Review Article

Role of Medicinal Mushroom Lentinula Edodes (Shiitake) in Nutrition, Nutraceutics and Enthnopharmacology

Abstract:

Lentinula edode (shiitake mushroom) is the medicinal macro-fungus popular in Japan and China. It is the second most well- known edible fungus in the global markete after Agaricus Bisporus. Because of presence of dietry fibers, vitamins, proteins, minerals and carbohydrates, shiitake mushroom have significant nutritional worth. It is commonly cultivated in winter season and known as "elixir of life". Bioactive compounds such as polysaccharides, amino acid derivatives, sterols, glycoproteins, chitin and sulfurous compounds are all extracted from shiitake mushrooms. Some of these are lentinans, eritadenine and KS-2-α- mannan peptide etc. Shiitake mushroom is used therapeutically to cure cancers, cardiovascular disorders, viral and fungal infections, hepatitis, hypertension and hepatic disorders. Shiitake mushroom have also grown in popularity as a result of their unusual and well-liked flavor.

Keywords: Lentinula edode, Agaricus Bisporus, KS-2-α- mannan peptide,

Introduction:

Mushrooms, like other fungi, are unique in the living world since they are neither plants nor animals. They have been assigned to the kingdom of Myceteae. Mushroom is a macrofungus with a characteristic fruiting body that can be epigeous or hypogeous and large enough to be seen and plucked by hand (Chang, S.T. & Miles, P.G., 1992). For humans, mushrooms are being used not just as food, but also in nutraceuticals, pharmaceuticals and cosmeceuticals. According to present day estimates, there are minimum 12,000 kinds of mushrooms in the globe, with 2000 of them being edible. Commercially developed mushroom species number around 35, with approximately 200 wild species utilized for therapeutic determinations (Beulah, G.H., *et al*., 2013).

Furthermore, the presence of specific bioactive components makes these mushrooms medically helpful, from immune system strengthening to the restore and avoidance of life-threatening disorders such as malignancies, cerebral stroke, heart disease and hypertension. The most general form of mushroom is umbrella shaped, which is, Lentinula edodes (Wasser, S.P., & Weis, A.L., 1999).

Shitake is a Japanese word that combines the words takes (mushroom) and shii (castanopsis cuspidate), a type of chestnut tree. Shitake has been known the "king" or "monarch" of the mushrooms in Japan, where the best products have been saved for royalty for ages. This denotes a dish of superior taste and quality (Jones, K., 1995).

These days, the majority of shitake growth is based on oak species. The shii tree was one of the principal types used in one part of japan in previous years, hence the name shii-take (Harris, B., 1986). There are also some other names for shitake like black forest mushroom, black mushroom, shiang-ku mushroom and golden mushroom (Breene, W.M.,1990). The scientific name of shiitake mushroom is L.edode.

Shitake is now one of the world's top five most popular edible mushrooms only the button mushroom Agaricus Bisporus produces more (2 million tons). Shitake mushrooms which are widely grown in East Asia are now gaining popularity around the world (Chang, S.T., 1999)(Stamets, P., 2000). Miles joseph Barkeley, a British botanist contributed to the Shitake's renown as a highly appreciated food plant (1803-1889). The latin name of the shitake mushroom was to lately altered to lentinula Edodes (barkeley) pegler, although this had little effect on its populatrity (Jones, K., 1995).

Dr. Mori added that Shitake was utilized in oriental traditional medicine to improve circulation and strength, and that 15th and 16th century soldier priests in Japan ate the mushroom as part of a stew with meats and vegetables (Mori, K., 1974). Shitake was traditionally used to deal chronic rheumatism, brain hemorrhages, heart illness, intestinal worms, poor circulation and fatigue (Jones, K., 1995) (Hobbs, C., 2002).

In 1986, approximate 314,000 metric tons of shitake mushrooms were grown; Japan (51%), China (38%), Taiwan (10.2%), Korea (0.3%), and United States (0.1%) were the major countries which gave rise to it (Chang, S.T., 1999***)***. Shitake can grow in the winter season and in regulated conditions throughout the year it can produce (Chang, S.T., 1999). It is commonly grow in South-East Asia. In tropical-subtropical weathers, it is produce on deceased timber of different fallen trees including acer, fagus, castanopsis, and populus, etc (Staments, P., 1993) (Royse, D.J., 1996).

Substrate is essential for mushroom production because it lacks chlorophyll. For the production of shitake mushroom, Swadust is the most common base component in artificial substrate formulation (Miller, M.W. & Jong, S, C., 1987). Because the oak's log are not comfortably accessible or too much expensive in Pakistan so, its cultivation is constricted (Abbas, A.).

The main goal of writing this review is to explore shitake mushroom because of its great nutritional value. Active constituents in shitake composition approach in market which can put back different artificially prepared marketed medicines. Along with its remarkable medicinal qualities, shitake have grown in popularity as a result of their unusual and well-liked flavor.

History:

In China`s forests shiitake production begins 1000 years before by utilizing cut logs naturally immunized by the fungus. During the Sung Dynasty (960-1127) emprores this mushroom production in China. Wu San Kwung praised as the creator of shiitake agriculture by history. In China approximately each shiitake cultivating village has a shrine in tribute of Wu San Kwung (Miles, P.G. & Chang, S.T., 1997). In former China, past documents suggested shiitake mushroom uses where it was known as "hoang-mo" or "Ko-Ko".

These days Japan is the number one exporter of shiitake mushroom productions. In the year 199 A.D, it was presented by the local community of Japan, to the emperor of

Chuai(Hobbs, C., 2002).Much technological advancement has been established, used in production of shiitake over the years. The favorable outcomes of this fungus have been notable for from the 1940s.(Chang, S.T., 1978). Cottage industry in Japan is currently the major site of shiitake cultivation which in 1978 used almost 2 million cubic meters of firm tree trunks and grown $1.1 billion in sale markete (Royse, D.J., *et al*., 1985). In 1953, shiitake cultivation in Taiwan developed fastly due to rise in natural log production and plastic bag culture. These days, some producers of shiitake in Canada and United States cultivate it under regulated conditions by using synthetic logs (F, Zadrazil., *et al*., 1983).

In 1974, advantages of shiitake was known by the health food industry in America, when a great mycologist Kisaku Mori,D.Agric., wrote a book in English "Mushrooms as Health Foods" (Mori, K., 1974). The United State becomes the 3rd greatest importer of dried shiitake mushroom in Japan. Though, shiitake mushrooms had heard of, or eaten only by a little fraction of Americans. Now shiitake produced abundantly in all Southeast Asia countries (Vasser, S,P., &Weis, A.L., 1997).

Classification:

The classification of mushroom shiitake is;

Kingdom	**Fungi**
Phylum	Basidiomycota
Class	basidiomycetes
Order	Agaricales
Family	Agaricaceae
Genus	Lentinus
Species	Edodes

Table I: Classification of Shiitake mushroom (Boer, C.G.,*et al*., 2004).

Shiitake is a timber decomposing basidiomycetes growing in open clusters on dead logs of a vast variety of fallen trees. It grows basically on wide leaf trees particularly chestnut, shii, maple, beech, ironwood, and gum, oak, and mulberry, cottonwood in a hot and humid environment (Wasser, S.P., & Weis, A.L., 1997).

Nutritional role of shiitake (L.edodes):

Shiitake mushrooms have great nutritional importance. Because of high content of proteins, with essential amounts of fibers and vital amino acids, L.edodes are known to have significant nutritional worth. Wu-Rui of the Ming Dynasty said in his book "Ri Youg Ben Cao" that shiitake enhances basic energy, beat the energy of body liquids, heals fever and kept starvation off (Ch, H., 1996)(Wasser, S.P., & Weis, A, L., 1997).

Dietary fibers in shiitake:

Shiitake stipe because of its high substance of dietry fiber has its utilization in useful food sources, stated by Nieto in 2012 (Nieto, R.J., *et al*., 2012).

Water soluble and insoluble compositions of dietry fibers are present in shiitake. Non-soluble dietry fibers in L.edodes contained polyuronide, heterosaccharides, chitin, hemicellulose and lignin. Water soluble dietry fibers include proteins with all essential amino acids and B-glucans (Heleno, S. A., *et al*., 2012). Shiitake are useful in cardiovascular disease because they reduce the levels of total cholesterol by their soluble and non-soluble fibers (Rajarathnam, S., *et al*., 1998).

Soluble dietry fiber has significant role in physiological functions of humans, including preventing issues of GI tract, lowering blood pressure and cholesterol and preventing the onset of certain cancers. Insolube dietry fiber improves role of intestine by enhancing faecal bolus and increasing intestinal peristalsis in general (Mizuno. Y., 1999).

The fiber present in shiitake stem is composed of polysaccharides of long chain length approximately interconnected to the cell wall. These polysaccharides include hemicellulose, mannans, chitin and β-glucans (Manzi, P., & Pizzoferrato, L. 2000). In animals, function of liver and enhancement in hepatitis B antibody production is because of a proportion of polysaccharides from L.edodes (Wasser, S.P., & Weis, A.L., 1997). Shiitake mycelia draw out KS-2 which is a active polysaccharide against cancer treatments (Fujii, T., *et al*., 1978).

1. **Vitamins in shiitake:**

A beneficial amount of vitamins is also present in it. These include vitamin B1 , B2, B12, C, D and E. Shiitake mushrooms have comparatively high amount of nutrients in their dried form. Quantity of nutrients and bioactive compounds present in shiitake vary according to their fruiting body situations, substrate presence and ways of cultivation. Fresh fruiting mushrooms contained 88-92% water, carbs, proteins, fatty acids (lipids) and vitamins. Mushrooms have high amounts of vitamins particularly vitamin D and vitamin B like B1, B2 and B12 (thiamin, riboflavin and niacin) respectively (Przybylowicz, P., *et al*., 1990)(Ch, H., 2000).

Designated by current studies, vitamin D amounts which are required on daily basis even greater amounts than that of every day needs are provided by these mushrooms when they are under specific circumstances are revealed to ultraviolet light (Phillips, K.M., *et al*., 2011). Ergosterol after UV light exposure gives calciferol (vitamin D2).

2. **Proteins in shiitake:**

Easy way to approximate the nutritional value of mushroom is by measuring the amount of essential amino acids. (Food and Agriculture Organization,1970)(Food and Agricultural Organizaion 1973) Studies on nutritional value of shiitake mushrooms have been done in restricted figures; most of the journal's assertions only relate proteins of mushrooms with other vegetables and meat (Rosye, D.J., & Schisler, LC., 1980)(Crisan, E., *et al*., 1978).

3. **Minerals:**

Polysaccharides which can soluble in water are 1-5% total of shiitake's dried mass. Minerals which are present in L.edodes are magnesium, calcium, copper, potassium, iron, zinc and phosphorus (Stamets, P., 2000). Sodium present in lower amounts in shiitake, so it is favorable for peoples with hypertension disease (Cheung, P. C., & Lee, M.Y., 2000).

Specific odor of shiitake mushroom was recognized as 1,2,3,5,6 pentathiepane. Mizuno says that monosodium glutamate, sugars, organic acids, peptides with less molecular weight is the components which makes this mushroom's flavor appetizing (Mizuno, T., 1995).

Role of different compounds present in shiitake:

For macrophages to activate more effectively, Lentinan present in shiitake persuit the complement cascade which breaks C3.When an individual comes into contact with pathogens, Lentinan plays role to modulate the response to inflammation

(Wong, K.W. C., 2005). Shiitake abstract have antibacterial properties, boosting the host's resistance to infections (Rao, J. R., *et al*., 2009)(Mantovani, M.S., *et al*., 2008)

Shiitake mushroom extracts prevent microorganisms of mouth that cause periodontal disease and cavity. E.coli and bacillus subtilis growth is inhibited by lenthionine, which contribute to the shiitake's flavor (Zaura, E., *et al*., 2011)(Lingstrom, P., *et al*., 2012). The quantity of Lenthionine present in L.edodes prevents platelet accumulation, according to the Nihon's University in Japan. Peoples who take L.edodes mushroom in their diet have been proven to have a low risk of thrombosis. (The health benefits of Shitake mushrooms, 2011)

It was demonstrated by scientific studies that eritadenine from L.edodes are helpful in decreasing the levels of LDL (low density lipoproteins) cholesterol in the body and in blood. In one week, it lowers the levels of cholesterol in blood by 25% (Wasser, S.P., & Weis, A.L., 1999). Shiitake mycelium contain a molecule lignin which is favourable in the treatment of AIDS and hepatitis B (Jong, S.C., *et al*., 1993). L.edode mycelia (LEM) and Lentinan are given by both mycelium and fruiting body of shiitake are anti-tumor and immune system strengthening compounds (Yang, B.K., *et al*., 2002). Enzymes intricated in medicinal removal and metabolic alteration of mutagenic chemicals are overexpressed by antioxidant function of shiitake mushroom (Fanelli, C., *et al*., 1984).

Zhang characterized the standard of powders derived from stem of shiitake in 2012. In comparison to the stem of shiitake, this study found pileus (cap) offers more nutritional advantages due to its higher protein content (Zhang, Z., *et al*., 2012).

Cultivation:

Shiitake (also known as Xiang gu in Chinese) can be grown on both natural and synthetic logs. It has now surpassed as the world's most cultivated fungus since 2002 (Quimio, T.H., *et al*., 1990)(Stamets, P., 2000). Shiitake was regarded the "elixir of life" by the seniors of the Japanese kingdom as it enhanced validity and energy (Campbell, A.C., *et al*., 1999).

China begins with harvesting and drying of L.edodes. In China, it is the greatest growing edible mushroom. 'Plastic bag method' was used for high quality production of shiitake (Luo, X.C., 2004). Japan was the huge cultivation country of shiitake in 1983 with total of 82.8% cultivation of this mushroom in the world (Chang, S.T., 2005). For bed log cultivation of shiitake, different plants have been utilized (Royse, D,J., 1985)(San Antonio, J.P., 1981).

The cultivation method involves, from the chosen host tree species inoculating the mycelia with a combination of bark and wood, and then putting them under soil. The Chinese are thought to have transferred this gardening technique to Japan during the sixteenth century (Suzuki, H., *et al*., 1990). In Japan, mostly shii trees were used in formr years but these days different oak species are used for cultivation (T,Ito., 1978). By using 'synthetic log' procedure in 1987 Chinese gain on Japan as great growers of shiitake in the world.

Bed logs are immunized among 15 to 30 days of fell down and in the most favorable way, generally cut up in the autumn (Nutalaya, S., *et al*, 1981). In Japan, trees immunization sliced up into trunk (logs) of approximately 1m length approached before they possibly cut up and entrusted in the woods (T, Ito., 1978). The best log diameter

could be in the rank of 7-15 cm (Nutalaya, S., *et al*., 1981).

The cultivation of shiitake is split up into two important phases.

1-In first phase, comprises preparing the fruiting and stock cultures, grain based medium for mushroom growth and spawn planting.

2-Second phase involves synthesizing the substrate for mushroom growth. These days, the wood timber (log) and artificial sawdust bag are the most frequently acquired commercial cultivation methods (Royse, D.J., 1996)(Stamets, P., 2000) (Mizuno, T., 1996).

Various types of wastes from agro-industrial process have also been utilized in shiitake growth, including crushed maize cobs, sunflower seed hulls, coffee and hazelnut husks, wheat straw, either alone or in combination with other by-products (Mizuno, T., 1996)(Philippoussis, A. N., *et al*., 2003)(Elisashvili, V. I., *et al*., 2015).

Synthetic logs for shiitake cultivation:

These days, shiitake are commonly grown in artificially prepared substrates, which are generally made of oak placed in senitizeable polypropylene packs to produce "synthetic logs" (Royse, D.J., 1996).

Artificial substrate often consisting of a combination of wheat straw and small to medium sized pieces of wood. To grow mushrooms on artificial substrate, substrate in plastic bags is sterilized in a strong heated container (autoclave), and then cools it down, and then immunizing with mycelium (spawn). The period it takes for the mycelium to fully occupy the substrate, known as spawn run, varies from 12 to 3 months. After the spawn run, the plastic packs removed and the synthetic logs are exposed to growing environment. After being placed in the growing rooms they will typically start to develop within 2 to 3 week (Fuzisawa, N., & Hattori, K., 1979)(Royse, D.J., *et al*., 1983)(Co., Shiitake mushrrom., 1980)(Patrick., Z.A., *et al*., 1983).

Natural logs for cultivation of shiitake:

Bed logs are infected within 15 to 30 days of being felled and typically cut in the autumn. Trees chopped and even before the right immunization time remained in the woods. The logs are prepared for inoculation once they have been chopped to the proper size (Chang, S.T., & Hayes, W.A., 1978).

Cultivaters make holes in the tree trunk (log) to match the size of the wood-chips substrates. The wood-chips coated in warm wax to keep them from drying out, pushed into the holes. Sawdust spawn is also occasionally substituted as a substrate. The time for spawn run varies from 6 to 9 months. Then the logs are frequently moved to the production room. The growing room is often wetter and colder than spawn run rooms. The alteration in environment creates an ideal setting for mushroom cultivation and production (Nutalayas, S., & Pataragetvit, S., 1981).

Bioactive compounds derived from shiitake mushroom:

Mushrooms have a diverse range of bioactive chemicals with significant medicinal promise for the avoidance and treatment of a variety of illness (Elkhateeb, W.A., *et al*., 2019). Bioactive compounds known as secondary metabolites have been found in high molecular weight molecules including peptides and polysaccharides (Finimundy, T.C., *et al*., 2014). Because of the inclusion of polysaccharides, sterols,

triterpenes, flavonoids and fatty acids, edible mushrooms have been identified as useful foods (Chegwin, C., & Nieto, I., 2004).

Fruiting bodies and mycelia of shiitake have yielded a number of bioactive compounds with diverse biological functions (Chang, S.T., 1999)(Smith, J., *et al*., 2002). The important bioactive chemicals derived from shiitake are polysaccharides (Eritadenine, Lentinan, Ergosterols, β-glucans and chitin), sterols, sulfurous compounds, glycoproteins (LEM and LAP) and many other compounds. Anticancer, blood pressure, renal tonic, body's help against disease fighting, cholesterol regulation, anti-hepatotoxicity, control of diabetes, protection against viruses, parasites and bacteria are a few examples of biological activities performed by these bioactive agents (Wasser, S.P., & Weis, A. L., 1999).

Bioactive compounds	**Role of bioactive compound**
Polysaccharide-Lentinan (β-D-glucans)	Anti-cancinogenic effects, Anti-HIV effects
Glycoproteins (LEM& LAP)	Anti-tumor action, Used to treat Hepatitis B patients
EP3	Anti- herpes simplex action, Anti- HIV effects
Sterols (Ergosterol)	Hypolipidemic effects, Bone growth and calcium absorbance effects
Polysaccharide KS-2-α-mannan peptide	Anti-tumor action
Polysaccharide (Chitin)	Anti-microbial activity
Lenthionine (Sulfurous compound)	Anti-fungal action Anti-bacterial action
Lavostatin	Inhibit HMG-CoA reductase
Eritadenine (Amino acid derivative)	Cardiovascular effects (Lowers blood serum cholesterol levels)

Table II: Bioactive compounds dericed from Shiikate and their role until 2020 (Chihara, G., *et al*., 1969)(Shavit, E., *et al*., 2009)(Gordon, M., *et al*., 1995) (Hobbs, C., 2000)(Pegler, D. N., 1983)(Tochikura, T. S., *et al*., 1988)(Suzuki, H., *et al*., 1989)(Jones, K., 1998)(Perera, C. O., *et al*., 2003)(Chen, J., *et al*., 2015) (Fuiji, T., *et al*., 1978) (Yen, M. T.,*et al*., 2007)(Yoshid, H., *et al*., 1986).

1. Amino acid derivative (Eritadenine):

Shiitake mushrooms give Eritadenine, a secondary metabolite formerly known as lentysine and lentinacin. Eritadenine is a by-product of nucleic acid that was initially segregated from the shiitake's fruiting body as a cholesterol lowering constituent (Chibata, I., *et al*., 1969)(Saito, M., *et al*., 1975). Chibata and Rokujo recognized this chemical as Lentinacin and Lentysine, respectively, after it was derived for the first time from shiitake (Rokujo,T., *et al*.,1970).

Eritadenine is generated mostly by the L.edode basidiomycete. It is 2(R), 3(R) – dihydroxy-4- (9-adenyl) – butyric acid (Saito, M., *et al*., 1975). In humans, the shiitake mushroom reduces the levels of blood cholesterol because of presence of a chemical eritadenine. In people tested in the trial feeding 90g of fresh shiitake mushroom every day for one week decreased serum

cholesterol by 12% (Suzuki, S., & Oshima, S., 1976).

Eritadenine was found in shiitake's fruiting body at 400-700 mg/ kg of dry matter, according to research (Saito, M., *et al*., 1975). Enman found 3.2-3.6 mg/g level of eritadenine in shiitake,s dried form in 2007, demonstrating the relevance of the mushroom as a bioactive agent (Enman, J., *et al*., 2007). In earlier research, the quantity of eritadenine detected in fruiting bodies of shiitake mushroom was higher in pileus cap (0.5-0.7 mg/g) than the stem (0.3-0.4 mg/g) (Vitanyi, G., *et al*., 1998).

This chemical has been widely researched in mice and rats to see how it affects blood cholesterol levels (Shimada, Y., *et al*., 2003).It appears to lower BSC (blood serum cholesterol) in rats through speeding up the metabolic breakdown of ingested cholesterol and its secretion from the body, rather than by inhibiting cholesterol production (Jasrotia, N., *et al*., 2012). The results showed that a diet with 0.005% eritadenine may dramatically lower the levels of serum cholesterol (Koki, T., *et al*., 1974).

Eritadenine has no effect on triglycerides in serum. Nonetheless, in rats, it dramatically lowers cholesterol and plasma phospholipids. Current research state that eritadenine lowers metabolism of linoleic acid and affects blood phosphatidylcholine in rats (Sugiyama, K., & Yamakawa, A., 1996). It may altering the metabolism of liver phospholipids and act as a hypocholestrolemic metabolite (Sugiyama, K., *et al*., 1995).

Although several research has been done, the mechanism of action of Eritadenine in lowering cholesterol levels is still unknown. Eritadenine works by preventing cholesterol from being liberated from tissues or it has been thought to speed up elimination of cholesterol from blood by boosting tissue absorption, but it has no effect on cholesterol production in the liver (Enman, J., 2009).

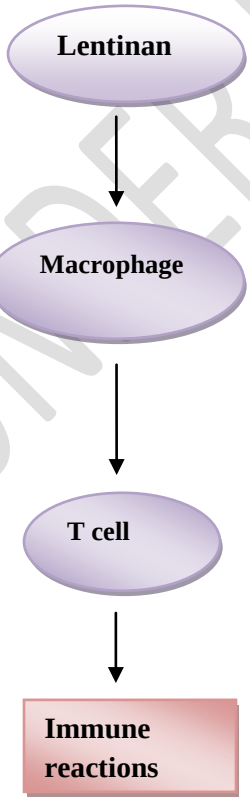
2. Polysaccharides (Lentinan):

Lentinan identified in Japan in 1985, as water soluble, protein free polysaccharide produced from the shiitake fruiting body and authorized for the cancer treatment, particularly stomach cancer. Important polysaccharides of lentinan are β-1,6-D-glucans and β-1,3-D-glucans (Shavit, E., *et al*.,2009). Chihara derived this anticancer polysaccharide in 1970, and after the lentinus genus which include the shiitake fungus called it "lentinan". The anticancer activity of lentinan was first demonstrated in CD-1 mouse transplanted with S180 (Chihara, G., *et al*.,1969). Lentinan causes the immune system to get activated by stimulating macrophages, helper T lamphocytes, natural killer cells and other short lived cells (effector cells), when given orally. So the antitumour action of lentinan is due to the activation of host,s immune system (Shavit, E., *et al*., 2009)(Wong, K.W.C., 2005). It is alkali-liable, can soluble in water and resistant to heat.

During cancer's treatment (chemotherapy) lentinan orally given to patients. Medical studies reveal that those who were given lentinan showed improved chemotherapeutic capabilities, growth of cancer was stoped and patient's life was wxtended. In three patients with untreatable cancer of stomach, the lentinan demonstrated a significance increase in life duration (Mashiko, H., *et al*., 1992)(Shiitake, O., 2005). Only glucose compounds are found in lentinan, which has a triple helix structure with mainly (1-3)-glucose connections in the routinely branching backbone and –(1-6)-glucose side chains (Wasser, S.P., 2002).

In animal samples, lentinan seemed to be a new class of host defense potntiators (HDP),

enhancing a variety of auto-immunity frameworks and shielding hosts from the adverse effects of traditional treatment approaches with no harmful side effects (White, R. W. D., *et al*., 2002)(Ngai, P.H., & Ng, T. B., 2003). In an open label medicinal research in Japan, lentinan seems to be extremely successful in treating a condition called "low natural-killer cell syndrome" (LNKS), with signs that are quite similar to CFS (chronic fatigue syndrome) in the US (Aoki. T. Y. H. K. R., *et al*., 1987). Lentinan can be used with some transient adverse effects in conjugation with the anti-HIV medication Videx (DDI), however it generated considerable enhancement in numbers of T lymphocyte cells in HIV patients (Gordon, M., *et al*.,1995). Lentinan suppresses liver metastasis in C26-carcinoma mice via activation of Kupffer cells, according to a recent study. In animal samples, lentinan not only inhibit cancer causing viruses and chemicals but also reduces cancer spread and outbreak (Ooi, V. E., & Liu, F., 2000). **Figure I:** Action of Lentinans



3. Glycoproteins (LEM and LAP):

Glucose, mannose, xylose, galactose, arabinose and fructose are found in LEM and LAP, both are glycoproteins. The crushed mycelia of L.edode is used to create light brown powder termed as "L.edode mycelium" (LEM). The powder product formed by the addition of 4 volumes of Ethanol to a water solution of mycelium was then termed as "LAP". The LEM production was around 6 gram/1kg of medium. LAP yield was 0.3 g per gramme of L.edode mycelium (Mizuno, T., 1995).

In both peoples and animals, L.edode mycelium and LAP showed potent antitumour action when administred intravenously and orally. Vitamin B molecules, derivatives of nucleic acid and ergosterol are also found in L.edode mycelium (Suzuki, H., *et al*.,1990)(Hobbs, C., 2000). Both L.edode mycelium and LAP can be used to treat Hepatitis B and work by stimulating the immune system of the patient (Singer, R., 1986)(Pegler, D. N., 1983)(Mizuno, T., 1996).

In vitro, L.edode mycelium showed anti-HIV activity, leading to the discovery of the most powerful HIV-inhibtor (Tochikura, T. S.,et al., 1988)(Suzuki, H., 1989). By fractionating LEM, an immunoactive molecule known as EP3 was currently produced. EP3 is a lignin based compound that contains almost 80% lignin and 10% carbs and 10% protein. The active ingredient is thought to be a carboxyl-rich lignin, which is water soluble. So the biological activity was lowered by the elimination of lignin and was unaffected by the elimination of other two compounds (Mizuno, T., 1995).

EP3 in vitro, demonstrated anti-Herpes simplex action and totally inhibited HIV from destroying T helper cells (Jones, K.,

1998). EP3 constituent EPS4 is significantly more powerful. 12.2 percent sugar, 3.2% proteins and majority of lignins make up the EPS4 (Suzuki, H., *et al*., 1989). Lignins are the basic elements of plant fibers, including polysaccharides (Lin, S.Y., *et al*., 1990).

4. Sterols (Ergosterol):

Shiitake mushrooms have a lot of ergosterol in their cell membranes, from which vitamin D is derived. The ergosterol content of the shiitake stalk is 3.57 mg/g, whereas the ergosterol content of the shiitake hat is around 17 mg/g of dry weight (Perera, C. O., *et al*., 2003).

From acetone elicit of fruiting bodies of shiitake, Chen et al. extracted and recognized six sterols along with ergosterol (Chen, J., *et al*.,2015). Vitamin D deficiency is widespread across the world. It is essential for the accumulation of minerals on the bone matrix for bones growth and for absorption of calcium. Ergosterol changes to vitamin D when shiitake mushrooms are subjected to UV-light or simply placed in the sun light, according to several studies (Jasinghe, V.J., *et al*., 2005).

5. KS-2-α-MannanPeptide: (polysaccharide)

KS-2, an orally affecting polysaccharide bounded by protein, water soluble or peptidomannan whose short peptide is coupled to α and β – mannose. It is the most significant mycelium constituent that has yet to be discovered (Fujii, T., *et al*., 1978).

The amino acids serine, alanine, proline and threonine make-up this α – mannan peptide. By extracting cultivated L.edode mycelia warm water and then precipitating it with ethanol was produced KS-2 polysaccharide (Mizuno, T., *et al*., 1995)(Mizuno, T., 1996).

Intravenously and intraperitoneal injection of KS-2 inhinited the development of Sarcoma 180 and Ehrlich ascetic tumours in mice, along with inducing interferon in the blood (Fuiji, T., *et al*., 1978). Immunomodulating function of KS-2 protect the person from infections of viruses and bacteria (Suzuki, F., *et al*., 1979).

Macrophages from KS-2 served animals were found to have apoptosis inducing action and activation of macrophage when they are inoculating with IFN in vitro turned into tumoricidal. The reports demonstrated that KS-2 in vitro does not kill the tumour cells directly through changes in cell morphology, although the procedure of action of KS-2 is still unknown (Hobbs, C., 2000)(Mizuno, T., 1996)(Fuiji, T., 1978).

6. Chitin: (polysaccharide)

Shiitake stem become an important material containing a great amount of chitin after they have been dried and powdered. Chitin and chitosan are being prepared by stalk of L.edodes. From dried shiitake stem, Yen et al, extracted 36.72 percent purified chitin in 2007. Chitin and chitosan are both active against microbes, for biological degradation of organic molecules, compatible with living tissues, maintainance of the stability needed to function properly and replacement of missing tissue layers (Yen, M. T., & Mau, J.L., 2007). In shiitake, dietry fibers contained water insoluble molecules like chitin. Chitin is present as component of cell wall and can only be extract with acids, bases and salts. It plays role in the polysaccharide make-up of L.edodes (Yoshida, H., *et al*., 1986).

According to Yen and Mau's findings, chitosan derived from the chitin can be employed as a substance that reduces damage due to oxygen, as a component of food or in the business of medicine. The researchers discovered that chitosan made

from shiitake stem exhibits hydroxyl radial hunting and Fe2+ chelating properties (Yen, M.T., & Mau, J.L., 2007).

7. Lenthionine:(sulfurous compound)

Morita et al. identified lenthionine, as a distinctive fragrant constituent from dehydrated shiitake fruiting bodies (Morita, K., *et al*., 1967).

This sulphur carrying peptide has strong action against fungi and bacteria and its secondary metabolite (BMSMDS) Bis (methylsulfonyl) methyl disulphide, (Yasumoto, K., *et al*., 1971) has a high prohibitive action in case of gram-positive and gram-negative bacteria (b.Subtilis, E.Coli and S.aureus). (Hatvani, N., 2001).

Chloroform fragments of powdered fresh shiitake were also contained sulfur compounds by chen *et al*., (Chen, C.C., & Ho, C.T., 1986). In rats, CCl4 generate severe hepatic damage which is inhibited by lenthionine. Furthermore thrombocyte accumulation was reduced by lenthionine in vitro tests (Fukushima-Sakuno, E., 2020).

8. Lavostatin:

Lavostatin- α secondary metabolite with values ranging from 0.27 to 32.7 mg\100g of dry weight have been found in the fruiting bodies of shiitake by different studies (Kala, K., *et al*., 2020)(Chen, S.Y., *et al*., 2012).

A liver enzyme that catalyses synthesis of cholesterol and lowers serum cholesterol is (HMG CoA) reductase which is selectively inhibited by lavostatin. Different types of mushrooms as well as shiitake, have been found to contain lavostatin (Lo, Y.C., *et al*., 2012)(Lin, S.Y., *et al*., 2013).

Therapeutic applications of shiitake:

Since the Ming Dynasty, the therapeutic qualities of shiitake have been researched (1369-1644) (Kues, U., & Liu, Y., 2000). Shiitake is one of the most well-studied and well-known medicinal mushroom. It's the origin of a number of well- known therapeutically proved preperations, particularly including L.edode mycelial, culture medium wastes, polysaccharides and lentinan (Wasser, S.P., & Weis, A.L., 1997)(Mizuno, T., 1995)(Mizuno, T., 1996).

L.edode is medically used to treat illnesses including tumour, seasonal allergies, major or long term disorders in immune system, diabetes, recurrent flu and fever, mycosis, loss of bladder control and bronchitis. The most important medicinal benefits of this amazing fungus.

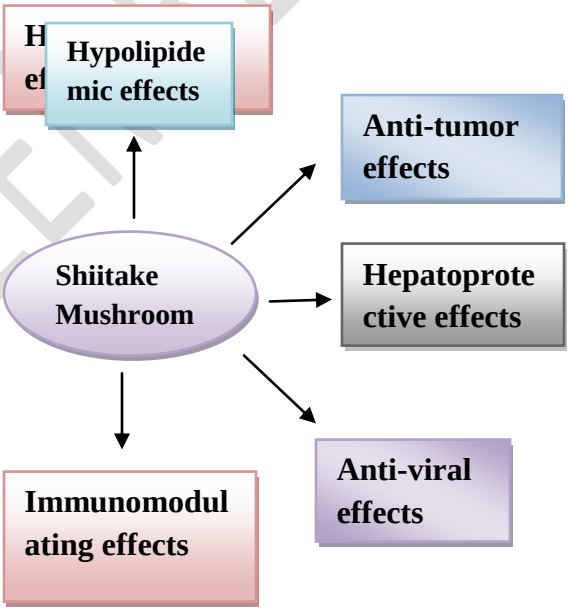


Figure II: Different therapeutic effects of shiitake mushroom

1. Shiitake effects against tumour:

Chihara was the one, who report on the mushroom's anticancer effects. Chihara claiming that "lentinan" was nearly totally degenerate the heavy sarcoma 180 tumours

and various other types of cancers including synergic host's tumor system as well as methylchloranthrene generated fibrosarcoma (Chihara, G., *et al*., 1970). β-glucans can stimulate significant tumor fighting chemicals including activation of limulus coagulation factor G, and macrophages causing them to produce nitric oxide (Wong, K. W. C., 2005).

Lentinan has significant efficacy not just against synergic cancers like sarcoma-180, but also inhibit transformation of healthy cells to cancer cells (oncogenesis) by different chemicals and viruses (Chihara, G., *et al*., 1987). Shiitake mycelium draw out and 5-fluorouracil mixture showing a extraordinary chemo-preventive approach in colon malignancies and p53 (tumour suppressor protein) also offers a significant role in preventing tumours growth (Wu, C, H., *et al*., 2007). Macrophages, CD4+ cells, NK cells and different effector cells get activated when β-D-glucan attaches to leucocyte surface or with certain blood proteins. When effector cells are activated interleukins (type of cytokines) and interferon proteins (part of natural defenses) are produced. All of these factors boost the antibodies production. As a result, activation of immune system of host causes lentinan's anticancer activity (Yap, A. T., & Ng, M. L., 2001).

In animals, refined polysaccharides cause the removal of sarcoma malignancies after 5 weeks and significant tumor regeneration (Yap, A. T., & Ng, M. L., 2003). In rats, injection of lentinan reduces the rate of malignancies by 80% (Wasser, P., & Solomon., 2005). It was shown that antitumor impact of lentinan requires an active thymus gland and a healthy immune system (Pegler, D. N.,1975)(Earle, F, S., 1909). Experiments in laboratory suggest that nervous system containing 5-hydroxytryptamin receptors, serotonin, catecholamines substances and histamine as well as the hypothalamic-pituitary-adrenal axis (HPA axis) play a role in anticancer activity of lentinan (Hobbs, C., 2000)(Wasser, S. P., 2002)(Yap, A. T., & Ng, M. L., 2001).

Shiitake produced L.edode mycelium (LEM), which was taken orally, was used to create a water soluble active material JLS-18, lignin rich polysaccharide (Shavit, E., *et al*., 2009). LEM and JLS-18, both polysaccharides are used for cancer treatments (Yamamoto, Y., *et al*., 1997). By using lentinan stimulating immunocytes in treatments of cancers in mice that lack T-helper cells including athymic mice, β-cell lacking mice led in tumor development suppression (Yap, A. T ., & Ng, M. L., 2003). It's impossible to determine if shiitake when taken as constituent of a healthy diet, may help to prevent cancer. Anticancer investigations using shiitake so far have been quite fascinating, and they do show promise for giving tumor therapeutic control.

2. Shiitake effects against cardiovascular diseases:

In western societies, congestive heart failure is the leading cause of death. L.edodes were found to reduce blood serum cholesterol, according to Yang (Yang, B. K., *et al*., 2002) and Hobbs (Ch, H., 1996)(Hobbs, C., 2000). Shiitake mushroom through a component called eritadenine has been shown to decrease cholesterol levels in blood. Eritadenine reduces the levels of all low density and high density lipoproteins (Breene, W. M., 1990). Several studies have shown that the shiitake speede up lipid build-up in the liver by liberating them from blood circulation along with the reduction of blood free cholesterol and hypertension (Ch, H., 1996)(Hobbs, C., 2000)(Mizuno, T., 1996).

Eritadenine appears to lower BSC in mice through speeding up metabolic decomposition of cholesterol and its elimination from body rather than by preventing production of cholesterol (Wasser, P., & Solomon, 2005). Eritadenine speed up the elimination of serum cholesterol by either blocking tissue excretion or by increasing absorption of tissue (Enman, J., *et al*., 2008).

In animals, eritadenine has also been found to decrease lipid and cholesterol levels in the blood. Hypocholesterolemia (low density cholesterol levels (LDL-C) than total cholesterol) is a key component that contributes to Atherosclerosis (Smith, J., *et al.*, 2002). In the quest for a possible natural medication, in case of lowering blood cholesterol levels, the quantity of eritadenine in shiitake was measured (Tokita, F., *et al*., 1972).

The efficacy of shiitake in reducing BSC (blood serum cholesterol) was also evaluated in human patients, besides to animal testing. 12 percent of mean blood cholesterol levels are reduced in young woman by consuming 90 grammes of fresh shiitake for seven days. Similarly, 7 percent of blood cholesterol is reduced by consuming 9 grammes of powdered shiitake and 6 percent by taking dried shiitake irradiated with ultraviolet radiations (Suzuki, S., & Oshima, S., 1976).

3. Shiitake effect against viral diseases:

Antiviral compounds were initially discovered in mushrooms by Goult and colleagues in 1960 (Goulet, N. R., *et al*., 1960). Lentinan and its by-products increased the patient's tolerance to viruses, including AIDS causing pathogens (Chihara, G., 1992)(Ngai, P. H., & Ng, T. B., 2003). Viruses like Ad12, retrovirus and vesicular stomatitis virus (VSV) - Encephalitis virus can all be inhibited by lentinan (Ooi, V. E., & Liu, F., 2000).Proteinase inhibitors are anti-retroviral medicines found naturally in shiitake fungus (Ichimura, T., *et al*., 1998).

For centuries, shiitake was thought to be a cure-all for the viral rhinitis. Few scientific studies has lately been discovered to show the action of shiitake again common cold was 46 percent, which was compareable to the action of popular antiviral medeicine amantadine hydrochloride whose acton is 40 percent against influenza. It's also been stated that a liquid draw out from shiitake can stop the polio virus from multiplying (Johl, P. P., *et al*., 1995). Lentinan inhibited the surface expression of HIV on T lymphocytes cells more effectively when combined with AZT (3'-azido3'-deoxythymidine) than did AZT solely. In vitro, in a variety of HSCs it can improve the efficacy of AZT on human immunodeficiency virus replication (TOCHIKURA, T. S., *et al*., 1987).

Shiitake's secondary molecule eritadenine regulate metabolism of cholesterol also shows antiviral effects (Wasser, S. P., & Weis, A. L., 1999). Antiviral properties have been found in water soluble lignins derives from EP3 and EPS4 from L.edode mycelium (HANAFUSA, T., *et al*., 1990). In animals, Herpes simplex virus spread was prevented by LEM and its novel lignin-rich molecule, JLS-18 (Sarkar, S., *et al*., 1993). JLS-18 may be useful in the therapeutics of AIDS and hepatitis B patients because of its strong action (Yamamoto, Y., *et al*., 1997).

In vitro, lentinan and its sulfated deriatives had significant action against HIV, preventing replication of viruses and multinucleate cell formation. Host defense peptides like lentinan can also be used to inhibit the progress of signs of AIDS in carriers. LEM has been demonstrated to

enhance the antiviral activity of AZT and to reduce HIV contamination in cultured human T helper cells. LEM extracts was discovered, for macrophages activation and boost the development of Interleukin-1, although the exact procedure of its activity is unknown (Yang, B. K., *et al*., 2002)(Tochikura, T., *et al*., 1988).

4. Immunomodulating effects of shiitake:

Former research has shown that lentinan activates various immune functions in the host to achieve anticancer effects instead of directly targeting tumour cells. In utmost of the animals studied, lentinan can generate a 90 percent depletion in tumour size or total remission (Li, Q., *et al*., 2021)(Chihara, G., *et al*., 1969). Lentinan work as host defense potentiators, enhancing or restoring host cell sensibility to hormones, lymphocytosis and different physiologically active molecules by increasing the divergence, growth and development of cells engaged in host defensive systems (Yap, A., T., *et al*., 2003)(Yap, A., T., *et al*., 2001).

Lentinan infusion resulted in increased natural killer (NK), Lymphokine Activated Killer and Cytotoxic T Lymphocytes activity and Delayed Type Hypersensitivity feedback against cancer antigen (Hamuro, J., 1985). After particular identification of cancer cells, lentinan can increase the potentiation of the reaction of parent T cells and macrophages to cytokines generated by specific lymphocyte types (Chihara, G., 1992). Unlike different specific immunostimulants, lentinan belongs to a distinctive class of DT-cell-oriented assistans that include macrophages. At this time the first reaction of lentinan in the human body are unknown. But, various serum protein constituents, including complement C3, ceruloplasmin and hemopexin, show a transient but noticeable increase in the α- and β-globulin areas (Wasser, S. P., *et al*., 1997)(Yap, A.T., 2003).

Immunomodulation through generating immune responses of macrophages and T-cells moderate the anticancer efficacy of the polysaccharide L-II on mice implanted S-180. In a well-known model sample of Listeria monocytogenes infection in mice, Kupfahl et al. investigated the impact of lentinan. The findings revealed that lentinan most likely, by interleukin-12- moderate the enhancement of the particular antilisterial CD8 T-cell reaction and boosts the defensive CD8 T-cell reaction against L.monocytogenes (Kupfahl, C., *et al*., 2006).

A rise in the stimulation of general inflammatory reactions, like the synthesis of acute phase protein (APP), has been described as one of lentinans numerous biological actions. Other biological actions of lentinan include

1-In vivo vascular dilation and bleeding

2-Helper T-cell activation and production

3-Enhancement in IL-1 and IL-3 immune moderators and in migration inhibition factors (MIF).

4-Boosting the range of gastric cancer patients` PBM (peripheral blood mononuclear) cells to produce interleukin-1α, interleukin-1β and tumor necrosis factor-α (Wasser, S.P., *et al*.,1996) (Yap, A.T., *et al*., 2003)(White, R. W. D., *et al*., 2002).

5. Effects of shiitake for hepatoprotection:

On dimethylnitrosamin-damaged rat, the liver protective effects of ethanol extraction and warm-water extraction of L.edodes mycelia were investigated (Akamatsu, S., *et al*., 2004).

The levels of AST and ALT in the serum were reduced in both fractions. In mice, these fractions inhibited the α-SMA (alpha-smooth muscle action) or heat-shock protein 47 upregulation and was somewhat suppressed the overabundance of collagen fibrils. In addition, both fractions suppressed the growth of outlying mice hepatic stellate cells (HSCs) and it is crucial for hepatoprotective action. Polysaccharides like LEM and Lentinan have shown to be effective in the treatment of severe long lasting hepatitis and increase the antibodies manufacturing against hepatitis B patients (Mizuno, T., 1995).

Injecting LEM into rats inhibited the growth of a malignant liver tumor (Mizuno, T., 1996)(Smith, J., *et al*., 2002)(Amagase, H., 1987) . The liver have been shown to be protected by unprocessed extracts of L.edodes cultures (Ch, H., 2000)(Mizuno, T., 1996)(Wasser, S.P., *et al*., 1999).

A chemical Kojic acid present in high quantities in shiitake mushroom targeted at lightening our skin. It is naturally changed to hydroquinone, which helps to light spots and aging scars from our skin. Also stated by, Skincare-News.com, shiitake mushroom ingredients appealing on skin makes our looks better. Shiitake along with taking care of body's inside organs also decrease the inflammation of skin, found as a constituent in skin lotions and creams (Rahman, T., & Choudhury, M.B.K., 2012).

Shiitake mushroom utilization also helpful in weight loss. Studies of American Heart Association show that, taking a proper balanced food which includes these beneficial shiitake mushrooms will be the great remedy in weight loss process (Rahman, T., & Choudhury, M/B.K., 2012).

DISCUSSION:

Mushrooms play an important role in human life as they are not only used as food but also play key role in pharmaceutical and nutraceutical industries. There are various kinds of mushrooms approximately 12,000 species of which 2000 are edible (Beulah, G.H, *et al*, 2013).

Most common type of mushroom is Shiitake (Lentinula edode) which is umbrella shaped in structure. This mushroom has been called "King" or "monarch" in Japan because of its great anti-tumour, antihypertensive and antimicrobial activities (Jones, K., 1995). Shiitake is also known as shiang-ku in China and shii-take in Japan and are mainly grown in East Asia countries (Chang, S. T., 1999) (stamets, S. P., 2000).

Dr. Mori said that shiitake in pharmacology used to improve circulation, heart illness, fatigue, brain hemorrhage and intestinal worms (Mori, K. 1974). Nutritional compounds most commonly present in shiitake are carbohydrates, proteins, water, fats, minerals and vitamins (Hobbs, C., 2002). Shiitake grows commonly in winter but it can grow throughout the year under favourable conditions (Chang, S. T., 1999). Shiitake production begins thousand years before in China. Wu Sang Kwang was known as the founder of shiitake agriculture (Miles, P.G. & Chang, S. T., 1999). This mushroom grows mainly on deciduous trees and shii tree is one the trees which sheds their leaves yearly, therefore it was named shiitake (Boer, C. G., *et al*., 2004).

Water soluble and insoluble dietry fibers like polyuronide, chitin, lignin, amino acids and β- glucans are all present in shiitake (Heleno, S. A., *et al*., 2012). Vitamins specially vitamin D and vitamin B such as B1, B2 and B12 are all present in L.edodes. Calcium, Copper, K, iron, Zn and P are the minerals present in shiitake (Stamets, P., 2000). Organic acids, peptides, monosodium

glutamate and sugars are the constituents which makes this mushroom's aroma appetizing (Mizuno, T., 1995). It can be cultivateded both on natural and synthetic logs and was called the "elixir of life" (Campbell, A.C., *et al*., 1999). Plastic bag method (Luo, X. C., 2004) and bed log cultivation are the methods used for cultivation of shiitake mushroom.

Important bioactive compounds derived from shiitake are polysaccharides, (lentinan, β-glucans, eritadenine, and chitin) sterols, (ergosterol) sulfurous compounds and glycoproteins (LEM and LAP) with different biological functions. (Smith, J., et al., 2002) Shiitake lowers the levels of blood cholesterol because of a chemical eritadenine present it it (Suzuki, S., & Oshima, S., 1997).

Antitumour activity of shiitake is because of a presence of compound lentinan. Lentinan activate the host's immune system by stimulating helper T cells, macrophages, NK cells and different effector cells when asministrated orally (Shavit, E., *et al*., 2009) (Wong, K.W.C., 2005). LEM and LAP are glycoproteins extract from shiitake mycelium are used to treat Hepatitis B. Both proteins show anticancer action when given orally (Suzuki, H., *et al*., 1990) (Hobbs, C., 2000). Shiitake mushroom have ergosterol in their cell membrane from which vitamin D is obtained (Perera, C. G., *et al*., 2003). KS-2 extract from shiitake mycelia inhibit the development of Sarcoma-180 and protect the host from infections of bacteria and viruses because of its immunomodulating function (Fuiji, T., *et al*., 1978) (Suzuki, F., *et al*., 1979).

Chitin from shiitake stalk protects against microbes and help to replace missing tissue layers (Yen, M. T., & Mau, J. L., 2007). Lenthionine from shiitake fruiting bodies protect against gram-positive and gram negative bacteria (Hatvani, N.., 2001). Lavostatin – a secondary metabolite inhibits (HMG CoA) reductase which catalyze the synthesis of cholesterol and reduces blood cholesterol levels. Shiitake mushrooms are used therapeutically to treat diseases including tumour, viral and bacterial infections, cardiovascular disorders, diabetes and disorders of immune system etc. Lentinan inhibit the Sarcoma -180 tumours development (Chihara, G., *et al*., 1970). Shiitake mushroom extract eritadenine lowers blood cholesterol and hypertension by releasing lipids from circulation to the liver (Ch, H., 1996) (Hobbs, C., 2000) (Mizuno, T., 1996).

Lentinan enhances the host resistence to viruses and AIDS (Ngai, P. H., & Ng, T. B., 2003). Eritadenine also shows antiviral effects. Herpes Simples Virus was also destroyed by LEM and JLS-18 (Sarkar, S., *et al*., 1993). Hepatoprotective effects shown by lentinan and LEM. Both are favourable in the treatment of hepatitis (Mizuno, T., 1995).The potential of this mushroom is undoubtedly most crucial in modern biotechnology.

Conclusion:

The shiitake mushroom has been explained in literature as a macro-fungus with great capability for nutrition, nutraceutics and medicinal values. Therapeutic applications of this mushroom are favorable in treating severe disorders like cancer, hypercholestrolemic issues and hepatitis. Shiitake produces useful bioactive metabolites and they act as significant biomedical drugs. There is still various areas of L.edode need further research for future perspectives.

NOTE:

The study highlights the efficacy of "traditional medicine" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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