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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, antidiabetic, 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 aspects[1]. In India, mushrooms are used as an important component of folk medicine and Ayurveda[2,3]. *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 tons[4]. 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

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amino acids, polysaccharides (lentinan, â-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].

Table 1. Composition of *L. edodes* (per 100 gm Sample) [16, 62].

S. No.	Components	Concentration
1	Ash	6.0gm
2	Carbohydrate and Fibre	64.4gm
3	Energy	411 Kcal
4	Fat	2.1gm
5	Moisture	4.7gm
6	Protein	22.8gm
7	Calcium	127mg
8	Chromium	140 µg
9	Copper	0.9mg
10	Iron	20.1mg
11	Magnesium	200mg
12	Manganese	5.1mg
13	Phosphorus	439mg
14	Zinc	4.3mg
15	Ascorbic acid	2.1mg
16	Folic acid	0.03mg
17	Niacin	2.6mg
18	Pro-Vitamin D Ergosterol	679 µg
19	Ribolflavin	20.15mg
20	Thiamin	0.05mg

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)-á-D-glucans, (1-3)-, (1-6)-â-bonded heteroglycans, heteromannans, heterogalactans, etc. In addition, it also contains several free sugars, including glycerol, trehalose, mannitol, arabitol, 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, á-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

Table 2. Main compounds found in *L. edodes* mushrooms. (63, 64, 65)

Fatty acid	Free sugars	Polysaccharides	Amino acids	
Linoleic	Arabinose	Heteroglycans	Glutamate	Leucine
Palmitic	Glycerol	Heterogalactans	Threonine	Valine
Oleic	Arabinol	Heteromannans	Arginine	Alanine
Stearic	Mannose	Heteroglycans	Cysteine	Glycine
Myristic	Mannitol	Xyloglucans	Histidine	Lysine
Arachidic	Glucose	Polyuronide	Aspartate	Serine
Linolenic	Fructose	â-glucan	Isoleucine	Proline
Tetradecenoic	Trehalose	Chitin	Phenylalanine	Tyrosine

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-á 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, â1-3-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 aureus*[33]. 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, Benzoic acid derivatives, and Quinolones	69
ß-glucans, Chitins, Eritadenine, Lenthionine, Ergosterol, Proteins/Peptides	66
Octanal, Pentanal, Hexanal, Furfural, Vinyl propionate, Geranylacetone, Hexanoic acid, Octanoic acid, Benzoic acid, 2-Cresol, Toluene, Styrene and Ethylbenzene	69
Phenylacetaldehyde, 3-methylbutanal, butanoic acid, dimethyl trisulfide, pentanoic acid, phenylacetic 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 [37]. A previous study demonstrated that lentinan exhibited therapeutic effect against gastric cancer[15]. 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 [38]. 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.[39] and shown to be immuno-modulators that can improve the phagocytic function of macrophages and the host tumor defence mechanisms without detrimental effects [40].

Anti-Atherosclerotic Activity

Atherosclerosis is intricately associated with excessive intake of cholesterol-filled food

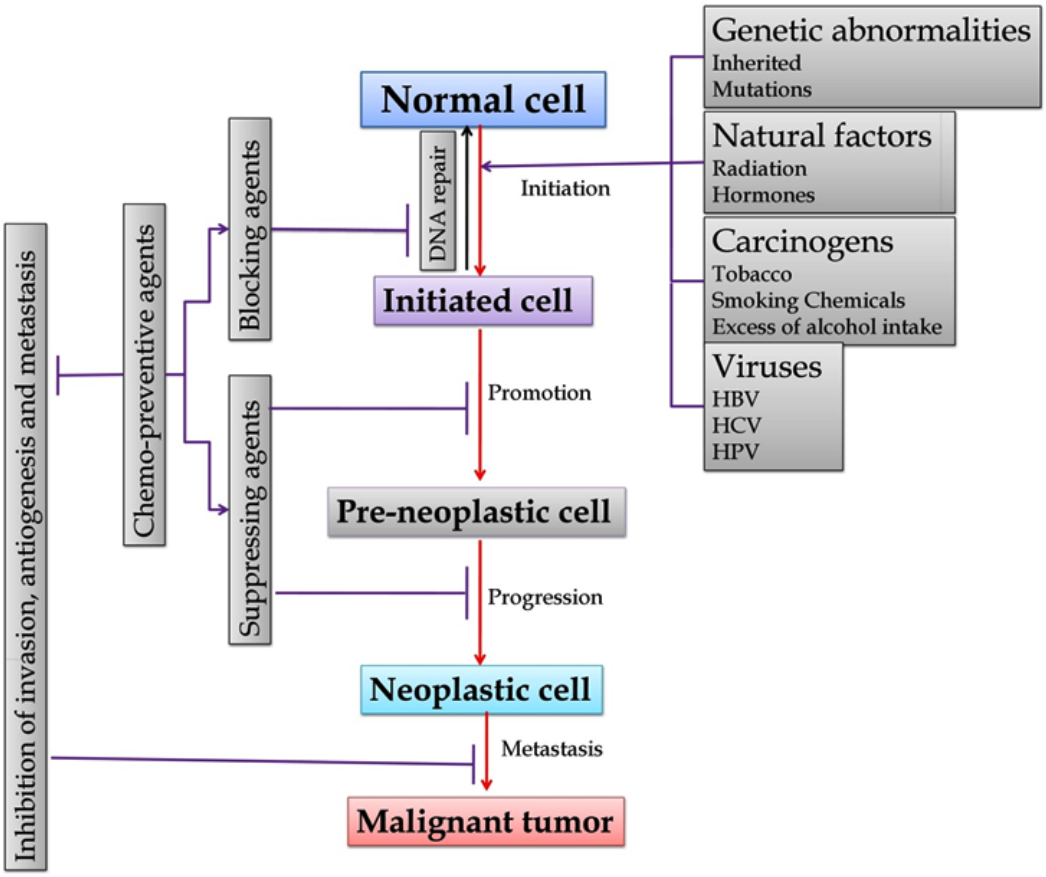

Fig. 1. Phases of carcinogenesis. Carcinogenesis can be classified into at least three stages. The first stage of carcinogenesis is caused by an irreversible genetic changes, including mutations, transversions, transitions, and/or minor DNA deletions. The reversible stage of promotion involves changes in the expression of the genome mediated by promoter-receptor interactions rather than changes in the structure of DNA. Karyotypic instability and malignant development describe the final irreversible stage of progression. Proto-oncogenes, cellular oncogenes, and tumour suppressor genes are all important targets during the stages of carcinogenesis, with changes in both alleles of the latter occurring only during the advancement stage

products and overproduction of oxidized low-density lipoproteins (LDL [41]. 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 [42]. The anti-atherosclerotic activity of *L. edodes* indicates its therapeutic product as an anti-atherosclerotic agent against cardiovascular diseases [43, 19].

Antioxidant Activities

Oxidation reactions lead to formation of free radicals, which, in turn, damage cells. Antioxidants not only prevent the formation these free radical intermediates, but also get oxidized themselves to prevent such oxidation reactions [18]. Previously, Choi et al., [44] 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 [45]. Hence, *L. edodes* has been shown to exhibit potent antioxidant property.

Antidiabetic and Hepatoprotective Effects

Previously, Yang et al. [46] 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*.[47] 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[46,48]. Various other studies have also suggested *L. edodes*-derived polyphenols as potential components with hepatoprotective effects [49,50].

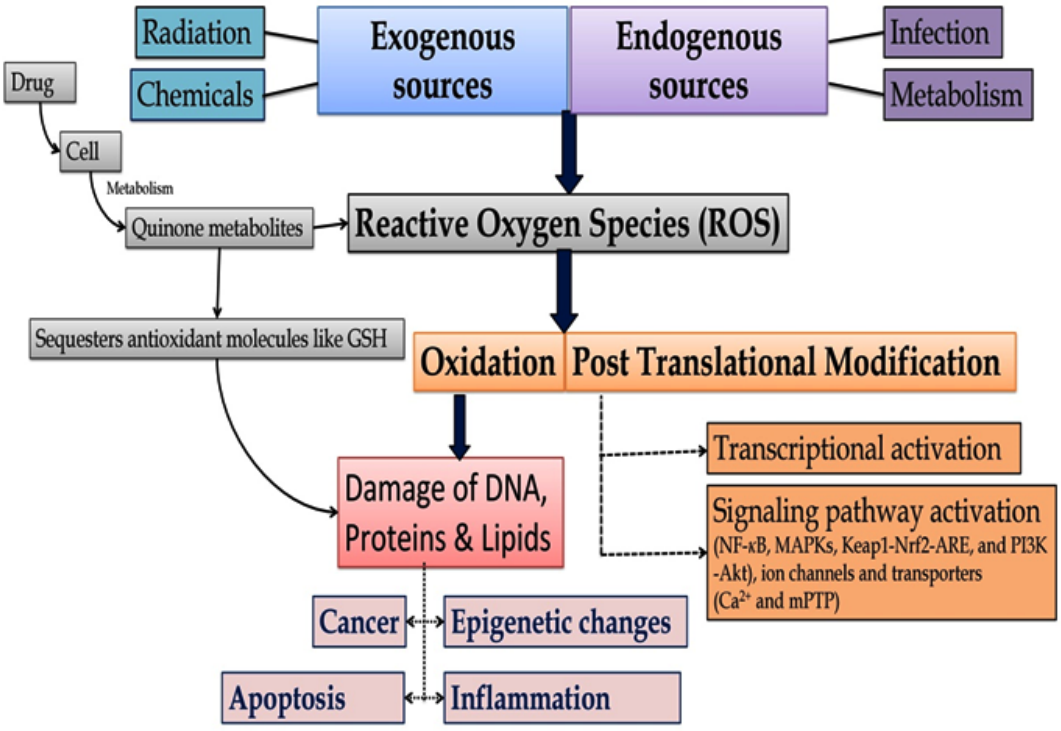

Fig. 2. The mechanism of ROS generation and its importance in the apoptosis of cancer. ROS produced by either exogenous sources (radiations & chemicals) or endogenous sources(Infection & metabolism) or drugs such as through cellular mitochondria, can induce DNA damage through oxidation(cancer, apoptosis, 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 [51]. 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.*[27] 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 immune-modulatory 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. [52] 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

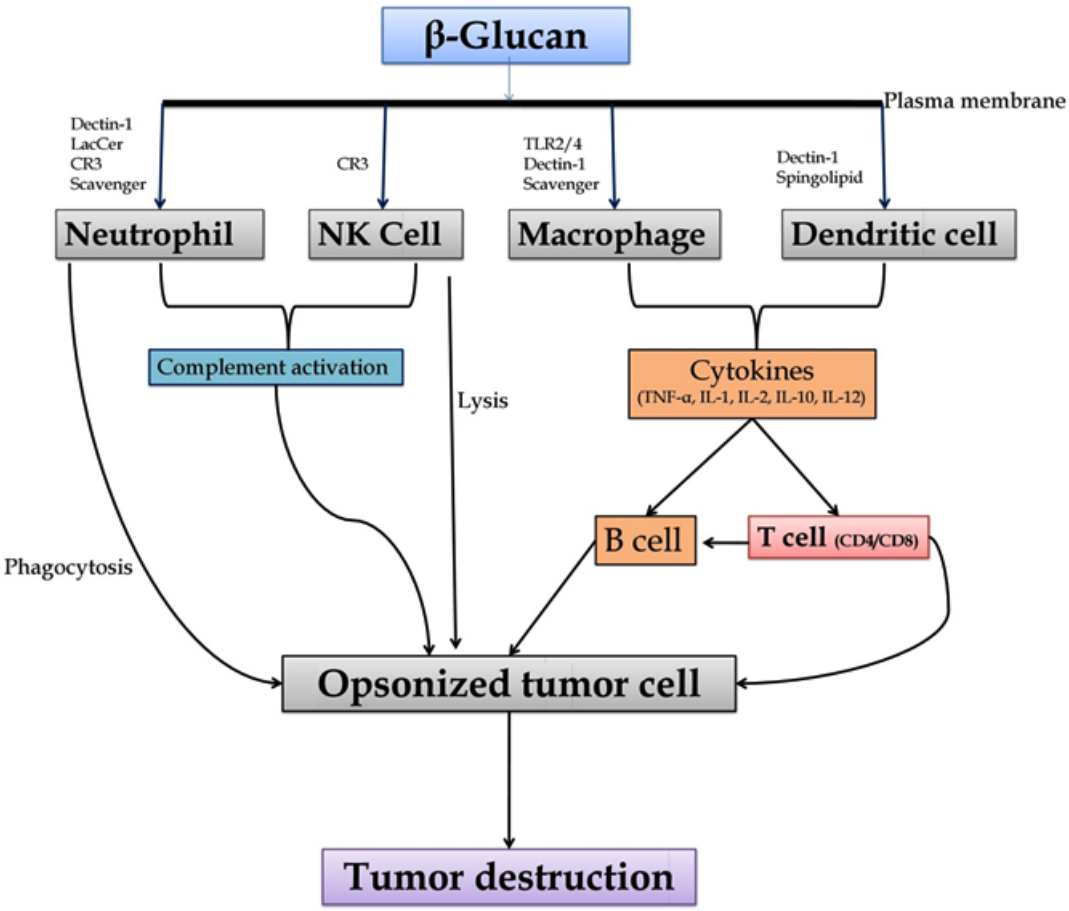

Fig. 3. Schematic representation of possible pathways regulated by â-glucan to attenuate cancer cells. Beta-glucan acts through the activation of innate immune cells which triggers the immune response, resulting in the inhibition of tumor growth and metastasis

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 patients[53] and recurrent breast cancer patients[54]. A phase II study revealed that administration of lentinan, in conjugation 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

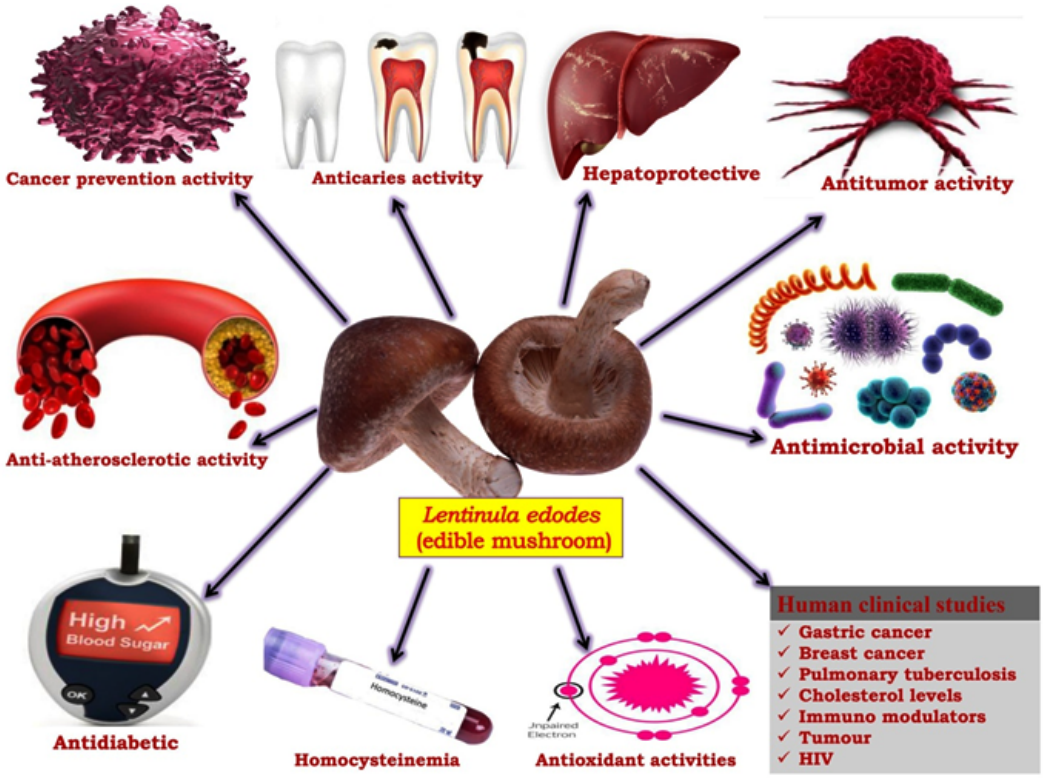

Fig. 4. Possible therapeutic activities of *Lentinula edodes* (edible mushroom)

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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