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A Review on General Nutritional Compounds and Pharmacological Properties of the *Lentinula edodes* Mushroom

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Abstract

***Lentinula edodes* is a macrofungus with great potential for therapeutic applications and serves as a model for investigating functional fungi properties and isolating pure compounds for pharmaceutical use. Mushrooms have a great nutritional value and present medicinal molecules including polysaccharides, terpenoids, sterols and lipids, that participate actively in several human disorders and modulate mechanisms involved in the immune system regulation. This review will focus on general nutritional compounds and pharmacological properties of *L. edodes*.**

Keywords

***Lentinula edodes*, *β*-Glucans, Therapeutic Applications, Review**

1. Introduction

Over the past 25 years, new natural drugs have been approved for the treatment of human diseases. Natural products play a very important role in the process of discovery and development of drugs, including the treatment of chronic diseases such as cancer [1]. For hundreds of years, medicinal mushrooms are used as decoctions and essences, and are applied as alternative medicine in Korea, China, Japan and eastern Russia [2]. A wide variety of compounds that occur naturally have proven active to protect against the development of tumors [3] and inflammatory processes [4]. The most investigated compounds are polysaccharides which are present in the whole structural composition mushrooms, among many effects are the antitumor and activation of the host

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immune response [5]. A number of polysaccharides have been isolated from basidiomycete [6] and are represented as homo- and heteropolymers, especially *β*-configuration glucans. One of the active compounds responsible for the immune effects is in the form of complex polysaccharides known as *β*-glucans, which are ubiquitously found in bacterial cell walls or yeast [7] [8]. The genus *Lentinula* sp. grows in gregarious on fallen wood of a wide variety of deciduous trees, in a warm, moist climate. Most of these are raised for artificial cultivation of shiitake mushroom and occurs naturally throughout Southeast Asia [9]. *Lentinula edodes* species is the most famous (**Figure 1**), and has been used as a model to investigate the functional properties and isolate pure compounds for pharmaceutical use.

L. edodes has shown to present medicinal compounds, including polysaccharides, terpenoids, sterols and lipids, which are effective in treating various tumors and infections, among other activities which are still being studied [10].

In vitro and *in vivo* investigations have demonstrated the medicinal effect of glucans as modulators of humoral and cellular mediators of interleukin (IL), activators of macrophages, T-helper and natural killer (NK), protecting the body against bacteria, viruses, fungi and parasites. Modulation of the anti-inflammatory response has also investigated [5]. In Japan, *β*-glucan is used as natural immunostimulant for cancer treatment since 1980. *β*-Glucans are also effective against allogeneic, syngeneic, and even autochthonous tumors [11].

The literature has reported the presence of various compounds such as fractionated extract from mycelium *L. edodes* (LEM) and the aqueous precipitate extract extracted from the mycelium (LAP). Both LEM and LAP contains various sugars such as galactose, arabinose, xylose, mannose and fructose, among others [12]. These extracts have revealed a strong anti-tumor activity *in vivo*. From the fractionation of LEM, lignin (80%), carbohydrates (10%) and protein (10%) are obtained, together with a complex known as EP3 immuneactive [9] [13].

From the harvest of the mycelium, we also obtained amino acids (serine, threonine, alanine and proline), the KS-2 peptide, *α*-mannan, which are capable of inducing the production of interferon and effectively inhibit the development of cancer [14] [15].

Numerous clinical trials are currently under study in the USA and several European countries. Others *Basidiomycetes* species also present biologically active compounds of *β*-glucans like Pleuran for *Pleurotus* sp and Lentinan for *L. edodes* [16]. Some of these important effects will be discussed in this review.

2. General Nutrition Componentes of *L. edodes*

Mushrooms have a great nutritional value since they are quite rich in protein, with an important content of essential amino acids and fiber. The dietary fiber present in *L. edodes* (Shiitake) consist of soluble and insoluble structures. In the water-soluble are found the *β*-glucans and proteins. In the non-soluble fraction, salts are extracted only with acids or alkalis, and found the polyuronide (acidic polysaccharide), hemicellulose, *β*-glucan chains with heterosaccharide, lignin, and chitin. They also provide a nutritionally significant content of vitamins (B1, B2, B12, C, D, and E) [17]. Are shown in **Table 1** the main compounds. The aroma components include alcohols, ketones, sulfides, alkanes, fatty acids, among others [13] [18]. The main constituents which are volatile like matsutakeol (1-octen-3-ol) ethyl, n-amyl ketone and the characteristic aroma of shiitake was identified as 1,2,3,5,6-Pentathiepane [19]. Edible mushrooms are a high nutritional quality of food and have been used as an

Figure 1. Morphology of the *Lentinula edodes*.

Table 1. Main compounds found in edible mushrooms.

Fatty acid	Free sugars	Polysaccharides		Trace elements	
		Soluble	Insoluble	Vitamins	Minerals
Linoleic	Trehalose	Heteroglycans	heteroglycan	Pro-vitamin D-2	Fe
Palmitic	Glycerol	Heterogalactans	polyuronide	Pantothenic acid	Mn
Tetradecenoic	Mannitol	Heteromannans	*β*-glucan	B1	Ca
Oleic	Arabinol	Xyloglucans	Chitin	B2	K
Stearic	Mannose			B6	Zn
Myristic	Arabinose			B12	Cd

alternative to dietary protein supply in countries with high malnutrition rate. The chemical and nutritional characteristics of mushrooms vary in function after harvest, and processing.

3. Immunomodulation and Anti-Tumour Effects of *L. edodes*

Edible mushrooms have been reported to generate beneficial effects on health and in the treatment of disease through its immunomodulatory and antineoplastic properties [20]-[22].

Investigations related to the presence of anti-tumor substances present in mushrooms started in Japan in the late 1960's. Evaluations conducted with macrofungi confirmed the effectiveness of the extracts of the fruiting bodies and mycelia in the inhibition of various cancer cell lines [2] [23]-[25]. The immunomodulatory effects of the mushrooms are well described in the literature and are related to the increased function of monocytes in the production of Interleukin-1 [11] [26] and expression of cytokines. Molecules like glucans are relatively resistant to the stomach acid and are trapped by macrophage receptors present on the intestinal wall as the dectin-1, the toll-like receptor 2 (a class of proteins that play a role in immune system) and lactosylceramides The *β*-glucans with its various structures have different affinities for these receptors to elicit different host responses [16]. *In vivo* studies showed that the analysis of cytokine expression after administration of *β*-glucan isolated from *L. edodes* (lentinan) revealed a significant increase in mRNA levels of Interleukin-1*α*, interleukin-1*β*, tumor necrosis factor-*α* (TNF-*α*) and interferon-*δ* (IFN-*δ*).

This result indicates a good response in the homeostasis of various diseases (**Figure 2**) [27] [28].

To date its anti-tumor activity remains unclear as some authors relate this activity with increasing cell-mediated immune response [29] [30]. However, other authors have shown anti-tumor activity with a direct effect on the cell, without involving the immune system [31].

In a study to investigate the effect of lentinan on T cells, when administered intraperitoneally, resulted in complete tumor regression in mice inoculated with cells FBL-3 (erythroleukemia).

The immunological effect was further confirmed when the inhibition of tumor growth stopped by administration of monoclonal antibodies against CD4 and CD8 prior to administration of *β*-glucan [32] [33]. These effects could be helpful in a number of disease states, but the significance of some of these findings in terms of potential medicinal value still has to be established [34]-[36]. A recent clinical study showed that chemo-immunotherapy using lentinan prolongs the survival of patients with advanced gastric cancer, as compared to chemotherapy alone [37]. In a study conducted by Lee *et al.* [38] crude water-soluble polysaccharides obtained from *L. edodes* by hot water extraction and ethanol precipitation activated macrophages and showed the increased of nitric oxide (NO), cytokines and phagocytosis expression.

An innovative strategy was suggested by Chen [39], using *β*-glucans to deliver nanoparticles containing chemotherapeutic agents to the site of the colon cancer and, thus, improving the therapeutic efficacy.

The anti-tumour effects of shiitake feed in murine models has interact with the effects of lentinan, which has been reported to prevent both chemical and viral carcinogenesis [40] [41].

Hazama *et al.* [42] demonstrated the efficacy of oral administration of lentinan in the treatment of advanced colorectal cancer (**Figure 3**). Shimizu *et al.* [43] also revealed good results in advanced pancreatic cancer, both with increased parameters of survival. Multicenter studies also looked at the effectiveness of the administration of lentinan in patients with hepatocellular carcinoma, resulting in increased survival time of these patients [44] [45].

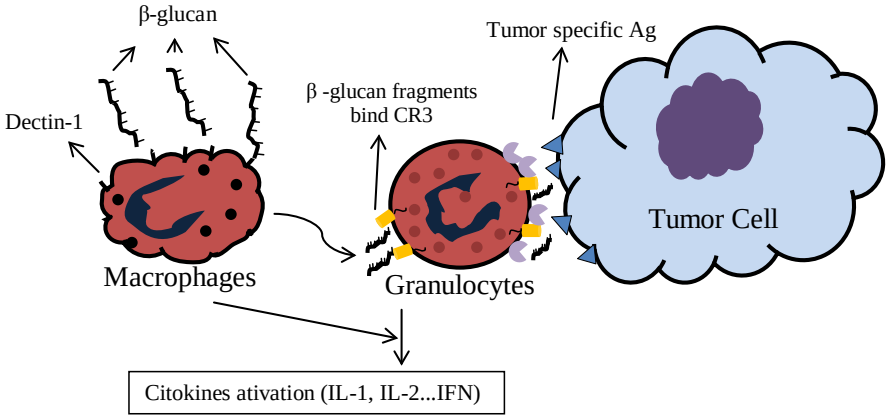

Figure 2. Immune system activation and cytokine production.

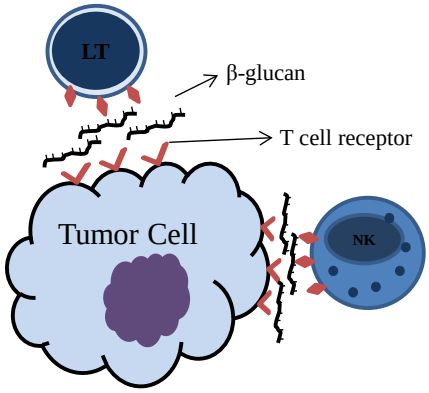

Figure 3. Neutralization of immunosuppressive factors.

Yamaguchi *et al*. [46] suggests the concomitant use of *L. edodes* mycelia (LEM) extracts to chemotherapy, resulting in a synergistic action to improve the quality of patients life. Another compound derived from the extract of *L. edodes*, the Active Hexose Correlated Compound (AHCC), also proved effective as adjunctive therapy in patients with cancer [47]-[49]. According to Ritz [49], oral supplementation with AHCC demonstrates a potential clinically relevant agent that enhances the immune system.

Studies have shown that some active substances present in *L. edodes* exert a protective effect against mutagenesis and carcinogenesis [50]. Aqueous extracts of *L. edodes* demonstrated direct inhibition of the proliferation of breast cancer cells *in vitro* and show to have immunostimulating properties in terms of mitogenic activity and co-mitogenic (**Figure 4**) [51]. In addition, antimutagenic and antigenotoxic effects evaluated by micronucleus and the comet test showed that extracts of shiitake have a antigenotoxic and antimutagenic activity *in vivo* [52] [53].

However, further studies to define the relationship between exposure to the mutagen, the required amount of Shiitake mushroom intake and the frequency of mutations, are still needed [52]. Basically, their antitumor abilities are influenced by the molecular mass, branching configuration, conformation, and chemical modification of the polysaccharides [36].

4. Antioxidant Effects of *L. edodes*

Our body has antioxidant defense systems that are often insufficient to completely prevent the damage caused by oxidative stress [54]. Thus, natural products such as mushrooms containing bioactive compounds can be used to help reduce such damage in the body [55]. As nutraceuticals, they activate endogenous protective system, generation important antioxidant role for the homeostasis of the organism [18] [35] [54]. Several studies have demonstrated the antioxidant properties of *L. edodes* for different; the extract on conditions. Study has performed

tests with aqueous extract of the fruiting body [24], fractions of different molecular weight of polysaccharides [56], crude extract of polysaccharide (LEP) [57] [58] and exudates obtained from the mycelium (DE) [59]. All reports have shown antioxidant activity with high phenolic content (**Table 2**).

5. Antiviral Activities of *L. edodes*

Recent studies have determined the antiviral activity of extracts from LEP on the replication of poliovirus type 1 (PV-1) and bovine herpes virus type 1 (BoHV-1) and the results were anti-virus activity in promoting [60].

The isolated compound lentinan suppressed the activity of HIV-1 reverse transcriptase. In combination with antiretroviral 3'-azido-3'-deoxythymidine (AZT) lentinan suppressed the in vitro expression of surface antigens of HIV more efficiently compared to AZT monotherapy. It was also shown that it can increase the *in vitro* anti-retroviral effect on HIV replication [61].

Tochikura *et al.* [62] tested many substances using non-sulfated polysaccharides (EP-LEM) and achieved inhibition for HIV-1, HIV-2 and HTLV-1. In another study, various fractions of LEM caused inhibition of infectivity and cytopathic effect of HIV [63] [64]. The mechanism of action is unclear, but it suggests that it may be related to activation of macrophages and stimulation of IL-1 [9]. A list of different extracts and its anti-viral activity is shown in **Table 3**.

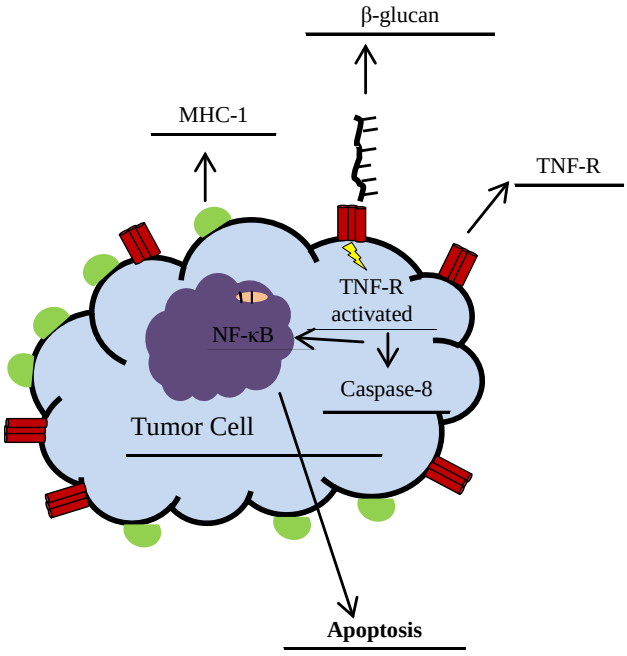

Figure 4. Direct action for induction of apoptosis and increased expression of MHC-1.

Table 2. Positive response against tumor cell line using different extracts of *L. edodes*.

Extract	Cell line	Reference
Low temperature aqueous total extract	Hep-2, HeLa *in vitro*	[24]
Isolated Lentinan	FBL-3 erythroleukemia cells	[81]
Methanol aqueous total extract	*In vitro* cell line MCF-7	[51]
Mycelia-oral ingestion	Mouse (Colon-26)	[82]
Mycelia-oral ingestion	Mouse (B16 melanoma)	[83]
Isolated α-(1,4) glucans	A549 *in vitro*	[28]
Ethyl acetate fraction	MDA-MB-453, MCF-7, MCF-10F, RPMI-8226, IM-9 *in vitro*	[84]

Table 3. *L. edodes* mycelia extracts and anti-viral activity.

Extract	Microorganism	References
Isolated lentinan derivate sulphated	West Nile virus	[10]
Hot water total extract Ethanolic total extract	Poliovirus type 1 (PV-1)	[60]
Isolated polysaccharide	Bovine Herpes virus type 1 (BoHV-1)	[63]
Isolated lentinan Isolated laccase	HIV-1	[64] [85]
Polysaccharide sulphated Polysaccharide nonsulfated	HIV-2	[61] [62]
Glycyrrhizin sulphated Lentinan sulphated	HTLV-1	[62]

6. Antimicrobial Activities of *L. edodes*

It has been reported that extracts of shiitake possess antibacterial activity enhancing host immunity against infections [34] [50] [64] [65]. Hatvani [63] used solvents like chloroform and ethyl acetate in dried mushroom and demonstrated bactericidal activity. Lenthionine, a cyclic organosulfur compound partially responsible for the taste of shiitake showed inhibitory effects against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli.* Several studies have shown the ability of the extract of *L. edodes* to inhibit oral pathogens, mainly causing cavities and gingivitis [66]-[70].

According to Spratt *et al.* [71], the fraction of low molecular weight (LMM) isolated from the aqueous extract of *L. edodes* also has potential activity against oral pathogens *in vitro*. A list of different extracts and its antimicrobial activity is shown in **Table 4**.

7. Other Biological Activities of *L. edodes*

The hypoglycemic effect of an exo-polymer produced from a submerged culture of the *L. edodes* mycelium was investigated in rats with induced diabetes, and obtained a reduction in plasma glucose level compared to the control group. The reduction of cholesterol and triglyceride was also observed [72]. In a study by Akamatsu *et al.* [73], fractions obtained from aqueous extraction of *L. edodes* was examined for its hepatoprotective effect in injured rats. The reduced levels of aspartate aminotransferase and alanine aminotransferase in the blood were observed. These hepatoprotective effects are explained by the presence of polyphenols contained in fractions [72] [74] [75]. Polyphenols contained in both fractions are considered to be potential candidates for expressing the hepatoprotective effects [35] [76].

Cardiovascular disease is the leading cause of cholesterol levels in the blood throughout the world and is an important risk factor for the high mortality, therefore hypocholesteremic effects are of great importance. The ability of shiitake in lowering sanguine cholesterol was first reported in the 1960s [12]. To date, some studies demonstrate the ability of *L. edodes* in both decrease very low density lipoproteins (VLDL) as well as high density lipoproteins (HDL), preventing the increase of blood pressure [45] [77].

The consensus is that regular consumption of fruits and vegetables reduce the risk of cardiovascular disease (CVD). This is due to the antioxidant activity and immunomodulation exerted by these class of food [78]. Evidence also shows that mushrooms may protect against chronic disease like CVD. Oxidative stress and inflammation are closely linked to atherogenesis [68]. The mechanism of action is due to a significant reduction in binding of quiescent monocytes and also stimulated by cytokines [78] [79].

The main active component isolated from *L. edodes* associated to this function is the eritadenine. It reduces the lipid components of serum lipoproteins both in animals and in humans [80]. According to Isoda *et al.* [44], the oral administration of this compound proved to be effective and demonstrate low toxicity, although only 10% is absorbed in the gastrointestinal. As intravenous administration, it proved completely ineffective, and quickly eliminated from circulation and excreted by the kidneys.

8. Conclusion

The *L. edodes* is a macrofungus, that presents a variety of nutrition compounds, with great potential for therapeutic application. The activity and use of this macrofungus are unquestionable in some of the most important

Table 4. *L. edodes* extracts against antimicrobial activity.

Extract	Microorganism	References
Low molecular weight	*Actinomyces naeslundii*	[69] [86]
Dry aqueous extract total	*Bacillus cereus*	[65]
Dry aqueous extract total	*Bacillus subtilis*	[65] [87]
Dry aqueous extract total	*Enterococcus faecalis*	[65]
Isolated liquid medium	*Listeria monocytogenes*	[87]
Dry aqueous extract total	*Staphylococcus aureus*	[65]
Dry aqueous extract total	MRSA	[65]
Low molecular weight	*Fusobacterium nucleatum*	[86] [69]
Isolated liquid medium	*Klebsiella pneumoniae*	[87]
Isolated liquid medium	*Proteus mirabilis*	[87]
Ethanol extract total and dry aqueous	*Pseudomonas aeruginosa*	[65]
Low molecular weight	*Yersinia enterecolitica*	[86]

areas of applied biotechnology. Medicinal value of mushroom intake has become a matter of great significance, particularly in preventing or treating serious chronic conditions such as cancer and cardiovascular disease. From a pharmacological point of view, safety is the primary issue and research in this direction is desired. To date, *L. edodes* has shown to present a great potential for the production of useful bioactive metabolites that serve as a rich resource for drugs. Further research however is needed to establish content and bioactivity of the many compounds found in edible mushrooms.

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