Maitake mushroom (Grifola frondosa) is a Basidiomycete fungus belonging to the order Aphyllophorales, family Polyporaceae (1, 2). The name maitake is Japanese and means dancing mushroom. In English, the fungus is also known as hen-of-the-woods or sheep’s head. The fruiting body of maitake often occurs as a heavy mass at the base of stumps and on the roots of oaks, elms, persimmons, and other trees. Parts of northeastern Japan are especially hospitable for maitake, although human foraging and landscape alternation have combined to limit availability of this fungus in the wild. Maitake can also be found in the northern temperate forests of Asia, Europe, and eastern North America (3). Because of its enticing taste, maitake has been praised and consumed by the Chinese people for hundreds of years. Moreover, the medicinal properties of maitake have been asserted for years and many such claims have been corroborated with scientific analysis. For instance, maitake has been shown to have antitumor effects, immune regulatory activity, anti-hyperliposis, as well as specific infection effects on diseases such as hepatitis (1). The most important compounds in maitake are the polysaccharides β-glucans, especially β-1,6- and β-1,3-glucans, which are usually referred to as D-fraction or MD-fraction, respectively. Maitake provides B vitamins, ergosterol/provitamin D2, magnesium, potassium, calcium, unsaturated fatty acids, phosphatidylerine and other phospholipids, as well as protein.

This summary takes a brief look at the medicinal properties of maitake, and includes review of its use in attenuating tumor growth and mitigating the downside effects of chemotherapeutic drugs. Also discussed is the immunomodulatory benefits of maitake, its potential use in treating diabetes and HIV, and its antioxidant properties.
ANTITUMOR EFFECT

Maitake fractions in particular seem to have a specific antitumor action, potentially slowing the growth of tumors in the colon, lungs, stomach, liver, prostate, brain, and other organs. Researchers of maitake have identified several ways that maitake can counter cancer: (a) by protecting healthy cells from becoming cancerous; (b) by helping to prevent metastasis; and (c) by slowing or stopping the growth of tumors. A fourth potential use of maitake is to enhance the benefits of chemotherapeutic drugs while reducing the undesirable side effects. Common side effects of chemotherapy include hair loss, pain, and nausea, among other adverse reactions. Figure 1 shows how chemotherapy combined with maitake ameliorates many of the acute downsides of cancer treatment (3).

A study by Masuda et al. (4) demonstrated that D-fraction of Grifola frondosa in combination with cisplatin (i.e., CDDP, a widely used anticancer drug with serious side effects), significantly enhanced antitumor and antimetastatic activity compared to CDDP alone. Although CDDP treatment resulted in decreased total weight of the body and the spleen in particular, D-fraction reduced weight loss in comparison to control treatments that lacked maitake exposure. In addition, CDDP-treated mice with D-fraction showed a relatively lower loss of immunocompetent cells such as macrophages, dendritic cells (DCs), and natural killer (NK) cells. D-fraction in combination with CDDP not only increased the number of immunocompetent cells, but also induced interleukin (IL)-12p70 production by splenocytes, resulting in increased NK cell activity. These results indicate that D-fraction exhibits antitumor and antimetastatic activity by strongly enhancing innate immunity. Moreover, this study shows that D-fraction can reduce nephrotoxicity, which is one of the major dose-limiting toxicities of CDDP. Because D-fraction in combination with CDDP not only enhances antitumor and antimetastatic activity but also reduces CDDP-induced myelotoxicity and nephrotoxicity, the combined treatment of D-fraction with cisplatin should be useful in the treatment of cancer.

Figure 1. Amelioration of chemotherapeutic side effects by D-fraction (n=455) (3).
Lin et al. (5) used a colony forming units assay of normal mice to test the dose-response to maitake D-fraction on bone marrow suppression caused by the chemotherapeutic drug doxorubicin (DOX). Normal mouse bone marrow CFU-GM progenitor cell activity was significantly increased in the presence of D-fraction in the dose range of 50–100 Ag/ml. The study further showed that toxicity of DOX on bone marrow is attenuated by D-fraction. Even without DOX, bone marrow cell viability is dramatically decreased within 24 h without the support of in vitro growth factor. Moreover, Lin and colleagues observed that D-fraction protected the bone marrow progenitor cells from irreversible damage associated with prior DOX induced toxicity, suggesting that D-fraction supports maintenance or viability of bone marrow progenitor cells in the face of DOX toxicity. Furthermore, D-fraction treatment promoted the recovery of hematopoiesis from bone marrow following pretreatment with DOX. These data indicate that D-fraction directly affects bone marrow cell survival from DOX and that D-fraction of maitake has the potential to reduce hematopoietic suppression induced by chemotherapy.

Kodama et al. (6) investigated the benefits of D-fraction and mitomycin-C (MMC), an anticancer agent with deleterious side effects, in tumor-bearing mice. They demonstrated that by enhancing the T helper (Th)1-dominant response, D-fraction decreases the amount of MMC required to manage cancer. Although further studies are required to clarify whether combined therapy using D-fraction is effective, this study has indicated a potential benefit when applied with MMC in the therapy of patients with cancer.

The sulfated derivate (S-GAP-P) of water-insoluble polysaccharide produced by maitake was tested with the anticancer chemotherapeutic agent cyclophosphamide (CTX). S-GAP-P exhibited distinct anti-proliferative effects on human gastric carcinoma SGC-7901 cells and induced apoptosis in a dose-dependent manner, but had no effects on mouse sarcoma S180 cells. The in vivo experiments showed that S-GAP-P significantly inhibited tumor growth and enhanced macrophage phagocytosis in S180-bearing mice. It is noteworthy that S-GAP-P could accelerate the antitumor activity of CTX and partially reverse the immunocompetence induced by CTX.

A result reported by Matsui et al. (8) suggests that, in addition to activating immunocompetent cells, D-fraction also has an antitumor effect, i.e., the reduction of carcinoma angiogenesis. However, an earlier study reported that angiogenesis is essential for the carcinoma cells as the means of securing nutrient composition, oxygen supply, and emission of metabolic wastes; thus, the antitumor effect of D-fraction is caused by the reduction of angiogenesis. Moreover, they showed that the TNF-α produced by macrophages causes direct damage to carcinoma cells as well as stimulating macrophages to produce a vascular angiogenesis factor. Matsui and colleagues suggest that D-fraction enhances TNF-α production by macrophages, which implies that induction of vascular angiogenesis and the antitumor effect of D-fraction are closely related processes.

**IMMUNOLOGICAL EFFECTS**

Numerous studies have confirmed that maitake has remarkably beneficial effects on immune function. For instance, maitake promotes the action of not only macrophages, but it also enhances a variety of other constituents of immune-related function such as NK cells and cytotoxic T-cells that attack tumors. Maitake also increases the immune-related efficiency of these cells by increasing IL-1, IL-2, and lymphokines.
In a phase I/II dose-escalation trial conducted by Deng et al. (9), 34 postmenopausal breast cancer patients of age 38–77 who were free of disease after initial treatment, were enrolled sequentially in each of five cohorts. Maitake liquid extract was taken by mouth twice daily for 3 weeks at 0.1, 0.5, 1.5, 3, and 5 mg/kg. Peripheral blood was collected at days −7, 0 (i.e., prior to the first dosing), 7, 14, and 21 for ex vivo analyses. The primary endpoints were safety and tolerability. In this trial, Deng and coworkers showed that (a) oral administration of maitake mushroom extract is associated with significant changes in certain immunologic parameters in the peripheral blood; (b) maitake extract appears to have a stimulatory effect on some parameters and a suppressive effect on others; and (3) the “optimal dose” of maitake extract, i.e., the dose associated with the largest immunological effect, varies for different immunological parameters. The result of this phase I/II trial of breast cancer survivors showed that oral administration of maitake medicinal mushroom extract over a 3-week period is well tolerated. No dose-limiting toxicity was experienced up to 10 mg/kg per day. However, the intermediate doses (5–7 mg/kg per day) were associated with the most striking functional changes, including increased production of IL-2, IL-10, TNF-α and IFN-γ by subsets of T cells. These results suggest that this medicinal mushroom extract is more appropriately viewed as an immunomodulator, rather than as an immune enhancer.

**SKIN BENEFITS**

In a controlled design with rats, Xu et al. (10) found that treatment with maitake polysaccharide is beneficial for those with skin diseases. Skin TNF-α, IgG content, T lymphocytes and caspase-3 mRNA were compared between different groups of rats.
In a search for functional cosmetic ingredients from mushrooms, Lee et al. (2) produced five groups of polysaccharides by submerged culture of maitake and investigated their diverse biological activities. These bioactivities included efficacy of antioxidants, free radical scavenging after UV irradiation, proliferation of fibroblasts, and collagen biosynthesis. Most polysaccharides had antioxidant and free radical scavenging activities after UV irradiation. The result suggests that maitake polysaccharides can be potent ingredients for cosmetic and other biological applications.

TREATMENT FOR HIV

In the late 1980s, Japanese researchers determined in a non-controlled animal trial that oral doses of maitake D-fraction exhibited an enhancing effect on helper T-cells, the target cells of HIV. This was one of the earliest clinical indications that maitake may be a potential treatment for HIV. In November, 1991, a sulfated maitake fraction was found to be active in a preliminary anti-HIV drug screening test conducted by the National Cancer Institute (NCI). According to the In Vivo Testing Project of the NCI's Developmental Therapeutics Program, the maitake test compound showed significant dose-dependent antiviral activity. Although the sulfated maitake fraction resembled the anti-HIV potency of AZT (zidovudine, formerly azidothymidine), it was not considered a promising treatment because of potential in vivo cellular toxicity. More recently, however, much of the research into the immunomodulating effects of D-fraction supports its potential use against HIV. The D-fraction was also the subject of a recent long-term human study on its potential benefits to HIV-infected patients.

DIABETES TREATMENT

Polysaccharides of maitake have been shown to lower blood glucose in diabetic mice, suggesting their potential use in treating diabetes sufferers. Konno et al. (11) investigated a blood sugar-reducing effect of maitake polysaccharides that may be associated with activation of insulin receptors in insulin-targeted cells.
A study by Hong et al. (1) showed that α-glucan of maitake (i.e., MT-α-glucan) has hypoglycemic and hypolipidemic activity in the mouse model of type 2 diabetes. Treatment with MT-α-glucan at 300 or 100 mg/kg decreased levels of fasting plasma glucose, triglycerides, cholesterol, and free fatty acid. MT-α-glucan also improved the proliferative response of macrophages and IL-1. Moreover, MT-α-glucan also increased levels of serum insulin and enhanced the proliferative response and IL-2 production of splenocytes induced by concanavalin A (ConA). Hong and colleagues also showed that MT-α-glucan improves immune function that has been disrupted in type 2 diabetes. This improvement is manifest in protective immune reactions and by decreasing levels of β-cell-destroying immune factors, which in turn attenuate the degree of injured β-cells in the pancreatic islets, and consequently exert a protective effect on pancreatic β-cells.

A subsequent study by Hong et al. (12) explored the protective effect of MT-α-glucan on NIT-1 pancreatic β-cells damaged by streptozotocin (STZ) in vitro. Moreover, the protective action of MT-α-glucan on pancreatic β-cells under oxidative stress and NO in vitro were also investigated. The study demonstrated that MT-α-glucan protects pancreatic β-cells damaged by streptozotocin (STZ) in vitro. This mechanism may promote cellular defense by decreasing lipid per-oxidation and NO toxicity, increasing antioxidant enzyme activity and, consequently, preserving the integrity and function of pancreatic β-cells.

**ANTIOXIDANT EFFECTS**

A study by Chen et al. (13) reports the antioxidant activities of three main polysaccharides fractions prepared from maitake fruiting body. The results were collected in different in vitro assay systems and included the scavenging effects on DPPH radical, hydroxyl radical and superoxide radical, the reducing power, the ferrous ions chelating effect, and the ability to inhibit the rat liver lipid oxidation. Together these assays demonstrated that purified fractions of maitake polysaccharides are effective antioxidants. Hence, maitake polysaccharides can be used as an easily accessible source of natural antioxidants, as a food supplement, or in the pharmaceutical and medical industries.

Fan et al. (14) analyzed the relationship between the physical properties and antioxidant activity of polysaccharides extracted from maitake with boiling water and enzymolysis. The highest antioxidant activity was exhibited by extracts prepared with combined enzyme extraction. The correlation analysis between antioxidant activity, polysaccharide content, protein content, and molecular weight (Mw) or viscosity indicated that Mw had a more important role in antioxidant activity. Overall the results indicate that the combined enzyme polysaccharide extracts can be developed as a natural antioxidant.
Maitake is a Basidiomycete fungus that often occurs at the base of stumps and on the roots of oaks, elms, persimmons, and other trees. Maitake can be found in the northern temperate forests of Asia, Europe, and eastern North America. It is well known for its enticing taste, but there is now increasing interest in the medicinal properties of this fungus. The most important compounds in maitake are the polysaccharides β-glucans, especially β-1,6- and β-1,3-glucans.

Maitake researchers have identified several ways that the fungus can counter cancer: (a) by protecting healthy cells from becoming cancerous; (b) by helping to prevent cancer metastasis; (c) by slowing or stopping the growth of tumors; and (d) by working in conjunction with cancer treatment to diminish the unwanted side effects of chemotherapeutic drugs. Several studies have shown that D-fraction of maitake exhibits antitumor and metastasis-inhibiting activity by strongly enhancing innate immunity.

D-fraction directly protects bone marrow cells exposed to the cancer-fighting drug DOX. It is more accurate to view maitake extract as an immunomodulator rather than as an immune enhancer. Much of the research into the immunomodulating effects of D-fraction supports its potential use against HIV.

Studies have shown that α-glucan of maitake has hypoglycemic and hypolipidemic activity in the mouse model of type 2 diabetes, and that purified fractions of maitake polysaccharides have effective antioxidant activities.

DISCLAIMER

Statements throughout this publication have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease process.
REFERENCES


