Medical Mushrooms: There's A Fungus Among Us!

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Mushrooms have played important roles in the development of human civilization.

- Mushrooms have, over the millennia, provided an easily-harvested forest edible that has been cultivated and commercialized into the multi-billion dollar global industry it is in the world today.
- Mushrooms have been used by indigenous peoples as folk medicines for as long as they have been collected and used for food; they have also served as medicines prior to the age of pharmaceuticals.
- Mushrooms have provided an other-worldly experience to many, who from that experience glimpsing into alternate universes, have created imaginative and unique music, books, artwork, and social systems that have left an indelible mark on human culture and society.
- Mushrooms have been the source of many fatal poisonings over the millennia, and are still a common source of ER visits in the summertime for both people and their pets.

Today, the nutraceutical and pharmaceutical industries are learning as much as they can about the beneficial properties of these specialized fungi, in a rush to bring newer and better medicines to market. (1) Today's presentation is to provide the veterinarian with a foundation of knowledge about mushrooms in general and their properties in general.

Medicinal Mushrooms

Medicinal mushrooms are macro-fungi found mainly in the class Basidiomycetes, with a few found in the class Ascomycetes. Medicinal mushrooms are becoming more commonly available in the natural products marketplace as the evidence of their value to the immune system and disease management, including cancer, becomes better understood through basic research and clinical trials.

Basidiomycete Genus

Polypores

Ganoderma lucidum (AKA: Reishi, Ling zhi)
Grifola frondosa (AKA: Maitake; Hen of the Woods)
Inonotus obliquus (AKA: Chaga)
Coriolus versicolor (AKA: Turkey Tail, *Trametes versicolor,* Yun Zhi)

Gills

Lentinus edodes (AKA: Shiitake)
Agaricus spp. (*Agaricus blazei* Murrill, *Agaricus braziliensis*)
Pleurotus ostreatus (Oyster mushroom)

Teethed

Hericium erinaceus (AKA: Lion's Mane, Monkey Head Mushroom, Hedgehog Mushroom)

Ascomycete Genus

(Sac-formers)

Cordyceps sinensis, cordyceps militaris
Tuber melanosporum (AKA: Black Truffles)
Morchella esculente (AKA: Morels)

It is important to understand the complex life cycle of the mushroom. Starting the life cycle is the spore-bearing "fruiting body", which is what we commonly associate with the name and the shape of a "mushroom." The spores are the reproductive "seeds" of the macro-fungus. Once the fruiting body drops its spores on a suitable substrate, the germination of the spore develops into a tube, the tip of which secretes enzymes which digest the substrate and provide nourishment to the growing tube.

This filamentous tube is called a "hypha" (plural="hyphae"), and, as it digests and grows into the substrate it branches multiple times and will fuse with other hyphae from other spores germinating from the same fruiting body. This complex tangled mass of hypha is called "mycelium". The mycelium is the vegetative stage of the Basidiomycete or Ascomycete, and it continues to grow into the substrate as long as there is a supply of nutrients to nourish it and environmental conditions are favorable for its growth. When conditions change, the mycelium produces hyphal knots, which are the first stage in the development and growth of the fruiting body. The hyphal knot then goes through stages of development, first becoming organized as a "primordium" and then developing into the "pin-head" which is the first differentiation into a pre-mushroom shape. It continues to mature, finally resulting in the fruiting body, which contains the spores. The cycle repeats itself as long as there is sufficient food for the mycelium and the environmental conditions remain favorable to growth. (10)

Dead or rotting wood provides one of the most common substrates for the growth of the mycelium, which literally digests the wood. The mycelium thus "eats" itself into the wood and becomes indistinguishable from the substrate itself. It's impossible to separate the mycelium from the substrate. The Cordyceps mushroom uses the body of the caterpillar as its substrate, and sends its fruiting body out of the caterpillar body. The fruiting body has a distinctive spear-like appearance as it emerges from the soil where the dead caterpillar had been. The caterpillar fungus *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*) is one of the entomogenous Ascomycetes and parasitizes the larvae of Lepidoptera to form the well-known traditional Tibetan medicine "yartsa gunbu" or, in traditional Chinese medicine, dong chong xia cao ("winter worm-summer grass") Lepidoptera are moths and butterflies. The fungus attacks the larva of some species of insects (Fam. *Hepialidae*), and converts each larva to a sclerotium, from which the fruiting body grows.

Mushroom growers use live mycelium as their seed. This is termed "spawn". This live mycelium is propagated on a carrier material. Spawn has historically been produced on many different carrier materials, including sawdust and various grains. Grain is one of the most common carriers due to its small size and ease of mixing into bulk mushroom growing substrates. Mushroom growers do not grow mushrooms on grain. Sterilized grain is inoculated with live mycelium which grows and covers the grain. Spawn is commonly used as a "seed" to grow mushrooms (the fruiting bodies) on their native substrate: sawdust, wood, or compost. The traditional path to growing mushrooms has been to use the spawn to inoculate a mushroom substrate, and then harvest the fruiting bodies (mushrooms).

A contemporary manufacturing process for growing fungal mycelium involves growing the fungal mycelium on grain, and then harvesting the mycelium with the grain, drying this biomass and then grinding it to a powder. This powder is being sold as "mushroom" powder, but since there are no mushrooms (fruiting bodies) in the powder, it is more appropriately called "fungal mycelium biomass" (according to a recent AHPA definition of the words "mushroom" and "mycelial biomass", since it contains both fungal mycelium and quite a bit of grain.)

In several studies analyzing and comparing the constituents of medicinal mushroom fruiting bodies grown on their native substrate, wood, with a mycelial mass grown on grain, some interesting findings have been reported which speak to the comparative medicinal potency of these two production techniques. The components of the mushroom that are usually measured as an estimate of potency such as beta glucans, triterpenoids, ergosterol were generally lower in the mycelial biomass than in the mushroom fruiting bodies. (10)

But first, a discussion of the naturally-occurring compounds found in basidiomycetes and ascomycetes will provide a better understanding of the findings of these comparative studies.

β-glucans

The most medicinally-beneficial compound found in mushrooms are the β-glucans. These are structural components of the cell wall of fungi and yeast, and are also found in the cell walls of seaweed and grains. β-glucans are polymers of the simple glucose molecule. They are named by the sites of the bonds between the glucose molecules. Not uncommonly they may exhibit complex branching, but may also be found unbranched. β-glucans compose up to 50% of the cell wall material on a dry matter basis. The linkages and branching are specific to each species of mushroom, and convey the specific properties of that species. Commonly we see a linkage in fungal species between the first and third carbon in the glucose molecule resulting in a 1,3-β-D-glucan. Cross linkages and branching are attached at various points. In fungal species both 1,3-β- and 1,6-β- linkages are present, which is unique and characteristic of fungi. There can be considerable variation in the complexity of the cross-linkages and branching from species to species. The 1,3-β-glucans and 1,3:1,6-β-glucans are bound to chitin and chitosan by 1,4 linkages. Additionally, there can be tertiary structures linked to the glucose molecules such as triple helixes which provide increased activity. (11)

After oral administration of β-glucans, the 1,3-1,6-β-glucans bind to receptors on the intestinal macrophages, which then carry the β-glucans to other organs such as spleen, lymph nodes, bone marrow and reticuloendothelial tissues in general. The macrophages metabolize the β-glucans into smaller, more immunologically active metabolites which bond to and activate bone complement receptors (CR3) on marrow granulocytes (stem cells), thus increasing immune competence. (11)

α-glucans (5)

α-glucans, are also present in the fungal cell wall and are found in three different configurations:

1. Structural fibers: 1,3-α-glucans attached to 1,3:1,6-β-glucans
2. Starch (1,4-α-glucans)
3. Glycogen (1,4-α-glucan and 1,6-α-glucan)

The α-glucans provide nourishment for sporulation, and help to prolong the survival of the spores through blocking their oxygen intake to slow metabolism. α-glucans, unlike β-glucans, are ubiquitous in the plant kingdom, not specific to yeast, fungi, grain and seaweed.

The molecules that make up the cell wall of fungi and yeast provide a specific recognition factor that allows them to be recognized not just by other yeast and fungi, but other plants, and humans as well. The recognition of fungi and yeast based on their cell wall molecular characteristics is an innate immune response in both plants and animals to the very old threat of fungal invasion and infection. Fungal infections can be very destructive with a high mortality, thus the immune system of all organisms needed to learn early in their evolutionary development to identify and protect against fungal infections, or else risk death. It is the branched chain 1,3:1,6-β-glucans, mannans and glycoproteins that provide the molecular recognition factors that trigger the immune response.

Other Compounds Contained in Mushrooms

A number of different compounds can be found in the cytoplasm of the mushroom cell, such as terpenes, alkaloids, phenolic compounds, proteins and fatty acids. *Ganoderma spp*. are known for their bitter taste, a result of the powerful triterpene molecules produced by this mushroom, which have demonstrated powerful immune enhancing properties in multiple studies. Ganoderma is known in Japanese as “Reishi” or the Emperor of Mushrooms.

These “triterpenoids”, in addition to being very bitter, have some very potent medicinal properties: Hepatoprotective, lipid lowering, antioxidant, inhibition of histamine release by mast cells, anti-inflammatory activity and a synergistic effect on immune activation in combination with β-glucans. Mushrooms known to contain triterpenoids include *Ganoderma* spp., *Chaga* and *Antrodia.* Triterpenoid analysis in these species can help to determine quality and confirm mushroom identification.

Nucleosides such as adenosine, guanosine, uridine and cytidine are found in varying amounts in most of the Basidomycetes. One of the active principles in the medicinal mushroom *Cordyceps* spp. is a nucleoside called cordycepin, which is an identifying compound for *Cordyceps militaris*, but not for *Ophiocordyceps sinensis*, a closely related species. Cordycepic acid is not considered to be a marker compound for *Cordyceps* spp. It is in fact the sugar mannitol, and is present in most plants and fungi. (12)

Other compounds such as alkaloids and sterols can also be found in mushrooms. One sterol is ergosterol, a compound found in all mushrooms. Testing for ergosterol is one way to document that there may be fungal contamination of grain. Ergosterol is a precursor in the formation of vitamin D_2 which is catalyzed by exposure to UV light, except in dogs and cats, who lack the enzyme to allow this conversion of either ergosterol or cholesterol that is present in the skin of most mammals.

The oyster mushroom (*Pleurotus*) and other species as well have been found to contain cholesterol lowering molecules that are naturally occurring in the mushroom. This effect is caused by mevinolin, which is a secondary metabolite found in many fungi and all medicinal basidomycetes. Mevinolin is now patented under the trade name: Lovistatin™ as a cholesterol-lowering drug.

Comparison of Fruiting Body Medicinal Compounds to Mycelial Mass Medicinal Compounds

When fungal mycelium is grown on grain (AKA: mycelial biomass), the harvested material is dried and ground into a powder that may contain as much as 50% carbohydrates from the grain. It's impossible to separate mycelium from grain, as the mycelium feeds upon and invades the grain for its nourishment. (5)

Within the nutritional supplement industry there is controversy regarding the relative value of mycelium grown on grain versus fruiting body content of bioactive immune modulating constituents. Objective studies indicate that mushrooms contain much more β-glucan and secondary metabolites such as triterpenoids that are found in *Ganoderma* than mycelium in general and especially as regards the content of mycelium grown on grain. However, proponents of mycelial-based products contend that it's not all about the β-glucan content, and that mycelium as an actively growing organism contains valuable bioactive materials. This author's primary problem with mycelium grown on grain is the large amount of α-glucan (starch) sourced from grain. Many patients have problems handling grain in their diets, and cancer patients need to keep their carbohydrates low to not promote cancer growth. It would be nice to have a clinical study comparing the health benefits of fruiting bodies versus mycelial mass grown on grain. It should also be noted that pure mycelium, without being grown on grain, is a common commercial product in China.

McCleary discussed the fact that the measurement of total dietary fiber and dietary fiber components (resistant starch, resistant, non-digestible oligosaccharides [fructan and galactooligosaccharides] β-glucan, native and chemically modified polysaccharides of plant and algal origin; galactomannan, chemically modified celluloses, agars, carrageenans and other plant polysaccharides such as psyllium gum) was subject to errors based on the contamination of enzymes. As an example, he noted that the contamination of certain preparations with cellulase can result in significant underestimation of dietary fiber samples containing β-glucan. (17)

In a follow-up study published 6 years later, McCleary compared the enzymatic measurement technique he had critiqued in his previous paper cited above using a technique he had developed with controlled acid hydrolysis, using H_2SO_4 followed by the use of specific reagents. This study demonstrated this technique itself to be a more accurate means of measurement of α- and β-glucan content in mushrooms and mycelial products. (18)

Of particular interest in McCleary's study is that he used this technology to measure α- and β-glucan content of a variety of commercially-available mushroom and mycelium on grain products, as well as some standards such as glucose, wheat starch, grain-based β-glucans, purified yeast β-glucan and others. He found a substantial difference in the samples he studied between the content of β-glucan and α-glucan in mushrooms versus mycelium on grain products. These results are summarized in the table below.

TABLE COMPARING Glucan Content in Mushrooms* versus Mycelial Products**

Sample	Total glucan %	α-glucan %	β-glucan %
*Ganoderma lucidum**	54.2	0.2	54.0
*Cordyceps militaris**	36.5	1.9	34.3
16 Basiomycete species blend**	69.5	66.4	3.2
7 Basiomycete species blend**	73.7	72.5	1.3
*Ganoderma lucidum***	44.6	22.6	22.0
*Ganoderma lucidum***	87.7	83.2	4.3
Cordyceps sp.**	64.8	53.9	10.9

Cordyceps sp.**	65.5	64.0	1.5
Control (*A. niger* mycelium) **49%** β-glucan	51.9	1.0	**50.9**

In a study using the McCleary enzymatic measurement technique described above, Chilton carried it a bit further by analyzing 60 samples representing commercial products containing 6 different species of basidiomycetes and ascomycetes for β-(1,3)(1,6)-glucans, α-glucans, and ergosterol. Chilton's test results objectively demonstrated that mushroom fruiting bodies contain much more β-glucan than fungal mycelium grown on grain, and much less α-glucan than grain-grown mycelium for all of these 60 samples. (20)

Bak et al. (19) compared the β-glucan content in different sections of the fruiting body and mycelia of *Lentinus edodes* (Shiitake) cultivars. What they determined parallels McCleary's results. The fruiting body samples were in the range of 24.86% - 55.91% β-glucan and 0.7%-8.17% α-glucan. The mycelium measured in the range of 15.59% - 27.09% β-glucan and 1.46-7.9% α-glucan. In this study the mycelium was grown on potato agar, not grain [as in McCleary], indicating that the grain-based mycelial products contain less β-glucans and more α-glucans.

In a study performed comparing the medicinal compounds found in fruiting bodies grown on their native substrate of wood to the mycelial grown in liquid culture medium, it was found by Nitschke (8) that there were 3.7 times more 1,3:1,6-β-glucans and 2.3 times more total β-glucan content in the fruiting body of shiitake than in the mycelial biomass of the same species. They found this to be true of most medicinal and edible mushrooms except for the button mushroom, *Agaricus bisporus*.

Mycelium grown on grain has not been proven through comparison studies to have the same potency as the mushroom/fruiting bodies of the same fungal species with regards to β-glucans, triterpenoids, ergosterol and the other active compounds. The mycelial-grain biomass does contain substantially more α-glucans (carbohydrates) than are present in naturally-occurring mycelium not grown on grain. Patients on a low carbohydrate diet, or a no-grain diet, or for those who have cancer and are avoiding starches so as not to promote cancer growth, may want to avoid using these [mycelium grown on grain] products that contain substantially higher levels of grain-based carbohydrates. Alpha-glucans also contribute little to the medicinal benefits of mushrooms. (5)

A 2015 study compared the biological activity of medicinal mushroom (MM) products purchased in the US marketplace. Sixty percent of these products were mycelium on grain and 40% were hot water extracts of the fruiting body. The activation of toll-like receptor 2 (TLR2) was measured. Activation of this immune receptor indicated that a MM product had immune-modulating biological activity by the measurement of TNF-α increase after administration. In general, it was found that the hot water mushroom extracts were able to induce significantly higher levels of both TLR2 and TNF-α activity than the mycelium on grain products. (6)

What is the Best MM Extract Format to Use?

Lu et al. in a recently published paper showed that the aqueous extracts (hot water extracts of fruiting bodies) promote the cytotoxic activity of NK Killer cells against cancer cells, but ethanolic extracts will inhibit that activity. (21) This is an important consideration when choosing a MM product, in addition to the actual content of immune modulating constituents.

MEDICAL MUSHROOM MATERIA MEDICA (2) (12) (15)

<u>Agaricus blazei</u>

Scientific name: *Agaricus blazei* Murrill

Common names: Royal Sun **Agaricus**, Himematsutake, Kawariharatake, Songrong.

Constituents: Ergosterol, α-glucans; β-glucans; glucomannan, proteoglucans, riboglucans,

Applications: Anti-cancer (Utero-cervical, especially), immune, interferon and interleukin enhancing, anti-viral, cholesterol reducing, blood sugar modulating

Most unique property: Proven cancer preventative: A study of 2,018 pre- and post-menopausal woman, 50% diagnosed with cancer, the other half without detectable cancer were given 10 grams (1/3 ounce) of fresh button mushrooms or four grams of dried. 64% reduction in the risk of breast cancer was noted in the fresh mushroom group and only slightly lowered for the dried mushroom group. The decreased risk in breast cancer went up to 90% if the women also drank green tea regularly. (16)

Cordyceps spp.

Scientific name: *Cordyceps sinensis; Cordyceps militaris, Cordyceps capitata*

Common names: **Cordyceps**, Caterpillar fungus, Tochukaso, Dong Chong Xia Cao ("Summer grass, winter worm"), Chongcao, Yartsa gunbu

Constituents: Cordycepin, galactomannans, polysaccharides, sterols, beta glucans, a number of other as yet un-characterized non-polysaccharide compounds

Applications: Anti-tumor, immune enhancement, anti-leukemia, enhance NK T cell function, cholesterol reducing properties, cardiotonic properties, relax bronchiolar constriction, improves physical performance, treats asthma, TB, and pulmonary inflammation, thins phlegm, antioxidant, anti-viral, Lymes' disease, renal protective, hepatosupportive.

Most unique property: **Has an affinity for the lungs and kidneys.**

Coriolus versicolor

Scientific name: *Trametes versicolor, Coriolus versicolor*

Common names: **Turkey Tail**, Yun Zhi, Kawaratake

Constituents: β-glucans, PSK (protein-bound polysaccharide, β-(1,4)-D-glucan protein) (commercially known as Krestin), PSP (polysaccharopeptide)

Applications: Immune enhancement, anti-tumor, anti-viral, anti-bacterial, anti-oxidant

Most unique property: Univ. of Penn. veterinary college study in naturally occurring hemangiosarcoma found better results in this pilot study for survival time with the PSP extract of the Coriolus versicolor mushrooms versus with chemotherapy alone.

PSK vs PSP extracts: **PSP** is a water-soluble, low-molecular-weight cytotoxic polysaccharide that is isolated from this mushroom. It has been found to have anti-viral (HIV), Anti-tumor, and immune modulating properties as a biological response modifier (BRM), inducing interferon, interleukin-2 and T-cell proliferation. It differs chemically from PSK by having rhamnose and arabinose, and PSK has fucose. **PSK** (Krestin) is widely sold in Asia as an anti-cancer drug. In a 1997 study, 224 patients with gastric cancer and 262 patients in 1994 were treated with chemotherapy and then treated with Krestin. Results demonstrated a dramatic reduction in recurrence, an increase in disease-free-interval, and was cost effective too. PSK provides some chemoprevention to cancer for healthy cells, and sensitizes cancer cells to chemotherapeutic agents. (13) (14)

Maitake

Scientific name: *Grifola frondosa*

Common names: **Maitake**, Kumotake ("Cloud mushroom"), Mushikusa, Hen-of-the-Woods

Constituents: 1,6 β-glucans (Grifolan); 1,4 and 1,3 β-glucans; acidic- and hetero- β-glucans, mannogalactofucan, mannoxyloglucan, xyloglucan, n-acetylgalactosamine-specific lectin ("GFL")

Applications: Anti-tumor (liver, breast, prostate, colorectal), anti-diabetic, anti-viral (HIV)

Most unique property: Highly prized as an edible mushroom for its taste, has an affinity for stomach and spleen conditions, hemorrhoids, calms the mind and nervous system, (for instance, neuralgia, palsy) and can help with arthritis.

Ganoderma

Scientific name: *Ganoderma lucidum*

Common names: Reishi (Divine mushroom); Ling Zhi (spirit plant or tree of life mushroom), mannentake (mushroom of immortality), varnished conk

Constituents: Ergosterols, β-glucans, triterpenoids (ganoderic and ganoderenic acids), ganoderans, mannogalactoglucans, Ling Zhi-8 protein

Applications: Anti-neoplastic, inhibits histamine release, anti-hypertensive (like ACE inhibitor), inhibits cholesterol synthesis, anti-inflammatory, apoptotic, antioxidant, inhibits viral reproduction, anti-microbial, immune modulating, anxiety/insomnia, allergies, liver support; rheumatoid arthritis, anti-aging, anti-diabetic

Most unique property: Special affinity for the lungs and liver. Considered one of the most important medicinal mushrooms

Shiitake

Scientific name: *Lentinus edodes*

Common name: **Shiitake**, Xiang Gu, Black Forest mushroom

Constituents: β-glucan = "Lentinan", galactoglucomannan; hetero-glucan protein = "LEM", eritadenine, α-mannan peptide "KS-2"; glycoproteins, RNA fractions; ergosterol (provitamin D2)

Applications: Immuno-modulating; increases NK t cell activity, increases interferon, anti-viral, liver supportive. Lentinan is used as an injectable in human oncology patients in Asia, but has also been found to be effective orally, reduces cholesterol, anti-bacterial

Most unique property: Most popular and most studied of all of the medicinal mushrooms.

Chaga

Scientific name: *Inonotus obliquus*

Common name: **Chaga**, Polyporus obliquus, Poria oblique, Clinker polypore.

Constituents: Protein-bound polysaccharides (Xylogalactoglucan), Lanostanoid triterpenoids and other sterols and steroids (betulin, flanosterols, inotodiol), inositols, lactones, melanin.

Applications: Anti-tumor (breast, lung, cervical, stomach, liver), antiviral, anti-tuberculosis, digestive, inflammatory bowel disease, diabetes, ulcers cardiotonic and liver supportive, psoriasis

Most Unique Property: A distinctive black fungus that grows a black, cankerous mass called a sclerotium, that grows specifically on birch trees and which cannot be cultured or cultivated commercially. This brittle hard mass was boiled as a tea, and the boiled mass remaining was pounded into a poultice to prevent infection and help recovery from toxicity. Widespread ethnobotanical use, from Eurasia and Russia, Siberia, US and Canadian First peoples, Norway, Finland, England

Lion's Mane

Scientific name: *Hericium erinaceum*

Common name: **Lion's Mane**, Monkey's Head, Yamabushitake, Houtou

Constituents: Cyanthane derivatives, erinacines, hericenones, β-glucans, galactoxyloglucan, mannogluxylan, xylan, ergosterol

Applications: Anti-neoplastic, immune modulation, nerve growth regeneration, anti-microbial, Parkinson's disease, used to treat atrophic gastritis.

Most unique property: Erinacines, compounds unique to Hericium, stimulate neurons to regrow which is being studied for Alzheimer's Disease, senility, repairing neurologic trauma, increasing
cognitive abilities, improving muscle/motor response pathways.

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