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Traditional Uses, Phytochemistry and Biological Activities of *Agaricus blazei murrill*: A Comprehensive Review

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Abstract

Agaricus blazei murrill is an important medicinal and edible mushroom species, widely cultivated in Japan and native to Brazil. Different *in vivo* and *in vitro* studies describe its ant mutagenic and immunomodulatory properties however, it is not still clear that what chemical substances and biological pathways are responsible for these properties. It is assumed that the polysaccharides phytocomplex may be responsible for the antitumor and immunostimulant activities, through an opsonizing biochemical pathway. *A. blazei* is used to cure dermatitis, hepatitis, diabetes, therosclerosis, hyperlipidemia, and cancer in traditional medicine. The present review provides a comprehensive review on traditional, phytochemical and pharmacological aspects of *A. blazei*.

Keywords: *Agaricus blazei*; Phytochemical constituents; Pharmacological activity; Traditional uses

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Introduction

The *Agaricus blazei Murill* a basidiomycete fungus, belonging to the *Agaricaceae* family, is native to southern Brazil and was introduced to Japan around 1950s [1]. In 1945, an American mycologist named William Alphonso Murrill described *A. blazei* in 'Quarterly Journal of the Florida Academy of Science' [2]. It is now commonly cultivated in Japan, China and Brazil [3,4] and used to cure atherosclerosis, hepatitis, hyperlipidaemia, diabetes, dermatitis, cancer and several other diseases [5]. Several clinical studies proved its significant effects on immune system. It increases the number of white blood cells, activity of natural killer cells, and production of tumor necrosis factor-alpha. Sodium pyro glutamate and ergo sterol, an antitumor and anti-angiogenic substances are also identified in this species which cut off the blood supply to tumors and inhibit angiogenesis [6]. *A. blazei* favours the humid, hot-house environment of its native Brazil. *A. blazei* popularly known as "Himematsutake" or "Brazilian mushroom" has been traditionally used as a health food supplement for the prevention of cancer, diabetes, hyperlipidemia, arteriosclerosis and chronic hepatitis [7]. In recent years, the mushroom is used in Japan as an adjuvant in cancer chemotherapy [8]. Polysaccharide is one of the main chemical constituents of *A. blazei* [9]. The content of polysaccharides contains many kinds of water-soluble fractions such as β-(1-6)-D-glucan and β-(1-3)-glucan with β-(1-6)-glycosyl branching. It is well known that β-D-glucan is the key compound for expression of the antitumor activity and immune modulating functions [10]. Various studies also revealed that the *A. blazei* extracts significantly inhibit the growth of various types of tumor cells, including sarcoma-180, Lewis lung carcinoma, Ehrlich ascites carcinoma, and Shionogi carcinoma in mice *in vivo* [11,12] and human ovarian cancer HRA cells *in vitro* [13]. The extracts also showed anti-tumor activities related to induction of apoptosis, cell-cycle arrest, inhibition of tumor-induced neovascularization, immunopotentiation and restoration of tumor-suppressed host immune system [13-15] and inhibition of human leukemic cells [16,17]. Bactericidal and fungicidal effects of Agaricus sp. have also been reported [18,19]. The available information on this species was collected from scientific databases such as PubMed, SciFinder, Science Direct, Scopus, Web of Science, and Google Scholar. The search terms used for this review included *Agaricus blazei*, phytochemical composition, traditional uses, activity, pharmacology, and toxicity.

Literature Review

Botanical description

Pileus subcylindric to subexpanded, scattered or gregarious, 7-9 cm broad; surface finely scaly, cremeous to ochraceous, margin glabrous, white, even, entire, projecting 5 mm.; context white, unchanging. 1-1.5 cm thick, not amygdaline; lamellae free, inserted, close, 5 mm broad, entire, pale; spores ellipsoid or ovoid, smooth, dark, opaque, about 5 × 4 µm; sterile cells on edges of gills scarce, hyaline, irregularly elavate; stipe equal, solid, white, ochraceous when bruised, 5-6 × 1.5-2 cml annulus large, white, median, simple [2].

Chemical constituents: *Agaricus blazei* contains agaritine [20], α and β-glucans [21,22], phenylhexane derivatives (1, 2), benzoylergostane (3), N-benzoyl-L-leucine methyl ester (4), ergostanes, incisterol [23], blazeispirols A(1), B(2), C(3), D(4), E(5), F(6), X(7), Y(8) and Z(9) [24], acetic, aconitic, benzoic, citric, fumaric, malic, oxalic, α-ketoglutaric, Ergosterol, C Vitamin, B1 Vitamin, B2 Vitamin, B9 Vitamin, B12 Vitamin, PP Vitamin [25], polysaccharide WABM-A-b [26].

Pharmacological activities

Anti-cancer activity: Matsushita and co-workers studied the anti-cancer activity of the hot water extract of *A. blazei* against human pancreatic cancer cell lines such as MIAPaCa-2, PCI-35, and PK-8 and the immortalized human pancreatic duct-epithelial cell line, HPDE. They observed that HPDE was less sensitive, i.e., more resistant, to AbE than pancreatic cancer cell lines. The GI50 values of AbE treatment for the tested cell lines were 0.015% for MIAPaCa-2, 0.012% for PCI-35, 0.009% for PK-8, and 0.094% for HPDE which indicated that AbE significantly and specifically inhibited the proliferation of pancreatic cancer cells relative to that of normal duct-epithelial cells [27].

Kim et al., obtained various hydro alcoholic extract at room temperature (25°C) and from fruiting bodies of *A. blazei* (80°C) and studied their anti-tumor effects against human acute promyelocytic leukemic cell line NB-4 by using MTT assay. Among the tested extract, 70% (v/v) ethanol-water, 80◦C (JAB80E70) extract exhibited highest 82.6% suppression of growth of NB-4 calls with lowest IC50 value of 82.2 µg/ml [1].

Protective effect: Song et al. evaluated the protective effect of the polysaccharides isolated from aqueous extract of *A. blazei* (ABP) were against Cd-induced damage on the testis of chicken. They observed ABP improved Cd-caused testicular tissue damage by increasing the SOD and GSH-Px activities decreasing the Cd accumulation and MDA content, mRNA levels of TNF-α, IL-1β, and IL-6, and protein expressions of HSP60, HSP70, and HSP90 [9].

Hepatoprotective effect: The ethanolic extract of *A. blazei* mushroom (AbM) was evaluated for hepatoprotective effect against CCl4-induced liver injury in Male albino rats of Sprague-Dawley strain (120-150 g) by given orally in a dose of 0.5 g/kg body weight daily for 30 days, 48 hours. The CCl_4 treated groups showed decrease levels of serum LDH5 (29.33), ALT (16.25), AST (05.70), GR (39.22), Vitamin C (mg/g) (228.12), Vitamin E (0.35), MDA (nmol/mg prot.) (11.36) and GSH (nmol/mg prot.) (14.65) compared to the control. This effect was reversed in the animal groups that were given AbM only and during treatment with CCl4 (therapeutic group, protective group). Malondialdehyde serum levels were significantly elevated in CCl4-treated groups as compared with control groups. Also, in therapeutic group and protective group where CCl4 was given side by side with mushroom, levels of malondialdehyde were found higher than control group. On the other hand, malondialdehyde, of animals treated with AbM alone remained within the levels of the control group [28].

Anti-neurotoxic effects: The methanolic extract of *A. blazei* showed effective anti-neurotoxic activity on rotenone-induced Parkinson's disease in male Albino mice (25-30 g). The extract (50, 100, and 200 mg/kg b.w.) significantly improved the behavioral status of mice and showed neuroprotective effect by enhancing the depleted dopamine levels and minimizing the deleterious effect of neurotoxin as compared to control [29].

Apoptotic effect: The polysaccharides isolated from aqueous extract of *A. blazei* (ABP) were evaluated for apopototic effect on Cadmium-Induced apoptosis in Chicken. It was found that the ABP significantly increased the PBL apoptosis rate, mRNA levels of caspase-3 and Bax expression, while the expression of Bcl-2 was significantly reduced after 20, 40, and 60 days treatment. However, Bax/Bcl-2 ratio was significantly increased in the Cd group compared with control group [P29]. Similarly, isolated polysaccharides from *A. blazei* (ABP-Ia) were also evaluated for apopototic effect against human osteosarcoma cell lines (HOS) and normal human osteoblast cell line (NHOst) by using MTT assay. At 100, 200 and 400 µg/ml of ABP-Ia was significantly induced apoptosis in a dose-dependent manner in the HOS cells. However, ABP-Ia had no or minor inhibitory and cytotoxic effects on NHOst cells even at the high concentration of 400 µg/ml [30].

Anti-genotoxic effect: Dried powdered mycelial from *A. blazei* was evaluated for anti-genotoxic effect against hydrogen peroxide induced DNA damage in human peripheral blood cells by using comet assay. The anti-genotoxic effects of *A. blazei* were examined by pre and post treatment of mushroom with H_2O_2. At 500 µg/ml, pre-treatment of powder exhibited slightly significant reduction in number of damaged cells and attenuation in comparison to the control cells (treated with 50 µM H_2O_2). However, at 250, 500 and 1000 µg/ml, all the tested concentration, significantly decrease the mean number of cells with DNA damage when compared with quercetin 100, 250, and 500 µg/ml, used as positive control [31].

Anti-oxidant effect: The antioxidant activity of *A. blazei* dried powdered extract was evaluated by using hydroxyl radical scavenging, reducing power and DPPH assay. Different concentration i.e., 0.062, 0.125, 0.25, 0.5, 1 and 2 mg/mL showed concentration-dependent but moderate reducing power ability i.e. 0.33, 0.62, 0.80, 0.99, 1.70 and 3.16%. At 2 mg/ml, mushroom showed only 3% inhibition of DPPH free radicals as compared to Trolox (96.25%). In hydroxyl radical scavenging assay, at tested concentration range, *A. blazei* showed IC50 values of 0.196 mg/ml and Trolox used as standard exhibited 60% inhibition with IC50 value 0.023 mg/ml [31].

Similarly, the ethanolic extract, ethyl acetate and hydroalcoholic fractions were evaluated for their antioxidant activity by using DPPH and ABTS assay. Ethanolic extract, ethyl acetate and hydroalcoholic fractions were exhibited powerful antioxidant effect with IC50 values of 7.9, 7.61 and 7.24 µg/ml (in DPPH assay),

and 22.82, 21.61 and 20.73 µg/ml (in ABTS assay), respectively as compared to trolox and uric acid used as reference [32].

Another study, γ-irradiated methanolic extract of *A. blazei* was evaluated for anti-oxidant effect by using DPPH, reducing power, hydroxyl radical scavenging and chelating assay. At 7.5 and 10.0 mg/ml, the antioxidant activities of methanolic extracts from 2.5 to 20 kGy γ-irradiated *A. blazei* increased by 19.9-55.7% and 8.8-35.7%, respectively. The methanolic extract from 20 kGy γ-irradiated *A. blazei* showed the best antioxidant activity (83.6%) at 10 mg/ml. However, the antioxidant activities were 98.8% at 10 mg/ml for ascorbic acid, 91.4% at 0.5 mg/ml for BHA and 94.8% at 0.5 mg/ml for α-tocopherol. For 0, 2.5, 5, 10, 15 and 20 kGy of irradiation, EC50 values in antioxidant activity were 27.6, 26.4, 21.4, 18.4, 19.3 and 20.3 mg sample/ml; EC50 values in reducing power were 3.15, 1.88, 4.92, 1.88, 2.30 and 2.93 mg sample/ml; EC50 values in scavenging ability against DPPH radicals were 0.92, 0.96, 0.93, 0.81, 0.84 and 0.89 mg sample/ml; EC50 values in scavenging ability against hydroxyl radicals were 18.1, 28.6, 25.3, 23.5, 23.0 and 25.4 mg sample/ml; EC50 values in chelating ability against ferrous ions were 2.23, 2.98, 2.82, 2.22, 2.14 and 2.35 mg sample/ml, respectively [33].

The ethyl acetate extract showed stronger antioxidant activity, as well as inhibition of α-glucosidase, compared to ethanol extract of *A. blazei* using 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and hydroxyl radical scavenging assays and the reducing power using K3Fe(CN)6 *in vitro* [34]. Ethyl acetate extract also showed a better protective effect on hepatic antioxidant activity and recovery of the impaired pancreatic tissues [35].

Leishmanicidal activity: The aqueous extract of *A. blazei* was evaluated for leishmanicidal effect against *Leishmania amazonensis, L. chagasi* and *L. major promastigote* and amastigote-like stages. It was observed that the tested extract exhibited leishmanicidal effect against tested species with IC50 values of 67.5, 65.8, and 56.8 µg/ml for promastigotes stage and 115.4, 112.3, and 108.4 µg/ml for amastigotes, respectively [36].

Wound healing effect: The polysaccharides of *A. blazei* were evaluated for their burn wound healing effect on Sprague-Dawley rats. At 50 and 100 mg/kg b.w. dose, polysaccharides exhibited 45.7 and 63.2% recovery rate of skin wound as compared to control. The burn wound in rats' skin induces the expression of IL-1β mRNA. Thus, the increase in the accumulation of macrophages in the burn wound area by the application of *A. blazei* polysaccharides suggests that a decreased production of IL-1β by macrophages may be related to the acceleration of wound repair [37].

Cytotoxic effect: The isolated compound agaritine from *A. blazei* was evaluated for cytotoxic effect against human monocytic leukemia U937 (human monocytic leukemia cell line; RCB0435) cell line by using MTT assay. The optical density of cells treated with agaritine for 48 h decreased by about 60% compared to the untreated cells, and this decrease was almost the same as that of Arabinosylcytosine (Ara-C) treatment for 24 hours. The death of agaritine-induced cell was partially inhibited by the coexistence of caspase-3 inhibitor. Cells treated with agaritine showed a 1.2 or 3.0 fold increase in caspase-3, 1.4 or 3.3 fold increase in caspase-8, and 1.4 or 4.8 fold increase in caspase-9, respectively, as compared to untreated cells. After 24 h of Ara-C treatment, all caspase activities increased 5.1-8.9 fold compared to untreated cells. Release of cytochrome c was increased in U937 cells incubated with agaritine for 48 h or Ara-C for 24 hours [20].

Guterres et al. studied the extract of *A. blazei* in lung cells of Chinese hamsters, in which 3 mg extract residues were diluted in 400 mL of dimethyl sulfoxide and 4600 mL of PBS, and a final concentration 60 mL/mL of this solution was applied to the comet assay. They observed a significant reduction of DNA damage caused by methyl methanesulfonate [38].

Angeli, et al. demonstrated that β-glucans extracted from *A. blazei* did not exert genotoxic or mutagenic effects at concentrations of 7, 21 and 63 µg/mL, and that there was also a dose-dependent protective effect against DNA damage caused by benzo[a]pyrene (20 µM) in a human hepatoma cell line (HepG2) by a comet assay [39]. Silva, et al. studied the expression of CASP-9 in HepG2 cells treated for 6 h with non-sulfated β-glucans (50 mg/mL) extracted from *A. blazei*, and indicated that expression of β-glucans did not influence apoptotic cells [40].

Ex *vivo* experiments demonstrated that the Andosan extract (containing *A. blazei* (mycelium) (82.4%), *Hericium erinaceus* (14.7%), and *Grifola frondosa* (2.9%)) had a cytotoxic effect on primary myeloma cells, and also on myeloma and leukemia cell lines *in vitro*, probably caused by cell cycle arrest [41].

Anti-mutagenic effects: The anti-mutagenic effect of aqueous extracts of *A. blazei*, obtained at ice-cold (2-8 °C), room temperature (20-25°C) and warm (60°C), was evaluated against Methyl Methane Sulfonate (MMS) induced mutation in Chinese hamster lung V79 cells by using comet and Micronucleus (MN) assay. At 0.05, 0.1 and 0.15% concentrations, extract were used in MNS pre-treatment and post-treatment and result compared with negative control (PBS). In pre-treatment, the tested extracts exhibited anti-mutagenic effect in V79 cells in comet assay. However, in micronucleus assay, tested extracts exhibited efficient anti-mutagenic effect against MMS-induced number and percentage of MN with decreased frequent of micronuclei ranged in concentration dependent manner between the ranging from 61.5 (room temperature 0.1% tea in post-treatment) to 110.3% (co-treatment with warm and ice-cold 0.15% tea) [42].

Anti-inflammatory activity: The anti-inflammatory activity of aqueous and alkaline extracts of *A. blazei* was evaluated against nystatin induced paw edema in rats (150-200 g). At 300, 400, and 500 mg/kg of alkaline and aqueous extracts significantly inhibited 19, 33, and 39% and 12, 38, and 56% edema formation, respectively, as compared to control group. The aqueous and alkaline extracts (400 mg/kg) also decreased the ulceration index by 21.88% and 28.63% when compared to the control group [10].

Anti-diabetic effect: The β-glucans isolated from dried fruiting bodies of *A. blazei* was evaluated for anti-diabetic effect on streptozotocin induced diabetes in Sprague-Dawley rats (200 to 230 g). At 2% dose of β-glucans, significantly increased the levels

of insulin secretion 3.79 ng/ml from pancreatic islets as compared to control 0.21 ng/ml [21].

Immuno-potentiating activity: The aqueous extract of *A. blazei* was evaluated for immuno-potentiating effect (antibody production) against sheep red blood cells antigen by using hemolytic plaque-forming cells (PFC) method. At 25 mg/kg dose, extract significantly increased the number of PFC in spleen (1.11 × 108 cells/spleen) when compared with control group (0.98 × 108 cells/spleen) [43].

Hyperlipidemia effects: The water extract of the total *A. blazei* Morrill acidic polysaccharides (WABM-A) was isolated from WABM using DEAE-cellulose, and subsequently purified using sepharose CL-6B to obtain the acidic polysaccharide WABM- A-b. In comparison with the model group, WABM-A significantly reduced the serum levels of total cholesterol, triglycerides and LDL-C, increased the serum levels of HDL-C, and up regulated the liver expression of PPARγ, LXRα, ABCA1, and ABCG1 in rats with hyperlipidemia. The *in vitro* experiments showed that in comparison with the model group, WABM-A-b-H significantly reduced the levels of total cholesterol and triglycerides in HepG2 cells induced by oleic acid, and significantly up regulated the protein expression of PPARγ, LXRα, ABCA1, and ABCG1 [26].

Conclusion

Several studies describe that *A. blazei* is rich in b-glucans which showed significant immunostimulatory activity however; we can't deny the presence of other substances which can be involved in immunostimulatory activities. So, it become necessary to isolated and identifies other clinically beneficial substances to explore other pharmacological benefits of *A. blazei* as per its high consumption in popular medicine.

References

1 Kim CF, Jiang JJ, Leung KN, Fung KP, Bik-San Lau C (2009) Inhibitory effects of *Agaricus blazei* extracts on human myeloid leukemia cells. J. Ethnopharmacol 122(2):320-326.

2 Murrill WA (1945) New florida fungi. Quarterly Journal of the Florida Academy of Sciences. 8(2):175-98.

3 Kuroiwa Y, Nishikawa A, Imazawa T, Kanki K, Kitamura Y, et al. (2005) Lack of subchronic toxicity of an aqueous extract of *Agaricus blazei Murrill* in F344 rats. Food Chem Toxicol. 43(7):1047-1053.

4 Mizuno T (1995), Agaricu blazei Murill: Medicinal and dietary effects. Food Rev Int. 11(1):167-172.

5 Firenzuoli F, Gori L, Lombardo G (2008) the medicinal mushroom *Agaricus blazei murrill*: Review of literature and pharmaco-toxicological problems. Evidence-Based Complementary and Alternative Medicine. 5(1):3-15.

6 Halpern GM (2007) Healing mushrooms. Square One Publishers, Inc. Feb 15.

7 Kawamura M, Kasai H, He L, Deng X, Yamashita A,et al. (2005) Antithetical effects of hemicellulase-treated *Agaricus blazei* on the maturation of murine bone-marrow-derived dendritic cells. Immunology 114(3):397-409.

8 Yoshimura K, Ueda N, Ichioka K, Matsui Y, Terai A, et al. (2005) Use of complementary and alternative medicine by patients with urologic cancer: A prospective study at a single Japanese institution. Supportive care in cancer. 13(9):685-690.

9 Song Y, Zhang R, Wang H, Yan Y, Ming G (2018) Protective effect of *Agaricus blazei* polysaccharide against cadmium-induced damage on the testis of chicken. Biological Trace Element Research. 184(2):491-500.

10 Padilha MM, Avila AA, Sousa PJ, Cardoso LG, Perazzo FF, et al. (2009) Anti-inflammatory activity of aqueous and alkaline extracts from mushrooms (*Agaricus blazei Murill*). J. Med. Food 12(2):359-364.

11 Ohno N, Furukawa M, Miura NN, Adachi Y, Motoi M, et al. (2001) Antitumor β-glucan from the cultured fruit body of *Agaricus blazei*. Biol Pharm Bull. 24(7):820-828.

12 Takaku T, Kimura Y, Okuda H (2001) Isolation of an antitumor compound from *Agaricus blazei Murill* and its mechanism of action. J Nutr. 131(5):1409-1413.

13 Kobayashi H, Yoshida R, Kanada Y, Fukuda Y, Yagyu T,et al. (2005) Suppressing effects of daily oral supplementation of beta-glucan extracted from *Agaricus blazei Murill* on spontaneous and peritoneal disseminated metastasis in mouse model. J Cancer Res Clin. Oncol. 131(8):527-38.

14 Kimura Y (2005) New anticancer agents: *In vitro* and *in vivo* evaluation of the antitumor and anti-metastatic actions of various compounds isolated from medicinal plants. *In Vivo*. 19(1):37-60.

15 Kimura Y, Kido T, Takaku T, Sumiyoshi M, Baba K (2004)Isolation of an anti-angiogenic substance from *Agaricus blazei Murill*: Its antitumor and antimetastatic actions. Cancer Science. 95(9):758-764.

16 Jin CY, Moon DO, Choi YH, Lee JD, Kim GY (2007) Bcl-2 and caspase-3 are major regulators in *Agaricus blazei*-induced human leukemic U937 cell apoptosis through dephoshorylation of Akt. Biol Pharm. Bull 30(8):1432-1437.

17 Kawamura M, Kasai H (2007) Delayed cell cycle progression and apoptosis induced by hemicellulase-treated *Agaricus blazei*. Evid. Based Complementary Altern. 4(1):83-94.

18 Rosa LH, Machado KM, Jacob CC, Capelari M, Rosa CA, et al. (2003) Screening of Brazilian basidiomycetes for antimicrobial activity. Mem Inst Oswaldo Cruz. 98:967-974.

19 Vogel FS, McGarry SJ, Kemper LA, Graham DG (1974) Bacteriocidal properties of a class of quinoid compounds related to sporulation in the mushroom, Agaricus bisporus. Am J Pathol. 76(1):165.

20 Akiyama H, Endo M, Matsui T, Katsuda I, Emi N, et al. (2011) Agaritine from *Agaricus blazei Murrill* induces apoptosis in the leukemic cell line U937. Biochimica et Biophysica Acta (BBA)-General Subjects 1810(5):519-525.

21 Kim YW, Kim KH, Choi HJ, Lee DS (2005) Anti-diabetic activity of β-glucans and their enzymatically hydrolyzed oligosaccharides from *Agaricus blazei*. Biotechnology letters 27(7):483-487.

22 Zhang A, Deng J, Liu X, He P, He L, et al. (2018) Structure and conformation of α-glucan extracted from *Agaricus blazei Murill* by high-speed shearing homogenization. International Journal of Biological Macromolecules. 113:558-564.

23 Ueguchi Y, Matsunami K, Otsuka H, Kondo K (2011) Constituents of cultivated *Agaricus blazei*. Journal of Natural Medicines. 65(2):307-312.

24 Hirotani M, Sai K, Hirotani S, Yoshikawa T (2002) Blazeispirols B, C, E and F, des-A-ergostane-type compounds, from the cultured mycelia of the fungus *Agaricus blazei* Phytochemistry. 59(5):571-577.

25 Rózsa S, Măniuțiu DN, Poșta G, Gocan TM, Andreica I (2019) Influence of the Culture Substrate on the *Agaricus blazei Murrill* Mushrooms Vitamins Content. Plants. 8(9):316.

26 Li Y, Sheng Y, Lu X, Guo X, Xu G (2020) Isolation and purification of acidic polysaccharides from *Agaricus blazei Murill* and evaluation of their lipid-lowering mechanism. International Journal of Biological Macromolecules. 157:276-87.

27 Matsushita Y, Furutani Y, Matsuoka R, Furukawa T (2018) Hot water extract of *Agaricus blazei Murrill* specifically inhibits growth and induces apoptosis in human pancreatic cancer cells. BMC complementary and alternative medicine. 18(1):1.

28 Al-Dbass AM, Al-Daihan SK, Bhat RS (2012) *Agaricus blazei Murill* as an efficient hepatoprotective and antioxidant agent against CCl4-induced liver injury in rats. Saudi J Biol Sci. 19(3):303-309.

29 Venkatesh Gobi V, Rajasankar S, Ramkumar M, Dhanalakshmi C, Manivasagam T, et al. (2018) *Agaricus blazei* extract abrogates rotenone-induced dopamine depletion and motor deficits by its anti-oxidative and anti-inflammatory properties in Parkinsonic mice. Nutr Neurosci. 21(9):657-666.

30 Wu B, Cui J, Zhang C, Li z A (2012) polysaccharide from *Agaricus blazei* inhibits proliferation and promotes apoptosis of osteosarcoma cells. Int J Biol Macromol. 50(4):1116-1120.

31 Živković L, Borozan S, Čabarkapa A, Topalović D, Ciptasari U, et al. (2017) Antigenotoxic properties of *Agaricus blazei* against hydrogen peroxide in human peripheral blood cells. Oxid Med Cell Longev.

32 Oliveira of, Vellosa jr, Fernandes AS, Buffa-Filho W, Hakime-Silva RA (2007) Antioxidant activity of Agaricus blazei. Fitoterapia (Milano) 78(3):263-264.

33 Huang SJ, Mau JL (2006) Antioxidant properties of methanolic extracts from *Agaricus blazei* with various doses of γ-irradiation. LWT-Food Science and Technology 39(7):707-716.

34 Wei Q, Zhan Y, Chen B, Xie B, Fang T,et al. (2020) Assessment of antioxidant and antidiabetic properties of *Agaricus blazei Murill* extracts. Food Sci Nutr. 8(1):332-329.

35 Wei Q, Huang L, Li J, Chen B, Xie B, et al. (2020) The beneficial effects of *Agaricus blazei Murrill* on hepatic antioxidant enzymes and the pancreatic tissue recovery in streptozotocin-induced diabetic rats. J Food Biochem. 44(5):13170.

36 Valadares DG, Duarte MC, Oliveira JS, Chávez-Fumagalli MA, Martins VT, et al. (2011) Leishmanicidal activity of the *Agaricus blazei Murill* in different Leishmania species. Parasitol Int.60(4):357-363.

37 Sui Z, Yang R, Liu B, Gu T, Zhao Z, et al. (2010) Chemical analysis of *Agaricus blazei* polysaccharides and effect of the polysaccharides on IL-1β mRNA expression in skin of burn wound-treated rats. Int J Biol Macromol. 47(2):155-157.

38 Guterres ZD, Mantovani MS, Eira AF, Ribeiro LR, Jordão BQ (2005) Genotoxic and antigenotoxic effects of organic extracts of mushroom *Agaricus blazei Murrill* on V79 cells. Genet Mol Biol. 28:458-463.

39 Angeli JP, Ribeiro LR, Bellini MF, Mantovani MS (2009) β-Glucan extracted from the medicinal mushroom *Agaricus blazei* prevents the genotoxic effects of benzo pyrene in the human hepatoma cell line HepG2. Arch Toxicol. 2009 83(1):81-86.

40 Silva AD, Sartori D, Macedo Jr FC, Ribeiro LR, Fungaro MH, et al. (2013) Effects of β-glucan extracted from *Agaricus blazei* on the expression of ERCC5, CASP9, and CYP1A1 genes and metabolic profile in HepG2 cells. Hum Exp Toxicol. 32(6):647-654.

41 Tangen JM, Holien T, Mirlashari MR, Misund K, Hetland G (2017) Cytotoxic Effect on Human Myeloma Cells and Leukemic Cells by the *Agaricus blazei Murill* Based Mushroom Extract, Andosan. Biomed Res Int.

42 Menoli RC, Mantovani MS, Ribeiro LR, Speit G, Jordão BQ (2001) Antimutagenic effects of the mushroom *Agaricus blazei Murrill* extracts on V79 cells. Mutat Res Genet Toxicol Environ Mutagen 496(2):5-13.

43 Nakajima A, Ishida T, Koga M, Takeuchi T, Mazda O (2002) Effect of hot water extract from *Agaricus blazei Murill* on antibody-producing cells in mice. Int Immunopharmacol. 2(8):1205-1211.