

# Polysaccharides Extracted from *Agaricus blazei* Murill as Applicable Drugs in Biomedicine

Yuchen Wei\*

Haide College, Ocean University of China, Qingdao, China

\*Corresponding author: weiyuchen@stu.ouc.edu.cn

**Abstract.** *Agaricus blazei* Murill (ABM) is a type of basidiomycete mushroom with various of nutrition including polysaccharides, ergosterol, sterols, minerals, vitamins, proteins and some phenolic compounds. As a kind of edible mushroom, ABM is also rich in a variety of potential pharmacological applications with administering the extraction contained in its fruiting body or mycelium. On the other hand, even if the ingredients and chemical structures of the ABM have been discovered deeply, the related drug extracted by the *Agaricus blazei* Murill is rare. This review aims at summarizing the immunoregulation benefits and anti-inflammation advantages of *Agaricus blazei* Murill polysaccharides (ABMP). With  $\alpha$ -glucans and  $\beta$ -glucans as dominant bioactive polysaccharides, ABMP shows evidence in natural killer (NK) cells, macrophages with activating a comprehensive array of signal pathways and protecting creatures from inflammation. Whereas some of the biological mechanisms related to ABMP still remain controversy or conflicts. Furthermore, the experiments about the extractions of ABM may still have limitations in purifying, making some potential mechanisms or reactions unclear and have not been found. Therefore, more data about the ABMP, especially the clinical trials and the further purification of ABMP, is needed to be explored and analyzed.

**Keywords:** Mushroom; Polysaccharides; Innate immune system; Inflammation; Oxidative stress.

## 1. Introduction

Edible Mushroom is widely welcomed around the world due to its low calories and high contents of nutrition such as vitamin, minerals, unsaturated lipids, proteins and other bioactive components. Recently, the polysaccharides of mushroom are gradually well focused by scientists for their wide ranges of potential pharmacological applications, such as Grifron-D, Lentinan and Krestin for anticancerous medical treatment as well as activating lymphocytes with the use of heteroglycan in mushroom, enhancing the immune systems in an organism. ABM is a type of edible basidiomycetes mushroom that is first discovered in Florida, the United States of America but it is a type of native food in Brazil. Since ABM is worldwide spread, it is also called “Ji-Songrong” or “Baxi-Mogu” in Chinese and “Himematsutake” in Japan [1].

ABMP is various in ABM not only the fruit body but also in the mycelium. Evidences have proved the existence of uronic acid, mannose, trehalose, arabitol, galactose, and glucose is in the ABM as essential elements of ABMP [1]. Furthermore, more complex polysaccharide structures such as  $\alpha$ -glucans,  $\beta$ -glucans, AbEXP1-a, AbMP-II- $\alpha$ , AbMP-II- $\beta$ , FA-1-a- $\alpha$ , FA-a- $\beta$  and FI0-a- $\beta$  can be well extracted from ABM as potentially bioactive parts of ABMP [1]. On the other hand, emerging properties also reported that  $\beta$ -glucans and  $\alpha$ -glucans are the predominant, while  $\beta$ -glucans has higher level than the latter. Polysaccharides in ABM reveal great immunoregulation activities, anti-inflammatory function and antioxidant function together with negligible side-effects, providing considerable application prospects in large ranges of diseases related to the dysfunction of immune systems.

This review mainly focuses on immune system, especially the innate immune system, and anti-inflammatory regulation influenced by ABMP. The former part initially discusses the advanced cytotoxicity of NK cells in experiments and further mechanisms in macrophages with the effect of ABMP or related extracts. In another aspect referring the anti-inflammation, two types of the inflammatory protection effects due to the ABMP are mentioned. Although ABMP seems effective

in enhancing the immune system and protecting organs from inflammation, advancing the purification technology of ABMP together with further studies are required.

## 2. ABMP in Immune System

The immune system, especially the innate immune system, can be affected by ABMP through enhancing the cytotoxicity in NK cells. NK cells are a type of lymphocytes with tumoricidal activities. Table 1 has given some researches related to the ABM extractions, all of which contains ABMP. Emerging evidences have indicated that after the oral administration of  $\beta$ -glucan or extractions from ABM, such as aqueous extracts and ethanol-insoluble fractions, NK cells and spleen cells in mice being detected are generally activated. Moreover, Youminamochi et al. also find the same result [2]. The author set several groups of mice with different characteristics including wild-type (WT) group, RAG-2-deficient group and the group with interferon- $\gamma$  (IFN- $\gamma$ ) deficient. Only the first and the second type of mice are detected increased cytotoxicity after they are oral administered the extraction from the fruiting-body of ABM. However, these parameters are inhibited by the addition of anti-interleukin-12 (anti IL-12), which is a cytokine that is secreted by macrophages, and it can be induced by ABMP or relative extracts.

**Table 1.** Researches related to the ABMP administration, indicating an increase of immune activities in mice.

Extraction	Target Objects	Target Cells	Absorption Mode	Consequence	Reference
$\beta$ -glucan plus Immune-Modulating Nutrients	patients	NK Cells	\	Activated	[3]
Ethanol-Insoluble Fraction from the <i>A.blazei</i> Extracts	\	Murine Spleen Cells	\	Increased Natural Killer Activity	[4]
The Extraction from The Fruiting-Body of ABM	WT Mice	NK Cells	Oral Administration	Higher Cytotoxicity	[2]
The Extraction from The Fruiting-Body of ABM	RAG-2-Deficient Mice	NK Cells	Oral Administration	Higher Cytotoxicity	[2]
The Extraction from The Fruiting-Body of ABM	IFN- $\gamma$ Deficient Mice	NK Cells	Oral Administration	No Specific Effect	[2]

The secretion of cytokines in macrophages can be influenced by the administration of polysaccharides of ABM by recognized by inflammasomes or the macrophages themselves. IL-1 $\beta$  is one of the cytokines produced from macrophages, while its production can be enhanced by the ABM via the activation of inflammasome and a series of mechanisms followed by. The study detected the secretion of IL-1 $\beta$  in THP-1 macrophages after the administration of ABM extraction. Comprehensive experiments in this study indicate that the inflammasome NLRP3 with normal function is activated by ABM extraction, stimulating the caspase-1 and finally secreting the cytokines IL-1 $\beta$ , while IL-1 $\beta$  is mediated by caspase-1. Signal pathways mediated by TLRs from macrophages can also be affected due to the bind of ABMP and TLRs. TLR2 and TLR4, for instance, are pathogen recognition receptors (PRRs) located in the cell membranes of macrophages to recognize pathogen associated molecular patterns (PAMPs) linked to bacteria, fungi as well as virus, which means that some PAMPs can bind with TLR-2 or TLR-4 as ligands and the interaction can stimulate some pro-inflammatory signaling pathways, such as a dependent signaling pathway named MYD88,

stimulating the release of NF-kappa B (NF- $\kappa$ B) and causing innate pro-inflammatory responses eventually [5]. Polysaccharides in ABM, such as  $\beta$ -glucans, are able to bind with TLR-2 and TLR-4 receptors, stimulating the cytokines genes and promoting the efficiency of immune response [6]. Further evidences indicate that  $\beta$ -glucans can bind to TLR-2 (e.g.,  $\beta$ -1,6-glucans) and dectin-1 (e.g.,  $\beta$ -1,3-glucans) which is famous for its anti-fungal function, enhancing the immune system activities as a result [7,8]. Bagheri et al. also indicate the activation of the NF-kappa B (NF- $\kappa$ B) pathway may happen after the stimulation of TLR-2 indirectly [5]. However, Bertollo et al. argue that the activity of NF- $\kappa$ B may be inhibited due to the LMW-ABP, a type of micromolecular polysaccharide in ABM, so that the expression of adhesion molecule E-selectin is decreased, inhibiting the cancerous cell immigration, and the apoptosis signals in cancer cells with the increased sensitivity of chemotherapeutic drugs may be induced because of the inhibition of NF- $\kappa$ B [9]. In addition, T cells, especially Th cells, are influenced by ABMP as well. Accepting cytokines due to the ABMP, Th1 cells can be activated and therefore B cells and other types of adaptive immune cells can receive signals from Th1 cells, upregulating the activity of adaptive immune system eventually [10].

### 3. The anti-Flammatory Function of ABMP

Inflammatory is a series of physiological response to the xenobiotics or microorganisms and it can be roughly classified into two groups: acute inflammation and chronic inflammation [11]. Acute inflammation is an explosive process, which lasts from several hours to a few days, and it can be detected by the physiological syndromes including higher permeability of blood vessels, the migration of phagocytic leukocyte to the inflammatory tissues and the leakage of the plasma protein or fluids in microcirculation, as well as the stimulation of NF- $\kappa$ B and cytokines associated with inflammation. For example, TNF- $\alpha$  as well as IL-1 $\beta$ , etc. On the other hand, when the process of inflammatory is over-stimulated or long-lasting, this may even more easily lead to the chronic inflammation [11]. Inflammation is crucial to the human immune system that can enhance the activity of leukocytes, but it may also cause the damage of tissues and even lead to serious diseases. Therefore, measures of inhibiting the syndrome of inflammation are requested.

When it comes to the function related to inflammation, ABMP has two-side effects, causing contradictory results of experiments in different conditions. Some in vitro experiments indicate that the expression of cytokines will be enhanced, such as TNF- $\alpha$  and interleukin, which induce the inflammation if cells are exposed to the ABM extraction rich in ABMP [12]. In vivo experiments, to the opposite, shows a decrease of the level of main inflammatory cytokines [13]. This may be due to the digestion of polysaccharides in stomach and increasing anti-inflammation reactions after the final absorption of low level of ABMP which reduces the proinflammation cytokines.

#### 3.1. ABMP in Acute Inflammation

Large scales of experiments have proved significant effects of the ABMP in acute inflammation directly or indirectly [14,15]. Padilha et al. set a comprehensive array of experiments to discover the anti-inflammatory function in rats [14]. The study mainly includes the nystatin induction of paw edema, the induction of granulomatous tissue and the experiment of gastric ulcers. Although the granulomatous tissue induction experiments show the inhibited result about such tissues, the experiments of paw edema and gastric ulcers indicate the decrease of edema and less ulcer comparing to the control group, indicating the positive effect on decreasing the syndrome of inflammation [14]. This study also holds an experiment about arthritis, which will be discussed in chronic inflammation. Moreover, Hu et al. indicate that the expression of mRNA of inflammatory cytokines is significantly decreased in the liver of chicken induced by the cadmium after the administration of ABM extracts, though the level of mRNA is evidently higher than the ones in homeostasis [15]. This demonstrates that the ABMP can directly relieve the inflammatory condition by mildly inhibiting the expression of the DNA segments related to TNF- $\alpha$  and IL-1 $\beta$ . Since the expression of pro-inflammatory cytokines can induce the iNOS production, eventually produce nitric oxide, one of the pro-inflammation signals,

oral absorbing the ABMP may indirectly reduce further inflammatory pathway [16]. Additionally, cell adhesion molecule ICAM-1 can also be moderately controlled by ABMP. The experiment of Wang et al. show that the overproduction of ICAM-1 can be downregulated slightly in ovariectomized rats that absorb the water-soluble ABMP, meaning that the leukocyte may have more hurdles to enter the tissue from blood vessels since the reduced expression of ICAM-1 [17].

### 3.2. ABMP in Chronic Inflammation

Chronic inflammation may be induced by a variety of reasons such as long-term stimulation of xenobiotic or infections failed to be solved by endogenous protective mechanism or oxidative stress, etc. Although few studies prove that ABMP can participate in the repair mechanism in chronic inflammation, the protective effect of ABMP can be seen indirectly by lower the level of factors related to chronic inflammation. Padilha et al. hold the experiment about arthritis in their study, showing valid downregulation of the edema both in aqueous and alkaline extracts of ABM groups of rats comparing to the control group [14]. Further testing are held by Sucheska et al. [18]. In this study, three of the experimental groups is mainly divided, while each of which is separated into two sub-groups including controlled and enteritis suffered. Eventually, the experiment indicates that most of the cells, including granulocytes and monocytes that related to the innate immune system and inflammation, have a decrease in enteritis groups after the oral intake of  $\beta$ -glucan derived from oat, no matter high molecular weight or low molecular weight, which can be confirmed indirectly that the syndrome of inflammation is moderately controlled after the addition of components related to ABMP such as  $\beta$ -glucan [18].

Oxidative stress is also a potential origin that finally leads to the chronic inflammation and it also involved in the chronic inflammatory illness [19]. Oxidative stress is a consequence when the reactive oxygen species (ROS) in cells and tissues is overproduced and cannot be neutralized by the antioxidant system, causing the damage of cellular molecules including DNA, proteins and lipids. The damaged production of protein, in some cases, can act as inflammatory factors and enhance the inflammation by releasing itself as a pro-inflammatory signal such as peroxiredoxin 2 (PRDX2). After being activated, the PRDX2 can be induced to release even more, stimulating the production of TNF- $\alpha$  in macrophages though PRDX2 may not participate in the mRNA synthesis related to the PAMP including LPS in classical inflammatory response [19]. ABMP has ability to scavenge the activity of ROS, which is one of the pathways for ABMP to decrease the level of inflammation especially the one which is chronic. In Hu et al. study mentioned before, the SOD activity is increased in Cd affected chickens absorbing the  $\beta$ -glucan [15]. According to Suchecka et al., a decreasing level of GSH is detected in enteritis rats after orally administrating low molecules of  $\beta$ -glucan and higher molecules of  $\beta$ -glucan while the level of relative enzyme named GPX and molecule GSSH reduced from GSH has little change [18]. This makes it possible that the oral administration of  $\beta$ -glucan has potential effects to reduce the GSH level, and reduce the release of peroxide. On the other hand, a moderate decrease of the SOD concentration is also indicated by the same research after absorbing the  $\beta$ -glucan and the phenomenon although it seems contradictory to the Hu et al. experiment [15]. Moreover, evidences have indicated that partly repairment of cells and tissues in the liver of chickens has happened after the oral administration of ABMP [15]. In the report of the study, though the structure of the liver section is similar to the section which is influenced by Cd, there are less erythrocytes and vacuolar degeneration, which means the permeability of the blood vessels are decreased moderately [15]. This indicates potential effects on reducing the diffusion of erythrocytes and protect tissues and cells from edema through downregulate the osmotic pressure.

## 4. Conclusion

ABMP has been proved their multifunction in various studies. They have obvious and positive effects no matter in immunoregulation, anti-inflammation or oxidation resistance, meaning that the application of ABMP in health-caring and medical treatment is of great potential. Nevertheless, some

of the pharmacological mechanisms related to ABMP, such as NF- $\kappa$ B signaling, still remain controversy or conflicts of whether the ABMP eventually activates or inhibits its secretion. Moreover, the experiments about the extractions of ABM may still have limitations in purifying, making some potential mechanisms or reactions unclear and have not been found. Thus, more statistics about the ABMP, especially the clinical trials and the further purification of ABMP, are needed to be explored and analyzed.

## References

- [1] Huang K, El-Seedi H, Xu B. Critical review on chemical compositions and health-promoting effects of mushroom *Agaricus blazei* Murill[J]. *Current Research in Food Science*, 2022.
- [2] Yuminamochi E, Koike T, Takeda K, et al. Interleukin-12-and interferon- $\gamma$ -mediated natural killer cell activation by *Agaricus blazei* Murill[J]. *Immunology*, 2007, 121(2): 197-206.
- [3] Lee J G, Kim Y S, Lee Y J, et al. Effect of immune-enhancing enteral nutrition enriched with or without beta-glucan on immunomodulation in critically ill patients[J]. *Nutrients*, 2016, 8(6): 336.
- [4] Zhong M, Tai A, Yamamoto I. In vitro augmentation of natural killer activity and interferon- $\gamma$  production in murine spleen cells with *Agaricus blazei* fruiting body fractions[J]. *Bioscience, biotechnology, and biochemistry*, 2005, 69(12): 2466-2469.
- [5] Bagheri V, Askari A, Arababadi M K, et al. Can Toll-Like Receptor (TLR) 2 be considered as a new target for immunotherapy against hepatitis B infection?[J]. *Human Immunology*, 2014, 75(6): 549-554.
- [6] Oliveira Lima C U J, de Almeida Cordova C O, de Tolêdo Nóbrega O, et al. Does the *Agaricus blazei* Murill mushroom have properties that affect the immune system? An integrative review[J]. *Journal of medicinal food*, 2011, 14(1-2): 2-8.
- [7] Kurniawan D, Sargowo D, Tjokroprawiro A, et al. The interaction of  $\beta$ -glucan on Dectin-1 receptor or TLR-2 might have the potency to activate function of Treg Cell and production of anti-inflammatory cytokine[J]. 2020.
- [8] Kalia N, Singh J, Kaur M. The role of dectin-1 in health and disease[J]. *Immunobiology*, 2021, 226(2): 152071.
- [9] Bertollo A G, Mingoti M E D, Plissari M E, et al. *Agaricus blazei* Murrill mushroom: a review on the prevention and treatment of cancer[J]. *Pharmacological Research-Modern Chinese Medicine*, 2022, 2: 100032.
- [10] Lin M H, Lee K M, Hsu C Y, et al. Immunopathological effects of *Agaricus blazei* Murill polysaccharides against *Schistosoma mansoni* infection by Th1 and NK1 cells differentiation[J]. *International Immunopharmacology*, 2019, 73: 502-514.
- [11] Arulselvan P, Fard M T, Tan W S, et al. Role of antioxidants and natural products in inflammation[J]. *Oxidative medicine and cellular longevity*, 2016, 2016.
- [12] Gonçalves J L, Roma E H, Gomes-Santos A C, et al. Pro-inflammatory effects of the mushroom *Agaricus blazei* and its consequences on atherosclerosis development[J]. *European journal of nutrition*, 2012, 51: 927-937.
- [13] Markovina N, Banjari I, Popovic V B, et al. Efficacy and safety of oral and inhalation commercial beta-glucan products: Systematic review of randomized controlled trials[J]. *Clinical Nutrition*, 2020, 39(1): 40-48.
- [14] Padilha M M, Avila A A L, Sousa P J C, et al. Anti-inflammatory activity of aqueous and alkaline extracts from mushrooms (*Agaricus blazei* Murill)[J]. *Journal of medicinal food*, 2009, 12(2): 359-364.
- [15] Hu X, Zhang R, Xie Y, et al. The protective effects of polysaccharides from *Agaricus blazei* Murill against cadmium-induced oxidant stress and inflammatory damage in chicken livers[J]. *Biological Trace Element Research*, 2017, 178: 117-126.
- [16] da Silva Campelo M, Neto J F C, Lima A B N, et al. Polysaccharides and extracts from *Agaricus brasiliensis* Murill—A comprehensive review[J]. *International Journal of Biological Macromolecules*, 2021, 183: 1697-1714.

- [17] Wang P, Li X T, Sun L, et al. Anti-inflammatory activity of water-soluble polysaccharide of *Agaricus blazei* Murill on ovariectomized osteopenic rats[J]. *Evidence-Based Complementary and Alternative Medicine*, 2013, 2013.
- [18] Suchecka D, Harasym J P, Wilczak J, et al. Antioxidative and anti-inflammatory effects of high beta-glucan concentration purified aqueous extract from oat in experimental model of LPS-induced chronic enteritis[J]. *Journal of Functional Foods*, 2015, 14: 244-254.
- [19] Hussain T, Tan B, Yin Y, et al. Oxidative stress and inflammation: what polyphenols can do for us?[J]. *Oxidative medicine and cellular longevity*, 2016, 2016.