Lentinula Edodes (Edible Mushroom) as a Nutraceutical: A Review

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Lentinula edodes (L. edodes) is the globally second most widely consumed mushroom that is well-known for its therapeutic potential and is a commonly used experimental fungus model. This review was focused on the benefits, efficacy, and potential mechanism of action of the extracts from L. edodes as described in the previous studies. With limited information on the health-related benefits of L. edodes, several investigators have now diverted their attention towards this macrofungus. Several studies have now revealed its antitumor, immune-modulating, antitumor, antiviral, antimicrobial, cholesterol-regulating, anti-atherosclerotic, anti-diabetic, antioxidant, and homocysteinemia activities.

Keywords: Lentinula edodes; Mushroom; Shiitake; Polysaccharides.

Several cultures around the world have utilized mushrooms as highly nutritional and medical food item. In Asia, mushrooms are widely used as a medicinal ingredient and several studies have been conducted on their medicinal aspects1. In India, mushrooms are used as an important component of folk medicine and Ayurveda2,3. L. edodes, also known as flower mushroom, Shiitake, winter mushroom, golden oak mushroom, emperor mushroom, and Chinese black mushroom has been cultivated for thousands of years. In the last two decades, L. edodes production has raised substantially from 2.68 to 10.8 million tons4. Biochemically, the dried extracts of L. edodes comprise 58-60% carbohydrates, 20-23% proteins, 9-10% fibre, 4-5% ash, and 3-4% lipids (Table 1)5. Several studies have demonstrated the antitumor, immuno-regulation, anti-inflammatory, antioxidant, and blood pressure lowering activities of L. edodes 6, 7, 8, 9. In addition, L. edodes contains
amino acids, polysaccharides (lentinan, α-glucans), minerals, vitamins, choline, adenine, hexose (Table 2) 10, 11.

*L. edodes* has long been used as an important ingredient of the Oriental folk medicine for the treatment of several diseases and disorders, such as flu, tumours, high blood pressure, cardiovascular disorders, obesity, sexual dysfunction, ageing, respiratory diseases, diabetes, etc. in Japan 12, 13. According to a 2019 study, around 88,832 tons of *L. edodes* was produced in 2018, which accounted for around 19% of total mushroom production in Japan 14.

Belonging to the Basidiomycetes division, this white-rot fungus is commercially cultivated on logs placed on the forest floor (outdoors) and on synthetic sawdust substrates (indoors). Recently, the indoor cultivation has emerged as the primary *L. edodes* production method; however, the traditional log cultivation still contributes substantially to overall *L. edodes* production 13, 14.

**L. edodes Composition**

Previously, the investigators have been able to isolate several bioactive compounds from *L. edodes* that are beneficial to the health 15. Table 1 enlists the compounds present in the fruit bodies of *L. edodes* 16. Apart from the glycogen-like polysaccharides, *L. edodes* contains lentinan, antitumor polysaccharides, (1-4)-(1-6)-α-D-glucans, (1-3)-, (1-6)-β-bonded heteroglycans, heteromannans, heterogalactans, etc. In addition, it also contains several free sugars, including glycerol, trehalose, mannitol, arabinol, arabinose, and mannose. The dietary fiber from *L. edodes* is composed of both water-soluble and water-insoluble materials. It also contains various aromatic compounds, such as alcohols, sulphides, ketones, alkanes, etc. 17. The characteristic flavour of the shiitake mushroom is attributed to its component organic acids, such as malic acid, α-keto-glutaric acid, fumaric acid, oxalic acid, acetic acid, lactic acid, glycolic acid, and formic acid 18. *L. edodes* contain numerous biocomponents that possess pharmacological potency against various disorders and cancer. (Table 3) 19.

**Cancer Prevention Activity**

The cancer prevention effects of mushroom polysaccharides were first observed by the farmers who primarily grew medical mushroom. These farmers exhibited around 40% lower cancer-related mortality rate compared...
to general population 20. In a previous rodent study, the impact of L. edodes-derived lentinan on the hepatic expression of Cytochromes P450 (CYPs) was observed. The researchers reported down regulation of the expression and activity of constitutive and 3-methylcholanthrene-inducible CYP1A, along with promotion of synthesis of tumour necrosis factor-α in test animals 21. Apart from being an immune-potentiator, lentinan is also known to prevent in vivo anticancer drug-induced chromosomal damage. A previous study demonstrated that treatment with L. edodes fruit body extract suppressed the in vivo mutagenicity of N-ethyl-N-nitrosourea and cyclophosphamide 22. Most of the cancer-related studies have focused on lentinan as the major anticancer compound present in L. edodes. It is currently being used as an anticancer agent to improve the outcome of cancer therapy. Interestingly, a previous study reported that when administered orally, α1-3-glucanase and lentinan fail to impart any antitumor activity in mammals 23.

Anticaries Activity

Caries is a bacterial infection characterized by tooth lesions. Caries-causing bacteria synthesize insoluble bio adhesive polysaccharides, which form a plaque that, in turn, mediates Streptococci accumulation and adherence to the dental surface. Streptococci produce organic acids that trigger enamel demineralization. Then, secondary invaders easily invade the deeper tissues of the tooth, producing caries lesion. Most important caries-inducing species include Streptococcus mutans, Streptococcus sobrinus, Actinomyces, and Lactobacillus 24. Caries incidence is affected by several factors, such as oral hygiene, susceptibility to demineralization, and diet habits 25. The growth of caries-inducing microbes is also suppressed by the presence of fluoride. On the other hand, sucrose promoted the formation of caries, as it acts as a substrate for both biofilm production and lactic acid formation. Treatment with L. edodes extracts inhibited the adherence capability of Streptococci, enhanced biofilm disruption, and suppressed the formation of biofilm. Another study reported mushroom-derived adenosine to inhibit the formation of biofilm 26. It contains sweetening agent called erythritol.27 Sesquiterpenes, steroids, anthraquinone, benzoic acid derivatives, and quinolones present in Shiitake extracts inhibit the growth of S. Mutans 28. This bacteriostatic action is carried out by the inhibition of DNA synthesis which is in agreement with a previous study 29.

Antimicrobial Activity

Mushrooms are well-known to exhibit antibacterial activity 30. Previous studies have demonstrated the antimicrobial activity of L. edodes extracts and or culture; however, majority of these studies were focused on micro organism including Gram-positive bacteria 31,32. A previous study demonstrated that lenthionine, a cyclic compound that partially contributes to the characteristic L. edodes taste, exhibited inhibitory effects against Bacillus subtilis, Escherichia coli, and Staphylococcus aureus33. Previous studies have also shown L. edodes-mediated inhibition of oral pathogens 34. Further studies reported antiviral activity of L. edodes culture medium. For instance, sulphated lentinan ameliorated HIV-induced cytopathic effects 35. Rincão et al. 36 suggested that aqueous and ethanolic extracts of L. edodes and L. edodes polysaccharides acted at the initial replication stages of the bovine viral diarrhoea, bovine herpes virus infection of the

| Table 3. Bioactive compounds present in L. edodes mushrooms |
|-------------------------------------------------------------|
| **Bioactive components**                                    | **Reference** |
| Erythritol, Adenosine, Sesquiterpenes, Steroids, Anthraquinone, | 69            |
| Benzoic acid derivatives, and Quinolones                     |               |
| β-glucans, Chitins, Eritadenine, Lenthionine, Ergosterol, Proteins/Peptides | 66            |
| Octanal, Pentanal, Hexanal, Furfural, Vinyl propionate, Geranylacetone, | 69            |
| Hexanoic acid, Octanoic acid, Benzoic acid, 2-Cresol, Toluene, Styrene and Ethylbenzene |          |
| Phenylacetaldehyde, 3-methylbutanal, butanoic acid, dimethyl trisulfide, pentanoic acid, phenylactic acid and vanillin | 70            |
| Copalic acid                                                  | 68            |
| Carvacrol                                                    | 67            |
mucous membranes (BoHV-1), and polio virus infection (PV-1). Therefore, these extracts and polysaccharide are considered as potential sources of novel antiviral compounds.

**Antitumor Activity**

Mushrooms are well-known to be highly efficient functional food and potential therapeutic products. A previous study demonstrated that lentinan exhibited therapeutic effect against gastric cancer. Administration of *L. edodes*-derived polysaccharides in conjugation with the chemotherapeutic drugs significantly enhanced the drug efficiency among cancer patients without any substantial liver, renal or bone marrow dysfunction. Administration of lentinan prior to the chemotherapeutic drugs led to improved outcome among advanced or recurrent gastric cancer patients in terms of tumour regression, prolongation of life, and immune enhancement. Lentinan, a â-(1,3)-D-glucan, was first isolated from *L. edodes* by Mizuno et al. and shown to be immuno-modulators that can improve the phagocytic function of macrophages and the host tumor defence mechanisms without detrimental effects.

**Anti-Atherosclerotic Activity**

Atherosclerosis is intricately associated with excessive intake of cholesterol-filled food.
products and overproduction of oxidized low-density lipoproteins (LDL). In addition, to reduce the risk of atherosclerosis, The European Food Safety Association (EFSA) recommends two types of functional foods namely â-glucan (L. edodes) and phytosterol. The anti-atherosclerotic activity of L. edodes indicates its therapeutic product as an anti-atherosclerotic agent against cardiovascular diseases.

**Antioxidant Activities**

Oxidation reactions lead to the formation of free radicals, which, in turn, damage cells. Antioxidants not only prevent the formation of these free radical intermediates, but also get oxidized themselves to prevent such oxidation reactions. Previously, demonstrated that exposure to high temperatures significantly increased the overall antioxidant activities of L. edodes. Another study showed that low molecular weight sub-fraction of aqueous L. edodes extract exhibited inhibition of lipid peroxidation in animals. Hence, L. edodes has been shown to exhibit potent antioxidant property.

**Antidiabetic and Hepatoprotective Effects**

Previously, showed that treatment with the L. edodes culture-based exo-polymer substantially increased the levels of plasma insulin by 22.1% by and decreased the levels of plasma glucose, total cholesterol, and triglycerides by 21.5%, 25.1%, and 44.5%, respectively. In another study, Akamatsu et al. investigated the hepatoprotective effects of various fractions of aqueous L. edodes extract in rodents. They observed a decline in the blood levels of alanine aminotransferase and aspartate aminotransferase, which attributed to the presence of polyphenols. Various other studies have also suggested L. edodes-derived polyphenols as potential components with hepatoprotective effects.

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**Fig. 2.** The mechanism of ROS generation and its importance in the apoptosis of cancer. ROS produced by either exogenous sources (radiations & chemicals) or endogenous sources (Infection & metabolism) or drugs such as through cellular mitochondria, can induce DNA damage through oxidation (cancer, apoptosis, epigenetic changes & Inflammation) or cause post-translational modifications (Transcriptional activation & Signaling pathway activation) on cellular proteins.
Homocysteinemia

Homocysteine is synthesized during methionine metabolism. Several studies have shown significant association between enhanced homocysteine levels (homocysteinemia) and various ailments such as bone-related disorders and cardiac failure. It has previously been shown that homocysteinemia enhance susceptibility to endothelial injury, which results in tissue, ischemic injuries, and metabolic imbalances. Several neuronal degenerative and cardiovascular diseases have also been attributed to homocysteinemia. *L. edodes* has previously been shown to be effective against lipid metabolic and vascular diseases, including homocysteinemia, lipidaemia, and hypertension. Yang *et al.* have demonstrated that various *L. edodes* components, such as eritadenine, can counter the effects of hyper homocysteinemia. Their study also suggested that these components regulate DNA methylation-related genes in mice.

Improves Human Immunity

*L. edodes* is cultivated for both its medicinal as well as culinary qualities. Its immunomodulatory effects have been demonstrated in various animal and *in vitro* studies; however, there have been limited number of human studies on this aspect. The consumption of *L. edodes* has been shown to improve immunity via enhanced cellular proliferation and activation and upregulate IgA levels. Dai *et al.* attributed these effects to *L. edodes*-mediated innate lymphocyte priming. They also suggested that this mushroom exhibited an anti-inflammatory environment, as evident by the expression of NKG2D and CD69 on innate cells.

Fig. 3. Schematic representation of possible pathways regulated by β-glucan to attenuate cancer cells. Beta-glucan acts through the activation of innate immune cells which triggers the immune response, resulting in the inhibition of tumor growth and metastasis.
T cells and downregulation of C-reactive protein levels. They proposed that decreased inflammation is beneficial to the host, as it may result in a less aggressive immune response, while retaining its pathogen-combating ability 52.

**Human Clinical Studies**

*L. edodes*-derived lentinan has been shown to exhibit antitumor activity and increases the survival time among gastric cancer patients53 and recurrent breast cancer patients54. A phase II study revealed that administration of lentinan, in conjunction with chemotherapeutic drugs significantly enhanced the drug efficacy in individuals with progressive cancer but without hepatic, renal, or bone marrow dysfunction 55. A follow-up phase III trial again revealed that administration of lentinan prior to chemotherapy led to significantly favorable outcomes in individuals with primary lesions and without prior chemotherapy 55. Lentinan has also been shown to exhibit protective effects against infectious diseases. The results of a previous study on pulmonary tuberculosis patients who had shed drug-resistant M. tuberculosis for a decade showed that the excretion of M. tuberculosis ceased after treatment with lentinan 56,15.

In another clinical trial, *L. edodes* fruiting bodies showed some cholesterol reducing effects. Administration of dried *L. edodes* at daily doses of 9 g and 90 g for one week led to a 7% and 12% decrease in serum cholesterol, respectively. Furthermore, daily intake of 90 g *L. edodes* and 60 g butter for a week led to a 4% decrease in the serum cholesterol levels 57. Another study revealed that intake of dried or fresh *L. edodes* led to a 9% reduction in cholesterol levels in individuals 60 years of age or older 57.

Immuno modulators are generally classified into immune stimulant, immune adjuvants, and immune suppressant 58. Mushrooms are a rich source of immune modulators. Previously, Uno et al.59 showed that oral administration of *L. edodes* normalized the levels of cytokines in phytohemagglutinin-stimulated peripheral blood lymphocytes. Won (2002),60 also reported around 20% increase in the NK-cells to total lymphocytes.
ratio after oral supplementation of *L. edodes*. Gordon et al. 61 showed good tolerability of HIV-positive patients to lentinan, with only mild side effects, particularly when infusion was carried out for over 30min.

**CONCLUSION**

In summary, several studies were demonstrated that *L. edodes* (edible mushroom) has significant therapeutic actions against various disorders. So, taking this data into consideration, *L. edodes* will become a prospective nutraceutical in future, if researchers concentrated on this and conduct further preclinical and clinical studies.

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**Conflict of Interest**

The authors declare that there is no conflict of interest regarding this paper.

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