BioBran, Immuno Modulating Rice Bran Arabinoxylan Compound: Functions and Evidence

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Introduction

BioBran (rice bran arabinoxylan) is a functional food material that has potent immunomodulatory effects. It is manufactured by modifying a hot water extract of rice bran, specifically by partially decomposing the water-soluble dietary fiber, hemicellulose B, with carbohydrate enzymes derived from *Lentinus edodes* mycelia. More than 70 papers on BioBran have been published so far, and it has been sold in more than 50 countries world wide through evidence-based sales development. Here, the functionality of BioBran is described based on data from these published academic papers.

1. Natural killer cell stimulatory activity

Natural killer (NK) cells are components of the innate immune system and attach to cancer or virus- infected cells without antigen presentation.

Subsequently, granules containing perforin and granzyme are released, which induce apoptosis by creating pores in the target cell membrane [1]. NK cell activity is reduced in cancer patients owing to a decrease or lack of these granules [2-4].

The oral administration of BioBran to healthy patients for 2 months increased NK cell

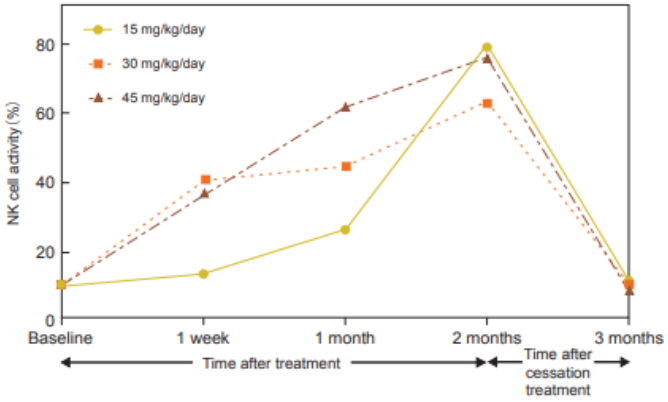

Fig. 1 Effect of BioBran on NK cell activation

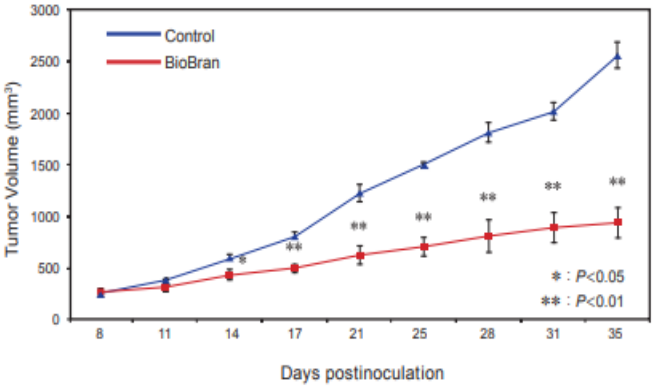

Fig.2 The effect of BioBran in inhibiting tumor growth

activity; however, NK cell activity decreased and returned to almost the baseline level one month after treatment discontinuation (Fig. 1) [5]. Animal studies have shown that BioBran increases NK cell activity. When BioBran was administered to elderly mice (18 months old) orally or via intraperitoneal injection, NK cell activity significantly increased. The NK cell stimulatory activity of BioBran may be attributed to the enhanced adhesion of NK cells to YAC-1 tumor cells and increased intracellular granules compared to those in untreated mice [6]. The administration of BioBran to mice transplanted with Ehrlich cancer cells also promoted NK cell activity and potently inhibited tumor growth (Fig. 2) [7].

2. Dendritic cell stimulatory activity

Immature dendritic cells take up antigens, including bacteria and viruses, via phagocytic activity. After phagocytosis, they move to the lymph nodes to mature, resulting in the presentation of antigens to T cells. This mechanism seems to be an important liaison between innate and acquired immunity.

BioBran reduced CD14, an immature dendritic cell marker, and increased CD83, a mature dendritic cell marker, in a dose-dependent manner [8]. These findings suggest that BioBran promotes dendritic cell maturation. BioBran also dose-dependently promoted CD80 and CD86 expression in dendritic cells and increased cytokine production from dendritic cells (IL-1β, IL-6, IL-10, TNF-α, IL-12p4 0, IL-12p70, and IL-2). Furthermore, it promoted $CD4^+$T cell proliferation and induced cytokine production (IFN-γ, IL-10, and IL-17) [9]. These results suggest that BioBran activates dendritic cells.

Dendritic cells expressing DEC-205 are present abundantly in the T cell regions of lymphoid tissues. DEC-205-positive dendritic cells and CD8+T cells play important roles in cancer and viral infections and are deeply involved in initiating adaptive immune responses [10,11]. BioBran increased DEC-205 expression in dendritic cells and type III IFN secretion in a dose-dependent manner. In addition, BioBran-treated dendritic cells induced granzyme B release in CD8+T cells [12].

3. T- and B-cell proliferation promoting activity

As mentioned above, BioBran has been found to enhance the activities of macrophages, NK cells, and dendritic cells. Next, we discuss how BioBran acts on immune cells of the adaptive immune system. We studied the effect of BioBran on T and B cell proliferation. Monoclonal cells (MNCs) of healthy subjects and leukemia patients were collected before and after BioBran administration, and the 3H thymidine incorporation into T and B cells after treatment with PHA and ConA, the T cell mitogens, and PWM, T and B cell mitogens was assayed. The results showed that BioBran promoted T and B cell proliferation in both healthy

subjects and leukemia patients [13, 14].

4. Anti-inflammatory action

In addition to its immunostimulatory and anti- inflammatory activity, BioBran has remarkable immunomodulatory activity. As mentioned above, BioBran treatment of Ehrlich carcinoma-bearing mice promoted NK cell activity and potently suppressed tumor growth. The anti-inflammatory activity of BioBran was evaluated in a similar Ehrlich carcinoma-bearing mouse model. BioBran treatment normalized the levels of the lipid peroxidation marker malondialdehyde (MDA), increased glutathione with antioxidant activity, enhanced the activities of antioxidant enzymes (glutathione peroxidase, glutathione- S- transferase, superoxide dismutase, and catalase), and suppressed the growth of tumor. These results demonstrate that BioBran possesses anti-inflammatory effects.

Radiotherapy is a major cancer treatment modality. It is associated with various adverse effects, including inflammation in the mouth, pharynx, and esophagus; vomiting; and depilation. In mice irradiated with radiation, BioBran was found to alleviate the adverse effects related to radiotherapy by preventing MDA and glutathione reduction, bone marrow cell reduction, spleen weight decrease, and body weight reduction [16]. However, these activities to alleviate the adverse effects may interfere with the therapy by inhibiting the tumor killing activity. A study in Ehrlich carcinoma-bearing mice showed that the effect of BioBran in promoting tumor regression is attributed to its tumor-cell apoptosis induction and inflammation-suppression activities [17].

5. Clinical trials

(1) Multiple myeloma

The effect of BioBran in multiple myeloma patients was evaluated in a randomized double-blind clinical study. The BioBran group consumed 2 g of BioBran daily, while the placebo group consumed the same amount of placebo for 3 months. In addition to a significant increase in NK cell activity, significant increases were observed in macytoid dendritic cells (mDCs), mDC/plasma cell-like dendritic cell (pDC) ratios, and Th1 cytokines, especially IL-1ß, IL-12, IFN-γ, and TNF-α [18]. In multiple myeloma patients, mDCs tend to return to normal levels after remission [19]. Therefore, the mDC/pDC ratio is an important parameter to evaluate improvement of symptoms. In addition, it is known that Th1 levels tend to decrease in cancer patients[18]. BioBran increased NK cell activity, mDC, mDC/pDC ratios, and Th1 cytokine production, all of which indicate the improved disease condition of patients.

(2) Hepatocellular carcinoma

Hepatocellular carcinoma patients were allocated into two groups: Group 1 that received conventional therapies (chemoembolization, percutaneous ethanol infusion, and a combination of these) and Group 2 that received conventional therapy + BioBran. The subjects in Group 2 consumed BioBran at 1 g/day for one year. The subjects in Group 2 showed a lower recurrence rate, increased two-year survival rate, decreased tumor marker α-fetoprotein (AFP), and reduced tumor volume compared with subjects in Group 1 (Table 1) [20].

Effect of treatment on tumor volume (whole groups). Data represent mean ± standard deviation.
%Change = 100× [(value after treatment) - (value before treatment)] / (value before treatment).

Treatment	Tumor volume (cm^3)	Patients		Treatment		%Change
		Number	%	Before	After	
CT	≦200	17	57	92.7 ± 12.3	97.6 ± 35	+5%
	>200	13	43	460.4 ± 76.1	454.9 ± 106.7	-1%
	10-1320†	30	100	252.0 ± 258.7	252.5 ± 324.3	+0.2%
CT+BioBran	≦200	22	58	125.9 ± 13.6	94.1 ± 22.3	-25%
	>200	16	42	481.7 ± 56.6	288.3 ± 47.9	-40%
	12-1200†	38	100	275.7 ± 234.1	175.8 ± 174.9	-36%

CT= Conventional Therapy

†Range of tumor volumes in group.

Table 1 The effect of BioBran on patients with hepatocellular carcinoma

(3) Head and neck carcinoma

As has already been described in this paper, the results of several animal studies demonstrated that BioBran alleviated the adverse effects caused by radiation treatment and suppressed tumor growth via apoptosis induction. These effects have also been observed in human clinical studies. The effect of BioBran in head and neck carcinoma patients treated with radiotherapy was evaluated in a randomized double-blind study. The BioBran group was administered BioBran at 3 g/day, and the control group was administered the same amount of placebo two weeks before the treatment, during the treatment, and two months after the treatment. The BioBran group showed better treatment outcomes than the control group, including significantly higher hemoglobin levels, hematocrit levels, red blood cell count, and platelet count; lower severity; significantly higher quality of life (QOL) scores; and better treatment outcome (Table 2) [21].

(4) Breast cancer

Breast cancer patients were allocated into two treatment groups: Group 1, which received chemotherapy only, and Group 2, which received chemotherapy + BioBran. Group 2 was administered BioBran 3 g/day one week before and one week after chemotherapy. Anorexia, malaise, nausea and vomiting, hair loss, and weight loss were alleviated in Group 2 compared

to Group 1. Furthermore, patients in Group 1 showed poorer health and required more blood transfusions than those in Group 2 (Fig. 3) [22]. These results demonstrate that BioBran reduces the adverse effects of chemotherapy.

Outcome	Placebo	BioBran	P-value
Mortality	11	0	0.000339377
Blood transfusions	17	1	0.00001
Hospital Admissions	21	2	0.000001
Metastasis	5	0	0.028733562
Infection	4	0	0.06043956
Progression	2	0	0.253846154

The number of the table shows applicable patients; 32 in the placebo group, and 33 in the BioBran group.
p-values displayed are based on Chi square test and Fisher's exact test.

Table 2 Clinical outcome of patient with head and neck carcinoma

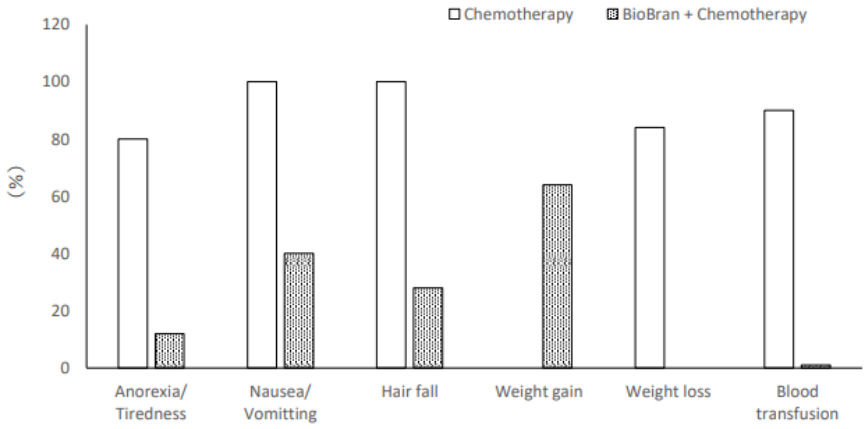

Fig. 3 Effect of BioBran on breast cancer patients

Discussion

Herein, we describe the functionality of BioBran based on studies published to date. In addition to its immunostimulatory activity, BioBran possesses immunomodulatory and anti-inflammatory activities. Thus, BioBran may be very useful in prevention and treatments against cancer and infections. With the aim of expanding knowledge on the potential benefits of BioBran, we have compiled a wide variety of data and studies, and we were therefore unable to explain each topic in substantial depth. This paper contains only a subset of the large number of studies on BioBran. We hope that as many people as possible will recognize the benefits of BioBran and take advantage of its potential. BioBran is expected to be effective not only for cancer and infections, but also for other diseases. We will perform further research on BioBran based on the findings of this paper.

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