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Maitake Mushroom (*Grifola frondosa*): Systematic Review by the Natural Standard Research Collaboration

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The objective of this study was to evaluate the scientific evidence on maitake, including expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing. This review serves as a clinical support tool. Electronic searches were conducted in 10 databases, 20 additional journals (not indexed in common databases), and bibliographies from 50 selected secondary references. No restrictions were placed on the language or quality of the publications. All literature collected pertained to efficacy in humans, dosing, precautions, adverse effects, use in pregnancy and lactation, interactions, alteration of laboratory assays, and mechanisms of action. Standardized inclusion and exclusion criteria were used for selection. Grades were assigned using an evidence-based grading rationale. There was a lack of systematic study on the safety and effectiveness of maitake in humans. However, based on popular use and supportive scientific data, three indications are discussed in this review: cancer, diabetes, and immunostimulation. Despite the lack of scientific evidence, maitake mushroom remains a popular agent in commercial products. Future randomized controlled trials are warranted.

Key words: *beta-glucan,* Grifola frondosa, *herbs and supplements, interactions, maitake, pharmacology, systematic review*

Maitake is the Japanese name for the edible fungus *Grifola frondosa*, which is characterized by a large fruiting body and overlapping caps. The name *maitake* stems from the Japanese word *mai*, which means "dance," and *take*, which means "mushroom." In Asia, maitake is used as a food and extracts are recommended medicinally for a number of health conditions, including arthritis, hepatitis, and human immunodeficiency virus (HIV). Some herbal experts describe medicinal mushrooms as behaving as adaptogens, which are agents that perform general, broad-based actions in the body to increase immunity, build endurance, and reduce fatigue. Recent attention has focused on possible immune and antitumor effects, and maitake is sometimes recommended to cancer patients.

Various fractions of the mushroom have been isolated in Japan over the past 40 years with the aim of isolating β-glucans with potent medicinal properties. These include the D-fraction and, more recently, the MD-fraction. The protein bound maitake D-fraction is the acid-insoluble, alkali-soluble, and hot water–extractable fraction,[1,2] with a molecular weight of about 1 million Daltons. The MD-fraction has a unique chemical structure and is thought to have fewer impurities than the D-fraction.

Polysaccharide constituents of maitake have been associated in animal studies with multiple bioactive properties. Extracts of maitake mushroom, particularly the β-glucan polysaccharide constituent, have been associated with immunomodulation in preclinical studies and are hypothesized to exert antitumor effects as a result of these immune properties. Human data are limited, and at this time, there is insufficient evidence to recommend for or against the use of oral maitake for any indication.

Methods

Natural Standard (<http://www.naturalstandard.com>) is a clinical resource tool that aims to provide clinicians and consumers with all of the evidence on safety and efficacy surrounding integrative therapies to allow health care professionals and consumers to make informed decisions about their health and the products they use. To prepare each Natural Standard review, electronic searches (June 2008) are conducted in 10 databases, including *AMED*, *CANCERLIT*,

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CINAHL, *CISCOM*, the *Cochrane Library*, *EMBASE*, *HerbMed*, *International Pharmaceutical Abstracts*, *Medline*, and *NAPRALERT*. Search terms include all of the common names, scientific names, and listed synonyms for each topic.* Hand searches are conducted in 20 additional journals (not indexed in common databases) and of bibliographies from 50 selected secondary references. No restrictions are placed on the language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) are consulted for access to additional references or ongoing research. All literature is collected pertaining to efficacy in humans (regardless of study designs, quality, or language), dosing, precautions, adverse effects, use in pregnancy and lactation, interactions, alteration of laboratory assays, and mechanisms of action (in vitro, animal research, human data). Standardized inclusion and exclusion criteria are used for selection. Data extraction and analysis are performed by health care professionals conducting clinical work and/or research at academic centers using standardized instruments that pertain to each review section (defining inclusion and exclusion criteria and analytic techniques, including validated measures of study quality based on the Jadad score[3]; see Table 1 for a description of validated grading scale for efficacy). Data are verified by a second reviewer. Blinded review is conducted by multidisciplinary research–clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the editorial board addresses conflicts and consults experts when applicable. The authors of studies are contacted when clarification is required.

Results

The popularity of maitake is largely due to its traditional use in Chinese cultures for its purported immunoenhancing

Table 1. Natural Standard Grading Scale

Level of Evidence Grade	*Criteria*
A (strong scientific evidence)	Statistically significant evidence of benefit from > 2 properly randomized controlled trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from ≥ 1 properly conducted meta-analysis, OR evidence of benefit from > 1 cohort/case-control/nonrandomized trials AND with supporting evidence in basic science, animal studies, or theory. *This grade applies to situations in which a well-designed RCT reports negative results but stands in contrast to the positive efficacy results of multiple other less well-designed trials or a well-designed meta-analysis, while awaiting confirmatory evidence from an additional well-designed RCT.*
C (unclear or conflicting scientific evidence)	Evidence of benefit from ≥ 1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,† OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from ≥ 1 cohort/case-control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically significant negative evidence (ie, lack of evidence of benefit) from cohort/case-control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit. *This grade also applies to situations in which > 1 well-designed RCT reports negative results, notwithstanding the existence of positive efficacy results reported from other less well-designed trials or a meta-analysis. (Note: If there are ≥ 1 negative RCTs that are well designed and highly compelling, this will result in a grade of "F" notwithstanding positive results from other less well-designed studies.)*
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e. lack of evidence of benefit) from ≥ 1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.†

Adapted from Natural Standard. Available at: http://www.naturalstandard.com (accessed February 2009).
Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication. Expert opinion and folkloric precedent are not included in this assessment. Evidence of harm is considered separately; the grades apply only to evidence of benefit.
†Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad and colleagues, in which a score below 4 is considered to indicate lesser quality methodologically.[3]

**Maitake synonyms/common names/related substances*: Beta-glucan, cloud mushroom, dancing mushroom, edible fungus, exo-biopolymers, *Grifola frondosa* HB0071, grifolan, Grifron® Pro D-fraction, king of mushroom, maitake PETfraction, Meripilaccae (family), MD-fraction, MDF, my-take, Polyporaceae (family).

effects. Surveys focusing on the prevalence of maitake are lacking in the available literature, although maitake has been casually mentioned in reports of adjunct or integrative approaches to cancer and is popularly marketed on Internet Web sites as having immunoenhancing effects. Our search methodology did not yield any high-quality human studies that qualified for inclusion. However, available animal and laboratory data suggested three areas of active research, as well as several theoretical or historical uses that lack sufficient evidence. Dosing, safety, interactions, and effectiveness results are discussed below.

Dosing

β-Glucan contents may vary between preparations. Various fractions of maitake, such as D-fraction, may be prepared via standardized processes, although it is not clear that different products are comparable. In adults, maitake has been taken as capsules, tablets, and liquid extract. Doses of 0.5 to 1 mg/kg daily of β-glucan from maitake have been taken in divided doses. Human study is limited, and safe and effective doses have not been established for commercial products or raw mushrooms. Insufficient evidence is available on the dosing used in pediatric populations.

Safety

Maitake has not been systematically assessed in humans with regular or high-dose use, and the effects are largely unknown. Safety in low doses is often assumed based on traditional use as a food. Maitake is likely unsafe when used in patients who are allergic or hypersensitive to maitake mushroom (*G. frondosa*) or any of its constituents. Should allergy arise, one case report documents the use of aerosol corticosteroid to treat occupational hypersensitivity pneumonitis caused by *G. frondosa*.[4] There is a lack of available evidence investigating the use of maitake in pregnant or lactating women.

In the absence of human reports, animal study suggests possible precautions and warnings. For instance, chronic oral use of maitake mushrooms in spontaneously hypertensive rats for 8 to 10 weeks was associated with reduced blood pressure.[5,6] Because various preparations (eg, whole maitake, D-fraction, MD-fraction, maitake, and vitamin C) have been used in both animal and human studies, it is unclear how the doses used in these animal studies (based on body weight) are comparable to doses used in humans. The clinical significance is unclear.

Animal research also suggests that oral maitake has hypoglycemic properties,[7–9] although human data are limited in this area.[10]

Interactions

Despite a lack of systematic study and reported interactions, maitake may interact with herbs, supplements, drugs, foods, or laboratory tests. The interactions listed below are theoretical and based on animal or laboratory studies. Human evidence is lacking in this area, although caution is advised.

- *Antidiabetic agents.* Animal research suggests hypoglycemic properties of oral maitake,[7–9,11,12] although human data are limited in this area. A reduction in fasting blood glucose was found in the subjects, but evidence is lacking to conclude on the degree of effect.[10]
- *Antihypertensive* agents. Animal studies have reported reduced blood pressure with chronic oral use of maitake mushrooms (8–10 weeks).[5,6] Human reports and/or interactions with antihypertensive agents are currently lacking in the available literature.
- *Antineoplastic agents.* Theoretically, maitake mushroom may work synergistically with antineoplastic agents, such as mitomycin C.[13,14] Based on laboratory and animal studies as well as manufacturer reports, there is controversy as to whether maitake mushroom can induce apoptosis or whether its main action is as an adaptogen or immunostimulant.[15–17]
- *Antiviral agents.* A novel antiviral (anti-herpes simplex virus) protein has been purified from an extract of *G. frondosa*.[18] The hepatitis B virus has been inhibited by D-fraction from *G. frondosa*, and a synergistic effect of combination with interferon-α in HepG2 2.2.15 has been observed.[19]
- *Immunosuppressants.* Based on animal and in vitro studies, maitake mushroom may alter the effectiveness of immunosuppressants.[16,20–23]
- *Interferons.* The hepatitis B virus has been inhibited by D-fraction from *G. frondosa*, and a synergistic effect of combination with interferon-α in HepG2 2.2.15 was observed.[19]
- *Food.* Insufficient evidence is available.
- *Laboratory tests.* Insufficient evidence is available.

Efficacy

Maitake has been used for hundreds of years in traditional medicine, but validation of its efficacy using randomized, controlled trials is lacking. Currently, there is preliminary evidence for cancer, diabetes, and immunostimulation, which is based on animal and laboratory data as well as case series. Summaries of findings are presented below, along with grades of effectiveness, which are based on objective grading criteria (see Table 1). A condition, disease, or function can

receive a grade when there is popular use in humans with or without supportive evidence from basic science or theory or emerging human evidence in the literature.

Cancer	C
Diabetes	C
Immunostimulation	C

Cancer

Maitake is a popularly used cancer therapy. Maitake extracts have been demonstrated in animal studies to stimulate immune function and potentially to prompt host-mediated antitumor activity,[24–30] although some small studies have not found any effects.[31] Multiple antitumor mechanisms have been proposed based on the results of in vitro and animal research.[16,17,22,28,32–39] According to Nanba, maitake has the strongest activity in tumor growth inhibition when administered orally and intraperitoneally.[13] In animal study, maitake extract D-fraction is effective not only on the inhibition against tumors already growing but also on the inhibition of formation of the secondary focus owing to metastasis of tumor cells in lymph and/or blood. Nanba conducted a nonrandomized clinical study to assess the effects of maitake D-fraction in 165 advanced cancer patients.[13] Patients received maitake D-fraction as crude powder tablets alone or in addition to chemotherapy. The author suggested that maitake is effective against breast, liver, and lung cancer but less effective against leukemia and stomach and bone cancers based on this study. For instance, tumor regression or significant symptom improvements were observed among 11 of 15 breast cancer patients, 12 of 18 lung cancer patients, and 7 of 15 liver cancer patients. If maitake was taken with chemotherapy, these response rates improved by 12 to 28%. Patients under the maitake treatment claimed improvement in overall symptoms one way or another, even when tumor regression was not observed. Various side effects from chemotherapy were ameliorated among 90% of the patients. Reduction of the pain was also reported from 83% of the patients. Lack of blinding and randomization, no definitions for tumor regression or symptom improvement, and an unclear description make interpretation of these results difficult. Kodama and colleagues reported the results of a case series in human patients with various types of cancer at a variety of stages.[40] A combination of whole maitake powder and the MD-fraction of maitake mushroom (containing β-1,6 glucan) was administered orally to subjects and was possibly associated with tumor regression or symptomatic improvement in 58% of liver cancer patients, 69% of breast cancer patients, and 63% of lung cancer patients. A < 20% improvement was observed for leukemia and stomach and brain tumors. However, the baseline patient characteristics and history of disease and therapy were not universally clear. Tumor regression was not according to standard accepted criteria, and symptomatic improvement was not well defined. In addition to unclear analysis, there are unresolved questions concerning the authors' descriptions of the cancer types and stages. Although the study is of interest, the lack of controls diminishes the clinical applicability of the results. Systematic human data are lacking in this area, although nonsystematic reviews suggest a theoretical basis for this use.[41–45] Therefore, a recommendation cannot be made either for or against the use of maitake for cancer treatment or prevention.

Diabetes

Multiple animal studies have demonstrated the hypoglycemic effects of maitake mushroom extracts. In insulin-resistant mice, a water-soluble maitake extract ("fraction X") has been associated with enhanced peripheral insulin sensitivity.[8] Decreased blood glucose levels and glucosuria and elevated serum insulin levels have been found with dietary maitake extract in experimentally diabetic mice.[7,9] Human evidence is limited in this area, and although a reduction in fasting blood glucose was found in the subjects, evidence is lacking to conclude on the degree of effect.[10] Without additional evidence, a recommendation cannot be made either for or against the use of maitake in the management of diabetes or hypoglycemia.

Immunostimulation

Animal research suggests possible immunomodulatory properties of oral maitake extracts. In preclinical studies, the D-fraction of maitake, a β-glucan extract, has been associated with activation of cellular immunity (specifically helper T cells), decreased activation of B cells, and increased production of interferon-γ, interleukin-12 p70, and interleukin-18 but suppression of interleukin-4.[16,20] Studies of antitumor effects have implicated maitake extracts in the enhancement of lymphocyte and macrophage activity. Reliable human data are lacking. Without additional evidence, a recommendation cannot be made either for or against the use of maitake as an immunostimulant.

Other

In addition to the indications described above, numerous historical or theoretical uses were found in the literature or in manufacturer claims, but they lacked sufficient evidence. These uses are presented here but not described in detail owing to insufficient available evidence: antifungal;

anti-infective; antiviral; arthritis[46]; bacterial infection[47]; chickenpox; diagnostic agent; hepatitis[46,48]; HIV; hypercholesterolemia[5,49,50]; hypertension[6]; snake bites; warts; and weight loss.

Conclusion

Based on this review, preliminary evidence suggests theoretical interactions and potential uses, but there is a lack of information corroborating the traditional uses of this medicinal mushroom. High-quality scientific evidence that investigates the safety and efficacy of maitake as an integrative therapy is recommended.

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