



Medicinal Mushrooms for Immunotherapy: The Power of Black Maitake Extract

Overview

Mushrooms have been used for centuries in Asia for their nutritional properties and as traditional medicines. Modern research supports the medicinal value of several types of mushrooms, including maitake, and medicinal mushrooms are used in clinical practice in Japan and China to augment certain therapies, including cancer treatments ^{1,2}.

Although the consumption of whole mushrooms provides health benefits, there is a growing market for the use of extracts of medicinal mushrooms as nutritional supplements with high therapeutic potential ³. Depending upon the mushroom species used as the source, the health benefits of mushroom extracts can include:

- antitumour and anticancer effects
- immunomodulation, including boosting the immune system
- reduction of cancer spread (metastasis)
- anti-oxidant effects
- anti-angiogenic effects
- antimicrobial properties
- anti-inflammatory properties
- lower cholesterol and blood glucose levels ⁴

The health benefits of medicinal mushrooms are achieved through various bioactive compounds, of which a group of polysaccharides called beta-glucans are of particular value. As will be discussed in this report, a substantial body of research indicates that beta-glucans can boost the immune response against cancer cells, reduce tumour growth, and enhance the effects of other cancer treatments.

A few facts about mushrooms...

Although they may appear physically similar to plants, mushrooms are fungi and belong to the same biological kingdom (the Kingdom Fungi) that includes yeasts and molds. There are thousands of species of fungi, and the term “mushroom” commonly refers to the fruiting bodies found in some members of the basidiomycetes, i.e., the Basidiomycota division of the fungal kingdom. Fruiting bodies are the reproductive structures for these types of fungi and contain spores that disseminate the species.

When spores find a suitable substrate, such as a tree stump or soil rich in organic matter, they germinate into hyphae, which are thread-like structures that constitute the major “unseen” portion of the fungi. A network of hyphae is called a mycelium (Figure 1), much of which remains embedded in the substrate that serves as the food source for the fungus (mushroom).

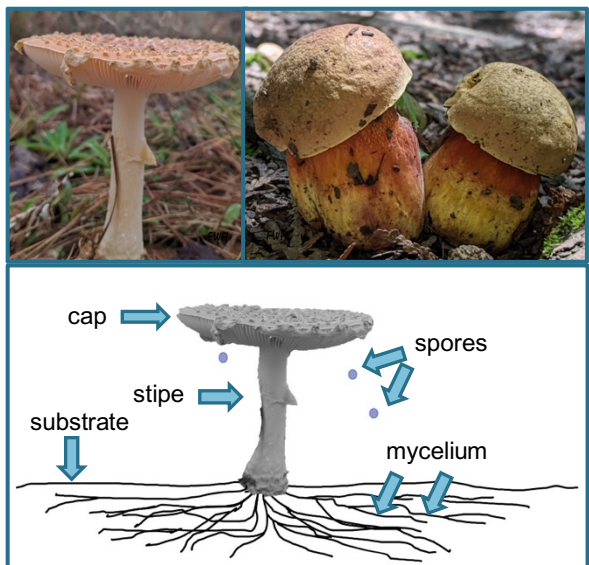


Figure 1. Upper panel: wild mushroom species with “cap and stipe” fruiting bodies. Lower panel: illustration showing mushroom parts and mycelium embedded in soil or other substrate.

Many basidiomycetes produce fruiting bodies with the familiar cap and long stem or stipe (Figure 1). In contrast, some basidiomycetes, such as maitake (Figure 2) and other bracket or shelf fungi, produce more layered fruiting bodies that can have a scalloped or ruffled appearance. Maitake, pronounced “my-ih-ta-kay”, is also known as the ram’s head mushroom or hen-of-the-woods and by its more formal species name of *Grifola frondosa*.

Maitake is both a medicinal mushroom and a popular culinary mushroom, especially in Asia, although it is native to the hardwood forests of Europe and eastern North America as well as Asia⁵. As discussed later in this report, maitake

has only been recently cultivated, and compared to most other cultivated mushrooms, the individual fruiting bodies of maitake can grow to enormous sizes (Figure 2), a benefit both in culinary terms and for extracting compounds of medicinal value.



Figure 2. Fruiting body of maitake (*Grifola frondosa*). The flower-like head of this mushroom is about 20 cm (8 inches) wide.

Mushrooms are excellent sources of protein, minerals, vitamins, and fiber. Additionally, they supply beneficial bioactive compounds such as beta-glucans, other polysaccharides, flavonoids, triterpenoids, and lectins, among others⁴. However, the abundance of bioactive compounds can vary depending on the species and also the fungal structure, e.g., whole fruiting body versus stipes^{6,7} (Figure 1). Maitake is a particularly good source of beneficial beta-glucans⁸, and maitake extracts are categorized as a natural health product by Health Canada⁹.

What are beta-glucans?

Like the starches and cellulose found in plants, beta-glucans (β -glucans) are polysaccharides, which are carbohydrates consisting of long chains of sugars (saccharides). In beta-glucans,

these chains are made of beta-D-glucose, which may be linked to sugar side chains, resulting in branched structures¹⁰ (Figure 3). Although beta-glucans are also found in plants, fungal beta-glucans are structurally different from those of plants and can also differ in size, structure, and complexity among various fungi.

A variety of beta-glucans from medicinal mushrooms have been shown to have immunomodulatory properties, that is, they can modify immune responses; however, their effectiveness and type of bioactivity differ depending on their specific structure^{2,11}.

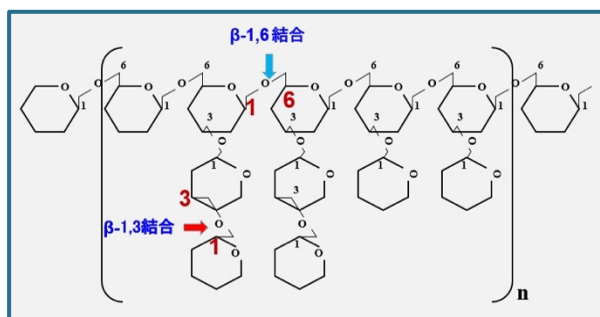


Figure 3. Structure of beta-glucan (β -glucan) from maitake. The complex structure of this β -glucan includes branching side chains and β -1,6 and β -1,3 linkages between the saccharide units. (Image: courtesy of H. Nanba)

Reported effects (bioactivities) of various beta-glucans include:

- stimulation of macrophages, natural killer cells, T cells, and other white blood cells that are important in fighting cancer and infectious diseases;
- enhanced production of immune-signalling proteins such as cytokines from white blood cells;
- inhibition of tumour cells and reduction of tumour cell spread;
- enhanced sensitivity of cancer cells to chemotherapy, among others^{4,12,13}.

Some of these bioactivities result from the binding of beta-glucans to specific receptors on immune cells^{2,8}. Additionally, clinical trials with beta-glucans from medicinal mushrooms report:

- increased stimulation of the immune system in patients with different types of cancers;
- reduction in side effects from chemotherapy;
- pain reduction;
- improvement in the quality of life and overall survival of cancer patients^{7,14}.

Notably, several fungal beta-glucans have been approved as adjuvant cancer therapies in Japan, Korea, and China, including a drug based on maitake beta-glucan^{7,14,15} (Figure 3).

What is known about the benefits of maitake immunotherapy in cancer and other diseases?

Multiple research studies report the immunotherapeutic benefits of maitake extracts for various diseases, with many of these studies suggesting therapeutic benefits against several types of cancer, such as:

- bladder cancer
- colon cancer
- breast cancer
- gastric cancer
- kidney cancer
- prostate cancer
- and systemic antitumour effects and inhibition of metastases¹⁶⁻²⁴.

Additional studies suggest benefits of maitake extracts in the treatment of diabetes type II, hepatitis B virus infection, and myelodysplastic syndromes (MDS)²⁵⁻²⁸. Notably, in mouse models of diabetes, maitake extracts improved glucose and lipid metabolism and protected pancreatic cells from oxidative damage^{26,27}. Overall, these studies support a range of health benefits of maitake extracts (Figure 4).

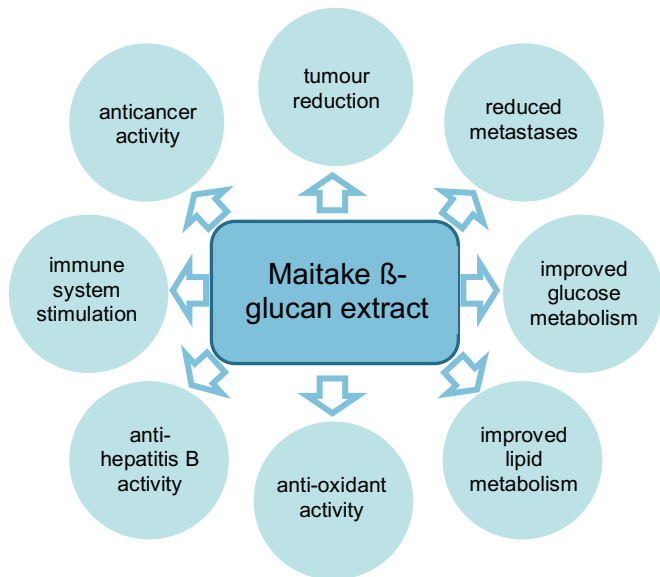


Figure 4. Health benefits of maitake beta-glucan extract indicated by research studies.

Some of the earliest experimental studies on the therapeutic potential of maitake were conducted in 1985 by Dr. Hiroaki Nanba and colleagues at Kobe Pharmaceutical University. Dr. Nanba's group prepared different fractions (separate portions) from the maitake fruiting body and found that some fractions exerted anticancer effects, enhanced the activation of macrophages, and also enhanced the production of cytokines ²⁹⁻³³

Administration of these active maitake fractions significantly reduced the development of cancer in mice exposed to a cancer-causing agent; in the control group that did not receive the maitake fractions, 93% of the mice developed cancer whereas the number was much lower (31%) in the group that also received maitake ³⁰, indicating that maitake helped to protect against the effects of the cancer-causing agent.

Dr. Nanba and colleagues also showed that active maitake fractions reduced the size of tumours in mice ²⁹. These active fractions contained large beta-glucans with a high degree of branching (Figure 3), features that are believed to enhance the ability of beta-glucans

to stimulate immune cells and induce cytokine production ^{7,32} (Figure 5).

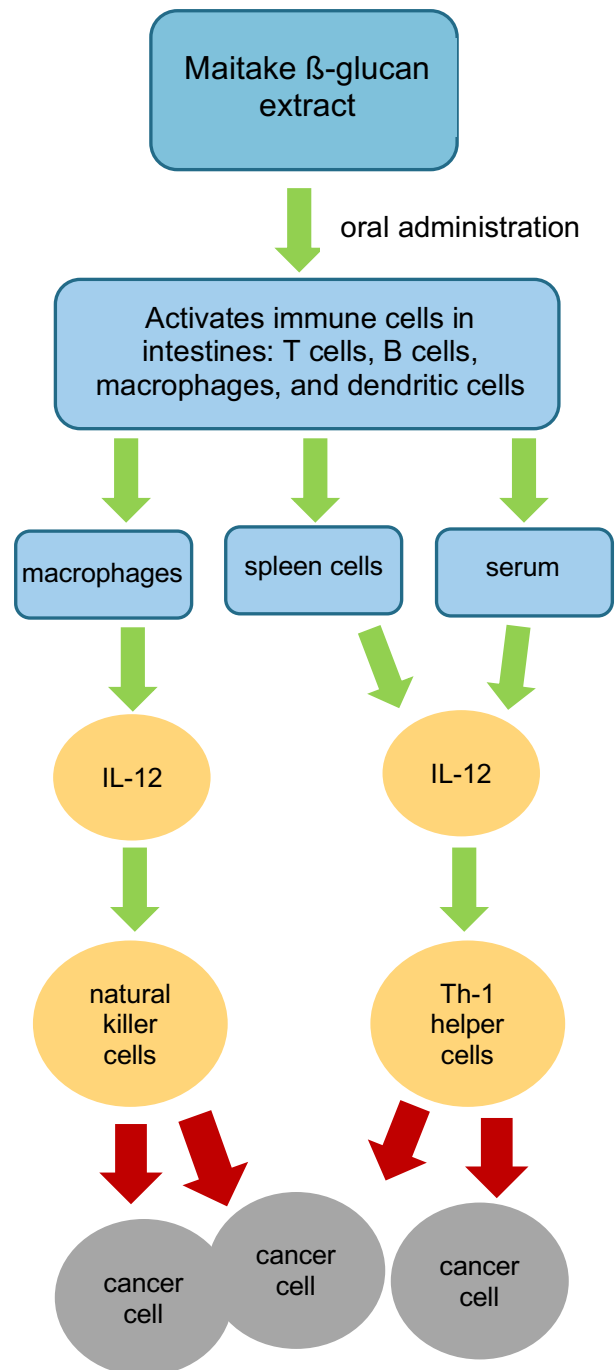


Figure 5. Effects of maitake beta-glucan extract on the immune system. Green arrows indicate activation of different components of the immune system, including the cytokine interleukin 12 (IL12). IL-12 and other cytokines stimulate white blood cells to fight cancer cells. (Image: based on illustration by H. Nanba, ref. 33)

Studies on cancer patients suggest that the suppression of tumours by active maitake fractions results from the activation of natural killer cells and increased presence of activated T cells (Figure 5), and from a reduction in special regulatory white blood cells that can suppress the immune system ^{16,34,35}. It should be noted that antitumour effects have been achieved using oral administration of maitake fractions (Figure 5) as well as by injection ^{16,29,30,36}.

Research Highlights:

In laboratory models, active maitake extract:

- reduced the development of breast cancer
- reduced the spread of breast cancer cells
- reduced the size of tumours
- increased the destruction of cancer cells

In a study that used a mouse model of breast cancer, administration of an active maitake fraction reduced the development of breast cancer by more than 60%, and animals that received this fraction exhibited less tumour invasiveness, had reduced growth of blood vessels to tumours (thereby reducing the supply of nutrients to the tumours), and also had improved overall survival ³⁶.

Although most studies suggest that the effects of beta-glucans on tumours result from the stimulation of the immune system ¹⁰, a 2017 study using the mouse model of breast cancer suggests that maitake active fractions may also work directly on tumour cells, causing a decrease in the viability and migration of tumour cells and reducing metastases (tumour cell spread) and tumour burden ³⁷.

Additionally, cancer cells, including breast cancer cells, exposed to maitake active extracts showed decreased viability and increased apoptosis (cell destruction) when compared to unexposed cells ^{22,38}. In laboratory models of tumour cell metastasis, maitake active extracts

also reduced the invasiveness of a highly aggressive type of breast cancer cell (triple-negative breast cancer cells) by 62% ³⁹ and reduced the size of tumours produced by breast cancer cells ^{39,40}. Further studies suggest that maitake active fractions can suppress the gene pathways involved in the proliferation of breast cancer cells and activate pathways that lead to tumour cell destruction ⁴¹.

Have any clinical trials been conducted using maitake extracts?

A phase I/II trial conducted at Memorial Sloan-Kettering Cancer Center in New York assessed the safety of oral administration of maitake extracts in breast cancer patients, and this study determined that the extracts were safe, well-tolerated, and showed no toxicity and that they also stimulated several types of immune responses in the patients ⁴².

A separate phase II trial by the same research group at Memorial Sloan-Kettering Cancer Center further demonstrated the safety of maitake active extracts as well as the beneficial immunomodulatory effects following oral administration of the extracts in patients with myelodysplastic syndromes ²⁸. Patients with these syndromes, which are bone marrow stem cell disorders, are at increased risk of developing acute myelogenous leukemia and pneumonia ²⁸.

What factors should you consider when choosing a maitake extract?

With any medical mushroom extract, including maitake extracts, the quality and content of the extracts are critical for the optimal reliability and effectiveness of the product ¹⁰. Factors that impact the quality of maitake extracts include growth conditions, extraction and purification

processes, and a consistent content of active beta-glucans. For example, because mycelium is embedded in the growth substrate, extracts prepared from mycelium can contain some of the substrate material, whereas extracts prepared only from **fruiting bodies** avoid these impurities.

Factors that impact the quality of maitake extracts:

- organic growth conditions
- fruiting bodies versus mycelium
- extraction methods
- good manufacturing processes
- presence of active beta-glucans

The extraction method is also important. In hydrothermal extraction, the maitake is crushed, dried, and the resulting powder is extracted with hot water to make a simple extract, which is then dried again. However, extracts prepared using this single-step process contain impurities and can also have lower concentrations of beta-glucans.

In contrast, **hydrothermal-ethanol extraction** is a **two-step** process that produces a purer product. After the hydrothermal extraction step, an ethanol extraction step is used to remove impurities and components that can potentially suppress the immune system. Essentially, this dual-extraction method can eliminate impurities that reduce the efficacy of the final product. The clinical trials described in this report use maitake extracts prepared using the two-step method.

Therefore, whether you plan to use maitake extract as a nutritional supplement, as an adjunct therapy for your cancer patients, or even for clinical studies, there are important questions to consider:

- What is the maitake source?

Where your maitake comes from, how it is grown, and whether it is organic are all

factors that impact the quality of the final product.

- Does the maitake producer use good manufacturing practices (GMP)?

The maitake extract should be produced using GMP and rigorous protocols that ensure the optimal consistency, safety, and reliability of the product.

- Does the maitake extract contain active beta-glucans?

Large and highly branched beta-glucans (see Figure 3) are key ingredients when considering maitake extracts for their immune-boosting properties. Additionally, these beta-glucans are major factors in the anticancer effects of maitake.

ProThera™ Black Maitake Extract for Immunomodulation

ProThera is the immunomodulating extract produced from the black maitake mushroom by Shogun Maitake Canada. ProThera comes in powder (Figure 6) and liquid forms and is prepared to the highest-quality standards.



Figure 6. ProThera black maitake extract (powder form).

Shogun's 15,000 square-foot facility is located in London, Ontario (Figure 7). They also have facilities in Japan. At these locations, they use state-of-the-art technology to replicate the **natural environmental conditions** found where maitake grows in the mountains of northeastern Japan. This involves optimizing the temperature, humidity, light, and even air flow (wind) to produce ideal growing conditions. Their techniques have been developed over decades by the founder, Yoshinobu Odaira, to optimize maitake quality.



Figure 7. Cultivation of black maitake at Shogun Maitake facility in London, Ontario, Canada.

Importantly, Shogun Maitake cultivates their maitake without pesticides or chemicals and thus provides consumers with **healthy and organic** maitake products. At Shogun Maitake, they harvest maitake by hand, selecting only the mushrooms that meet their high internal standards. Additionally, they specialize in **black maitake**, which is a rarer type of maitake and more difficult to grow than standard maitake.

Since 2015, Shogun Maitake has focused their facilities to supply fresh maitake to gourmet restaurants and grocery markets in eastern Canada and the US. They are now using their extensive experience in producing superior-quality maitake to produce natural nutritional supplements with medicinal value, including

ProThera.

ProThera is produced only from black maitake using GMP and rigorous protocols that are carefully monitored throughout the manufacturing process, from cultivation and harvesting through to extraction, drying, and packaging.

In fact, Shogun Maitake's protocols are based on the protocols established by Dr. Nanba to extract the active beta-glucans used in his ground-breaking research studies on the anticancer effects of maitake^{29,30} and that were subsequently used to prepare the maitake extracts used in clinical trials^{28,42}.

Only the maitake fruiting bodies are used to avoid impurities from the growth substrate and they do not use additives.

A dual-extraction process generates extracts of optimal quality. These stringent protocols are necessary to produce nutritional supplements with optimal consistency, safety, and reliability, and we take pride in using these protocols to produce ProThera.

However, it is important to note that not all maitake nutritional supplements are prepared using such stringent procedures. Some manufacturers purchase their maitake from farmers in various countries and have fewer controls over the cultivation conditions, including the use of pesticides, and less rigorous standards for harvesting and extraction, including the use of mycelium, which can result in maitake extracts of inferior quality and batch-to-batch variation.

In contrast, Shogun Maitake grows all of their own maitake in Ontario and Japan in indoor, environmentally-controlled facilities using organic farming methods.

Clinical Grade

Shogun Maitake's extracts were chosen for new clinical trials on the immunotherapeutic benefits of maitake in breast cancer, pancreatic cancer, and other diseases ⁴³.

Shogun Maitake's processes combine Canada's internationally respected agricultural and manufacturing standards with the discipline and attention to detail of Japanese technology and culture.



A Japanese garden – precision and elegance

Therefore, when you choose ProThera, you can be assured you have a product of exceptional quality and stability, a product of consistent efficacy, and most importantly, a product that contains the active beta-glucans known for their immune-boosting properties.

Features of ProThera Black Maitake Extract:

- Prepared from premium black maitake
- Organic farming methods with no pesticides
- Sourced only from fruiting bodies | no mycelium
- Dual-extraction method
- Stringent manufacturing processes
- Used in clinical trials



SHOGUN
MAITAKE

About Shogun Maitake Canada

The founder, Mr. Yoshinobu Odaira, was himself a maitake pioneer---and a visionary. In Japan, the maitake mushroom had been a valuable delicacy for centuries, and in the 1970s, Mr. Odaira wanted to grow fresh maitake on a large scale for the commercial market.

However, at that time, no one had been able to cultivate it, and the only available maitake was harvested from the wild.

Maitake has a rich aroma and taste that is incomparably flavourful. In my youth, it was a very rare and valuable delicacy, and so about 40 years ago, I thought of artificially cultivating maitake mushrooms.

Yoshinobu Odaira

To obtain a more sustainable and scalable source, Mr. Odaira spent many years trying to replicate the conditions found in maitake's natural environment, including the seasonal changes that are necessary for the mushroom to produce fruiting bodies. Eventually, after many attempts and careful refining of his techniques, Mr. Odaira was able to expand production from 350 kg of maitake per day to 110 tons per day!

Even after he had built one of the world's largest suppliers of fresh maitake, Mr. Odaira was not content. In addition to the value of maitake as a health food and good source of nutrients, he knew that maitake was used in herbal medicine, and he was convinced he could verify the special medicinal properties.

In 1982, Mr. Odaira approached Dr. Nanba of Kobe Pharmaceutical University and asked him to investigate the medicinal effects of maitake extracts. Mr. Odaira's belief in maitake was therefore a major impetus for the decades of research studies by Dr. Nanba's group and many other laboratories, research studies that have used modern techniques to demonstrate the anticancer properties and other health benefits of maitake.



Mr. Odaira standing proudly in his maitake facility

In 2015, Mr. Odaira founded the large-scale Canadian facility in London, Ontario. As a naturopath and entrepreneur, Mr. Odaira's passion was to utilize the nutritional and medicinal properties of maitake to benefit human health globally.

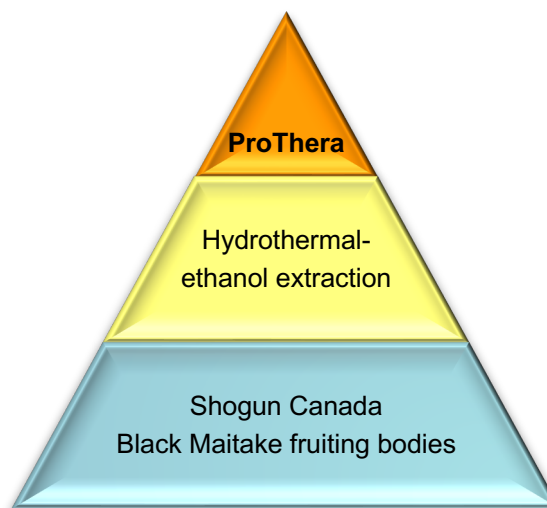
His vision was to take maitake extracts, which were already recognized by Health Canada⁹ as medicinal ingredient, and build a vertically integrated model of quality control where he oversaw everything from cultivation through to a

natural health product available to consumers in North America.

Today, Shogun Maitake uses Mr. Odaira's successful procedures to grow maitake on a large scale, thus providing a sustainable source of superior-quality maitake and maitake extracts.

We have the advantage of being able to manage everything from growing raw maitake mushrooms to manufacturing and selling supplements. In addition, many of the samples of maitake extracts used in maitake clinical trial data are what I have provided to each research institute in the past.
Yoshinobu Odaira

Now as CEO and President of Shogun Maitake Canada, Mr. Odaira continues his visionary leadership with the proud introduction of ProThera, the black maitake extract of exceptional quality.



A few words from Yoshinobu Odaira...

Since 1997, we have been selling maitake powders extracted using hydrothermal ethanol as raw materials to dietary supplement companies. To maximize the medicinal effect of maitake mushrooms, it is necessary to properly and strictly manage everything from cultivation to extraction of raw maitake mushrooms. The content of the extract is also very important.

According to clinical trials by Memorial Sloan-Kettering Cancer Center in New York, the appropriate daily intake of maitake extract is 6-7 mg per kg of body weight. For a person of 60 kg in weight, that would be about 400 mg a day.

However, many supplement companies use only small amounts of extracts in their products because maitake extracts are expensive to produce. Therefore, other maitake supplements on the market do not necessarily contain sufficient amounts of the active extract. Because of the inconsistent quality of maitake supplements from some suppliers, we saw a great need for an efficacious and reliable maitake extract for immunotherapy. So, we took advantage of my 40 years of experience in maitake cultivation and 35 years of experience providing maitake extracts with efficacy in medical research. The outcome of these years of experience is "ProThera", a product that brings together wisdom and knowledge for the health of humankind.

We are proud to be at the forefront of the world in technology that maximizes the medicinal properties of maitake. Forty-one years ago, I set my vision to develop stable mass production technology to supply high-quality maitake as a dietary supplement and for medical use. We confidently introduce you to the newly released supplements as an extension of my vision.

*As a supplier of high-quality maitake raw material to the world, we know everything about maitake from cultivation to dietary supplement production. We strongly believe that we will meet the expectations of our customers.
Yoshinobu Odaira*

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