

## **Awaking Our Innate Response: Immunocompetence and Maitake Mushroom**

**Larken Bunce, MS, Clinical Herbalist**

### **What is Maitake?**

Mushrooms are the fruiting bodies of fungi, the visible part of a much larger organism which also includes a generally unseen mycelia network. Mushrooms play a central role in the decomposition of dead plant matter and fallen trees and maintain symbiotic nutrient-sharing relationships with many plants, and so are essential to maintaining the health of a variety of ecosystems.<sup>1</sup> There are many thousands of species of mushrooms, about 700 of which are edible. Of those, approximately 50 are believed to be medicinal.<sup>2</sup> Many of the medicinal species come from the Polyporaceae family, so called because its members share a characteristically many-pored under-surface through which the fungus' spores (seeds) are released. (The polypore family has also amusingly been referred to as the "monkey's bench" family, as many are so woody that they are purported to be able to support a monkey!<sup>2</sup>) Other well-known medicinal polypores include reishi (*Ganoderma lucidum*), chaga (*Inonotus obliquus*), and turkey tail (*Trametes versicolor*), all of which grow in quantity in North America and are particularly abundant in my Vermont woods.

Of the polypores, one species has historically been prized for two reasons: 1) it is uniquely palatable and tender and 2) it has shown exceptional medicinal potency. This species, *Grifola frondosa*, is referred to alternately as "hen of the woods" by gourmet mushroom enthusiasts or as the "king of mushrooms" by some captivated by its medicinal value. The most common name for this species, however, comes from Japan: maitake—meaning "dancing mushroom"—which may refer to the delicate, fluttering nature of this mushroom's flesh.<sup>2</sup> Unlike other polypores, it is a tender edible species which would certainly not support a climbing monkey! Maitake does grow to be quite large, however, reaching as much as 100 pounds in one season of growth, but also weighing as little as five. Growing on the ground at the base of oaks or other deciduous trees in many parts of North America, maitake appears with white to gray-brown flesh forming spoon-shaped caps born on white stalks branching from a compound base.<sup>1</sup> Historically used in traditional Chinese and Japanese medical systems, as well as in Eastern European traditions, maitake has held an esteemed place in the global materia medica as a premier immunomodulating and tonic substance and is currently used extensively in many countries in a variety of supplement forms or prepared traditionally as a hot-water decoction.

### **Evolution of Maitake Research**

In the 1980s, while conducting research on shiitake (*Lentinus edodes*), Japanese mycologist Dr. Hiroaki Nanba of Kobe Pharmaceutical University discovered that the polysaccharides from maitake exhibited more marked antitumor activity than any of the other mushrooms he had studied. Also significant was that oral administration of maitake demonstrated activity equal to or greater than injected mushroom extracts, such as lentinan from shiitake.<sup>3</sup> In 1984, Nanba and colleagues discovered a unique polysaccharide fraction, present in both mycelia and fruiting body of maitake, which strongly stimulated macrophage activity. This particular extract of maitake came to be known as the "D-fraction" and was patented in Japan. The MD-fraction, a more purified and biologically active version of the D-fraction was later developed and patented. An X-fraction has also been isolated.<sup>3</sup>

Current interest in maitake and its isolated polysaccharide fractions, beta-glucans, is high. The proprietary MD-fraction, MaitakeGold 404<sup>®</sup>, is involved in a multi-phase, five year clinical trial to investigate its value in the treatment of breast cancer. This study is being funded by the National

*Originally published in the Summer 2009 issue of Unified Health, a practitioner publication of Innate Response (www.innateresponse.com).*

Institutes of Health (NIH) and carried out by Memorial Sloan-Kettering Cancer Center in New York. Ongoing research is also being conducted at the University of Louisville in Kentucky, in addition to continued investigations at Kobe Pharmaceutical University and other Japanese institutions.

### **Beta-Glucan Chemistry**

Fungi enzymatically decompose material as part of their feeding and defense mechanisms. Before digested food can be absorbed into a fungus' cells for use, pathogens and toxic substances must be neutralized as they pass through cell walls. It is believed that the polysaccharides and similar chemicals present in the cell walls which are responsible for protecting the fungus are also responsible for mushrooms' role in protecting human immunity.<sup>4</sup> Numerous medicinal mushrooms, as well as non-fungal herbs, contain immunomodulatory polysaccharides. However, beta-glucans, the polysaccharides found in shiitake (*Lentinus edodes*), reishi, turkey tail, maitake and others, have received particular attention for their potent immune-enhancing activity.

Beta-glucans are large and complex long-chain molecules composed of multiple spiraling chains linked in repeating patterns. The different ways in which the spirals and chains are linked create a variety of three-dimensional structures which are distinguished especially by their branching patterns.<sup>4</sup> The nomenclature for beta-glucans includes numbers that distinguish certain branching patterns from others, i.e. beta-1,3 or beta-1,4 branched chains. The numbers indicate which carbon atoms—of the 6-carbon glucose molecule that forms the backbone of beta-glucans—are linkage sites in the branching patterns (i.e. in 1,3 C1 is linked to C3 on the next glucose molecule). It is believed that the degree of branching, along with the molecular weight, solubility, viscosity and three-dimensional conformation, impacts the bioactivity of various beta-glucans, resulting in different, though likely overlapping mechanisms and strength of activity.<sup>5,6</sup> The D- and MD-fractions of maitake contain both a 1,6 main chain w/1,3 branches and a 1,3 main chain having 1,6 branches. Most mushrooms have only 1,3 chains with 1,6 branches.<sup>3</sup>

Because the structure of beta-glucans is central to their activity, and because these molecules are found within the indigestible cell walls (composed of chitin) of fungus, attention must be paid to the method of extracting the beta-glucans. The traditional, hot-water decoction of mushrooms releases the beta-glucans from the fibrous chitin without damaging their structure. Some modern products grind dried mushrooms or mycelia in an effort to liberate the beta-glucans from cell walls, but this mechanical friction may damage the branching structures or change other physical characteristics thought to confer particular activity. It remains unclear if methods other than those involving hot-water extraction at some stage of the process are effective in extracting intact and active beta-glucans.<sup>4</sup> Other constituents, however, are likely also important to the activities of maitake and may be made bioavailable in forms such as powdered or fermented fruiting body or mycelium. Whole mushroom extracts and powders are often taken alongside isolated fractions and have demonstrated important adjuvant and independent activity (particularly in hypertension and elevated cholesterol and triglycerides).<sup>7,8</sup>

### **Maitake and Beta-Glucan Impacts on Immune Function**

By examining traditional use and research over the past two decades, it is clear that maitake's potential benefits are wide-reaching. Maitake (and/or the beta-glucan fractions) has demonstrated impressive potential to enhance overall immunocompetence via strengthening host defense, as well as health outcomes in various chronic diseases, including cancers, liver disease, asthma, diabetes and HIV/AIDS. It may also mitigate cardiovascular risk factors, such as hypertension, obesity and elevated cholesterol and

*Originally published in the Summer 2009 issue of Unified Health, a practitioner publication of Innate Response ([www.innateresponse.com](http://www.innateresponse.com)).*

triglycerides,<sup>3</sup> as well as offer complementary therapy in systemic infection with such organisms as *Candida albicans* and *Listeria monocytogenes*.<sup>3, 9, 10</sup>

A great deal of research has investigated the manner in which maitake's beta-glucans interact with the immune system. Early researchers noticed that beta-glucans bind to receptor sites on macrophages (hence the importance of shape), stimulating their activity. Later, binding to other immune cells (such as natural killer (NK) cells and neutrophils) was also observed. Ongoing examination of beta-glucans in general, and maitake's D- and MD-fractions specifically, have revealed numerous complex and interrelated impacts on both innate and adaptive immune function in both *in vitro* and *in vivo* models, as well as in a handful of human trials. As these host defense mechanisms are at the heart of healthy relationship with our environment (impacting our responses to such threats as viral and bacterial infections and carcinogenesis), it becomes obvious why maitake is of ongoing interest to modern medicine. What follows is a summary of the currently understood mechanisms through which maitake exerts its actions.

In *in vitro* and *in vivo* models, maitake fractions have been shown to increase phagocytic activity of macrophages and granulocytes, even in quite small doses (ie, 2.6 micrograms).<sup>11</sup> Maitake fractions also both directly enhance NK cell activity, as well as stimulate activation of NK cells.<sup>4, 11, 12</sup> Administration of maitake fractions also increase expression of CD4+ T helper cells<sup>11</sup>, as well as cytotoxic T cells (Tc).<sup>3</sup>

In addition to directly stimulating immune cells, the fractions appear to potentiate synthesis and release of various cytokines, including interleukin (IL)-1beta, IL-2, IL-12, interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha.<sup>11, 13</sup> Recent research has also focused on improvement of antigen presentation by dendritic cells<sup>5, 12</sup> and activation of complement dependent cytotoxicity.<sup>10</sup>

### **Maitake and Cancer**

Maitake appears to address cancers through a multifaceted approach involving a combination of the above mechanisms. It protects cells initially by preventing mutation and carcinogenesis, inhibits metastasis of existing cancers and slows, stops or regresses the growth of tumors, through both its cytotoxicity and anti-angiogenic activity.<sup>3, 10</sup> Further, maitake demonstrates the ability to enhance chemotherapy treatment and to decrease its common side effects.<sup>3, 4</sup>

A non-randomized clinical study of 165 cancer patients (staged III-IV) using a combination of D-fraction and whole powder tablets demonstrated either tumor regression or significant improvement of symptoms in 7 of 15 liver cancer patients, 12 of 18 lung-cancer patients and 11 of 15 breast cancer patients. Combining maitake with chemotherapy further improved responses by 12-28%.<sup>14</sup> Prostate cancer may be a further application for maitake, as a recent *in vitro* examination of the combination of D-fraction with IFN-alpha caused a 65% reduction in cancer cell growth.<sup>15</sup>

In another non-randomized Japanese case series, 33 cancer patients staged II-IV were given either maitake MD-fraction along with whole mushroom tablets alone or in combination with chemotherapy. Regression or improvement of symptoms was again observed in 11 of 16 breast cancer patients, 7 of 12 people with liver cancer and 5 of 8 with lung cancer. In this study, a positive response was defined as one or more of the following: maintenance or reduction of tumor size; maintenance or reduction of number of lesions; prevention of metastasis; reduction in cancer size as measured via CT or MRI scanning by 1/2-3/4; reduction in tumor marker values by 1/3-1/2; enhancement of cytokine production

*Originally published in the Summer 2009 issue of Unified Health, a practitioner publication of Innate Response (www.innateresponse.com).*

(IL-1 and IL-2); and normalization of levels of immunocompetent cells (NK cells, macrophages, T lymphocytes).<sup>16</sup> This same study found, however, that maitake may be less effective in leukemia, stomach, bone and brain cancers.

It should be noted that brain cancer generally has an extremely low response rate to conventional treatment; however, the above 165-patient study found a 33% response rate to D-fraction plus whole mushroom. While this is less robust than responses found in other cancers, it offers significantly more value over conventional treatment (to which response in this study was 0%).<sup>14</sup>

While maitake and its fractions have demonstrated independent benefit, complementary use with chemotherapy appears to enhance both substances' effects. A murine study using the chemotherapeutic agent mitomycin-c (MMC) demonstrated a synergistic effect between MMC and maitake D-fraction and suggested that the MMC directly attacked tumor cells while maitake stimulated the immune system, thus enhancing effectiveness of treatment through a biphasic approach. The study showed an 80% reduction in tumor growth with use of only maitake compared to a 45% with chemotherapy alone. However, a 98% inhibition in tumor growth was observed with combined therapy.<sup>4</sup> A survey of 671 cancer patients demonstrated that combining chemotherapy with maitake consumption also reduced adverse side effects, such as hair loss, leukopenia, pain and nausea, thus improving quality of life while undergoing treatment.<sup>4</sup>

### **HIV/AIDS**

Because maitake exhibited enhancement of helper T cell activity in early animal models, it has long been considered a potential treatment for HIV. The National Cancer Institute found significant dose-related *in vitro* antiviral activity in a sulfated maitake fraction, potency being similar to the anti-HIV drug AZT. Since this research was conducted in the early 1990s, further investigations have supported the use of MD-fraction in HIV/AIDS, leading to a year-long study in 35 HIV-infected individuals. Six grams of whole maitake was compared to 4 g plus 20 mg MD-fraction. While effects on helper T cells (CD4+) and viral load varied, 85% of participants reported an increased sense of wellbeing regarding symptoms and diseases secondary to HIV infection. Nanba and colleagues suggested that MD-fraction works by directly inhibiting HIV while also stimulating host defense, reducing vulnerability to opportunistic infections.<sup>3</sup>

### **Safety**

Animal studies have noted the non-toxic nature of whole maitake and the polysaccharide fractions.<sup>16</sup> The recent phase I/II trial of MD-fraction conducted with breast cancer patients by Memorial Sloan-Kettering Cancer Center found no dose-limiting toxicity.<sup>17</sup> Coupled with a lengthy history of use in multiple traditions, these data point to the likely safety of maitake and its fractions for use in healthcare. However, caution may be advised in individuals using immunosuppressive agents until maitake's immunomodulating activities are fully understood.<sup>4</sup>

### **Dosing**

Various studies have confirmed that oral administration of maitake and fractionated beta-glucans are highly effective.<sup>11</sup> A daily dosage of 300-2,400 mg of a hot water extract, containing a minimum of 20% beta-glucans is suggested by some practitioners, based on existing research and traditional use. Maitake is best taken on an empty stomach in divided doses. For immune support, a viable dose of the maitake fractions would be 0.5 – 1 mg per kg (2.2 lbs) body weight per day.<sup>4</sup> For a 140 lb adult, the dose would

*Originally published in the Summer 2009 issue of Unified Health, a practitioner publication of Innate Response (www.innateresponse.com).*

then approximate 32 – 64 mg/day, the mid-range of which is equivalent to the amount found in about 12 g of maitake fruiting body.<sup>3</sup>

### Conclusion

While much research has focused on the use of the purified beta-glucan fractions of maitake, use of whole powdered mushroom in addition to fractions or alone has also demonstrated a variety of benefits. Particular applications of whole maitake are hypertension, liver disease, obesity and elevated cholesterol and triglycerides. It is also believed that the adaptogenic benefits of maitake are found only in whole mushroom.<sup>3</sup> If we look to the traditional use and effectiveness of long-decocted whole mushrooms, we might suspect that the complex composition of maitake, which includes a variety of polysaccharides and amino acids, contains synergistic chemistry which is not yet understood and which is likely essential to the overall activity and safety of this fungus. As with foods, whole herbs are most often best, particularly when used for general health maintenance. In the case of chronic disease, it seems the fractions are of great value and are rendered even more effective when paired with whole mushroom. Further, in what may be a model for healthcare in the future, a combination of whole maitake, isolated constituent and conventional drug therapy appears to be the optimum approach to some of the most significant health concerns of our time.

### REFERENCES

1. Lincoff GH. *The Audubon Society Field Guide to North American Mushrooms*. New York, NY: Alfred A. Knopf, Inc.; 1981.
2. Lieberman S, Babal K. *Maitake: King of Mushrooms*. New Canaan, CT: Keats Publishing, Inc.; 1997.
3. Mayell M. Maitake extracts and their therapeutic potential. *Altern Med Rev*. Feb 2001;6(1):48-60.
4. Stengler M. *The Health Benefits of Medicinal Mushrooms*. Laguna Beach, CA: Basic Health Publications; 2005.
5. Borchers AT, Krishnathurthy A, Keen CL, Meyers FJ, Gershwin ME. The immunobiology of mushrooms. *Exp Biol Med*. 2008; 233:259-276.
6. Tada R, Adachi Y, Ishibashi K, Ohno N. An unambiguous structural elucidation of a 1,3-beta-D-glucan obtained from liquid-cultured grifola frondosa by solution NMR experiments. *Carbohydr Res*. Feb 17 2009;344(3):400-404.
7. Kabir Y, Yamaguchi M, Kimura S. Effect of shiitake (*lentinus edodes*) and maitake (*grifola frondosa*) mushrooms on blood pressure and plasma lipids of spontaneously hypertensive rats. *J Nutr Sci Vitaminol (Tokyo)*. Oct 1987;33(5): 341-346.
8. Kubo K, Nanba H. Anti-hyperliposis effect of maitake fruit body (*grifola frondosa*). I. *Biol Pharm Bull*. Jul 1997;20(7):781-785.
9. Kodama N, Yamada M, Nanba H. Addition of maitake D-fraction reduces the effective dosage of vancomycin for the treatment of listeria-infected mice. *Jpn J Pharmacol*. Dec 2001;87(4):327-332.

Originally published in the Summer 2009 issue of *Unified Health*, a practitioner publication of *Innate Response* ([www.innateresponse.com](http://www.innateresponse.com)).

10. Akramiene D, Kondrotas A, Didziapetriene J, Kevelaitis E. Effects of beta-glucans on the immune system. *Medicina (Kaunas)*. 2007;43(8):597-606.
11. Vetvicka V, Vetcickova J. Immunostimulating properties of two different beta-glucans isolated from maitake mushrooms (*grifola frondosa*). *JANA*. 2005;8(3):33-39.
12. Masuda Y, Murata Y, Hayashi M, Nanba H. Inhibitory effect of MD-fraction on tumor metastasis: Involvement of NK cell activation and suppression of intercellular adhesion molecule (ICAM)-1 expression in lung vascular endothelial cells. *Biol Pharm Bull*. Jun 2008; 31(6):1104-1108.
13. Kodama N, Komuta K, Sakai N, Nanba H. Effects of D-fraction, a polysaccharide from *grifola frondosa* on tumor growth involve activation of NK cells. *Biol Pharm Bull*. Dec 2002; 25(12):1647-1650.
14. Nanba H, Kubo K. Effect of maitake D-fraction on cancer prevention. *Ann N Y Acad Sci*. Dec 29 1997; 833:204-207.
15. Pyo P, Louie B, Rajamahanty S, Choudhury M, Konno S. Possible immunotherapeutic potentiation with D-fraction in prostate cancer cells. *J Hematol Oncol*. Dec 4 2008;1:25.
16. Kodama N, Komuta K, Nanba H. Can maitake MD-fraction aid cancer patients? *Altern Med Rev*. Jun 2002;7(3):236-239.
17. Deng G, Lin H, Seidman A, et al. A phase I/II trial of a polysaccharide extract from *grifola frondosa* (maitake mushroom) in breast cancer patients: Immunological effects. *J Cancer Res Clin Oncol*. Mar 1 2009.