Mushroom Medicinal Value

Fungi produce a myriad of biologically active compounds, some of which are beneficial for human health. Consider that penicillin (from the fungus *Penicillium*) is among the most significant discoveries ever made by mankind. Some mushroom-producing fungi also produce antibiotics. For example, the commercialized antibiotic lefamulin, first discovered from the mushroom *Clitopilus*, is used to treat community-acquired bacterial pneumonia. Perhaps fungi synthesize these organic compounds to compete and survive in hostile environments teeming with other microbial life. In this lecture we will categorize some of the purported health effects of these compounds and look at the evidence for specific medicinal claims from individual mushrooms.

Mushrooms used for medicinal purposes have a long history. Recall Ötzi, the "Ice Man", who died about 5300 years ago in the Italian Alps, carried pieces of the birch polypore on leather thongs. He likely used them as an anesthetic and internal worm killer. Ancient Greeks (Hippocrates) and Romans (Pliny the Elder) praised mushrooms for anti-inflammatory and other health benefits. Medicinal benefits of mushrooms with vague reference to *Ganoderma* were described in China in *The Classic of Herbal Medicine* (*Shennong Bencaojing*) about 2,000 years ago.

In general, medicinally active compounds are extracted from mushrooms in hot water, alcohol, and/or organic compounds (e.g., ethyl acetate and chloroform). One of the most exploited compounds is beta-glucans, the soluble fiber sugar found in the cell wall of all mushrooms. Used to stimulate the immune systems, among other things, beta-glucan apparently differs slightly from one fungal species to another due to various proteins embedded in it and unique branching patterns. These features might give beta-glucan greater or lesser biological activity in the human body. The list of ailments supposedly affected by beta-glucans is extraordinarily long. How best to take advantage of these compounds? There is controversy about the relative concentration of beneficial compounds in growing mycelia versus compounds in fruiting bodies. Research to date hasn't provided a solid conclusion. One study demonstrated that certain genes are turned on only in the fruiting body. In another study the beneficial compounds were greater in mycelium than the fruiting body. Still other studies found no differences between mycelium and fruiting bodies. Does the age of the fruiting body influence the medicinal activity of the extracts? What about the type of substrate?

Unfortunately, there are very few long-term, replicated, non-biased, repeated clinical trials on the medicinal benefits of mushrooms. For example, in laboratory studies, beta-glucans from Reishi activates white blood cells of the immune system and destroys cultures of tumor cells of certain cancers, but these observations have not been demonstrated in the human body. Much more research is needed.

In the U.S., most fungal and herbal medicines fall into the category of Dietary Supplements, which are barely regulated by the FDA. This means the manufacturers of these supplements don't have to prove efficacy or even if they are safe. They can say anything when

they advertise as long as they include a disclaimer, often in tiny print, like, “These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” In fact, regulations are so relaxed that supplements may not have the ingredients listed on their labels! In a recent study, 14 of 19 Reishi supplements had no beta-glucans at all. Furthermore, even the manufactures of the supplement may not know the true identity of the fungus used for extracting medicinal compounds. For example, we use *Ganoderma lucidum* as the umbrella name for Reishi (or Lingzhi) but it is actually a complex of species. In 2012, the former *G. lucidum* in China was renamed *Ganoderma ling zhi*. This might matter because one species may have more of the biologically active compounds than another. And then there is the possibility of negative effects of supplements. Reishi extracts may not be recommended if you are pregnant, using an immunosuppressant, or taking a blood thinner, for example.

How do you know you are getting what you paid for? I attended a conference in China on medicinal mushrooms. While I was there, I visited a pharmacy off the beaten path (so it wasn’t a tourist trap of any sort), where one could expect to see a large variety of medicinal mushrooms. A small box of *Cordyceps* caught my eye. I paid a lot of money for this small box. It had a small clear plastic window where you could see the mummified caterpillars. Growing from one end of each caterpillar was the bottom of the stalk of *Cordyceps* so I confidently assumed the fungus was present. I carried my box of parasitized insects with great care on my return to the U.S. Finally back in Davis, I went to my lab at the University and opened the box to examine the *Cordyceps* under the microscope. The caterpillars were real but what should have been *Cordyceps* was a fungus-looking thing molded out of clay!

In no particular order, here are categories and some comments on medicinal mushrooms and their effects on laboratory animals and humans. The following is not an exhaustive treatise on medicinal mushrooms.

Weight Management/ Fiber

Mushrooms are low in calories. It makes sense, then, to include them in your diet if you want to lose weight. Mushrooms also have a low glycemic index. And we have seen that mushrooms are a good source of dietary fiber. These characteristics of mushrooms are beneficial for everyone but especially for diabetics.

There are also reports of more direct and active effects of mushrooms on weight loss. In a laboratory study, rats fed a diet high in fat lost fat tissue when they ate high doses of Shiitake mushroom powder. Maitake and Reishi extracts have also been used for treating obesity in lab animals but there are no human trials to back up the claim of weight loss. It should be noted that eating raw Shiitake can lead to skin dermatitis in a small percentage of the population. The beta-glucan lentinan found in Shiitake is blamed.

Anti-tumor/cancer Properties

The mushrooms of interest in this category are Reishi, Shiitake, Maitake, Oyster, Button and Turkey Tail. In 2008, Jedinaki and Silva (Int. J. Oncology) demonstrated that extracts of *Pleurotus ostreatus* suppressed growth of breast and colon cancer cells. In another study, lentinan, a beta-glucans from Shiitake, extended the life of liver cancer patients by about 3 months after the patients ingested the test material for 47 weeks compared to those who took lentinan for just 7 to 12 weeks (2009. J. Hepto-Gastroenterology 56:437-441). Lentinan apparently acts indirectly against cancer cells by activating killer cells of the immune system, among other ways. In a 2010 study, Maitake, Button, and Oyster mushrooms suppressed the growth of cancer cells, especially breast cancer. Shiitake mushroom ingestion was positively related to survival rates of stomach cancer patients in Japan by boosting the immune system. Since the 1980s, Shiitake extracts have been used in Japan to decrease the incidence of adverse effects of chemotherapy for cancer treatment.

In a study published in 2017, triterpenes from Reishi had anticancer effects on human prostate cancer cells (Oncol. Lett. 14:7467-7472). In contrast, lentinan had no effect on prostate cancer in a clinical trial. Other mushrooms with purported anti-cancer properties include Enoki, Maitake, and Turkey Tail (*Trametes versicolor*). The latter, which like Reishi is used solely as a medicinal mushroom, is used in China and Japan as part of cancer suppression therapy.

Anti-virus Properties

It is claimed that Reishi and Shiitake extracts target virus-infected cells while stimulating antibody production. Shiitake, in particular, may produce interferon-inducing compounds that stop viruses from multiplying. Maitake is also said to have antiviral effects.

There is interest in Shiitake extracts for management of the new coronavirus (Pierro et al., 2020. Possible therapeutic role of a highly standardized mixture of active compounds derived from cultured *Lentinula edodes* mycelia (AHCC) in patients infected with 2019 novel coronavirus. Minerva Gastroenterol Dietol. doi: 10.23736/S1121-421X.20.02697-5). For your interest only; not required reading.

Immune Enhancer

Your immune system is always working to clear your body of foreign infectious agents like viruses, bacteria, and various parasites. In age or when your health is compromised, the immune system begins to weaken. Apparently, mushrooms can boost the activity of components of the immune system, increasing the effectiveness of your body's defenses.

It has been reported that Reishi increases the production of your body's killer cells, which detect and destroy cancer cells and cells infected with viruses. In one study, patients with

advanced cancer experienced an increase in effectiveness of the immune system after receiving beta-glucan from Reishi.

Lentinan from Shiitake apparently also boosts the immune system. In a 2014 study (J. Am. Coll. Nutr. 2015;34(6):478-87), dozens of young adults were given dried Shiitake mushrooms. After 4 weeks of consuming the mushrooms, there was an increase in the number and effectiveness of T immune cells, killer cells, tumor necrosis factors, and a decrease in inflammation. In the 2017 book *Healing Mushrooms: A Practical and Culinary Guide to Using Mushrooms for Whole Body Health*, authors Isokauppila and Hyman state "These compounds act as immunomodulators… the shiitake mushroom has a polysaccharide that has proven to be more aggressive targeting HIV-infected cells than the most-used HIV-treatment pharmaceutical on the market and also effectively stimulates antibodies that counteract the effects of hepatitis B."

Other mushrooms with purported immune system-enhancing effects include Maitake, Lion's Mane, Enoki, and Turkey Tail. Extracts of the wild mushroom Chaga induced a rapid increase in macrophages, a type of white blood cell that removes foreign bodies from blood, in mice. In one study involving human patients and Maitake, results were mixed. Some patients had a boost in immune response while others experienced an inhibitory effect.

Anti-inflammatory

Reishi, Shiitake, Silver Ear Jelly, and Lion's Mane are mushrooms of interest in this category. In the trial mentioned above where dozens of people consumed Shiitake over 4 weeks, immune systems were improved, and inflammation was reduced. It is claimed that Reishi might have antihistamine effects that can lead to a reduction of inflammation (a help to allergy sufferers). Claims of alleviating allergies by Reishi have not been confirmed in clinical tests.

Blood Pressure Regulation/Cardio-vascular Benefits

In a published study (J. Nutr. Sci. Vitaminol. 1989, 35:91-94) high blood pressure in rats was significantly reduced by Maitake. The active compound is believed to be protein-bound beta-glucan. In the same study, Shiitake did not reduce blood pressure, but did lower cholesterol. Eritadenine, a compound found in Shiitake, apparently lowers lipid levels by modifying the way certain lipids are made in the liver.

The evidence for other mushrooms reducing blood pressure is inconclusive.

Cholesterol Management

One way to reduce cholesterol in your diet is to substitute mushrooms for meat since there is no cholesterol in mushrooms. But not only are mushrooms cholesterol free, they may have properties that lower cholesterol levels in the body. Beta-glucan reportedly interferes with the absorption of cholesterol into the bloodstream and may affect fat metabolism. In a small

Bangladesh study, cholesterol levels dropped in people who ate mushrooms on and off for 24 days; when mushrooms were excluded in the diet, cholesterol levels went back up (Mymensingh Medical Journal 16(1):94-9 · July 2007).

Lovastatin, originally identified in a species of *Aspergillus* and approved by the FDA in 1987 for lowering cholesterol, is now produced in a fermentation process using one of several fungi, including *Aspergillus*. Lovastatin inhibits an enzyme involved in cholesterol biosynthesis in the liver. Lovastatin occurs naturally in *Pleurotus ostreatus*, the white Oyster mushroom. In two lab studies, rabbits and rats were fed massive amounts of powdered Oyster mushroom, and in both cases their cholesterol levels were reduced. One cannot extrapolate these results to humans eating more realistic doses. In one study on humans, results were inconclusive.

In animal studies, total cholesterol levels were reduced by a diet that included mushrooms. LDL (the bad cholesterol) levels were lowered; HDL (the good cholesterol) levels were not affected in most studies. Eritadenine, a compound found in Shiitake, apparently lowers lipid levels by modifying the way certain lipids are made in the liver and lowers the amount of cholesterol circulating in the blood. In a lab study, rats fed Shiitake developed less liver fat, less plaque on artery walls, and lower cholesterol levels than rats not fed a mushroom-supplemented diet.

In lab studies, there was a drop in cholesterol levels in rats that were fed Reishi. Some claim that Maitake also reduces cholesterol but no good proof exists.

Antioxidants

Free radicals are unstable, highly reactive molecules (especially important is oxygen with unpaired electrons), produced by chemical reactions in the body, or by exposure to toxins in tobacco smoke, fried foods, pesticides, pollution, and to ultraviolet light. Free radicals can damage cells and DNA (but in fact free radicals are not all bad and are a natural byproduct in our cells). Antioxidants in foods can neutralize free radicals, reducing the risk of damage.

Two major antioxidants in mushrooms are ergothioneine and glutathione. Among foods in your diet, mushrooms have the highest amount of ergothioneine. Cooking mushrooms does not seem to significantly affect it. According to Robert Beelman of the Penn State Center for Plant and Mushroom Products for Health, “It's preliminary, but you can see that countries that have more ergothioneine in their diets, countries like France and Italy, also have lower incidents of neurodegenerative diseases, while people in countries like the United States, which has low amounts of ergothioneine in the diet, have a higher probability of diseases like Parkinson's Disease and Alzheimer's. Now, whether that's just a correlation or causative, we don't know. But, it's something to look into, especially because the difference between the countries with low rates of neurodegenerative diseases is about 3 milligrams per day, which is about five button mushrooms each day" (Food Chemistry, 2017; 233: 429). In this study, amounts of these two antioxidants varied between mushroom species. Porcini, a mycorrhizal mushroom collected in the wild, had the highest level of ergothioneine. Maitake had the highest level of glutathione;

Button mushrooms had lower amounts of these antioxidants than the wild mushrooms tested. However, Chanterelles collected in the wild had the lowest levels of all mushrooms tested.

In another study on antioxidants, King Oysters and Maitake, among common mushrooms, had the highest amounts of ergothioneine (Food Sci. Technol. 2012;47:274–278). The Button mushroom also had high levels of antioxidants, although some wild mushrooms, like Porcini, had more.

In a study on Parkinson's disease, one of twelve patients who took glutathione developed heart issues, illustrating the need to take caution with these active compounds. The group of control patients had more improvement than the groups taking glutathione. Care should also be taken with supplements of ergothioneine since little is known of its effect on humans. Ergothioneine is not made in the human body.

Hot water and alcohol beta-glucan extracts from Reishi also have purported antioxidant effects. Remember, Reishi is tough and bitter, so it is taken as a powder, capsule, or liquid.

In the produce section of the supermarket, mushrooms have more selenium, an essential antioxidant, than any other vegetable.

Although there are statements that antioxidants can slow the aging process, there are no data from studies with mushrooms or otherwise, to support those claims.

For more see, Kosharski, M. et al. 2015. Antioxidants of Edible Mushrooms. Molecules 10: 19489–19525.

Brain Health/Nerve Growth Factors

The focus on this health benefit is Lion's Mane. Compounds in this mushroom stimulate the synthesis of a protein called "nerve growth factor," which is critical for the growth and maintenance of neurons in your brain. In a small clinical study in Japan, 50 to 80-year-old men and women with mild cognitive impairment consumed tablets of Lion's Mane for 16 weeks. Relative to the control group, the group that ingested the tablets had increased test scores. When they stopped eating the tablets, this effect disappeared. Both short-term memory and visual recognition memory (recall of previously encountered events) seem to be positively affected by eating Lion's Mane. Because Lion's Mane has nerve regenerative properties, it is hoped that it might help prevent or reverse neurological diseases like Parkinson's, Alzheimer's, and dementia. In a study on mice, there was a suggestion that Lion's Mane decreased plagues in the cerebral cortex and hippocampus. If you are interested in this subject, see Ma et al. 2010. Hericenones and erinacines: stimulators of nerve growth factor (NGF) biosynthesis in *Hericium erinaceus*. Mycology 1:92-98.

Mental Health Therapy/Depression

The Magic Mushroom, *Psilocybe*, is the focus of current research at the Center for Psychedelic and Consciousness Research, John Hopkins University, on depression, anxiety, and fear. In clinical trials, the majority of patients who were given small and controlled doses of psilocybin experienced improved moods. There is also ongoing research on the benefits of psilocybin on post-traumatic stress disorder, anorexia, addiction, obsessive-compulsive disorder, and smoking and alcohol dependence. Preliminary results are promising.

For more information, see Lancet Psychiatry 2016; 3 619–27, on psilocybin and depression.

Managing Blood Sugar Levels

Mushrooms may be useful in managing blood sugar levels. In one study on mice fed a fat-inducing diet, extracts from *Cordyceps* lowered blood glucose levels by increasing insulin sensitivity (J. Diabetes Res. 2015:10. doi: 10.1155/2015/723190.723190). In another study, a *Cordyceps* polysaccharide lowered blood sugar in genetic diabetic mice. In a human clinical trial, there were no improvements in diabetic patients who were given extracts of Reishi.

General Vitality/ Stress Reducer

Reishi and *Cordyceps* are the mushrooms usually claimed to increase your energy levels and stamina and settle your uneasiness about the world. Some say that *Cordyceps* dilates the aorta, which increasing blood flow and so enhances one's endurance. Still others say *Cordyceps* stimulates the production of ATP, the compound that energizes chemical reactions in your body. There are studies that claim *Cordyceps* improves the performance of long-distance runners and improves exercise performance. The success of the Chinese women's swim team in the 1992 Olympics was attributed, in part, to drinking a tea made from extracts of *Cordyceps*. *Cordyceps* is also used as a sedative, stress reducer, and expectorant. It also reportedly relaxes muscles, improves liver cell functions, lowers cholesterol, stimulates the immune system, and reduces tumor growth (and this is a partial list!).

Reishi is also used to enhance one's energy level as well as reducing stress, but there is little scientific evidence to support these claims, although studies on mice indicate greater endurance. When I went to China to learn about medicinal mushrooms, I listened to a report on the following study. The researcher had two groups of 50 mice each, each group in a cage. One group was fed extracts of Reishi; the other not. The group fed Reishi had a red dot painted on their heads. The other group green. After a certain number of days, all the mice were tossed into a barrel 2/3^{rds} full of water. The mice had to keep swimming to survive. When they tired, they drowned. The mice with the red dots survived the longest. The conclusion? Reishi enhances endurance. A lot of experiments were of this nature; some were much more gruesome. If you think about it, there were problems with the experimental design of that trial. For example, a

cage of mice, no matter how many mice in each one, is one replication (not 50). It would have been much better to use five cages of ten mice each for each treatment. The diets of the different groups may have been influenced by other nutrients in the extracts, the trial should have been repeated, and there may have been bias in the experiment (that's complicated- there was pressure on the researcher to get positive results).

With or without data from well-planned, replicated, controlled, repeated trials, Eastern medicine uses a lot of mushroom products for enhancing general vitality.

Other Purported Health Effects

In Asia, the Wood Ear is used medicinally to thin blood. As a consequence of eating quantities of this mushroom, hemorrhages of the skin can occur, a condition known as the Szechwan Restaurant Syndrome (pink cheeks, for example). Reishi is reportedly used in Tibet to cure altitude sickness. Others claim it cures insomnia. The list of ills reportedly cured by Reishi is incredibly long, but this mushroom has a higher concentration of the supposedly beneficial chemicals per unit weight than other mushrooms and it remains the fungus of choice to many.

Oysters and some other mushrooms cause paralysis and death of nematodes in vitro. It is well known that Oysters in particular consume nematodes that inhabit the same wood that the fungus has colonized. A review of fungi and their antiparasite effects (e.g., inhibiting the vector of malaria) is found in Applied Microbiology and Biotechnology (2018) 102:5791–5810. A review on antimicrobials from Reishi is reported in Mycology (2017) 8:111–124.

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One of the principles of sound scientific inquiry is reproducibility of the results of an experiment. If I conduct an experiment and find a certain result, I need to repeat the experiment in space (hopefully) and time (certainly) so that when I publish the study, I can say the experiment was done at least twice and I got the same results. And I must carefully and with great detail include a description of the way I did the experiment in the Materials and Methods section of the paper. The paper cannot be published without those details because someone else must be able to repeat the experiment exactly like I performed it. If that person and the person after that can reproduce the results, then the conclusions become something we believe with great confidence, in other words, they are predictable. The results of many of the trials discussed above have not been repeated by other researchers. And some claims, despite well intentioned, may not be supported by experiments using rigorous standards that the scientific process demands. Furthermore, there are concerns that biases by the researchers or patients were not completely eliminated in some of these studies. Finally, there is a willingness of some people to make sweeping generalities from laboratory findings in test tubes, results from trials with animals, or studies with small number of humans. Repeated human clinical studies on the beneficial effects of mushrooms or their extracts, complete with nonbiased control groups, are often lacking. Hence, the health benefits of mushrooms are sometimes based on insufficient and incomplete data. All these concerns emphasize the need for more well-designed clinical trials on

medicinal mushrooms. Of course, this paragraph was written by someone who paid a lot of money for *Cordyceps* made of clay. So there's that.

For more on medicinal mushrooms and to access a long list of published studies, see "Scientific Research & Medicinal Fungi" By Dianna Smith. 2020. North American Mycological Association.