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Fermented grain products, production, properties and benefits to health

Yukiko Minamiyama [a,*], Shigekazu Takemura [b,1], Toshikazu Yoshikawa [c,2], Shigeru Okada [d,3]

[a] *Department of Food and Health Science, Graduate School of Medicine and Dentistry, Okayama University, 2-5-1 Shikata-cho, Okayama 700-8558, Japan*

[b] *Department of Hepato-Biliary-Pancreatic Surgery, Graduate School of Medicine, Osaka City University, 1-4-3 Asahimachi, Abeno 545-8585, Japan*

[c] *Department of Medicine, Kyoto Prefectural University, Kamigyo-ku, Kyoto 606-8566, Japan*

[d] *Department of Pathological Research, Graduate School of Medicine and Dentistry, Okayama University, 2-5-1 Shikata-cho, Okayama 700-8558, Japan*

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Abstract

Fermented foods such as Japanese traditional food "*miso* (fermented soy bean paste)" have been shown to be rich source of micronutrients with the potential to prevent various human diseases. We have introduced effects of a new dietary supplement of fermented grain foods mixture containing extracts from wheat germ, soybeans, rice bran, tear grass, sesame, wheat, citrus lemon, green tea, green leaf extract and malted rice under the trade name of antioxidant biofactor (AOB). Chemical analysis of AOB shows the presence of various phenolic compounds (catechins, rutin, genistin, daidzin, etc.). AOB has strong antioxidant properties and additional biological effects, which might be of importance in context with the prevention of degenerative diseases. This paper focuses on the effect of supplementing AOB in various animal models and humans.

Keywords: Dietary grain food; Fermented; Antioxidant

1. Introduction

The history of fermented foods and drinks dates back more than 4000 years. Wine already existed around 5000 BC, and original forms of soy source, and fermented milk existed around 3000–2000 BC. Microorganisms seeded in the environment were put to use for the fermentation and maturation of fermented foods. Regional differences in products, climate, culture, and other environmental factors have developed unique fermented products in various part of the world. At the same time, regional and racial differences have a big effect on whether some fermented products are considered good or disgusting. We introduce a newly developed fermented grain food supplement, "AOB" in Japan.

2. A unique processed grain food, "AOB"

2.1. History and its manufacturing process

We developed a unique processed grain food, antioxidant biofactor (AOB). Raw materials of AOB are: rice germs (18%), rice bran (15%), soybean (20%), adlay (7.5%), sesame (total 4%), wheat (9%), green leaves extract (Japanese radish leaf, green tea; 10%), citron juice (2.5%) and then mixed more sesame extract. They are roasted and fermented according to the regular technique of Chinese herbal medicine. The powder has a

* Corresponding author. Tel.: +81-86-235-7143; fax: +81-86-235-7148.

E-mail addresses: yukiko@med.osaka-cu.ac.jp (Y. Minamiyama), takemura@med.osaka-cu.ac.jp (S. Takemura), toshi@koto.kpu-m.ac.jp (T. Yoshikawa), okadas@cc.okayama-u.ac.jp (S. Okada).

[1] Tel.: +81-6-6645-3841; fax: +81-6-6646-6057.

[2] Tel.: +81-75-251-5503; fax: +81-75-252-3721.

[3] Tel.: +81-86-235-7141; fax: +81-86-235-7148.

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greenish yellow color. AOB is exported to America, Europe and China (including Taiwan) as a healthy food additive.

2.2. Antioxidative effects of AOB in vitro and ex vivo

AOB contains a variety of substances having antioxidant activity including flavonoids, α-tocopherol, vitamin C, tannins and others. (Table 1). We investigated its radical scavenger activities, and antioxidative properties on auto-oxidation of rat brain homogenates using electron spin resonance (ESR) [1].

Table 1
Chemical analysis of AOB ingredients

	Content (mg/100 g on a dry weight basis)	
	AOB	Basal diet
Trace elements		
Potassium	1400	870
Phosphorus	760	830
Magnesium	321	240
Iron	10.0	15.4
Calcium	203	1110
Sodium	55.5	240
Zinc	6.6	5.1
Phenolic compounds		
Rutin	33.0	–
Genistin	31.0	–
Daidzin	24.0	–
Hyperin	9.9	–
Isoquercitrin	4.6	–
Daidzein	3.0	–
Genistein	2.4	–
Kaemperol	n.d.	–
Quercetin, quercitrin	n.d.	–
Catechins[a]		
Catechin	n.d.	–
Epicatechin (EC)	63.5	–
Epigallocatechingallate (EGCG)	1190	–
Epicatechingallate (ECG)	282	–
Vitamins		
Ascorbic acid	282	4
Tocopherols	24.5	9.4
α	9.8	
β	1.9	
γ	9.0	
δ	3.8	
Retinol (IU)	n.d.	2117
Carotene	2.3	–
Vitamin B6	0.97	0.82
Vitamin B12	n.d.	5.1

These constituents were analyzed by Japan Food Research Laboratories and were authorized by the Japanese government. All values are indicated per 100 g of dried extracts of AOB. n.d., indicated "not detectable".

[a] Measurement: Osawa T. Laboratory, Food and Dynamics, Nagoya University.

The in vitro scavenging activity of AOB was investigated on superoxide, hydroxyl radical and a stable free radical, diphenyl-*p*-picrylhydrazyl (DPPH) using ESR spectrometer. A suspension of AOB was added directly to a superoxide generating system (hypoxanthine-xanthine oxidase; HX/XO) and ESR spectrum was taken using 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) as a spin trapping agent. The scavenger activity of AOB was dose-dependent. A high concentration of AOB completely scavenged DMPO–OOH signals. AOB inhibited DMPO–OH signal generated by Fenton's reaction, but its inhibitory manner was non-competitive. AOB also inhibited the DPPH radical. Brain homogenates were time-dependently oxidized by air oxygen during the incubation at 37 °C. AOB strongly inhibited the autooxidation (lipid peroxidation) of rat brain homogenates in vitro in a dose-dependent manner. The inhibitory effect of AOB was much stronger than ascorbic acid and α-tocopherol at the corresponding dose.

In an ex vivo study, superoxide scavenging activity of the plasma obtained from rats treated with oral dose of AOB 1–5 g for 3 days were higher than those obtained from non-AOB basal rats, and scavenging activity was dose-dependent of oral dose of AOB (Fig. 1).

AOB is prepared by the process of roasting and fermentation. Raw materials before processing have little effect on the inhibition of lipid peroxidation (Fig. 2). It is speculated that fermentation is necessary for the biochemical transformation of each ingredient into active low molecular weight substances.

2.3. Effects of a processed grain food on animal models

2.3.1. Effect on reperfusion injury in the kidney

Reactive oxygen species has been implicated in the tissue dysfunction after ischemia and reperfusion. Many radical scavengers were tested with this model. The effect of oral dose of AOB was investigated in rats fed AOB diet (5 g AOB in 20 g standard diet) for 7 days.

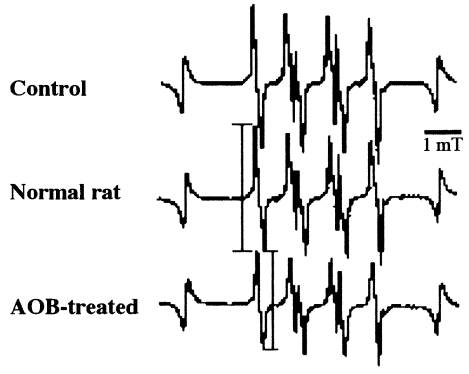

Fig. 1. O_2^- scavenging activity of plasma for animals fed on normal diet and AOB-containing diet. Superoxide was generated by 0.1 mM hypoxanthine and xanthine oxidase (0.1 U/ml). Data from [1].

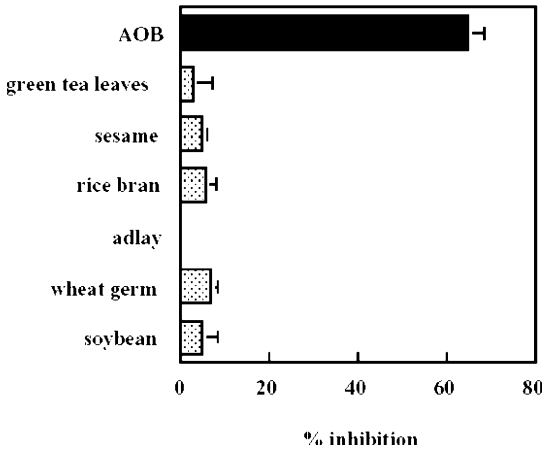

Fig. 2. Comparison of raw materials of AOB and processed AOB on the inhibitory effect of lipid peroxidation. Raw materials (10 μg/ml) of AOB and the processed AOB were examined for their inhibitory effects of rat brain lipid peroxidation. Values are mean ± S.E. of % inhibition of TBA-reactive substances with control level being 0%.

The model of 1 h occlusion and 24 h reperfusion of the left renal artery and vein was used. Ischemia followed by reperfusion induced high blood urea nitrogen (BUN) and renal failure in standard diet rats, but those indices of renal failure were strongly inhibited in AOB-fed rats (Fig. 3) [2].

2.3.2. *Effect on ferric nitrilotriacetate (Fe-NTA)-induced nephrotoxicity*

We have developed an experimental model of ferric nitrilotriacetate (Fe-NTA)-induced oxidative nephrotoxicity and renal cancer [3]. This model has been proved to be a good model for the evaluation of antioxidant food factors in vivo. Fe-NTA (7.5 mg Fe/kg) was given intraperitoneally to rats that had been fed an AOB diet (8%) for 10 days. Fe-NTA induced severe

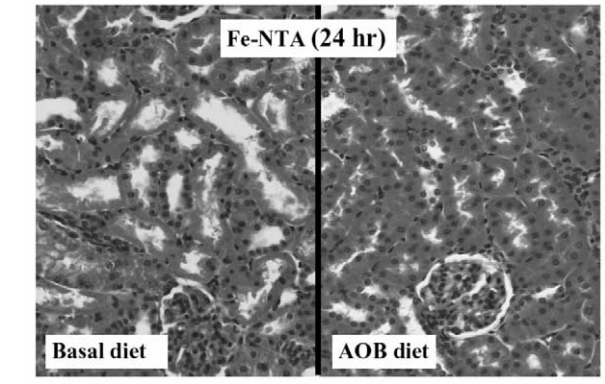

Fig. 4. Effect of AOB on Fe-NTA induced renal injury. Many of the proximal tubules in rats obtained 24 h after Fe-NTA injection showed a classic picture of acute tubular necrosis. Many of the tubules were without their nuclei.

proximal tubular damage in control rats without AOB, whereas in those fed an AOB diet tubular damage was minimal (Fig. 4) [4].

2.3.3. *Effect on cisplatin-induced renal and intestinal damages*

Oxygen free radicals play an important role in cisplatin-induced renal and intestinal injury. Intravenous administration of cisplatin (5 mg/kg) to Wistar rats significantly reduced body weight and elevated plasma levels of creatinine and BUN. Pathologically, extensive tubular necrosis, and regeneration in the outer stripe of the outer medulla 5 days after injection were observed. Pre-feeding of AOB (6.5% AOB containing diet) for 5 days markedly inhibited the renal dysfunction by cisplatin (Fig. 5). Furthermore, cisplatin induced severe small intestine injury (Fig. 6). This untoward effect of cisplatin was ameliorated by AOB feeding (6.5% AOB in the diet) [5].

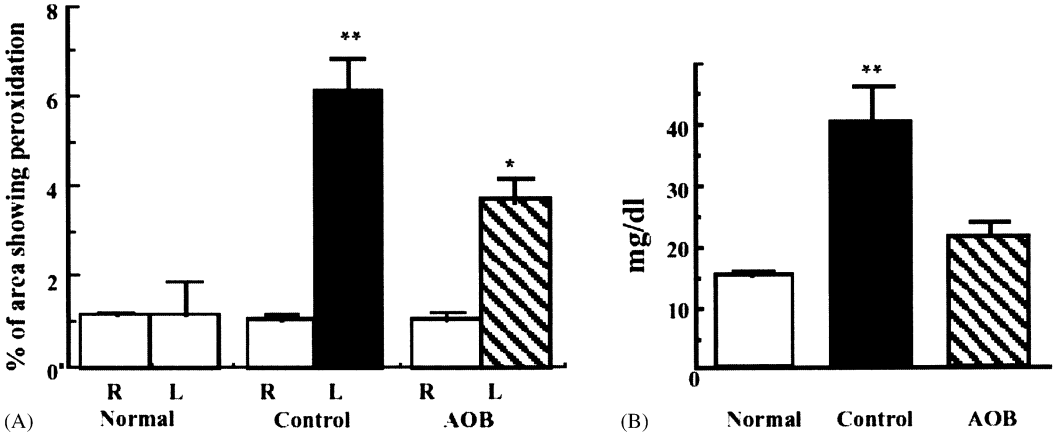

Fig. 3. Effects of AOB on renal injury induced by ischemia/reperfusion. Rats given oral administration of AOB-mixed diet, 5 g of AOB in 15 g normal diet/rat per day, were used and we compared them with control animals. After 5 g of AOB was given for 7 days, renal injury was elicited in male Sprague–Dawley rats (200 g) by 1 h occlusion and 24 h reperfusion of the left renal artery and vein. (A) Histochemical determination of lipid peroxidation with cold Shiff's reagent in the kidney using image analyzer. (B) Changes in levels of BUN. Values are mean ± S.E.M. *, $P < 0.05$; **, $P < 0.01$ vs. normal rats.

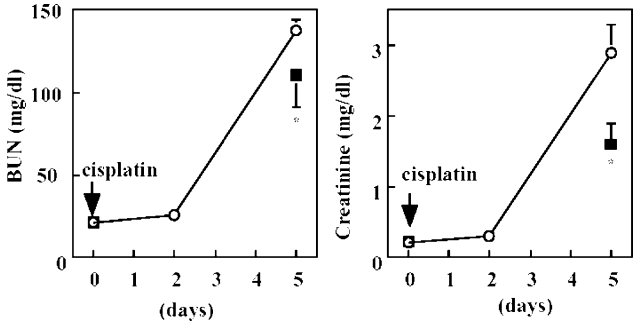

Fig. 5. Effect of AOB on cisplatin-induced renal failures. Cisplatin (5 mg/kg) intravenously administered to Wistar rats with or without AOB. Figure shows plasma levels of creatinine and BUN. Oral administration of AOB (6.5% AOB containing diet) for 5 days markedly inhibited the renal dysfunction by cisplatin. Open circle, cisplatin; closed square, AOB+cisplatin. *, $P < 0.05$.

2.3.4. Endotoxemic liver injury

The enhanced generation of free radicals and the decrease in endogenous antioxidants have been reported in patients and experimental animals with endotoxemia. Although therapeutic effects of various antioxidants, such as ascorbic acid, α-tocopherol, and *N*-acethylcysteine, have been tested for endotoxemic subjects, the results of their efficacy are conflicting. The following study was carried out to test the effect of AOB on lipopolysaccharide (LPS)-induced liver injury in the rat.

Intravenous administration of LPS induced liver injury with concomitant increase in hepatic generation of nitric oxide (NO) and 4-hydroxy-2-nonenal (HNE)-modified proteins and decrease in the reduced form glutathione (GSH) levels. HNE and its protein adducts have been demonstrated to be good markers for lipid peroxidation induced by reactive oxygen species. Administration of AOB significantly inhibited the LPS-induced hepatic injury (Fig. 7) and generation of HNE-modified proteins, and increased the survival rate of endotoxemic rats [1]. NO generation and plasma levels of tumor necrosis factor-α and interferon-γ were not affected. AOB also inhibited the LPS-induced decrease in hepatic GSH levels. Kinetic analysis revealed that AOB scavenged superoxide radicals and enhanced the regeneration of GSH.

2.3.5. The model of colon cancer metastasis in rat liver

Natural antioxidants have been shown to be rich sources of microchemicals with the potential to prevent human cancers. We examined ways in which dietary supplement of AOB may protect against colon cancer metastasis. The effect of supplementing AOB on the rat liver metastasis model of colon cancer was investigated. The group of model animals treated with cisplatin was also investigated to see the effect of AOB.

The day 5 of AOB (6.5%) supplementation in a basal diet, the rat colon cancer cells (RCN-H4) were injected beneath the capsule of the spleen and 1 min later rats were splenectomized. Three weeks after tumor cell inoculation, the rats were analyzed for liver metastases and other factors mentioned in the results. Some animals in both control and AOB groups were injected cisplatin (2.5 mg/kg, i.v.) twice at the first and second week after tumor cell inoculation. All rats had multiple

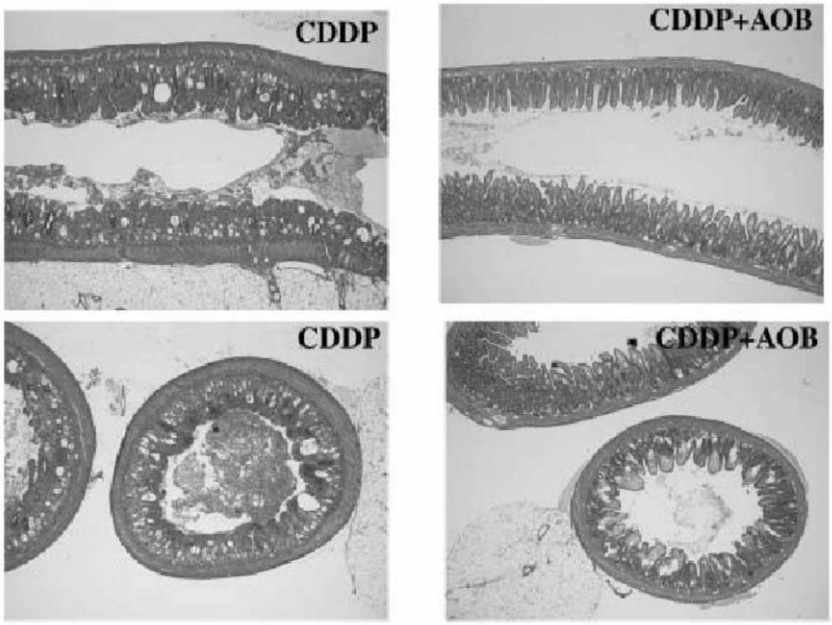

Fig. 6. Effect of AOB on cisplatin-induced small intestinal injury. Injection of cisplatin produced atrophic mucosa with fibrosis, inflammatory cell infiltration, lymph dilatation and regenerative epithelium 5 days after injection. This figure resembles the regenerative stage of inflammatory bowel disease. AOB (6.5% AOB containing diet) for 5 days markedly inhibited the injury by cisplatin.

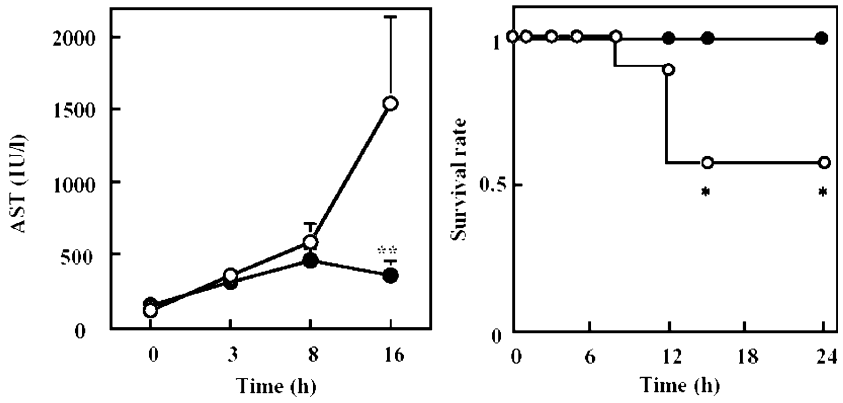

Fig. 7. Effect of AOB on LPS induced liver injury and survival. LPS (10 mg/kg) was intravenously administered into rats. Under light ether anesthesia, plasma samples were collected via the abdominal aorta at the indicated times. AOB was given orally for 3 days (1 g/day) with basal diet before the experiments. Values are means±S.E. ($n = 5–10$). Open circle, LPS-treated; closed circle, AOB-treated. *, $P < 0.05$; **, $P < 0.01$ as compared with LPS-treated group.

liver metastases. The number and the size of metastatic tumors were reduced by dietary AOB (Table 2) [6]. AOB treatment showed 5-fold increase of natural killer (NK) cell activity as measured by ^{51}Cr release. Immunohistochemical analysis and Western blot revealed that AOB decreased levels of proliferating cell nuclear antigen (PCNA), cyclin-dependent kinase (cdk) 2 and the phosphorylated retinoblastoma protein (pRb) in cancer cells. The growth inhibition of tumor cells by AOB seemed to be linked to the increase of immune function, cell proliferation inhibitory through G1 arrest by the modulation of cell cycle regulators probably through antioxidant characteristics of AOB. Combined use of AOB and cisplatin showed a significantly enhanced antimetastatic effect in this metastasis model as compared with the effect elicited by any component alone (Table 2). It is also worthy of mention that the synchronous treatment with AOB profoundly decreased the toxic side effects of cisplatin (gastrointestinal disorder, decreased weight loss, leukopenia, etc.).

In conclusion, AOB inhibited liver metastasis through the regulatory mechanisms of immune function and cell cycle. This product may be used as an adjuvant in the therapy of malignant neoplasia and other diseases caused by or following immune-deficiency.

Table 2
The number of tumors on the liver surface

	The number of tumors
Control	≥100
Cisplatin	44.0±9.4
AOB	21.8±6.6 ($P < 0.05$)
Cisplatin+AOB	14.0±6.7 ($P < 0.01$)

At the day 5 of AOB (6.5%) supplementation in a basal diet, the rat colon cancer cells (RCN-H4) were injected beneath the capsule of the spleen and 1 min later rats were splenectomized. Three weeks after tumor cell inoculation, the rats were analyzed for liver metastases. *P*-values indicated significance differences between cisplatin group.

2.3.6. *Paraquat toxicity*

Hirai et al. have reported that paraquat generated free radicals from the outer membrane of mitochondria [7,8]. The same research group reported that treatment of AOB as well as other antioxidants inhibited the paraquat toxicity both in vitro and in vivo [9]. Paraquat-treated (0.2 mM) human lung cultured cell line (A549 cells) were incubated with each of antioxidative drugs, trolox (0–2.0 mM), α-tocopherol (0–4.4 mM), AOB (0–1.0 mg/ml) and superoxide dismutase (SOD; 0 and 3000 U/ml) for 48 h. Trolox, α-tocopherol and AOB, improved A549 cell survival in vitro.

In vivo study was performed using mice that had received i.v. injections of 4.0 mg/kg trolox, 100 mg/kg α-tocopherol, 10 mg/kg AOB (water soluble fraction) or 5000 U/kg SOD, *b.i.d.* for 4 days ($n = 10$ each). An intraperitoneal injection of paraquat (50 mg/kg) resulted in a survival rate of 40% in mice at day 6 in control animals. Antioxidants, trolox, α-tocopherol and AOB significantly lowered the mortality rate (80% survival). SOD was not protective in vitro and in vivo. These results suggest that some antioxidants, which successfully reach the target cells can protect against paraquat poisoning.

2.3.7. *Aging related phenomena*

The free radical theory of aging was initially proposed by Harman half a century ago. However, administration of various antioxidants turned out to be ineffective in prolonging the life span of animals.

Trial study of AOB to prevent age-associated diseases was performed with some success. Professor Hosokawa et al. of Kyoto University examined the changes in tissues weight and macroscopic grading score in a series of phenotypically selected senescence-accelerated mice (SAMP1) with or without AOB supplemented food (10%) for 8 months, and compared them with a senescence-resistant line (SAMR1) that has the same

ancestral origin. SAMP1 showed significantly increased liver, kidney, spleen weight and grading score (blepharitis, conjunctivitis, fatty liver, amyloidosis etc.) compared with SAMR1 line. AOB supplementation in SAMP1 decreased organ weights and grading score to those of SAMR1 levels. Body weights were not so much different in all groups. The results are similar to those obtained by the calorie limitation except that the body weight was not affected. (Presented at the 12th Council for SAM Research in Kyoto).

2.3.8. Others

Professor Utsumi et al. in Kurasiki Adult Disease Hospital Research Center (presented at First AOB Meeting in Okayama) reported that AOB accelerated acethylcholine-dependent vascular relaxation in norepinephyrine-preconstricted rat aorta. The mechanisms might be the increase of active NO via superoxide scavenging activity of AOB and/or ODQ (a guanylate cyclase inhibitor)-inhibitable direct activation of guanylate cyclase in endothelium denuded vessels. The result is consistent with our previous report that a drop of blood pressure induced by NOC7 (a NO donor) was prolonged in AOB-treated rats [2]. These results suggest that AOB might improve some diseases associated with endothelium dysfunction such as atherosclerosis, hypertension.

2.4. Beneficial effects on human health

2.4.1. Chernobyl accident

The presence of clastogenic factors (CFs) in the plasma of irradiated individuals has been brought to light [10]. And they also reported that plasma levels of CFs increased in workers and children exposed to Chernobyl reactor accident [11]. They also reported that the plasma clastogenic activity of the Chernobyl liquidators was significantly reduced after treatment with AOB [12].

Twenty Armenians, who had been engaged as soldiers or civil workers in the clean-up of the Chernobyl reactor accident underwent CF-tests at random during their annual check-up. Their mean age was 40 years (25–59 years) at the time of starting this test. A medical questionnaire was given for all liquidators at the Institute for Radiation Medicine in Yerevan. AOB treatment started from the following day with the recommended dose of 6×3 g/day for 3 months. A second blood sample was taken at the end of AOB treatment. Additional samples were taken from 12 liquidators, who could be followed for 6, 9 and 12 months. Even after 12 months, clastogenic scores had still been low in AOB-treated liquidators. It was hypothesized that the anti-clastogenic effect was due to the antioxidant properties of AOB, since the clastogenic effects are mediated via free radicals.

2.4.2. Others

Clinical trial was conducted comparing AOB to placebo in patients with chronic hepatitis C by Professor Emerit in Paris University [13]. The levels of CF-test, lipid peroxidation, reduced GSH and alanine aminotranferase (ALT) in the plasma were compared before and after a 3-month-treatment with AOB. AOB treatment inhibited lipid peroxidation and increased GSH levels. ALT levels were significantly decreased by AOB, although they were not completely normalized. Decrease of ALT was more remarkable with the combination treatment of chronic hepatitis C with interferon (5 MIU) and AOB than with the treatment with interferon alone. The results obtained with other antioxidants, such as *N*-acetylcysteine or α-tocopherol, were not as good as those obtained by AOB.

3. Note added in brief

AOB contains many biofactors and has many bioeffects as results of roasting and fermentation of the raw materials. The mechanism of action and essential biofactors of AOB are under clarification in various research institutes.

Recently, other fermented products from wheat germ has reported to have protective action against experimental colon carcinogenesis [14] and human colon carcinoma [15]. Another group also reported that the fermented wheat germ extract controls tumor propagation primarily by regulating glucose carbon redistribution between cellular proliferation-related and cellular differentiation-related macromolecules [16]. Combined treatments with wheat germ extract and vitamin C-administered synchronously-profoundly inhibited the metastasis in all the applied tumor models, while treatments with vitamin C alone did not exert such an inhibiting effect on the metastasizing process [17]. Another group suggested that one of effective ingredients may be phytic acid in wheat bran which affects colon morphology, cell differentiation and apoptosis [18]. Thus, research on effectiveness and functional ingredients of fermented grain food are rapidly in progress.

However, there is no magic bullet for disease prevention. It may be the balance of whole diet that matters. AOB as well as fermented soy products should be viewed as just one part of a healthy diet.

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