

Health Beneficial Effects of Food Factors Can Be Applicable to Humans?

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Immunomodulating compounds in Basidiomycetes

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Mushrooms are distinguished as important food containing immunomodulating and anticancer agents. These compounds belong mostly to polysaccharides especially β -D-glucans. Among them, β -1,3-glucan with side chain β -1,6-glucose residues have more important roles in immunomodulating and antitumor activities. In this review, we have introduced polysaccharide mainly from *Lentinula edodes* and *Agaricus blazei* Murill with immunomodulating and antitumor activities. In addition, the mechanism of activation of immune response and signal cascade are also reviewed.

Key Words: Basidiomycetes, β -glucan, immunomodulating activity, antitumor activity, polysaccharide

Fungi are classified in the independent kingdom Fungi among other organisms. Fungi kingdom contains five main phyla including Ascomycota, Basidiomycota, Chytridiomycota, Glomeromycota and Zygomycota. Nowadays fungi are distinguished as important natural resources of immunomodulating and anticancer agents. With regard to the increase in diseases involving immune dysfunction, cancer, autoimmune conditions in recent years, application of such immunomodulator agents especially one with a natural original is vital. Generally, fungi are referred as “mushrooms” which are popular term for their fruiting bodies. Most mushrooms are commonly found in the shape of umbrella with pileus (Cap) and stipe (Stem) as shown in Fig. 1. Pileus is conical,

flat or even spherical. Sporophore usually present on the lower surface of pileus and composed of many thin layers stacked side by side. Some mushrooms also have pores.

In the 21st century, mushrooms have attracted attention as natural resources due to their low toxicity and high specificity to activate immune system in our body. The number of the mushrooms on Earth is estimated at 140,000. However, probably only around 10% of them are taxonomically known. Assuming that proportion of useful mushrooms among undiscovered and unexamined mushrooms is only 5%, this implies that 7,000 yet undiscovered species will be of possible benefit to mankind.⁽¹⁾ Mushrooms such as *Lentinula edodes*, *Ganoderma lucidum*, *Schizophyllum commune*, *Sclerotinia sclerotiorum*, *Fomes fomentarius* and many others have particularly been used as a traditional medicine to remedy different diseases for centuries in Japan, China and Korea.⁽²⁾ One of the first studies pertaining to the antitumor properties of Basidiomycetes mushrooms was carried out by Lucas and coworkers, who successfully applied an extract obtained from *Boletus edulis* fruiting bodies in the treatment of Sarcoma 180 in mice.⁽³⁾ Its effect was confirmed against many experimental tumors, including Sarcoma 180, mammary adenocarcinoma 755, leukemia L-1210 and Hela cell lines.⁽⁴⁾ Since then, the hot water extracts of these mushrooms have been widely used for treatment purpose in many Eastern countries. The most active constituents in these extracts are polysaccharides, which have been found to boost the human immune system, showing anti-cancer and anti-viral activities. Numerous studies have shown that the antitumor properties of biologically active compounds isolated from mushrooms are mostly attributed to polysaccharides.⁽⁴⁻⁷⁾ Their main source appears to be fungal cell walls. The most important polysaccharides from mushrooms were summarized in Table 1. It was made clear that most polysaccharides composed of β -D-glucan moiety as a main chain.

Evidences accumulated that the food factors influence the function of our immune system. Therefore, alternation of dietary components received a lot of attention as a tool which can improve our immune system. β -Glucans, which is one of the most attractive food factors possessing immunomodulating activities without adverse effect, are currently under investigation for this purpose. This review article concentrates on Basidiomycetes-derived polysaccharides that possessed immunomodulating activities.

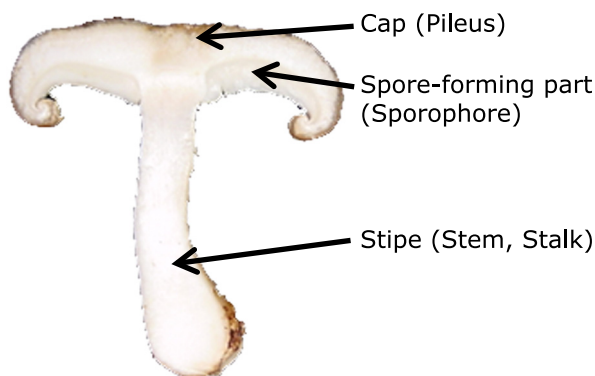
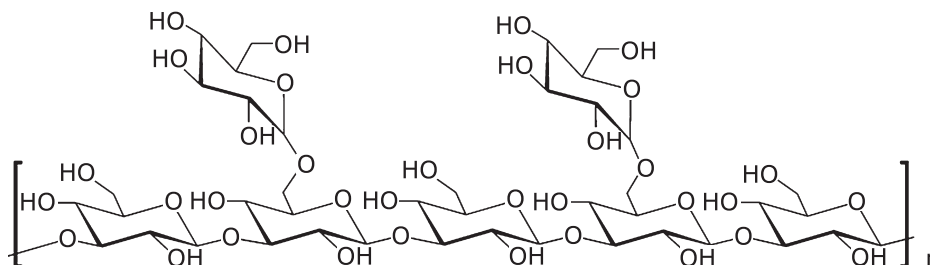


Fig. 1. Main mycological name of typical mushroom.

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Table 1. Polysaccharides isolated from mushrooms possessing some immunomodulating and antitumor activity

Mushroom	Polysaccharide structure	Reference
<i>Lentinula edodes</i>	(1→3)-β-D-glucan with (1→6)-β-D side chain	(8)
<i>Agaricus blazei</i>	(1→3)-β-D-glucan, heteropolysaccharides, polysaccharide-protein complex	(9)
<i>Grifola frondosa</i>	(1→6)-β-D-glucan with (1→3)-β-D side chain	(10)
<i>Ganoderma lucidum</i>	β-D-glucans, heteropolysaccharides, glycoproteins	(11)
<i>Flammulina velutipes</i>	Protein	(12)
<i>Hericium erinaceum</i>	Galactoxyloglucan-protein complex	(13)
<i>Schizophyllum commune</i>	(1→3)-β-D-glucan with (1→6)-β-D-glucosyl branches	(14)

**Fig. 2.** Structure units of lentinan.

Lentinula edodes

Lentinula edodes, the Shiitake mushroom, is one of the many very popular edible mushrooms in Japan. This mushroom is known as functional food. Lentinan, an antitumor polysaccharide, was isolated and purified from a hot water extract of *Lentinula edodes* fruit bodies.⁽¹⁴⁾ The structure of lentinan was reported as a (1→3)-β-D-glucan having two (1→6)-β-glucopyranoside branches for every five (1→3)-β-glucopyranoside linear linkages (Fig. 2).^(14–17) Lentinan is also known as a type of biological response modifier.⁽¹⁸⁾ Since lentinan did not show any direct cytotoxicity against tumor cells, its antitumor action is considered host-mediated.⁽¹⁹⁾ It is thought that lentinan augments the immune response through modulating phagocytes such as macrophages.^(20,21) It has been reported that lentinan possesses immunomodulating effect as it seems to activate variety of macrophage functions, e.g. some cytokines and superoxide anion production, phagocytosis, and cytotoxicity.^(22–25) Moreover, it has been reported that macrophages secreted tumor necrosis factor-α (TNF-α) through the stimulation by lentinan.⁽²⁶⁾ TNF-α is recognized as the primary cytokine produced mainly by activated macrophages; it is an important host defense molecule that affects tumor cells.⁽²⁷⁾ Hoffman *et al.*⁽²⁸⁾ observed that TNF-α was released from macrophages through a β-glucan mediated mechanism. Lentinan increases peritoneal macrophage cytotoxicity against metastatic tumors. It can initiate normal and alternative pathways of the complement system, splitting C3 into C3a and C3b, thereby enhancing macrophage activation.⁽²⁾ Recently, Xu *et al.*⁽²⁹⁾ investigated the effects of lentinan on the nitric oxide (NO) and TNF-α production in lipopolysaccharide (LPS)-stimulated murine RAW 264.7 macrophages. It was demonstrated that treatment with lentinan not only resulted in the striking inhibition of TNF-α and NO production in LPS-activated macrophage RAW 264.7 cells, but also the protein expression of inducible nitric oxide synthase (iNOS) and the gene expression of iNOS mRNA and TNF-α mRNA. Thus, there are many studies for the fascinating effects of lentinan on the responsiveness or function of the immune cells involved.

Recently, Mizuno *et al.*⁽³⁰⁾ have reported that lentinan exhibits

the immune suppressive effects such as intestinal anti-inflammatory properties using co-culture system composed of Caco-2 cells and RAW264.7 cells. When RAW264.7 cells were stimulated with LPS, interleukin (IL)-8 and TNF-α secretion increased. In this system, lentinan treatment on the apical side inhibited only IL-8 mRNA expression and its secretion without affecting TNF-α production from RAW264.7. Moreover, they demonstrated that lentinan exhibited different suppressive effects from fucoidan on IL-8 mRNA expression in Caco-2 through TNF-α production from RAW264.7 stimulated with LPS. As it has been reported that β-glucan is recognized through the dectin-1 receptor in intestinal epithelial cells,⁽³¹⁾ they speculated that the difference in receptors between lentinan and fucoidan which is a polymer of L-fucose linked by an α-1,2-linkage with a sulfate group mainly at the O-4 position⁽³²⁾ was due to the different suppressive effects on IL-8 mRNA expression in Caco-2.

The immunomodulating effects and/or indirect antitumor activity of lentinan are attributed to the activation of immune effector cells such as hematopoietic stem cells, lymphocytes, macrophages, T cells, dendritic cells, and natural killer cells involved in the innate and adaptive immunity. Lentinan can affect these cells via modulating cytokines secretion such as TNF-α which function as cell signal messenger. Humans and mice studies revealed that immune cells stimulated with lentinan increased cytokine production.^(33,34) It was also reported that lentinan can enhance the production of chemical messenger such as nitric oxide through TNF-α production.⁽³⁵⁾ Immunomodulating activity of lentinan may be linked to its hormonal modulating factors which can play a role in tumor growth. Aoki⁽³⁶⁾ showed that the antitumor activity of lentinan is strongly reduced by administration of thyroxine or hydrocortisone. Lentinan can also restore tumor specific antigen-directed delayed type hypersensitivity reaction. The mechanism of anti-tumor activity of lentinan is summarized in Fig. 3.⁽³⁷⁾

Agaricus blazei Murill

Agaricus blazei Murill is one of the most intensively studied medicinal mushrooms^(9,38,39) among others that used to treat many

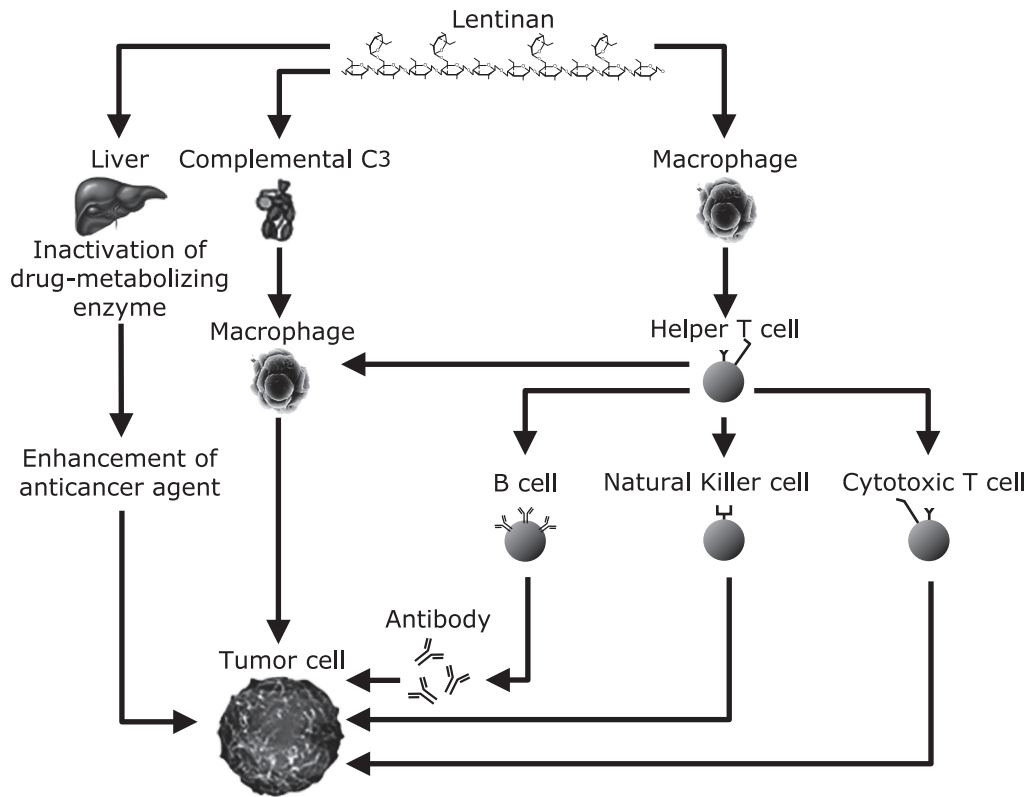


Fig. 3. Mechanism of antitumor activity of lentinan.

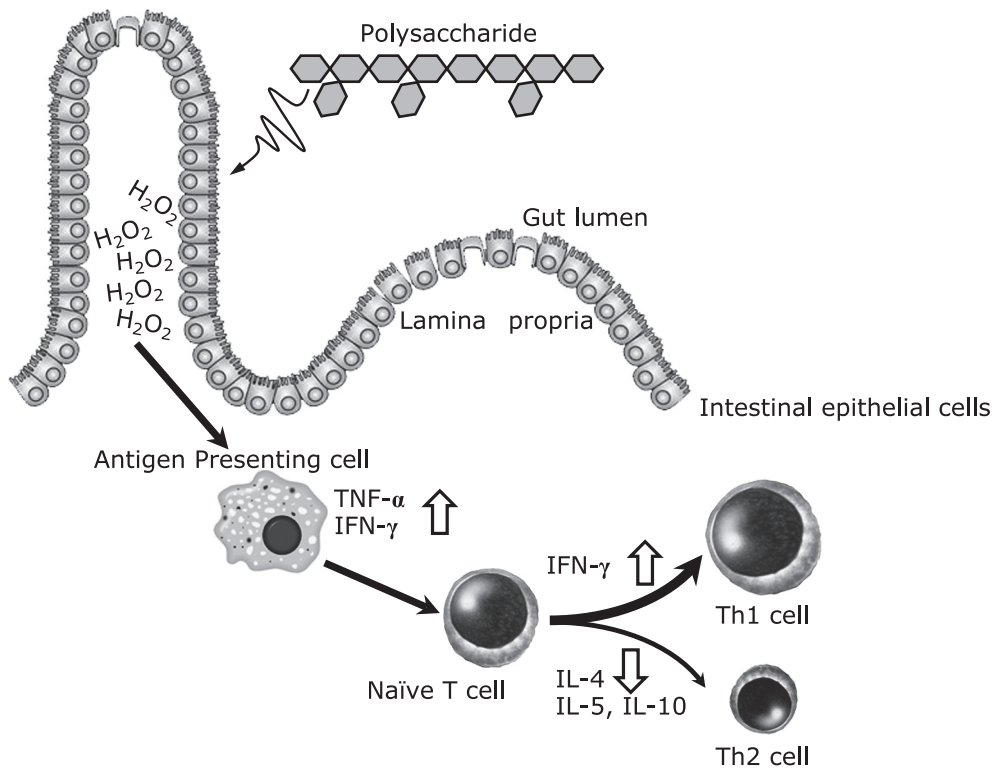


Fig. 4. Mechanism of Shift in Th1/Th2 balance to Th1 by *Agaricus blazei* Murill extract through intestinal epithelial cells. TNF- α , tumor necrosis factor- α ; IFN- γ , interferon- γ ; IL-4, -5 and -10, interleukin-4, -5, 10.

diseases.^(40–44) It was reported that the extract of *Agaricus blazei* Murill has potent antitumor activity in mice, postulated to be exerted through mediation of the host immune system by β -(1→6)- and β -(1→3)-glucan.^(9,45–48) These functions of *Agaricus blazei* Murill have been shown to indirectly affect the immune system.

Not only fruit bodies but cultured mycelia of *Agaricus blazei* Murill are also a source of antitumor polysaccharides. An antitumor organic substance “ATOM” was representative of *Agaricus blazei* Murill.⁽³⁹⁾ ATOM was highly effective on subcutaneously implanted Sarcoma 180 in mice, and was also activated against Ehrlich ascites carcinoma, Shionogi carcinoma 42 and Meth A fibrosarcoma. Mizuno *et al.*⁽⁴⁹⁾ has separated a new antitumor polysaccharide, β -(1→2)-; β -(1→3)-glucomannan, which acted against Sarcoma 180 from liquid cultured mycelium of *Agaricus blazei* Murill. It was reported that a similar polysaccharide was also obtained from submerged culture mycelium, in which the main component is glucose and mannose.

As mentioned above, antitumor polysaccharides researched in *Agaricus blazei* Murill fruit body, culture mycelia, or extracellularly produced in culture medium have a number of different chemical structures. Polysaccharides from fruit bodies possessed glucans with different types of glucose unit connections or heteroglucans. In contrast, culture mycelia contained glucomannan and mannan-protein complex was produced in a culture medium under submerged cultivation.

Recently, it was reported that oral administration of *Agaricus blazei* Murill possessed anti-allergic activity alleviating the severity of dermatitis and levels of serum immunoglobulin E (IgE) in NC/Nga mice, which developed atopic dermatitis-like skin lesions induced by repeated challenge with picryl chloride.⁽⁵⁰⁾ It was demonstrated that *Agaricus blazei* Murill increased interferon (IFN)- γ contents in serum. IFN- γ is a strong inhibitor of IgE synthesis and Th2 cell proliferation, as well as inducing differentiation from Th0 to Th1 cells. Moreover, *Agaricus blazei* Murill upregulated IFN- γ production and inhibited IL-4 secretion in spleen cells. These results suggested that *Agaricus blazei* Murill established Th1 dominance, which contributes to cellular immunity. Choi *et al.*⁽⁵¹⁾ demonstrated that the water extract of *Agaricus blazei* Murill fruiting body suppressed allergic edema after oral administration and reduced histamine release by direct incubation with mast cells. Bouike *et al.*⁽⁵²⁾ described that *Agaricus blazei* Murill suppressed IgE content in OVA-sensitized mice due to the activation of macrophages via intestinal epithelial cells (IEC) and subsequently promoted differentiation of naïve T cells into Th1 cells in the immune system. Also, they proposed the involvement of H₂O₂ as a second messenger in the cross talk between IEC and antigen presenting cells such as macrophages and dendritic cells (Fig. 4).

Other Mushrooms

A wide range of antitumor or immunomodulating polysaccharides of different chemical structure from Basidiomycetes mushrooms has been investigated with the exception of *Lentinula edodes* and *Agaricus blazei* Murill. The main varieties were listed in Table 2. *Grifola frondosa* is also one of the most popular medicinal mushrooms in Japan. This mushroom consisted mainly of β -(1→6)-; β -(1→3)-glucan⁽¹⁰⁾ and β -(1→3); β -(1→6)-glucan⁽⁵³⁾ as a water-soluble polysaccharide fractions which are antitumor polysaccharides. This fractions also included an acidic xyloglucan and three acidic glycoproteins with molecular weight of 20–100 kDa. Polysaccharides in *Grifola frondosa* composed of β -glucan with different side chain components. *Ganoderma Tsugae* is another medicinal mushroom of which polysaccharides have been investigated for antitumor activities. Water-soluble fractions contained 7 glycans with strong antitumor properties which were protein-glucogalactans complex with mannose and fucose residues.⁽⁵⁴⁾ As another edible mushroom, Mizuno *et al.*⁽⁵⁵⁾ reported

Table 2. Polysaccharides of higher Basidiomycetes possessing antitumor or immunomodulating activities

Species	Polysaccharides
<i>Agaricus blazei</i>	α -(1→4)-; β -(1→6)-glucan α -(1→6)-; α -(1→4)-glucan β -(1→6)-; β -(1→3)-glucan β -(1→6)-; α -(1→3)-glucan Mannogalactoglucan Riboglucan β -(1→2)-; β -(1→3)-glucomannan Glucomannan
<i>Agrocybe aegerita</i>	Linear α -(1→3)-glucan
<i>Amanita muscaria</i>	Linear α -(1→3)-glucan
<i>Armiariella tabescens</i>	α -(1→3)-glucan β -(1→6)-glucan
<i>Dictyophora indusiata</i>	α -(1→3)-mannan Fucomannogalactan
<i>Flammulina velutipes</i>	Galactomannoglucan
<i>Fomitella fraxinea</i>	α -(1→6)-mannofucogalactan
<i>Gahoderma tsugae</i>	Arabinoglucan
<i>Ganoderma lucidum</i>	β -(1→3)-glucuronoglucan Mannogalactoglucan Glucogalactan
<i>Ganoderma tsugae</i>	β -(1→6)-; β -(1→3)-glucan Xyloglucan Mannogalactofucan Mannoxylglucan
<i>Grifola frondosa</i>	Xylan Glucosylan Mannoglucosylan Galactoxylglucan Galactomannoglucan Xylogalactoglucan
<i>Hericium erinaceus</i>	β -(1→3)-; β -(1→6)-glucan Galactoglucomannan Galactomannoglucan
<i>Hohenbuehelia serotina</i>	Galactomannoglucan
<i>Inonotus obliquus</i>	Xylogalactoglucan
<i>Lentinula edodes</i>	β -(1→3)-; β -(1→6)-glucan Galactoglucomannan Galactomannoglucan
<i>Leucopaxillus giganteus</i>	Galactomannoglucan
<i>Lyophyllum decastes</i>	β -(1→6)-glucan
<i>Pleurotus citrinopileatus</i>	Arabinogalactan
<i>Pleurotus cornucopiae</i>	Mannogalactoglucan
<i>Pleurotus pulmonarius</i>	Xyloglucan Mannogalactoglucan Mannogalactan Glucosylan
<i>Polyporus confluens</i>	Xyloglucan
<i>Sarcodon aspratus</i>	Fucogalactan

that polysaccharide in *Sarcodon aspratus* showed the highest mitogenic activity among the eight mushrooms tested. Fucogalactan was identified as an active compound in *Sarcodon aspratus*. Moreover, this polysaccharide elicited the release of TNF- α from macrophage cell line RAW264.7 and its activity is higher than lentinan by approximately 4 fold. Thus, a number of different polysaccharides derived from Basidiomycetes exhibited antitumor and immunomodulating activities.

Conclusion

Mushrooms have been part of a diet for over 2,000 years. Traditional practices and scientific research have focused on mushrooms as a group of highly recommended dietary supplement and medicine due to their evidently nutritional values. Many mushrooms, if not all Basidiomycetes contain biologically and physiologically active polysaccharides. These polysaccharides are different in chemical structures but are consisted chiefly of β -glucans. It is evidently that structural features such as β -(1→3) linkages in the main chain of the glucan and additional β -(1→6) branch

portion are necessary for antitumor and immunomodulatory action. The antitumor activities of the polysaccharides from mushrooms have been proven to act by affecting different immune response in the host such as our body. A number of studies have proposed several antitumor mechanisms. However, it is widely expected that a more scientific approach is required to build up the theories. Scientific assessment of compounds contained in mushrooms will redound the prevention and treatment of lifestyle diseases including cancer.

Abbreviations

IEC	intestinal epithelial cells
IFN- γ	interferon- γ
IgE	immunoglobulin E
IL-8	interleukin-8
iNOS	inducible nitric oxide synthase
LPS	lipopolysaccharide
NO	nitric oxide
TNF- α	tumor necrosis factor- α

Conflict of Interest

No potential conflict of interests were disclosed.

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