and its derivatives, especially lentinan and LEM, have strong anti-tumor/ anti-viral activities, when taken both orally and by injection, both in animals and in humans. These substances were found to work by enhancing various immune system functions rather than attacking the tumor cells or viruses themselves.

Animal tests

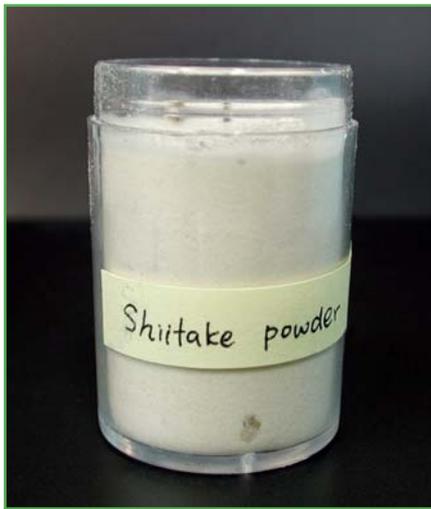


Figure 8. Powdered shiitake fruiting bodies

When powdered shiitake was fed to tumor-implanted mice as 10% of their normal diet, the growth of tumor⁸ was inhibited by 40% (Nanba *et al.*, 1987). When shiitake content was increased to 30%, tumor growth was inhibited by nearly 78%. When shiitake-supplemented feed (20%) was given a week after and on the same day of tumor implantation, the tumor inhibition rates were 53.9% and 72.4%, respectively. In a 1969 study by Dr. Chihara, the growth of Sarcoma 180 was inhibited by 67-81%, when aqueous shiitake extracts were injected or powdered dried shiitake was fed.

Lentinan is a most frequently studied substance due to its strong anti-tumor effects. Dr. Chihara (1970) found that when doses of 0.5-1mg lentinan per kg of body weight were administered to laboratory mice, Sarcoma 180 regressed or disappeared in 80-100% of the subjects. This purified polysaccharide has been shown to be non-toxic and enhance the immune response, inhibiting the growth of tumors⁹ in animal studies.

Besides lentinan, various polysaccharides extracted from *L. edodes* showed anti-tumor and immunostimulating activities. Ikekawa *et al.* (1969) found that an intraperitoneal¹⁰ injection of the freeze-dried water extract of shiitake (200mg/kg/day, for 10 days) produced an 80.7% tumor inhibition rate. Fuji *et al.* (1978) isolated a polysaccharide containing an α -mannan-peptide complex (KS-2) that strongly inhibited tumor growth when administered to mice both orally and intraperitoneally in doses between 1 and 100mg per kg of body weight.

Human clinical studies

Cancer patients suffer from severe side effects associated with cancer chemotherapy, as well as cancer. In clinical trials, when lentinan was administered to cancer patients during chemotherapy, tumor growth was inhibited, the effectiveness of chemotherapy was improved and patients' life spans were prolonged. In Japan, lentinan is approved for use as a drug to prolong the lives of patients undergoing chemotherapy for stomach cancer.

Lentinan was shown to increase the survival time for 3 patients with inoperable gastric cancer (Mashiko *et al.*, 1992; Shimizu *et al.*, 1981), and of women with recurrent breast cancer who have undergone surgical therapy (Kosaka *et al.*, 1985). In a randomized controlled trial, 275 patients with advanced or recurrent gastric cancer were given either one of two kinds of chemotherapy¹¹ alone or with lentinan injections. Statistically, the best results were obtained when lentinan was administered prior to chemotherapy (Taguchi *et al.*, 1981). In another group of 16 patients with advanced cancer, lentinan (4mg/week for 4 weeks) was injected into malignant peritoneal and/or pleural effusions¹². Eighty percent of the lesions showed clinical responses, and performance status¹³ was improved in 7 patients. The survival time for patients who responded immunologically to the treatment was 129 days and 49 days for those who did not respond (Oka *et al.*, 1992).

Researchers found lentinan produces its biological effects, including anti-tumor effects, anti-bacterial effects (tuberculosis) and anti-viral effects (HIV), not by attacking cancer cells, bacteria or viruses directly, but activating different immune responses in the host. Aoki *et al.* identified lentinan's immunostimulating effects in animal and human systems *in vitro*¹⁴ and *in vivo*¹⁵. Since the immune mechanisms behind various types of cancer are so complex and that highly purified substances are not subject to all situations or individuals, shiitake's immune system strengthening effects in animals and humans are briefly listed in Table 2.

⁸ Sarcoma 180 and MM-46. They are murine tumors.

⁹ Sarcoma 180 (Maeda *et al.*, 1974b; Togami *et al.*, 1982), ascites hepatoma 134 (Moriyama *et al.*, 1981), and Ehrlich carcinoma (Ying *et al.*, 1987)

¹⁰ administered by entering the peritoneum. Peritoneum is the serous membrane that lines the walls of the abdominal cavity and folds inward to enclose the viscera.

¹¹ mitomycin C with 5-fluorouracil or tegafur

¹² peritoneal/pleural effusion: an abnormal accumulation of fluid in the peritoneal and pleural space. Pleuron is the thin serous membrane that envelops each lung and folds back to make a lining for the chest cavity.

¹³ performance status: one of the indicators doctors use for assessing how a patient's disease is progressing and how the disease affects the daily living abilities of the patient and for determining appropriate treatment and prognosis

¹⁴ *in vitro*: in an artificial environment outside the living organism

¹⁵ *in vivo*: within a living organism

Table 2. Immune effects of lentinan *in vitro* and *in vivo* in animals and humans

Activity	Experimental Animal System		Human System	
	<i>in vitro</i>	<i>in vivo</i>	<i>in vitro</i>	<i>in vivo</i>
Humoral Factors				
Inhibition of immunosuppressive substance production	-	++	-	++
Immunopotentiative substance production	-	++	-	++
C3 splitting activity	-	+	-	-
Antibody production	-	+	-	+
Opsonin production	-	-	-	+
Production of colony-stimulating factor	+	-	-	-
Production of lymphocyte-activating factor (IL-1)	+	+	+	+
Inhibition of prostaglandin release	-	+	-	-
Interferon production	-(?)	+	±	-
Cellular Factors				
Natural killer cell activation	+	+	±~+	++
Activation of helper T-cells	-	+	+	++
Activation of killer T-cells	+	+	+	-
Activation of cytotoxic macrophages	-	+	-	+
Delayed-type hypersensitivity reaction	+	+~++	-	-
Mitogenicity	-	-	±~+	++

Sources: Aoki, 1984a,b; Takeshita *et al.*, 1993; Maeda *et al.*, 1974a; Tani *et al.*, 1992, 1993; Sendo *et al.*, 1981; Miyakoshi and Aoki, 1984a,b; Arinaga *et al.*, 1992; Fujimoto *et al.*, 1992; Sakamaki *et al.*, 1993.

Anti-viral effects

HIV / AIDS still remains as one of the greatest challenges of the modern medicine. Strong anti-viral activities of lentinan and LEM have drawn great attention in the medical community. LEM seems to be the stronger of the two. The major viral diseases studied in associated with anti-viral effects of *L. edodes* are Hepatitis B and HIV.

Animal tests

Lentinan has shown anti-viral activity in mice against viruses and virus-induced tumors¹⁶. Lentinan could also stimulate non-specific resistance against respiratory viral infections in mice. Notable protection was induced by lentinan administered through the nose before lethal influenza virus infection which could be confirmed by a reduction of the lung virus titres¹⁷. Lentinan also conferred complete protection against an LD75¹⁸ challenge dose of virulent influenza virus, and significantly prolonged the survival time in mice after an LD100 challenge administered through a vein.

Human clinical studies

Lentinan was successful in treating an HIV-infected patient with low helper-T cell and low lymphocyte counts and low NK cell activity. A drip infusion of lentinan restored these immune cell counts to normal (Aoki, 1984a). Lentinan is particularly active at augmenting helper-T cell activity (Akiyama *et al.*, 1981) and thus, assists HIV treatment.

LEM may also be useful in the treatment of AIDS. It has been shown to inhibit HIV infection of cultured human T-cells (Izuka, 1990), and it potentiates the effects of AZT (one of anti-HIV medications) against viral replication *in vitro* (Tochikura *et al.*, 1987). The mechanism of its action is not known for certain, but the extract was found to activate macrophages and stimulate the production of interleukin-1.

In addition to lentinan and LEM, water-soluble lignins with anti-viral and immunomodulating effects have also been isolated from shiitake mycelium (Hanafusa *et al.*, 1990). JLS, a new compound recently derived from the mycelium, showed the ability to block the release of infectious *Herpes simplex* virus type I in animals (Sarkar *et al.*, 1993). Shiitake contains water-solubilized lignin derivatives, such as EPS and EPS4, which have shown immunological and anti-viral activities not

¹⁶ VSV (vesicular stomatitis virus)-encephalitis, Abelson (Chang, 1981), and adenovirus type 12 virus-induced tumors (Hamada, 1981)

¹⁷ titer: concentration of a substance in solution or the strength of such a substance determined by adding to it a standard reagent of known concentration in carefully measured amounts until a reaction of definite and known proportion is completed

¹⁸ LD: lethal dose. LD 75 is the amount of drug it takes to kill 75% of the subject group.

only against *Herpes simplex* I and II, but also against equine encephalitis, polio virus, measles, mumps, and HIV (Suzuki *et al.*, 1989, 1990; Sorimachi *et al.*, 1990). In addition, an aqueous extract of the mycelium (known as JLS-18), consisting of 65-75% lignin, 15-30% polysaccharide, and 10-20% protein, inhibited the *Herpes* virus both *in vitro* and *in vivo* (Koga *et al.*, 1991).

Even for healthy folks, there are benefits in eating mushrooms. *The Star*, a Malaysian daily newspaper, reported on a pilot study by the National University of Singapore. The study showed that people who ate about 30g of shiitake mushrooms a day for four weeks were less susceptible to flu symptoms during the flu season in Singapore (*The Star*, October 30, 2000).

Anti-bacterial effects

Active compounds isolated from shiitake have shown potent anti-bacterial activities. Among them, lentinan is the most frequently studied compound as a promising anti-bacterial agent.

Animal tests

Lentinan is also effective against tuberculosis infections in the lungs of mice (Kanai and Kondo, 1981). It increased host resistance to infection with the potentially lethal *Listeria monocytogenes*¹⁹ (Aoki, 1984b).

Lentinan may afford protection against toxic stress from bacterial endotoxin²⁰. For instance, when lentinan was administered to rabbits with endotoxin, its clearance was increased (Yokota *et al.*, 1991).

Human clinical studies

For instance, in a study of 3 patients with pulmonary tuberculosis who had shed drug resistant *M. tuberculosis*²¹ bacteria for 10 years, after treatment with lentinan, the excretion of *M. tuberculosis* ceased (Usuda, 1981). These findings have been supported by several animal studies (Kanai and Kondo, 1981; Kanai *et al.*, 1980).

Hepatoprotective effects

Animal tests

Sugano *et al.* noted in their 1982 study that the injection of LEM slowed the growth of cancerous liver tumors in rats. Studies by Lin and Huang (1987) and Mizoguchi *et al.* (1987) also observed that polysaccharide fractions from shiitake demonstrated liver-protective action in animals.

Human clinical studies

In an unrandomized, uncontrolled clinical study by Dr. Amagase (1987), 40 patients with chronic hepatitis orally took 6g of LEM per day for 4 months. Hepatitis B symptoms were alleviated in all of the patients, and the virus was inactivated.

Cardiovascular effects

One unique amino acid, called eritadenine, is believed responsible for shiitake's ability to reduce cholesterol and lipids in blood (Yamamura and Cochran, 1974).

Animal tests

In a 1996 study, Dr. Kaneda found that blood serum cholesterol in lab mice was lowered by injection of hot water extract of shiitake. When eritadenine (0.005%) was added to the diet of rats, total cholesterol level was lowered by 25% in as little as one week (Chibata *et al.*, 1969). The cholesterol-lowering activity of eritadenine was more remarkable in rats on a high-fat diet than in those on a low-fat diet (Rokujo *et al.*, 1969). Eritadenine was found to accelerate cholesterol metabolism and excretion. It is highly expected as a potential anti-high blood pressure agent.

Human clinical studies

In a 1974 study by Suzuki and Oshima, 10 young Japanese women showed a decrease in serum cholesterol of 7% after one week on dried shiitake (9g). Another group who ate 90g of fresh shiitake showed a 12% drop in serum cholesterol after 7 days. A further study in young women on fresh shiitake (90g) for a week included butter (60g) in addition to the shiitake. In a control group of 10 women, only the butter was added to the diet for one week. In this group serum cholesterol showed a 14% increase, whereas the group on the shiitake and the butter showed a 4% decrease. A separate study found that people in their sixties or older showed a 9% drop in cholesterol, whether they took dried or fresh shiitake.

¹⁹ *Listeria monocytogenes*: a disease-causing bacterium that is food borne and causes an illness called listeriosis

²⁰ endotoxin: toxin produced by certain bacteria and released upon destruction of the bacterial cell

²¹ *Mycobacterium tuberculosis*: a bacterium causing tuberculosis in human

Toxicity and side effects

L. edodes is non-poisonous and safe, though some people may experience minor side effects or allergic reactions. Most common cases are shiitake dermatitis or diarrhea. They are associated with consumption of half-cooked or raw shiitake. During 17 years researchers have observed numerous cases of shiitake-induced dermatitis (Nakamura and Kobayashi, 1985; Ueda *et al.*, 1992). Nakamura (1992) reviewed the clinical manifestations, laboratory findings, and sources of shiitake dermatitis. It is known that people who work indoors in the cultivation of shiitake are prone to an immune reaction to spores called "mushroom worker's lung." Antibodies to shiitake spore antigens can be demonstrated in people who show symptoms. Protective masks can help, but not entirely eliminate, an eventual reaction to the spores after continued exposure (Van Loon, 1992).

A watery extract of the whole fruiting body is reported to lessen the effectiveness of the blood platelets in the process of coagulation, so people who bleed easily or who are taking blood thinners should use caution when chronically using shiitake or its water-soluble fractions (Yang and Jong, 1989).

In a phase I clinical trial of 50 patients with advanced cancer, 0.5-50mg/person/day lentinan was given by injection for 2 weeks. Minor side effects such as a slight increase in GOT and GPT liver enzymes²² and a feeling of mild oppression on the chest were caused at 5mg/day, but these disappeared after lentinan administration was stopped.

In a phase II trial, only 17 of 185 patients with advanced cancer had similar transitory side effects. Skin eruptions were noted in 7 cases, mild oppression on the chest, 6 cases, and mild liver dysfunction, 4 cases (Taguchi *et al.*, 1982).

In a follow-up phase III trial by the same researchers, 15 out of 275 patients experienced nausea and vomiting (2), heaviness in the chest (4), heat sensations (2), and one case each of face flushing, a rise in blood pressure, and heaviness in the head (Taguchi *et al.*, 1981b; Aoki, 1984b). Lentinan seems to be very safe when given to humans in the dosage range of 1-5mg/day once or twice a week by intravenous injection (Taguchi *et al.*, 1982).



Figure 9. Shiitake in everyday use **A:** Mushroom as stew ingredients **B:** Mushroom-flavored noodle **C:** Mushroom powder
D: Mushroom-flavored biscuit **E:** Mushroom chips

²² GOT: glutamine-oxaloacetic transaminase, GPT: glutamic-pyruvic transaminase. These liver enzymes are elevated for a variety of reasons. They are checked for suspected liver disease, also for suspected mononucleosis, or to monitor the effect of long term drug therapy on the liver.

Shiitake is used medicinally for diseases involving depressed immune function, including cancer, AIDS, environmental allergies, and frequent flu and colds. It also appears beneficial for soothing bronchial inflammation and regulating urine incontinence (Liu and Bau, 1980), as well as for reducing chronic high cholesterol. According to one prominent Japanese researcher, lentinan is an immunomodulating agent. For older persons, it serves as a general rejuvenating agent, no matter what the condition of their health. For young people, it presents a potent protection from overwork and exhaustion (Aoki, 1984b) or chronic fatigue syndrome. In Japan, lentinan is currently classified as a drug, whereas LEM is considered a food supplement.

As more clinical research on shiitake and preparations isolated from shiitake is published, the effective range of application will be more broadened. But the highly purified compounds including lentinan and LEM are subject to a particular situation or individual. Addition of shiitake to a daily diet is highly recommended to maintain good nutrition, to boost the immune system and to prevent various diseases. Shiitake containing almost all essential amino acids will serve as an excellent protein supplement.

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