## ➢ What is *Agaricus blazei* Murill?

Image: *Agaricus blazei* Murill (AbM)

*Agaricus blazei* Murill (AbM) is an edible mushroom species that was discovered in Piedade outside of São Paulo, Brazil. The mushroom was subsequently taken to Japan, where it was cultivated as a health supplement due to the observation that the indigenous folks ingesting the mushroom have fewer health issues than the general population.

AbM is essentially composed of five types of compounds: (1) amino acids including the nine essential amino acids, (2) minerals, (3) vitamins, (4) fatty acids and (5) dietary fiber.

## ➢ Is *Agaricus blazei* Murill safe to use?

AbM is an edible mushroom eaten in several Asian countries and is considered as a functional food. There is still some debate as to whether AbM may affect liver function in patients with advanced cancer[1], but for the most part, there have been no major side-effects and adverse events noted in many of the animal studies[2-4] and human clinical trials of AbM. In one study[5], 11 human volunteers were given a dose three times higher than the normal dose for six months. There were no noted statistically significant changes to the liver and kidney functions and no side effects from the long-term administration. In another study, 4 patients with chronic hepatitis B (in which liver enzyme levels may be increased as a possible sign of liver damage from the infection) were given an AbM extract at 1500 mg daily for 12 months[6]. The levels of the liver enzymes AST and ALT actually decreased in the study.

Specifically, the AbM extract from Atlas World has also been rigorously tested in the laboratory for safety. In an in vitro chromosome aberration test (which tests whether a certain compound has the potential to cause mutations), the Atlas World AbM extract, even at the highest concentration (5000 µg/mL) tested, did not induce chromosomal abnormalities. The results of a micronucleus assay in mice likewise showed that the Atlas World AbM extract was safe at the 2000 mg/kg/day highest dose tested. This 2000 mg/kg/day dosage for mice is equivalent to 140 g/day dosage for a 70 kg (or 154 pound) person.

- **How has *Agaricus blazei* Murill been used?**

  In folk medicine, the mushroom has been used against a variety of diseases including cancer, chronic hepatitis, diabetes, arteriosclerosis, and hyperlipidemia.

  Many of the putative medicinal effects of AbM have been studied by either *in vitro* experiments (experiments that were conducted in the lab but not in a live organism), *in vivo* animal experiments (experiments that were done in a live animal) or in human clinical trials. Below are examples of the medicinal effects of AbM that have been researched:

  - Immunomodulation[7]
    - anti-infection
    - anti-tumor[8]
  - blood sugar level control[9]
  - cholesterol level control

- **What is the evidence behind *Agaricus blazei* Murill extracts?**

  
  

  *Agaricus blazei* Murill mushrooms have a multitude of medicinal effects purported by folk medicine and through empirical use. Researchers have long since started studying the potential effects of this special mushroom in hopes of understanding the science behind some of its reputed medicinal properties.

  <u>Immunomodulation:</u>

  Researchers have found that AbM is loaded with immunomodulators, molecules that affect the way the immune system functions either by inhibiting or amplifying its response. For example, proteoglucans and β-glucans[10-12] (see table below of the active compounds contained in *Agaricus blazei* Murill), which are two types of carbohydrate (i.e. sugar) with widely studied immunomodulating properties, appear in high quantities within this mushroom species. Proteoglucans and β-glucans are known as potent stimulators of various types of immune cells, including macrophages[13-15], polymorphonuclear leukocytes[16], natural killer cells[17-18] and even CD4 and CD8 T cells[18]. In another study, mice that were given AbM also showed an increased number

of antibody-producing spleen cells, as well as an increased IgG antibody level in the blood (antibodies are an important part of the immune response system to infection)

and an increased number of T-cells in the spleen (T cells are a type of immune cell that play an important role in combating infections)[19].

| Unique polysaccharide compounds | Non-polysaccharide compounds |
|---|---|
| α-glucans | conjugated linoleic acid (CLA) |
| β-1,3-glucans (Beta-glucan subtype) | ergosterol |
| β-1,6-glucans (Beta-glucan subtype) | sodium pyroglutamate |
| β-1,3/1,6-glucans (Beta-glucan subtype) | |
| β-galactoglucans | |
| chitin | |
| proteoglucans | |
| protein-bound polysaccharides | |
| xyloglucans | |

Table: Active compounds contained in *Agaricus blazei* Murill

## Anti-infection:

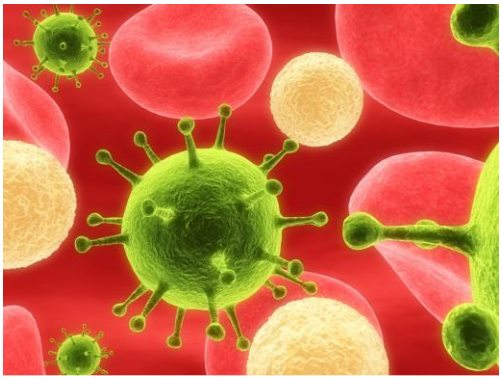

Image: Virus, red blood cells and white blood cells

Consequently, there has been a lot of interest in the possible therapeutic effects of AbM on infection. Research[20-21] has shown that AbM extracts appeared to enhance the body's immune response to viral antigens (an antigen is any substance that can stimulate an immune response) in DNA vaccines, increasing their effectiveness against the hepatitis B and foot-and-mouth disease viruses.

Investigators also examined the anti-infective effects of AbM extracts in bacterial infections. In one study[22] of pneumococcal sepsis (which is an illness characterized by an inflammatory response to a severe bacterial infection in the blood stream) in mice, various extracts of AbM were given through a catheter in the stomach prior to bacterial infection. One of the five different branded extracts performed statistically significantly well against sepsis in this mouse model by reducing the continued spread of bacteria in the bloodstream and increasing the survival rate. For comparison purposes, the control group of mice that were not given any AbM extracts all died within 5 days.

An AbM extract was similarly used in another animal experiment dealing with gram-negative bacterial sepsis through exposure to fecal solutions[23]. The resultant infection was graded from mild, moderate, to severe. For severe infections, the AbM extract

appeared to provide a significant protective effect by lowering the temperature, decreasing the spread of the bacteria in the blood and increasing survival.

In human clinical studies, AbM did not significantly change the number of natural killer cells. However, AbM did significantly increase natural kill cell activity[5]. Another study in humans has found an interesting effect of AbM on hepatitis C infections. In the study of patients with chronic hepatitis C that is resistant to IFN-α treatment, AbM extract taken for 1 week increased the receptor for IFN α and β molecules[24]. This increase in IFN receptors suggests that AbM might be able to make the INF- α resistant strain of hepatitis C more sensitive to IFN- α treatment.

Anti-tumor:

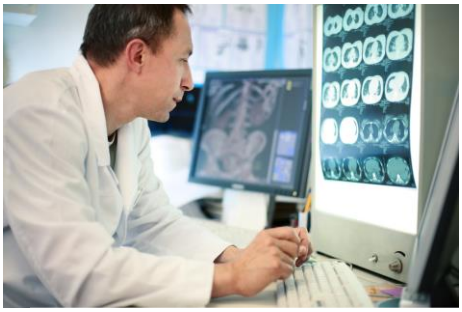

Image: Doctor looking at an X-ray

In addition to fighting off infections, the immune system also plays an important role in the fight against cancer. Therefore, the immunomodulating properties of AbM have likewise been of great scientific interest in cancer research. Proteoglucans and β-glucans have anti-tumor roles; in mouse models, they appear to promote tumor regression[25-26] and help against spontaneous metastasis in ovarian and lung cancer cells[27]. The mechanism of action of β-glucans may be due to their ability to activate natural killer cells and induce programmed cell death pathway. Furthermore, in the study of IFN-α resistant hepatitis C patients mentioned above, it was also noted that AbM extract also appeared to stimulate genes involved in antitumor defense[24]. Sodium pyroglutamate and ergosterol are two other examples of compounds isolated from AbM that likewise appear to have anti-tumor activity. They appear to inhibit the formation of new blood vessels inside tumor tissues (a process called neovascularization) and thus inhibit tumor growth and metastasis[28-29]. Finally, many of the polysaccharides (i.e. sugars) found in AbM have antioxidant capabilities[30] that allow them to scavenge for the free radicals that can damage cells and cause mutations.

There have been many studies about the effects of AbM on various cancers in mouse models that have shown favorable results, including connective tissue cancers[31],

ovarian and lung cancers[27], blood cell cancers[32] and liver, stomach and prostate cancers[33]. There has also been an NIH-sponsored study using Atlas World AbM extract in skin papilloma cancer[34] which yielded promising results suggesting antitumor promoting activity. In this study, the AbM extract from Atlas World used in either topical or oral form had protective effects compared to control mice that had

no preventive therapy. In both the topical AbM treated and orally treated group, tumor formation was delayed until weeks 7 and 8 respectively compared to 6 weeks with the control group.

In a human study, consumption of the AbM extract has been shown to promote natural kill cell activity and the quality of life in patients with gynecological cancers who were undergoing chemotherapy[35]. The results from a phase 1 clinical study regarding the use of AbM in cancer patients who are in remission support previous evidence that AbM powder is in general safe to use, excluding the possible allergic reactions, which occurred in 12% of the patients in the study and were mainly gastrointestinal allergic reactions[36]. Furthermore, another clinical trial showed that the daily intake of AbM granulated powder for six months improved the quality of life in cancer patients who are in remission[37].

Obesity, Diabetes and Hyperlipidemia:

Image: From left to right, a scale, a glucometer for measuring blood sugar and fatty foods.

The effects of AbM also extend to diabetes (a prevalent disease characterized by poor blood sugar control that over time may lead to organ damage) and hyperlipidemia (a prevalent condition characterized by high lipid levels that may lead to cardiovascular disease; lipids include cholesterol, HDL and LDL). Many research studies using animal models have shown the positive effects of AbM on blood sugar and lipid control. In one such study[9], rats that were fed a high fat diet gained weight, had high lipid and blood sugar levels and developed resistance to insulin, the hormone that is vital to blood sugar level control. However, there was some noted protection against

these adverse effects of a high fat diet when the rats were also given an AbM extract from Atlas World. The β-glucans found in AbM again appear to play and important role in body weight and blood sugar control[38].

Studies of Agaricus blazei in humans have yielded similar results. One study administered Agaricus blazei to 12 subjects for 3 months[5]. They found that patients had (1) a significant decrease in body weight and BMI, (2) a significant decrease in percentage body fat and percentage visceral fat and (3) a significant reduction in blood sugar and blood cholesterol level. In another clinical trial that included 72 patients with type 2 diabetes, the patients were given either AbM extract in combination with metformin and gliclazide (two commonly used diabetes medications) or a placebo pill in combination with metformin and gliclazide[39]. The trial used the homeostasis model assessment for insulin resistance (HOMA-IR) to measure the insulin resistance of the patients. After 12 weeks of treatment, the patients who received the AbM extract had a significantly lower HOMA-IR index (in other words, improved insulin resistance).

- **Why choose the Atlas World USA Agaricus Bio family of *Agaricus blazei* Murill?**

(1) Since 1995, Atlas World is the leading global manufacturer dedicated to AbM mushroom – and the one whose product was studied and used by NIH-sponsored researchers, which found our *Agaricus blazei* to be effective in healthy and safe immune modulation.
(2) Atlas World uses producers with over 70 years of fungi manufacturing experience.
(3) Mushrooms are DNA fingerprinted to ensure quality.
(4) Atlas World is JAS certified organic and USDA certified organic.

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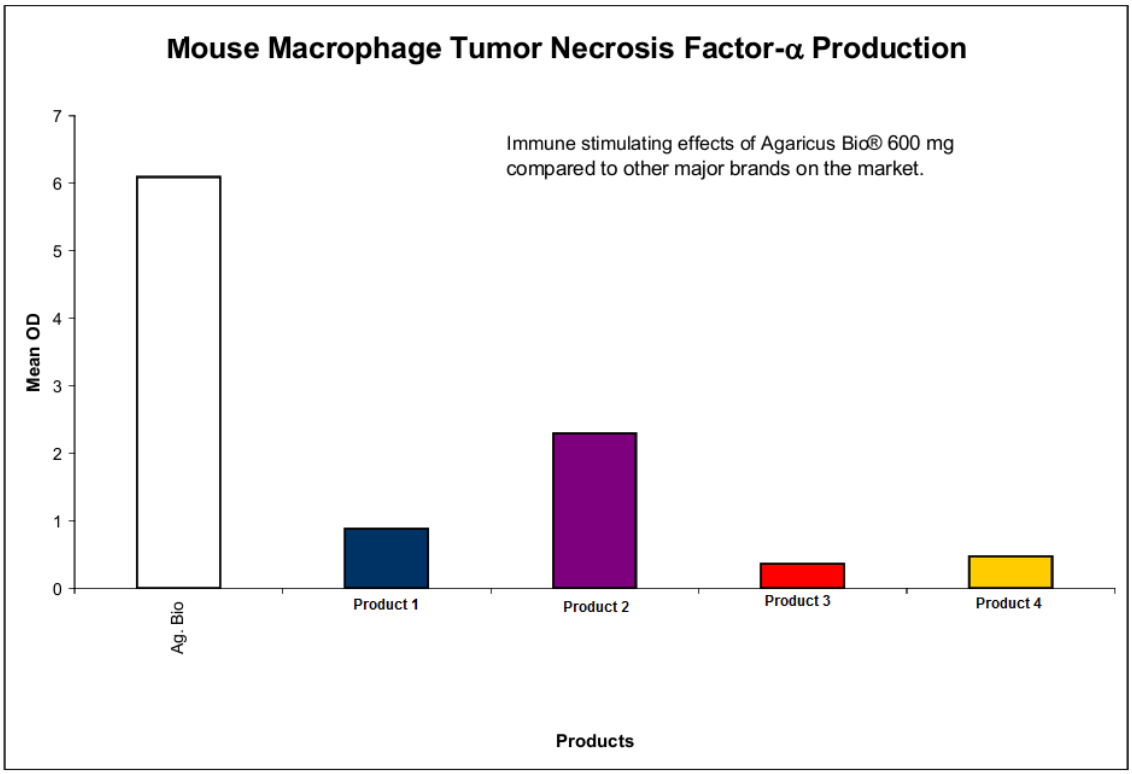
(5) The Agaricus Bio 600mg product has a higher optical density (OD) of mouse macrophage tumor necrosis factor-α production than other competitors (See figure below for the TNF- α Production Among Different AbM Products).

Figure: Mouse Macrophage TNF-α Production Among Different AbM Products.
(Internal Report – data available upon request)

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