Mushrooming Immunity & Mental Clarity



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Introduction

Mushrooms are fungi and those which possess medicinal properties have a unique and powerful role in natural medicine. Some species of mushrooms have been used as medicine for thousands of years. There is a natural synergy between fungi and herbs that can be exploited to make significant impacts on immune and cognitive function. This whitepaper will highlight maitake, chaga, reishi, cordyceps, lion's mane, as well as herbal synergists such as astragalus, gotu kola, holy basil and rosemary. Issues such as the extraction process for mushrooms and use of fruiting body versus mycelium will also be addressed.

What Exactly Are Fungi?

Fungi are not plants and they are not animals, but they have characteristics of both. Fungi are a unique kingdom which share metabolic traits with animals and structural traits with plants. Fungi, like animals, create carbon and energy from digestion of organic matter. This is different from plants, which create carbon via photosynthesis. Mushrooms do not photosynthesize. Mushrooms are plant-like in a structural sense, they look a bit like plants and have rigid cell walls, a characteristic of the plant kingdom. Fungi typically live within the ground. Mushrooms are actually the spore-bearing fruiting body from the fungi. Most of a mushroom's life is spend underground as the mycelium. Spores are released to facilitate propagation to new sites[1].

The Fungi Community

Mushrooms are connected to one another in long filaments, called hyphae. The hyphae spread through a substrate and form a net, or mycelium. Mycelia will continue to grow as long as there is substrate available. The largest mycelium is located in the northwest US and covers entire mountain ranges. Mycelia serve a very important role in the ecology of the world. Paul Stamets explains this quite well:

> "I believe that mycelium is the neurological network of nature. Interlacing mosaics of mycelium infuse habitats with information-sharing membranes. These membranes are aware, react to change, and collectively have the long-term health of the host environment in mind. The mycelium stays in constant molecular communication with its environment, devising diverse enzymatic and chemical responses to complex challenges.[2]"

Trees, for example, communicate by sending electrical impulses to one another via mycelia. If a tree is in danger, perhaps being eaten by an insect, it will generate an electrical impulse. That impulse is sent down through its trunk, picked up by mushroom mycelium, travelling through the mycelium and up through a trunk of a neighboring tree. That neighboring tree changes its chemical composition to deter that chewing insect. The result, thanks to the mushroom mycelia, is one tree protecting another.

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[1] Powell M. Medicinal Mushrooms: A Clinical Guide (Mycology Press, 2010)

[2] Paul Stamets – Mycelium Running: How Mushrooms Can Help Save the World

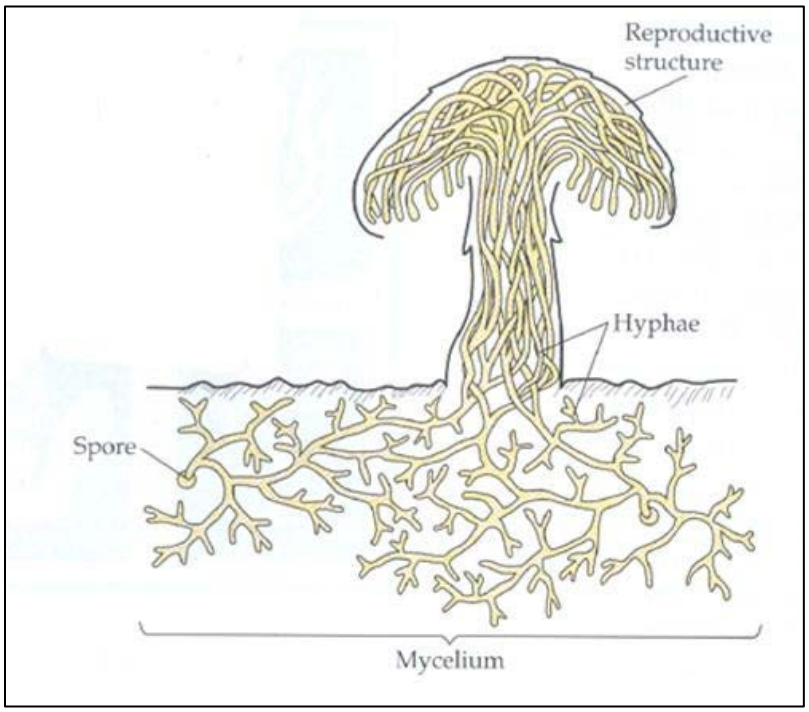

Figure 1: Parts of a mushroom

Mushroom Life Cycle

As mentioned previously, spores produce hyphae which grow together into a network called mycelium. As the hyphae gather themselves up into the stalk, they form the classic umbrella shaped mushroom, which is the fruiting body or reproductive structure of the fungi. The purpose of the fruiting body is to disperse spores. Spores live in the underside, or gills, of the mushroom. They are released into the air, find another area to germinate, go into the ground and form more hyphae. Eventually, along the hyphae, hyphal knots grow and ultimately grow into fruiting bodies once again.

The figure below illustrates the life cycle of a mushroom. Everything to the right of the line is in the primordium phase and would be considered mycelia, thus an extract from this part of the organism would be mycelial extracts. Everything to the left of the line would be considered fruiting body extracts. This becomes important to clinicians as related to extractions.

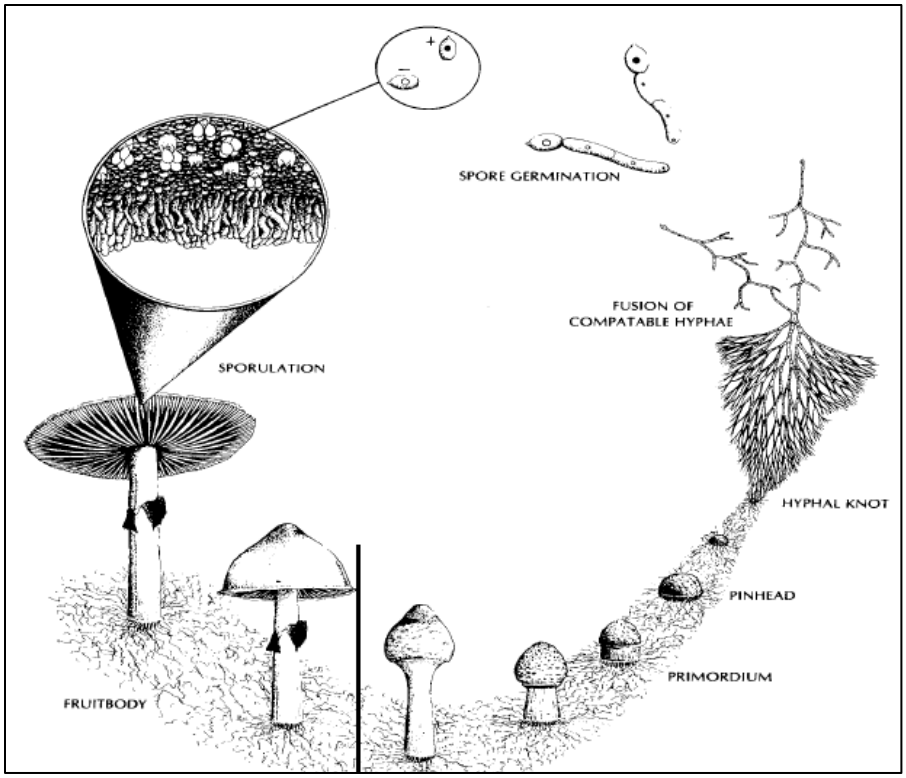

Figure 2: Mushroom life cycle

History of Medicinal Mushrooms

Mushrooms have been used for medicinal purposes across the globe for a very long time. Almost every healing tradition details the use of mushrooms. In Traditional Chinese Medicine, the use of mushrooms is extensively documented as early as 200AD. Medicinal mushrooms are documented by Dioscorides in 55AD, and have been a part of European herbalism since the mid-17th century. It's apparent there must be some unifying characteristics of mushrooms that allows them to have such broad applicability. One of these characteristics is called beta-glucans.

Biochemistry

All mushrooms contain polysaccharides as well as proteoglycans, which are a protein-bound polysaccharides. The typical polysaccharides in mushrooms are (1-3)-(1-6)-beta-glucans, which in fact are unique to yeast and fungi. They are composed solely of glucose and make up approximately 50% of the cell wall. Yeast derived 1-3 beta-glucans consist of a single twist, or helix, whereas mushroom-derived 1-3 beta-glucans are found as a triple helix and are said chemically to be three times more potent! So, although both are called by the same name, one could make the case that 1-3 beta-glucans in mushrooms are medicinally more powerful than those derived from yeast. There is some excellent data proving this factor.

A very comprehensive body of scientific research has demonstrated that beta-glucans are the main immunologically active compounds in mushrooms. Some mushrooms also contain significant quantities of other constituents, such as triterpenes and ergosterol.

Where Are Beta-Glucans Found

Beta-glucan polysaccharides found in mushrooms are fairly simple structures, yet they are very important medicinally.

Beta-glucans are found in all stages of the mushroom life cycle, but the greatest amount, 25-77%, are found in the fruiting body. Up to 21% are found in pure mycelium and approximately 6% are found in a mycelium on grain biomass[3]. The biomass is made up of the mycelium and the substrate that the mycelium is growing on. Because there is so much substrate and so little mycelium, there is very little beta-glucan present in a mycelium biomass product. Therefore, when looking for the medicinal benefits of beta-glucans, the fruiting body extracts are recommended.

Dosage Forms: Polysaccharide Extracts

The most simple, efficient and cleanest way to extract beta-glucans is to grind up the fruiting body and cook it in hot water for several hours. Next, evaporate the fluid and dry the residual. This will form the powdered fruiting body extract that can be encapsulated or tableted. This process can be done with more precision if mass produced. This process, called the hot water extraction, yields high polysaccharides but low triterpenes[4].

Another extraction process is ethanolic. The ethanolic process is not very good at extracting the polysaccharides, but very good at extracting triterpenes. Triterpenes are important constituents in certain mushroom species, for example reishi and chaga.

Finally, the combined extraction process, where there is an aqueous extract phase followed by an ethanolic phase, is used when the goal is to extract both the triterpenes and polysaccharides, for example with reishi.

Digestion

When beta-glucans, which are simple molecules, are extracted, they are non-digestible carbohydrates. In order to have them enter the blood stream, they must be fermented by intestinal microbial flora. Thus, the microbial ecology in a person's gut will influence, to some extent, the effect that mushrooms will have on a person. They can also bind, without being absorbed, to specific receptors of immune cells that will trigger a local immune reaction. That reaction can be internalized and propagated systemically. So, even without absorption you can have a systemic immune reaction.

[3] Powell M. Medicinal Mushrooms: A Clinical Guide (Mycology Press, 2010)

[4] Chilton J. Science and Cultivation of Edible Fungi. Int. Soc Mushroom Science, eds. Baars & Sonnenberg, 2016

Dosage Forms – Mycelium

Much of the clinical research on mushrooms is not technically on mushrooms, but rather on PSK and PSP pure mycelia that are produced using liquid fermentation technology. This process grows the mycelium in a nutritious liquid medium that is constantly aerated and stirred. When the mycelium is mature, it is separated from the fluid and concentrated using multiple extraction and purification steps. What is produced are highly active protein-bound polysaccharides.

PSK and PSP are purified, mushroom-derived 1-3 beta-glucans, but not whole mushrooms per se. PSK is protein linked and manufactured in Japan. PSP is peptide linked and manufactured in China. The majority of research on mushroom beta-glucans is actually on PSK or PSP. There is some question whether the PSK and PSP research is translatable to mushrooms. While some argue yes, there has been no known comparative studies on the relative efficacy of PSK versus a fruiting body extract. Also of importance, at this time PSK and PSP are not available in the United States.

Dosage Forms: Mushroom Mycelium Biomass

There is much controversy regarding mycelium on grain biomass. The biomass is created when mycelium is cultivated on a sterile, grain-based substrate, usually brown rice. Many commercial mushroom products in the United States are made with mycelium biomass[5]. Because the mycelium is so filamented, it gets imbedded in the grain and becomes nearly impossible to extract or remove from the grain. Thus, the entire biomass is milled to a powder, and because the beta-glucans are in such a low percentage (because the mycelium is such a small amount of that total substrate to begin with,) few beta-glucans are yielded. Therefore, products that are mycelium on grain biomass can run the risk of being adulterated with yeast beta-glucans. Oftentimes, yeast beta-glucans are added, which are much less expensive and not as effective as mushroom beta-glucans. In turn, there is some question about the clinical utility of mycelium based extracts. If a patient has used mushroom products previously, and has not had much success, check the product's ingredients. If it is a mycelial based product and/or has brown rice as an ingredient, this could explain why.

Fruiting Body Extracts

The fruiting body extracts of most mushrooms are full of beta-glucans, at approximately 25-77%. Additionally, there are other beneficial compounds found in different mushroom species. For example, maitake contains lectins which have been independently studied and found to have anti-tumor and anti-proliferative effects and also modulate immunity.

Chaga, which grows on birch trees, picks up some of the betulinic acid that grows on those trees and has fairly potent antiviral and anticancer properties against certain types of cancers. It is also anti-inflammatory.

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[5] Powell M. Medicinal Mushrooms: A Clinical Guide (Mycology Press, 2010

Reishi mushrooms contain triterpenes, which have very pronounced anti-inflammatory effects. As mentioned previously, triterpenes require alcohol to extract. Triterpenes and in-turn reishi mushrooms are very good at down-regulating TNFa and NFkB.

Cordyceps mushrooms have some unique adenosine compounds which are incorporated into ATP and have actually have been shown to increase stamina and endurance. They can also have an adaptogen effect.[6]

Lion's mane has some unique compounds, one of which is called hericenones, that stimulate nerve growth factor (NGF) which augment neuronal protection, development and cognitively[7].

From an immune perspective, mushrooms are interchangeable because of their beta-glucans. However, when looking at the whole organism it is important to look at some of the other compounds a mushroom has and pick the species specific to the specific indication of the patient.

The figure below details other beneficial effects of the fruiting bodies of mushrooms:

Mushroom	Beta-glucans	Other compounds
Maitake (Grifola)	✓	Lectins: agglutinate cells; anti-tumor, anti-proliferative, immunomodulatory
Chaga (Inonotus)	✓	Betulinic acid: antiviral, antineoplastic, anti-inflammatory Phenols: antioxidant
Reishi (Ganoderma)	✓	Triterpenes (down-regulates TNFa and NF-kB; hepatoprotective hypotensive)
Cordyceps (Cordyceps)	✓	Adenosine compounds: stamina, endurance, HPA adaptogen
Lion's Mane (Hericium)	✓	Meroterpenoids such as hericenones & Cyathane derivatives: stimulate Nerve Growth Factor (NGF) to enhance cognition Sterols (ergosterol): anti-angiogenic, anti-tumor

Mechanism of Action: Immunity

All Immune cells have receptors on their surfaces that are very specific for mushroom polysaccharides, and more specifically, for compounds found in the fruiting bodies of mushrooms. When the receptors are bound by those compounds the immune cell is stimulated. This makes sense when thinking about the fact that fungi causes disease. During

[6] Colson SN, et al. J Strength Cond Res. 2005;19(2):358.
[7] Sheng X, et al. Food Funct. 2017;8(3):1020, Furukawa S. et al. Tetrahedron Lett. 1994;35:1569
Mizuno T et al. Phytother Res. 2009;23:367

human evolution, people have evolved to have an immune activated defense against fungi. Thus, the human body is utilizing that defensive reaction against fungi in a medicinal manner when using mushroom products.

The innate immune system identifies infectious agents or compounds by means of pattern recognition receptors (PRR.) These receptors recognize pathogen-specific macromolecules called pathogen-associated molecular patterns (PAMPs.) Polysaccharides, particularly beta-glucans, are a PAMP, which stimulates the receptors on the immune cells and causes immune activation[8].

In the following diagram, the top figure displays the various receptors that are found on immune cells, in this case from a monocyte. These receptors are also expressed directly by natural killer cells representing the innate immune system. They are also directly expressed by neutrophils which also are directly phagocytosing immune cells. And when the monocyte is stimulated by the beta-glucan molecules, the monocyte becomes activated, now a macrophage. Further, beta-glucan stimulates dendritic cells and ultimately acquired T cell immunity. What's interesting is that the T cell side of the equation predominates, so the end result is a cell mediated immune response and an innate mediated immune response, in response to the beta-glucans[1].

[8] Guggenheim A, Wright K and Zwickey H. Integrative Medicine. 2014;13(1):32-44

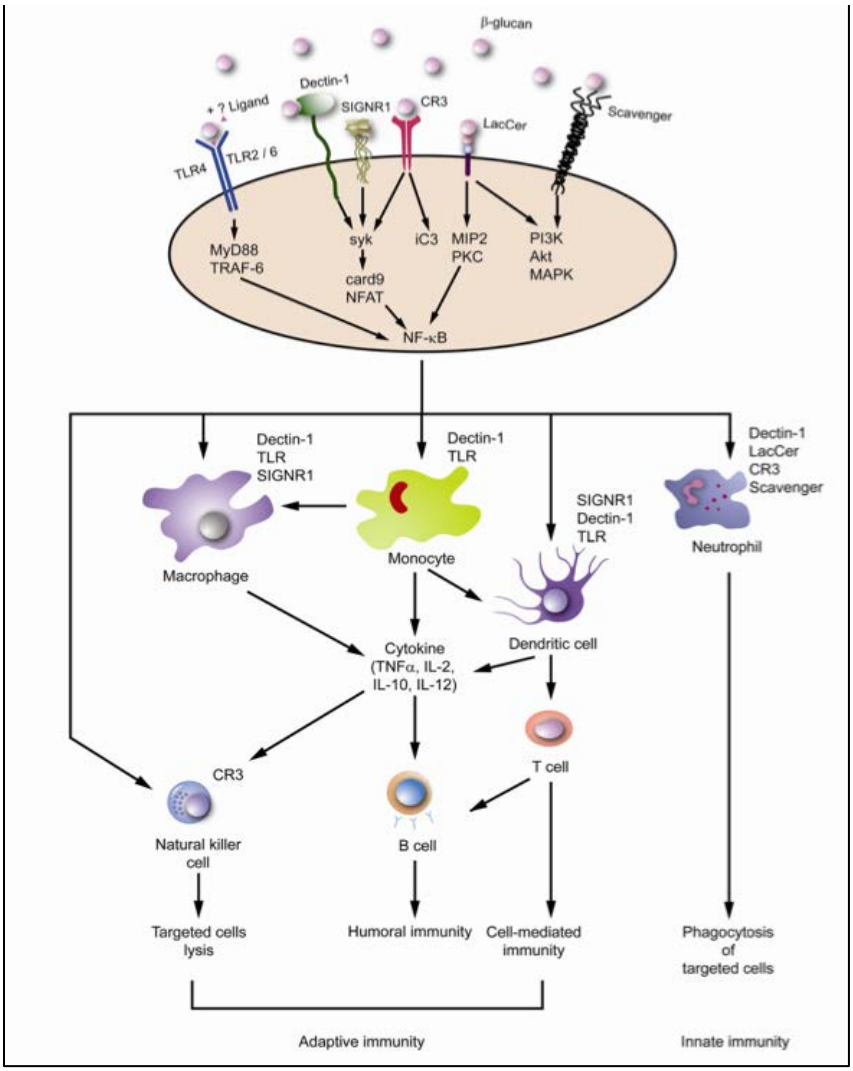


Figure 3: Immune Activation by Beta-Glucans

Mushrooms and Th1 Adaptive Immune Response

Mushrooms generally stimulate Th1 mediated immunity[9]. This means the mushroom is driving that direct cytotoxic immunity and not increasing antibody production. This is important because mushrooms should not aggravate auto-immune conditions. In fact, there is some proof that mushrooms may be indicated for people with auto-immune disease because oftentimes people with auto-immune disease have a relative deficiency of their cytotoxic immunity which mushrooms will selectively augment. This selective impact on cytotoxic immunity can be traced back to the fact that cellular receptor response, that PAMP originated response, ends up triggering certain cytokines, NF-kB in an antigen presenting cell, which then causes it to primarily produce more interleukin 12 and interferon gamma. Interleukin 12 and interferon gamma do not stimulate humoral immunity nearly as much as they stimulate

[9] Lull C. et al. Mediators of Inflammation. 2005(2):63-80.

cytotoxic immunity, which is why one ends up with cytotoxic immune predominated response under the influence of mushrooms.

Systemic Immunomodulation by Beta-Glucans

Although beta-glucans are not absorbed, some research suggests that a certain amount are leaked through to the blood stream after being digested. Even very low levels of beta-glucans will cause macrophages to engulf and circulate them, and transport them to the spleen, lymph nodes and bone marrow. The macrophages degrade the beta-glucans into very small fragments and then the fragments are released and taken up by other circulating immune cells which are, in a way, instructed to look for specific cells that are tagged with certain monoclonal antibodies and coated with inactivated complement 3b, such as malignant cells[10]. The following graphic illustrates this process:

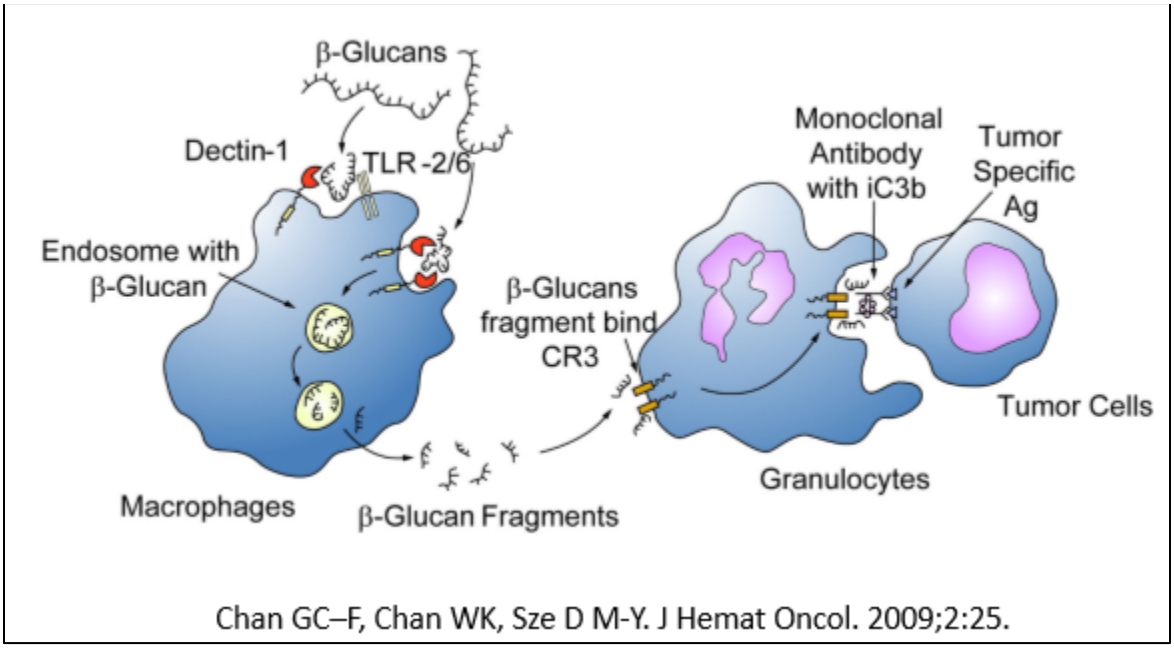


Figure 4: Proposed Immuno-Stimulation by Beta-Glucans. This explains one of the ways mushrooms are thought to be very effective against cancer, both and preventatively and even against established tumors.

Mushroom Contraindications

Side-effects of mushrooms are rare but can include rash, nausea and transient diarrhea, however these side-effects appear very, very infrequently.

People with mushroom allergies are typically reacting to airborne spores and therefore can take mushroom extracts without incident because the extracts are taken internally.

People with yeast overgrowth are often told not to take mushrooms, yet this seems to be unsupported by any evidence. Yeast overgrowth is a classic example of disordered immunity

[10] Chan GC–F, Chan WK, Sze D M-Y. J Hemat Oncol. 2009;2:25.

and taking mushrooms could reawaken the immune reactivity to some of these fungal pathogens and help people overcome their yeast overgrowth.

Further, mushrooms are safe in pregnancy, non-teratogenic and non-genotoxic.

Although this whitepaper is not focused on mushrooms as food, it's important to note there are some toxic compounds found in edible mushrooms. The best way to avoid these compounds is to cook the mushrooms prior to eating. Mushrooms are not foods that should be eaten raw.

Maitake Mushroom (*Grifola frondosa*)

Maitake mushroom is a great mushroom to consider. Most pre-clinical data research on maitake has been done by one group in Japan. They created an isolated polysaccharide from maitake (named D-fraction and MD-fraction) in combination with a powdered fruiting body extract. This particular extract has been shown to have a very strong cytotoxic effect on certain malignant cells. A dose-response in vitro study showed greater than 95% cell death within 24 hours with Maitake D-fraction greater than or equal to 480 micrograms/mL. Further, combinations of maitake D-fraction in a concentration as low as 30 – 60 micrograms/mL with 200 micrograms vitamin C, were as effective as maitake alone at 480 mirograms/mL, inducing greater than 90% cytotoxic cell death[11].

The bioactive beta-glucans from the maitake mushroom have a cytotoxic effect on prostate cancer cells, presumably through oxidative stress leading to apoptosis. Therefore, this unique mushroom polysaccharide may have great potential as an alternative therapeutic modality for prostate cancer.

It's debatable whether this is translatable to all maitake extract mushrooms. It could be said that this particular extract works and others are likely to work similarly.

Another study, PHAs II[12] consisted of eighteen patients with myelodysplastic syndrome (MDS) who received maitake extract derived from the fruiting body via hot water and alcohol extract. Myelodysplastic syndrome is a clonal disorder where the bone marrow fills with abnormal cells and result in low red and white blood cell counts and low platelets, as well as all of the dysfunction associated with these low counts. Eventually, MDS can become a life threatening disease. The MDS patients received a dose of 3g/kg of their body weight, a rather large dose, daily for 12 weeks. The study found that both the neutrophil and the monocytes were more active after taking the maitake treatment. This early study showed a definitively positive effect from the treatment. Additional reactive oxygen was produced and resulting in killing off some of the dysplastic cells.

A Phase I/II Japanese dose escalation study of thirty-four postmenopausal patients with stages I-III breast cancer who had been treated and were free of disease were included[13]. They were divided into five dosage arms of maitake fruiting body liquid extract at 0.1, 0.5, 1.5, 3.0 or 5.0

[11] Mol Urol 2000;4:7-13.
[12] Wesa KM et al. Cancer Immunol Innumother. 2015;64:237.
[13] Deng G, et al. J Cancer Res Clin Oncol. 2009;135(9):1215.

mg/kg twice daily for three weeks. The maitake was grown in a controlled environment and the fruiting bodies were extracted with hot water and alcohol. What they found was the intermediate dose, 5-7 mg/kg per day, had the best effect on increasing immune activity as measured by immune cytochromes: IL-2, IL-10 TNF-*α* and IFN-*γ* by subsets of T cells. Of note, there was both stimulatory (IL-2) and suppressive (IL-10) cytokine increase, but the stimulatory effect predominated. Also, the higher doses did not produce a greater effect. Additionally, it was discovered that maitake had blood-sugar and cholesterol lowering effects, too. Based on these studies, a recommended dose for the D-fraction maitake would be 35-150 mg/day or 4-6 g/day of the fruiting body extract.

Chaga (*Inonotus obliquus*)

Chaga mushrooms grow on birch trees. Chaga contains polysaccharides, 1-3 beta-glucans, it also absorbs betulinic acid from the birch tree bark. Betulinic acid is a specific pentacyclic triterpene and it has been shown to be a very potent anticancer agent inducing apoptosis, or cell suicide, in tumors of neuroectodermal origin. This includes melanoma, and neuroblastoma and medulloblastoma origin, which are found mostly in the pediatric population. There has also been some activity noted in in hepatoma cancers, ovarian cancer, glioblastoma and leukemia. Of note, the most common cancers seen in people are epithelial cancers, such as breast, lung, colon, prostate and renal cancers. Unfortunately these are not affected by betulinic acids.[14]

From its 1-3 beta-glucans, chaga mushrooms increase macrophage activity within the cells that are cytotoxically killed and directly killed by the acid. Much lipid peroxidation is seen, as is increased oxidated stress.[15]

Chaga – Preclinical Data

Unfortunately, there are not a lot of preclinical studies on chaga. A preclinical mouse study where betulinic acid was administered orally five times at the dose of 0.5 mg/kg showed an increase in many immune cells measured, including the total number of thymocytes, splenocytes, and lymphocytes of mesenteric lymph node cells. Further, this dose increased the percentage of mature thymic cells and decreased the percentage of immature thymic cells[16]. The recommended dose of chaga is 2-5 g/day of a powdered, aqueous extract. Chaga is highly recommended for patients with neuroectodermal tumors, specifically melanoma. There is no downside to using Chaga.

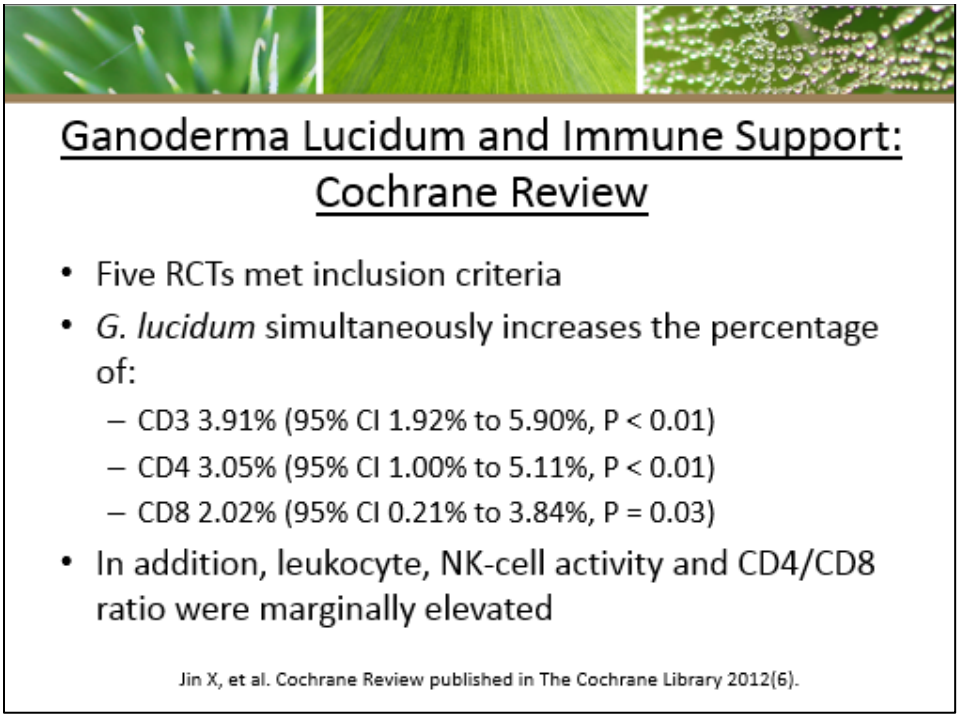
[14] Nat Med. 1995;1:1046., Ca Res. 1997;57:4596, Kim YR, Mycobiology, 2005;33(3):158,
[15] Yi J, et al. Pharmacol Rep. 2016;68(1):95
[16] Jine Y. et al. Pol J Vet Sci. 2012; 15(2):305.

Reishi (*Ganoderma lucidum*)

Reishi is a very popular mushroom for good reason. Animal studies have shown reishi to have very specific anti-tumor activity in a variety of cancer types[17]. It has been shown to inhibit the growth of cancer cells in sarcoma, colon, bladder, breast and prostate cancer[18].

An open label clinical trial of forty-seven patients with metastatic colorectal cancer were administered 5.4 grams/day of oral reishi for twelve weeks. There was a trend over those three months which showed increased counts, but also increased activity of both NK cell as well as some evidence of cytotoxic immunity. Thus, there was an indication of immune changes even in a short three month period in patients who are very immuno-compromised[19].

There is also a Cochrane review of reishi. Cochrane reviews are known to be very stringent in terms of the studies they complete and very conservative in their conclusions. In this review, five randomized control trials met inclusion criteria. The conclusions were that reishi did in fact increase the statistical significance of the activity of a variety of immune cell types, most were antigen presenting cells and T cells. The review also noted that people who received reishi concurrent with chemotherapy and radiation were 1.28% more likely to respond to the chemotherapy and radiation[20]. Further details are displayed below:



Other clinical trials have indicated that reishi has some effect against allergies, some anti-inflammatory actions, and some hepatoprotective actions, specifically inhibiting stellate cells. Stellate cells, when active, lay down fiber and start the process of fibrosis in the liver. These

[17] Lu et al. Cancer Lett, 2004. Nonaka et al. Biosci Biotechnol Biochem, 2006
[18] Lu et al. Oncol Rep, 2003, Nonaka, Ishibashi et al. Gan To Kagaku Ryoho, 2005
[19] Chen et al. Mol Pharmacol, 2006
[20] Jin X, et al. Cochrane Review published in The Cochrane Library 2012(6).

benefits are found in the triterpenes, thus reishi's best extracts should include an aqueous extract phase followed by an ethanolic phase (EtOH extraction.) Reishi triterpenes also have anticoagulant, hypotensive and possibly some sedative properties. Recommended dosage range is between 3-6 grams/day EtOH extraction.

Cordyceps (*Ophiocordyceps sinensis*)

Cordyceps is the most unusual mushroom as it is grown on an insect host. The photo to the left illustrates a caterpillar with a cordyceps mushroom growing out of it. When cordyceps is harvested naturally, the insect and the mushroom are recovered. In nature, cordyceps only grows at very high elevations, like the Himalayan Mountains, thus it is not very accessible and very expensive. Therefore, there has been much effort to cultivate cordyceps. The vast majority of cordyceps on the market is not grown on an insect host, but rather produced using liquid culture fermentation technology of cordyceps mycelium. The analytical testing and clinical testing between the cultivar and wild cordyceps showed similar results, thus cultivated cordyceps is considered to be a very good substitute. However, getting the exact speciation on cordyceps is quite difficult and there is some confusion surrounding it. DNA analysis will probably have a role, as mushroom understanding is evolved, to help clarify exactly what is being prescribed.

A placebo controlled trial of healthy male adults gave each a dose of 1.5 g/day of an ethanol extracted cordyceps capsule daily for four weeks. As expected, the cordyceps increased natural killer cells, lymphocytes, and increased cytochromes associated with immune activity. Overall, cordyceps increased cell-mediated, or TH1 dominated, immunity[21].

A retrospective study included sixty-seven kidney transplant recipients who were all on anti-rejection drugs (tacrolimus plus prednisone or mycophenolate mofetil plus cyclosporine A,) which means they were immunocompromised, purposefully. Twenty five of the sixty-seven also receive a dry powder preparation of cordyceps sinensis mycelium as part of their plan, post-transplant. Although there was no difference in survival rate, reject reactions or renal function, the cordyceps group had lower liver function tests, lower infection rates and higher T-lymphocyte counts ($P<0.01$.) This has led to the use of cordyceps in countries such as China and Japan for transplant recipients to augment their post-transplant experience[22].

Because of the adenosine compounds in cordyceps, clinical studies show it is an excellent mushroom for increased endurance, aerobic capacity and resistance to fatigue[23]. Animal studies have shown it improves asthma, improves spermatogenesis and success of IVF and

[21] Kang HJ, et al. J Med Food. 2015:18(10):1164.
[22] Abstract only, article in Chinese: Ding CG, et al. Zhongguo Xhong Xi Yi Jie He Za Zhi. 2009;29(11):975
[23] Colson SN, et al. J Strength Cond Res. 2005;19(2):358.

reduces insulin resistance[24]. It is recommended for patients who are fatigued for its adaptogen effect, in addition to its immune effect.

Lion's Mane (*Hericium*)

Lion's mane is another unique mushroom. It contains beta-glucans, thus giving it the ability to stimulate cell-mediated and humoral immunity, but it also contains hericenones and erinacines from its fruiting body and mycelium, which stimulate nerve growth factor (NGF.) NGF is very important in the human brain, it stimulates cholinergic nerve activity, protects our nerves against hypoxic stress, and improves neuron to neuron connectivity. As a result, when people have more NGF in their brain they have clearer thinking, their memory is improved, as is their mood[25]. This has been shown clinically in various studies.

A double blind, randomized, placebo controlled study (RDBCT) of thirty Japanese adults aged 50-80 who were all diagnosed with mild cognitive impairment, or early dementia partook in a four month study. They were randomized to receive four tablets, each containing 250 mg of the dried powder of the fruiting body, 1 gram per day, or placebo for sixteen weeks. Cognitive function scales were done at eight, twelve and sixteen weeks. At every time point, the cognitive scores in the lion's mane group were better than those of the placebo group. Four weeks after the intervention ended, when no lion's mane was administered, their cognitive scores started to decline back to baseline[26]. This indicates that the production of NGF was no longer being stimulated. Obviously, this is an important study, because of the last finding, it very clearly links the NGF stimulation effect to the mushroom and to the mechanism of the mushroom. Further, no adverse effects were noted.

In a similar RDBCT study of thirty menopausal women, taking 2 grams/day of powdered fruiting body extract for four weeks reduced depression and anxiety. This is presumed to be the result of an increase in nerve growth factor. Based on this study, a recommended dose of 3-5 grams of powdered fruiting body, approximately 1 tablespoon is suggested[27].

From an in-vivo, pre-clinical standpoint some additional actions have been documented with lion's mane:

- Cardioprotective: reduces oxidation of LDL, inhibits platelet aggregation
- Antidiabetic: reduces serum glucose and may reduce neuropathic pain
- Anti-fatigue: activates metabolism, specifically supporting glycogen storage in muscle and liver tissue
- Hepatoprotective: antioxidant, specifically in liver

[24] Holliday J, t al. Int J Med Mushr. 2008;10(3):219.
[25] Sheng X, et al. Food Funct. 2017;8(3):1020, Furukawa S. et al. Tetrahedron Lett. 1994;35:1569, Mizuno T et al. Phytother Res. 2009;23:367
[26] Mori K, et al. Phytother Res 2009;23:367
[27] Nagano M, et al. Biomed Res. 2010,31(4):231

- Anti-cancer: in-vitro activity against many cancer cell lines, exerts antiproliferative effect, synergistic with doxorubicin chemotherapy
- Immunomodulatory: activates dendritic cells and augments Th1 immunity[28]

Mushroom Nuances

There are other mushrooms that were not covered in this paper. For example, agaricus, the white button mushroom, is chock full of beta-glucans. The turkey tail mushroom, also known as coriolus, has outstanding anti-cancer actions, as well. These mushrooms should not be excluded.

To recap, maitake mushrooms are filled with beta-glucans, they increase cytoxic immunity and are recommended as a "go-to" mushroom for patients undergoing radiation therapy, which can decrease white cell count. The maitake fruiting body is also very good at preserving white blood cell count.

Chaga mushrooms have polysaccharides, the highly active triterpene, inotodiol and betulinic acid. Chaga is very specific for neuroendocrine types of cancer, like melanoma.

Reishi mushrooms are high in polysaccharides and triterpenes and is an excellent choice for good, solid immune restoration.

The polysaccharides and adenosine compounds in cordyceps are great for improving energy and acting as an adaptogen.

Finally, lion's mane with its polysaccharides, hericenones and erinacines is an excellent choice for immune and cognitive support.

Mushrooms and Plants

As mentioned, mushrooms and plants have a synergy in nature. Mushroom mycelia is the "net" that connects the forest and holds our ecosystem together. Mushrooms rely on decomposed plant organic matter for food and rely on plants to preserve shade and moisture. Combining mushrooms with botanicals medicinally, creates strong synergism.

Astragalus (*Astragalus propinquus*)

Astragulus is a deep, immune restoration herb. Patients who have cancer and/or chronic viral infections can benefit not only from mushrooms, but also astragalus. It is well studied, with fourteen human, clinical trials and studies to date. Much like mushrooms, astragalus improves innate immunity as well as cytotoxic T-cell immunity. Patients suffering from COPD, Graves'

[28] BioMed Res Intern, 2014;828149, Phytomedicine. 2010;17(14):1082, BMC Complement Altern Med. 2013;13:253, Exp Ther Med. 2015;9(2):483, J Agri Food Chem. 2015;63(32):7108, Process Biochem. 2013;48(9):1402

disease, sepsis, myasthenia gravis, cancer, SLE or Herpes Simplex Keratitis, can strongly benefit from astragulus [29].

A clinical study on astragalus and improving post-stroke fatigue, as well as social and cognitive functioning, offered positive results. The recommended dosage is 2.8 grams three times daily for 28 days.[30]

Schisandra (*Schisandra Chinensis*)

Schisandra can be considered a liver antioxidant combined with an adaptogen. It is good for improving endurance and energy, and protecting the liver from the effects of long term inflammation[31]. When working with patients with chronic viral infections, a combination of mushrooms and schisandra would be effective to really reach that long term inflammatory insult, specifically to the liver.[32] Anyone with hepatitis should also use schisandra. Coupling schisandra with a mushroom regimen could be very effective.[33] Schisandra has also been indicated for menopausal hot flashes and heart palpitations.

Turmeric (*Curcuma longa*)

Turmeric is another well studied botanical with over 85 human clinical trials to date. Curcuma, commonly known as turmeric, is very popular and for good reason. It is proven to have very pronounced and reliable anti-inflammatory effects. If looking for a way to modify the immune system so that more targeted immunity (cytotoxic immunity) is gained, and, at the same time reducing chronic, tissue-wide inflammation which could impede an immune response, curcuma combined with mushrooms is a very viable recommendation. The combination of an anti-inflammatory with a specific immunostimulatory action is desirable. Other indications of curcuma include cholesterol and lipid-lowering, a reduction in oxidative stress and lipid modification with metabolic syndrome.

Centella (*Centella asiatica*)

A very common consequence of cancer and its therapies is “chemo brain” which looks much like early dementia. The best way to combat this is by increasing nerve growth factor. Previously discussed, was lion’s mane which has been proven to increase NGF. Centella has been proven to increase memory and mood and is highly recommended to be used in conjunction with lion’s mane to increase NGF. In a RDBCT study of twenty-eight elderly patients taking a daily dose of either 250mg, 500mg or 750mg, the 750mg dose enhanced memory and increased self-rated mood[34].

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[29] Jiang D, Biomed Mater Eng. 2015;26suppl1:S2113. Brush J. Phytother Res. 2006;20(8):687.
[30] Liu CH, et al. J Ethnopharmacol. 2016;194:954
[31] Park JY and Kim KH. Climacteric. 2016;19(6):574
[32] Ciumasu-Rimbu M, et al. Rev Med Chir Soc Med Nat Iasi. 2012;116(3):790
[33] Chiu HF, et al. Phytother Res. 2013;27(3):368, Aslanyan G, et al. Phytomed 2010;17(7):494
[34] J Ethnopharmacol. 2008;116(2):325

Centella also has some anti-anxiety effects. Anxiety is very, very common in patients with cognitive decline. The more anxiety a patient has, the worse their cognition gets, so it is important to intervene. The recommended dose of centella is 1000mg twice daily[35].

Holy Basil (*Ocimum tenuiflorum*)

Prescribing holy basil is a great way to reduce anxiety and reduce feelings of stress and depression overall. In clinical studies people who take holy basil develop a sense of renewed confidence and courage to go forward and make changes in their life.
A study of thirty-five adults, with an average age of 38.4 years, took 500 mg of holy basil twice daily, after meals. Holy basil resulted in significant decrease in general anxiety and reduced feelings of stress and depression ($p<0.001$). Holy basil also increased motivation to make lifestyle and perception changes.[36]

A DBRC cross-over trial consisting of twenty-four healthy adults, showed an improvement in immune function over a four week period. Volunteers were given 300mg of ethanolic extract of holy basil or placebo. The IFN-gamma increased as did the IL-4, T-helper and NK cells.[37] Again, combining this botanical with lion's mane results in positive outcomes.

Rosemary (*Rosmarinus officinalis*)

Rosemary has also been shown to have a definite effect in increasing cognitive efficiency.
A RPCDB cross-over study of twenty-eight older adults, with a mean age of seventy-five, found that the lowest dose, 750mg, had a beneficial effect over placebo ($p=0.01$.) The effects of dried rosemary leaf powder on cognitive performance were assessed at 1, 2.5, 4, and 6 hours following placebo and 4 different doses of rosemary. There was also a 7 day washout period.

Surprisingly, the more dried rosemary the volunteers received, the worse they did. A dose of 6000mg actually had a significant impairing effect ($p<0.01$.)

The recommended dose, 750mg is just shy of 1/2 teaspoon. This is something patients can easily achieve in their daily diet. However, patients who do not like rosemary, or who have had too much of it in their daily diet, can just as effectively take it in supplement form.

[35] Nepal Med Coll J, 2010:12(1):8
[36] Bhattacharyya D. Nepal Med Coll J. 2008;10(3):176-9
[37] Mondal S. J Ethnopharmacol. 2011;136(3):452-6

Purchasing and Recommending Mushroom Products

It is very important, especially with mushrooms, that patients purchase quality products. Patients should purchase mushroom supplements through you - the practitioner - or at your recommendation so they are buying products that will be effective. Mushroom supplements should be extracted without the use of harsh solvents, and preferably a fruiting body extract to yield the most polysaccharides. A mycelium extract that does not say PSK or PSP or some other special name, is probably a biomass extract and will not have much of that very important 1-3 beta-glucan remaining in the product. A biomass extract will have rice grain or rice listed. If the product is still supporting a good amount of beta-glucan, it's important to determine where it is coming from, ask the manufacturer how it is being made. Is yeast beta-glucan being added? It is important to ask many questions.

About the Author

Dr. Lise Alschuler is a naturopathic doctor with board certification in naturopathic oncology and has been a practicing since 1994. She graduated from Brown University with an undergraduate degree in Medical Anthropology and received a doctoral degree in naturopathic medicine from Bastyr University. Dr. Alschuler is past-President of the American Association of Naturopathic Physicians and a founding and current President of the Oncology Association of Naturopathic Physicians. She also currently serves as President Emeritus on the board of the Naturopathic Post-Graduate Association. Dr. Alschuler works as an independent consultant in the area of practitioner and consumer health education. She maintains a naturopathic oncology part-time practice out of Naturopathic Specialists, based in Scottsdale AZ. Previously, she was the department head of naturopathic medicine at Midwestern Regional Medical Center – Cancer Treatment Centers of America. She was also the clinic medical director and botanical medicine chair at Bastyr, as well she was on the faculty of Southwest College of Naturopathic Medicine. In September 2000, Dr. Alschuler was named by Seattle Magazine as one of Seattle's Top Doctors. Dr. Alschuler received Bastyr University's Distinguished Alumni Award in 2005, and was given the President's Award from the Oncology Association of Naturopathic Physicians in 2007. In 2009, she was recognized as one of three Naturopathic Elders by Canadian College of Naturopathic Medicine. In May 2014, she was selected to receive an honorary degree in naturopathic medicine from the Canadian College of Naturopathic Medicine. She was also named Physician of the Year in August 2014 by the American Association of Naturopathic Physicians.

She is a frequent presenter to healthcare professionals and to the lay public in the United States and internationally. She co-created http://www.FiveToThrivePlan.comand co-hosts a radio show, Five To Thrive Live! on the Cancer Support Network and rebroadcast on I Heart

Radio Talk. Five To Thrive Live! features invited guests and provides the general public with information about living more healthfully in the face of cancer.

She believes that her job as a naturopathic physician and educator is to stimulate and support healing and wellness by utilizing the most natural and scientifically sound strategies possible. She believes that each person has the innate capacity to experience greater health and an exuberant life. She calls Tucson, AZ and Chicago, IL home. Learn more at http://www.drlise.net.