DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date:

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	Fucoidan
Firm:	Ocean Treasure Foods, Inc.
Date Received by FDA:	August 17, 2000
90-Day Date:	November 14, 2000

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on pubic display in docket number 95S-0316 after November 14, 2000.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT 82

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

OCT 30 2000

Masayo P. Kanstrup
President
Ocean Treasure Foods, Inc.
5853 S. Sherman Way
Littleton, Colorado 80121

Dear Mr. Kanstrup:

This letter is in response to your letter to the Food and Drug Administration (FDA), dated June 30, 2000, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act). Your letter notified FDA of your intent to market a product containing a new dietary ingredient named fucoidan. FDA received your complete submission on August 17, 2000.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully evaluated the information in your submission. Your submission contains evidence of history of use and other information that you assert is an adequate basis to conclude that a dietary supplement product containing fucoidan will reasonably be expected to be safe. The agency has significant concerns about the evidence on which you rely to support your conclusion. You state that mozuku has been used by the native population of Okinawa since antiquity for its health benefits. However, your submission lacks quantitative estimates of dietary exposure to mozuku and thus fucoidan in Okinawa. You also state that fucoidan is marketed as a dietary supplement and as a health drink in Japan. However, your submission fails to provide any information on dietary intakes and other conditions of use for

the dietary supplement and the health drink to assess the nature of exposure to the substance. In addition, your submission does not contain information on the post-marketing history of these products in Japan, including adverse effect monitoring, that could provide a basis to support that its use in the United States as a dietary supplement will be safe.

Although a search of the scientific literature reveals that fucoidan has been extensively studied, your submission includes information from a single animal study and a single human pre-market test. There are a number of limitations inherent in the animal study and your reporting of it. Therefore, it has limited usefulness in assessing the safety of fucoidan. For example, the study fails to describe the amount of mozuku or fucoidan extracts that were fed to the animals. In addition, the trial was designed to test the effect of fucoidan on the plasma concentration of cholesterol levels in rats fed a high cholesterol diet. It was not designed to test the toxicity of fucoidan. Importantly, short-term exposure studies in animals cannot predict effects of long-term exposure in humans. The pre-market test also has limited usefulness in assessing the safety of fucoidan. The greatest limitation is that the pre-market test did not provide information on the nature of, or details about, the evaluation of the subjects exposed to fucoidan. In addition, the test did not include specific study findings or quantification of data. Nonetheless, despite these shortcomings, the study results raise concerns about the safety of fucoidan under the conditions under which it may be marketed as a dietary supplement. The results of the test indicate that several participants complained of a warming effect in their stomachs. Although the effect was attributed to an intestinal reaction to the fiber found in fucoidan, the test sponsors failed to consider whether this adverse effect could be an inflammatory response. Additional information on the chemical composition, molecular weight and carbohydrate profile of the fucoidan that you intend to market as a dietary supplement would be useful in the interpretation of this effect.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that fucoidan, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains the new dietary ingredient fucoidan for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your submission will be kept confidential for 90 days from the date of receipt, and after November 14, 2000, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

Should you have any questions concerning this matter, please contact me at (202) 205-4168.

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements

Ocean Treasure Foods, Inc.
5853 S. Sherman Way, Littleton, CO 80121
Ph: 303-730-2849, Facs: 303-347-1833

August 11, 2000

Received 8/17/00
RFP

Dr. Roslyn Powers
Office of Special Nutritionals (HFS-800)
Center for Food Safety & Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, D. C. 20204

Re: "Fucoidan" Dietary Supplement Notification

Dear Dr. Powers:

This is in response to our conversation on July 11th regarding the need for additional safety information to be included in our dietary supplement notification.

We have been able to obtain safety data/information that was done prior to our parent company's introduction of Fucoidan to the Japanese dietary supplement market in October of 1999 under the name "Algia". Also included is information about other Japanese companies that use Fucoidan in their product's ingredients.

Enclosed herewith are three sets of our June 30th notification letter with additional information that we believe adequately addresses product safety issues. A series of four underwater pictures showing some of the mozuku farms in Okinawa that relate to our comment in paragraph 3 about the cultivation and commercial harvesting of mozuku are also included.

Sincerely yours,

Ocean Treasure Foods, Inc.

Masayo Kanstrup

Masayo P. Kanstrup, President

Ocean Treasure Foods, Inc.
5853 S. Sherman Way, Littleton, CO 80121
Ph: 303-730-2849, Facs: 303-347-1833

June 30, 2000

Office of Special Nutritionals (HFS-450)
Center for Food Safety & Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, D.C. 20204

Re: Notification of New Dietary Supplement

To Whom It May Concern:

In accordance with 21CFR Section 190.6 and Section 413 of the Federal Food, Drug, and Cosmetic Act, notification is herewith provided for the manufacture and distribution of a new dietary supplement. The following information is provided herewith.

1. Name and address of the manufacturer and distributor.

   Ocean Treasure Foods, Inc.
   5853 S. Sherman Way
   Littleton, CO 80121
   Ph: 303-730-2849, Fax: 303-347-1833

2. The name of the new dietary supplement: "Mozuku Fucoidan" or "Fucoidan"

3. Description of the product:

   Fucoidan is extracted from a particular kind of sea kelp ("mozouku") indigenous to the southern Japanese islands of Okinawa. Mozuku has been used as a food sources by the native population since ancient times. Despite the fact that Okinawans have a relatively high intake of cholesterol in their diet, Okinawan longevity is the earth's longest. Research seems to indicate that this may be attributable to their regular intake of significant quantities of mozuku in their diet. Okinawa mozuku is cultivated and commercially produced in Okinawa and its kelp farms supply almost all of the demand for the product in Japan (see photos).

Fucoidan is a polysaccharide that mainly contains fucose and sulfated fucose. It can be extracted . A substance called mucopolysaccaride is found in seaweed and makes these plants very "slippery". Oligosaccharide is one example, fucoidan is another.

(i) Ingredients: Upon extraction, fucoidan is processed, formed into 30 mg tablets and introduced by Hokugan Co., Ltd. as a dietary supplement in Japan in 1999 under the brand name "Algaia". Under an exclusive marketing agreement, Ocean Treasure Foods, Inc. will manufacture and distribute fucoidan as a new dietary supplement. Each tablet will contain 30 mg of fucoidan.

(ii) Recommended or Suggested Use: 3 to 6 tablets per day for general nutritional use and maintaining system balance. See "Algaia" supplemental information included herewith.

4. History, Safety Data and Published reference information:

a. History.

Mozuku has been in use by the native population of Okinawa since antiquity. Because of mozuku's apparent health benefits, it has been studied extensively in recent years by Japanese researchers and hundreds of articles about the beneficial health effects of seaweed have been conducted and published. In 1998 scientific research isolated a polysaccharide chain of fucose and sulfated fucose and it was given the name "Fucoidan". Fucoidan is used in Japan as a dietary supplement to promote general nutritional balance in the human system and is sometimes prescribed to ameliorate the negative effects of medical treatments.

b. Safety.

1. The ingredient Fucoidan was first introduced in health drinks and in tablet form in 1997 (see Hokugan K.K. translation attached). Presently there are seven (7) Japanese companies that market it as a dietary supplement. Four (4) cosmetic companies also use Fucoidan in various cosmetic products. Prior to Hokugan introducing Algia to the Japanese market safety testing was conducted on 21 people to determine any adverse health effects.

2. Many studies of Fucoidan that have been conducted by various colleges and universities, health and research institutes and independent companies. The research indicates that Fucoidan helped maintain normal levels of lipids and cholesterol - see report referenced and included herewith.

Oyo Tshitsu Kagaku, Journal of Applied Glycoscience, Volume 43, Number 2, pages 143-153 (1996). This is a summary of work done by various researchers from the University of the Ryukyus, Kagoshima University and the Okinawa Regional Study Center, University of the Air.

5. Signature of manufacturers and distributors designated representative:

Masayo Kanstrup

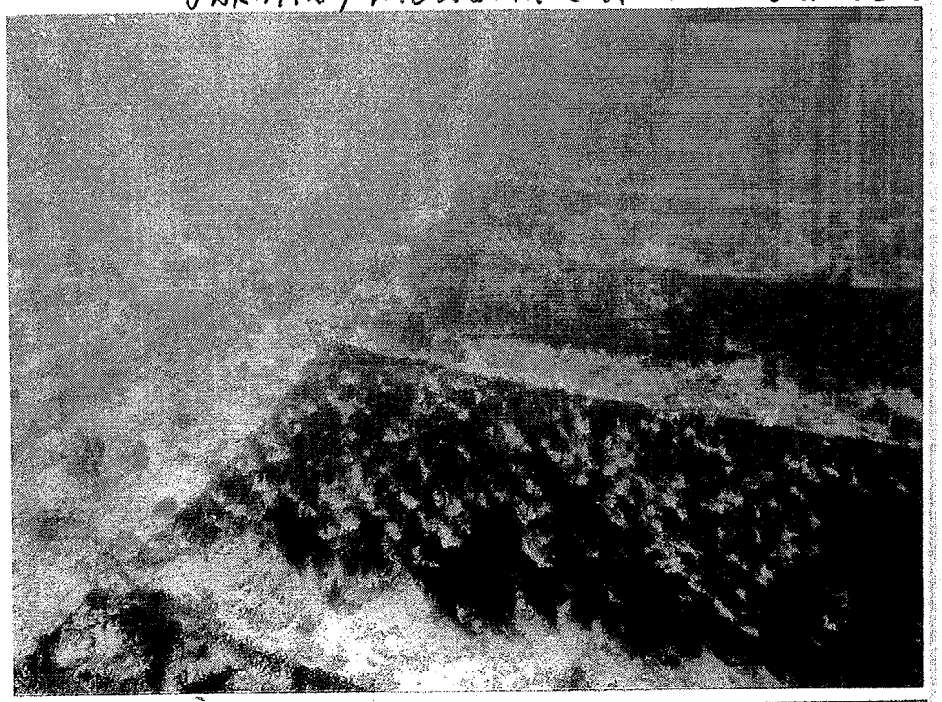
Masayo P. Kanstrup, President
Ocean Treasure Foods Inc.

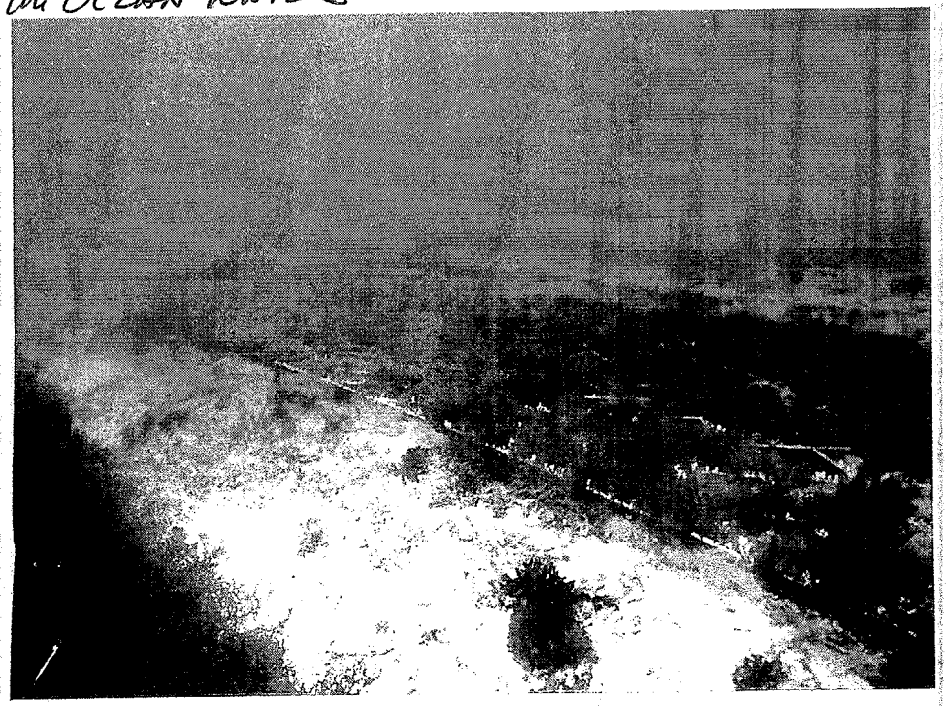
Phone: 303-750-2849, Fax: 303-347-1833

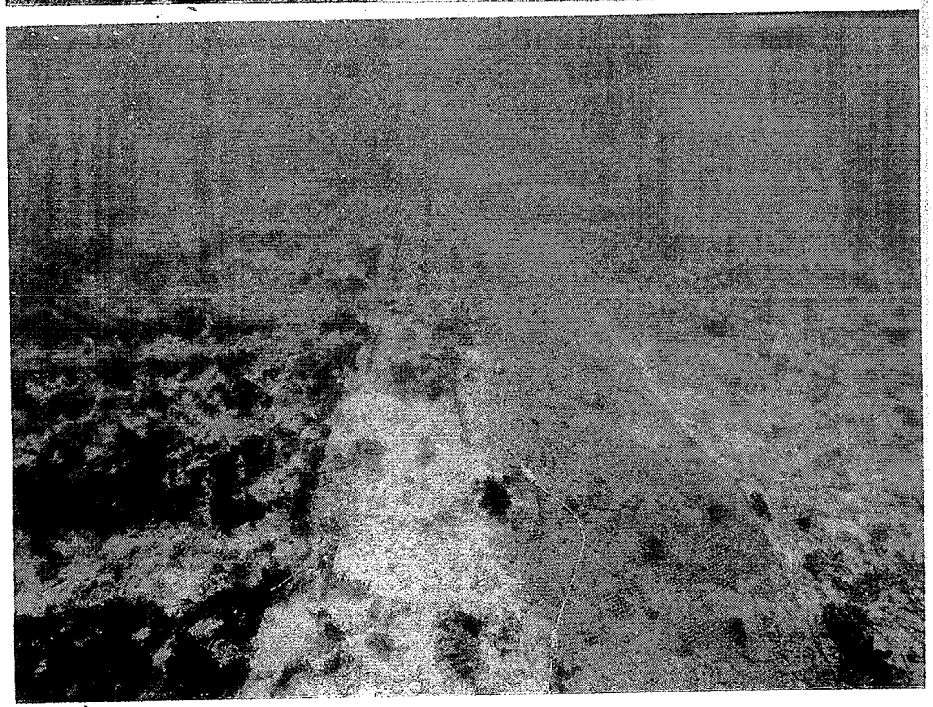
May 22, 2000

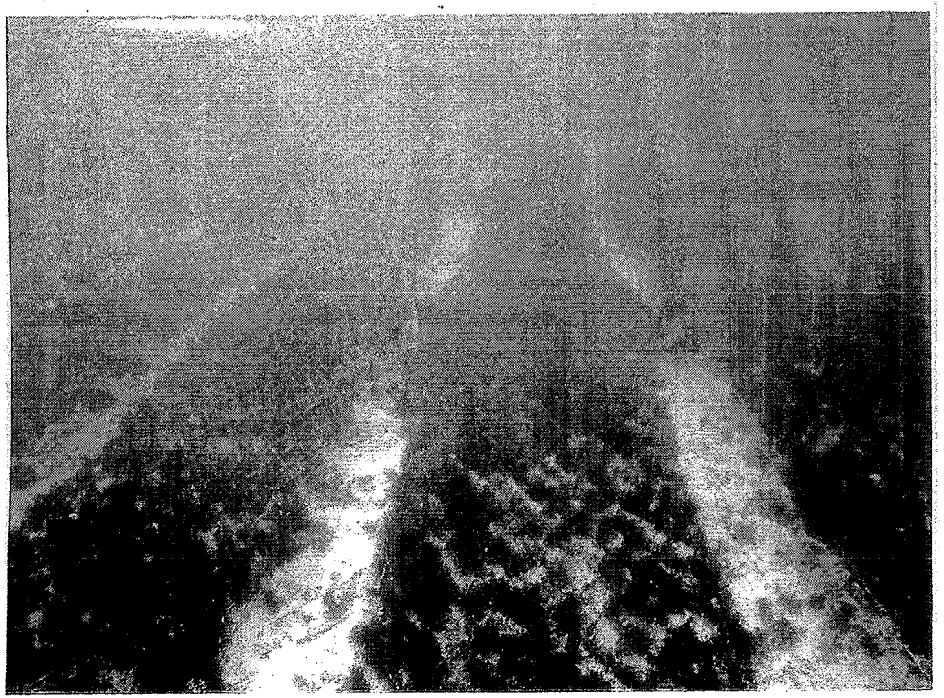
Algaia is a health supplement containing the polysaccharide fucoidan, a beneficial substance found in indigenous to Okinawa. To obtain the benefits of this substance, it is first extracted and then processed into highly digestible forms that are easy to take.

FARMING MOZUKU (OKINAWA) UNDER THE OCEAN WATER









Oyo Tshitsu Kagaku (J. Appl. Glycosci.) Volume 43 Number 2 P. 143 - 153 (1996)

Effects of Fucoidan Extracted from Okinawamozuku (*Cladosiphon okamuranus Tokida*) on the Plasma Concentration of Cholesterol in Rats Fed a High Cholesterol Diet

Megumi Uehara, Masakuni Tako, Yoshisugu Kawashima, Takao Fukunaga, Hirosi Syo, Isao Chinen, and Fujiya Honco

Department of Biosciences and Biotechnology, and Department of Environmental Sciences and Technology, College of Agriculture, University of the Ryukyus (I, Sunbaru Nishihara, Okinawa 903-01, Japan)

The effects of Fucoidan extracted from Okinawamozuku (*Cladosiphon okamuranus Tokida*) on serum cholesterol levels in cholesterol-fed rats were studied in comparison with those of cellulose. The liver weight of rats fed Fucoidan and Okinawamozuku diets was lower than in rats fed cellulose. The free and total cholesterol levels of serum for Fucoidan diets showed lower values than cellulose diets. However, HDL cholesterol levels of Fucoidan diets in serum showed higher values than those of cellulose diets (not significant). On the other hand, the total cholesterol levels of liver for Fucoidan diets also showed lower values than for cellulose diets. The serum cholesterol normalizing effect was estimated to be greater for Okinawamozuku diets in both serum and liver than for Fucoidan diets. These results suggest that Fucoidan and Okinawamozuku have serum cholesterol normalizing effects.

Corresponding authors reported the effects of fucoidan extracted and processed from Okinawamozuku (*Cladosiphon okamuranus Tokida*) and confirmed its physical and chemical characteristic *in the previous volume of this journal.*

Fucoidan, a polysccarides acid, 13.5% uronic acid and 11.9% sulfuric acid, molecular weight approximately 500,000, was added to L-Fucose and D-Xylose.

Okinawamozuku is cultivated and commercially produced in Okinawa (7,700 t in 1995) and had supplied 98% of demand of this nation (Japan). The demand peaked in 1991, however, in recent years, the demand for Okinawamozuku has been steadily declining.

Fucoidan contains a sulfuric acid base similar to heparin, which has been shown to be an anti-coagulant of blood, to lower serum cholesterol levels, and to suppress AIDS virus and tumor growth and produce anti-carcinogenic effects.

However, no report has been made on fucoidan extracted from Okinawamozuku. Thus, this report compared and examined the results of our experiments on the effect of Fucoidan extracted from Okinawamozuku and Okinawamozuku added to the experimental diets fed to high cholesterol diet-fed rats. The report also compares the effect on serum cholesterol levels and the total cholesterol levels of liver in high cholesterol-fed rats studied as well as cellulose-fed rats.

22 ± 1° C, and humidity was 60 ± 5% , with *ad libitum* access to water and rat chow. This environment was maintained 24 hours a day during the experiments.

Body weight and food intake of the rats were measured every other day. Feces was collected immediately before and at the conclusion of the experimental diets fed to the rats. After a 12-hour fast, on the last day of the experimental diet, rats were anesthetized with a nemputar, blood samples were drawn from the abdominal vein of the rats, plasma for the analysis was isolated by centrifugation, and subsequently it was supplied for analysis. At the same time, the liver and caecum (with its contents) were taken out, weighed, measured, and kept frozen and then stored until the analysis.

3. **Lipids analysis**

For analysis of the lipids in the plasma, Wako assay kits were used. Concentrations of free cholesterol, HDL cholesterol, total cholesterol, triglycerides and phospholipids were determined by using commercially available Wako assay kits (Wako Pure Chemical Industries, Ltd, Osaka, Japan):
(Free cholesterol with free cholesterol E - test Wako,
HDL cholesterol with HDL- cholesterol- test Wako,
total cholesterol with cholesterol E - test Wako,
triglycerides with triglycerides E - test Wako
and phospholipids with phospholipids C - test Wako).

4. **Analysis of the liver lipids**

The Folch method was employed for the extraction of liver lipids;
for the measurements, Sperr and Webb methods were used for free and total cholesterol, and Flecher method for triglycerides, and the Gomori method for phospholipids. The amount of cholesterol ether (%) was calculated from amounts of total cholesterol and free cholesterol in serum:
esterified cholesterol (%) =
(((total cholesterol - free cholesterol) / total cholesterol) × 100)

5. Analysis of neutral sterols in feces and bile acid

Rat feces were harvested, and neutral sterols and liver bile acid were extracted from freeze-dried rat feces. Ethanol was added. neutral sterols was extracted after ethanol extraction liquid was evaporated, then dried and solidified, thereupon extracted again to be measured with a gas chromatography.
A quantity of bile acid was measured at 340 nm, after ethanol extraction liquid was evaporated, dried and solidified, then dissolved again into a buffer. Subsequently, Hydroxysteoid dehydrogennase (Sigma) was added, and a reaction was allowed to proceed.

6. Statistical Analysis Methods

Our hypothesis was tested by using the single factor analysis tool, ANOVA (Analysis of Variance).
The data had been measured by previously described methods.
Subsequently, Fisher's Least Significant Difference (LSD) method was used.
Values are presented as mean ± standard deviation.

$p < 0.05$

were considered statistically significant.

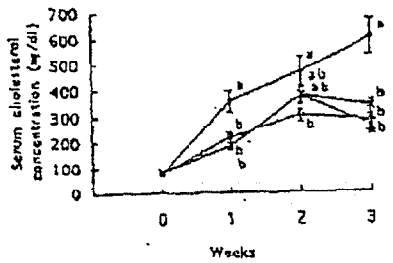


Fig. 1. Time course of changes in total-cholesterol concentration in serum.

Values not having the same superscript letters are significantly different ($p < 0.05$). ○, Mozuku; ▲, fucoidan; ★, guar gum; ◆, cellulose.

Table 1. Composition of the experimental diets (%)

	Mozuku	Fucoidan	Guar gum	Cellulose
Casein	20	20	20	20
Lard	5	5	5	5
Corn oil	5	5	5	5
Vitamin mix.*	1	1	1	1
Mineral mix.*	4	4	4	4
Cholesterol	1	1	1	1
Sodium Cholate	0.25	0.25	0.25	0.25
Cellulose	—	3	3	5
Mozuku	5	—	—	—
Fucoidan	—	2	—	—
Guar gum	—	—	2	—
Sucrose	58.75	58.75	58.75	58.75

* Vitamin mix., (in mg): retinyl acetate, 100.0; cholecalciferol, 0.25; tocopheryl acetate, 500.0; menadione, 520.0; thiamine HCl, 120.0; riboflavin, 400.0; phyridoxine HCl, 80.0; cyanocobalamine, 0.05; L-ascorbic acid; 3,000.0; D-biotin, 2.0; folic acid, 20.0; calcium pantothenate, 800.0; p-aminobenzoic acid, 600.0; nicotinamide, 600.0; inositol, 600.0; choline chloride, 20,000.0; cellulose powder, 73,057.7. * Mineral mix., (in %): $CaHPO_4 \cdot 2H_2O$, 14.56; KH_2PO_4, 25.72; NaH_2PO_4, 9.35; NaCl, 1.66; Ca-lactate, 25.09; Fe-citrate, 3.18; $MgSO_4$, 7.17; $ZnCO_3$, 0.11; $MnSO_4 \cdot 4-5H_2O$, 0.12; $CuSO_4 \cdot 5H_2O$, 0.03; KI, 0.01.

Results

1. The weight gain and food intake of rats

Table 2 shows effects of experimental diets exhibited by Table 1: weight gain, food intake, and liver and caecum weight.
There were no significant differences in any group's weight gain, but the guar gum diet-fed group showed slightly low values.

There were no differences in any group regarding diet efficiency, but for the intake of food, the mozuku diet-fed group and fucoidan diet-fed group showed significantly high values. And the weights of liver were significantly low in the guar gum diet-fed group and the mozuku diet-fed group; the fucoidan diet-fed group showed median values between the cellulose diet group and the guar gum diet-fed group.

Fucoidan diet-fed group showed the highest values in comparison with other groups.

2. Lipids concentration in plasma

Approximately 1 ml of rat's blood was drawn regularly and periodically from the tail vein for observation of daily changes in total cholesterol concentration in the rat's plasma.

Figure 1 shows time course of changes in total cholesterol concentration in serum.

Concentration of total cholesterol in rat's plasma for the mozuku and fucoidan diet-fed groups showed lower values in comparison with the cellulose diet-fed group, and the mozuku diet-fed group especially showed the lowest value.
Table 3 lists lipids concentration in serum.

Concentration of free cholesterol in the rat's plasma for the mozuku diet-fed group showed the lowest value. The next lowest value was shown by guar gum group, then followed by the fucoidan group, then cellulose.
(Table 3).

On the other hand, there were no significant variances in any group, but the mozuku and fucoidan diet-fed groups showed a tendency for higher values in comparison with cellulose diet-fed group, which showed lower values than other groups in the concentration of HDL cholesterol in rat's plasma.

But fucoidan, mozuku and guar guam diet-fed groups showed lower values in concentration of total cholesterol in rat's plasma in comparison with the cellulose diet group. And guar guam diet-fed groups showed significantly lower values than that of the cellulose diet group.

For the concentration of triglycerides, the fucoidan diet-fed groups showed significantly higher values than that of cellulose diet group.

For the concentration of phospholipids, mozuku and guar gum diet-fed groups showed significantly lower values than that of the cellulose diet group.

3. **Concentration of lipids**

The concentration of lipids is shown in Table 4.
The guar gum diet group showed lower value than other groups, although there were no significant differences in other groups.

The concentration of total cholesterol in rat's plasma for the mozuku diet-fed group showed the lowest value (see Table 4)..

Fucoidan diet-fed group showed a higher value in comparison with the mozuku diet.

But there were no significant differences with other groups (cellulose and guar gum).

For the concentration of triglycerides, the mozuku diet-fed group showed high value. The Guar gum diet-fed group showed the lowest value. ($p < 0.05$). Other groups had median values.

Fucoidan and guar gum diet-fed groups showed similar low values.

For the concentration of phospholipids, mozuku and fucoidan diet-fed groups showed significantly low values than that of the cellulose diet group.

4. **Neutral sterol in feces and concentration of bile acid**

Table 5 shows effects of mozuku and fucoidan on excretion of neutral sterol and bile acids.

Mozuku diet-fed group showed significantly high value in feces weight (dried) compared with other groups.

For the amount of excretion of neutral sterol and bile acids, the fucoidan diet-fed group showed the lowest value, the next lowest was the cellulose diet group, then guar gum diet group, followed by mozuku diet group in that order, but there were no significant differences among the groups.

Discussion

Okinawamozuku and fucoidan, which were extracted from Okinawamozuku with cholesterol (1.0 %), sodium cholate (0.25 %) were added to the experimental diets of high cholesterol-fed rats for 24 days. Their effects on serum cholesterol levels and liver bile, triglycerides, and phospholipids were measured and studied.
The weight gain of two groups of rats raised with Okinawa**mozuku** and fucoidan diets compared with the cellulose diets group were little bit higher but not significant, there were little impact on growth conditions of rats between any groups. On the other hand, the weights of livers were not significantly different between fucoidan and Okinawamozuku diet groups, but still showed lower values than the cellulose diets group.

The rats were fed fucoidan extracted from Okinawamozuku and Okinawamozuku. The experiment showed lower values of lipids in the blood serum and the liver weights in comparison with the cellulose diets group. Thus, this study resulted in the following consideration: that fucoidan and Okinawamozuku can suppress an increase in the serum cholesterol level. When cholesterol is absorbed from intestinal wall to bloodstream, in spite of the fact that lipids acid promotes the absorption of cholesterol, the study showed that fucoidan and Okinawamozuku prevent the absorption of cholesterol. Fucoidan and Okinawamozuku-fed groups of HDL cholesterol in serum were higher for fucoidan and Okinawamozuku fed groups (no significant value).
The concentration of phospholipids were lower than that of the cellulose diets group. Fucoidan showed the suppression effect of raising the level of phospholipids. However, Okinawamozuku-fed group of HDL cholesterol in serum was higher, but the concentrations of free and total cholesterol were lower than that of the fucoidan diets group.
Thus, the experiment showed that Okinawamozuku diets showed better results than that of fucoidan. This result is not conclusive, because it depended on the fact that different amounts of each substance added to the experimental diets:
Okinawamozuku, 5 % and fucoidan, 2 %.
The above result needs further investigations and examinations.

Although more than 7000 t of Okinawamozuku has been consumed as "sunomono" each year, its function has not been examined or studied.
It is important to note that mozuku contains plenty of fucoidan which drew recent attention, not only the mozuku itself, but glucose that is contained in mozuku which can expected to improve our health and life.
An examination of its potential function seems important for future investigators.

Summary

Fucoidan extracted from Okinawamozuku and Okinawamozuku were fed to rats and compared to the group that was fed cellulose diets. The experiment showed lower values of lipids in the blood serum and the liver weight for fucoidan and Okinawamozuku fed groups.

Following are results:

Fucoidan and Okinawamozuku-fed groups of HDL cholesterol in serum was higher, but the concentration of free and total cholesterol were lower than of cellulose diets groups.

As a result we concluded that fucoidan and Okinawamozuku possess the effect of suppression for raising serum cholesterol and lipids level in liver.

Table 2. Effects of experimental diets on the weight gain, food intake and liver and caecum weight.

	Body weight		Food		Liver weight	Caecum weight
	Intial (g)	Gain (g/24 days)	Intake (g/day)	Efficiency	(g/100 g B.W.)	
Mozuku	107.8±1.4	114.8±6.7	16.4±0.7[a]	29.1±0.5	5.1±0.3[a]	1.5±0.1[c]
Fucoidan	107.7±2.0	109.7±1.9	16.3±0.3[a]	28.0±0.2	5.0±0.0[a]	2.4±0.1[a]
Guar gum	107.5±2.7	102.2±4.3	14.7±0.4[b]	28.9±0.8	4.6±0.1[b]	1.9±0.1[b]
Cellulose	108.2±1.5	106.2±4.9	15.2±0.4[ab]	29.1±1.1	5.4±0.1[a]	1.2±0.0[c]

Different superscript letters show a significant difference at $p<0.05$.

Table 3. Lipid concentration in serum.

	Cholesterol				Triglycerides (mg/dl)	Phospholipids (mg/dl)
	Free (mg/dl)	Esterified (%)	HDL (mg/dl)	Total (mg/dl)		
Mozuku	21.0±3.0[b]	91±0.7	50.6±6.9	253±37.9[a]	79.1±3.3[ab]	148±13.2[b]
Fucoidan	31.4±3.0[ab]	91±0.4	57.2±6.2	338±19.9[a]	94.5±5.8[a]	177± 5.0[ab]
Guar gum	27.7±3.4[b]	91±0.7	54.6±7.8	289±15.8[b]	81.7±6.0[ab]	148± 7.5[b]
Cellulose	43.6±6.4[a]	91±0.4	47.4±5.5	478±47.8[a]	76.4±4.3[b]	209±19.2[a]

Different superscript letters show a significant difference at $p<0.05$.

Table 4. Lipid concentration in liver.

	Cholesterol			Triglycerides (mg/g)	Phospholipids (mg/g)
	Free (mg/g)	Esterified (%)	Total (mg/g)		
Mozuku	6.41±0.69	90±1.1	61.7±1.7[b]	40.6±6.3[a]	18.8±1.2[ab]
Fucoidan	7.09±0.49	89±0.7	63.3±1.2[b]	30.3±3.5[ab]	17.4±0.8[c]
Guar gum	5.73±0.58	91±1.0	62.6±1.6[b]	26.7±3.0[b]	19.9±0.7[ab]
Cellulose	6.84±0.79	91±1.1	73.8±3.0[a]	35.0±2.2[ab]	21.5±0.8[a]

Different superscript letters show a significant difference at $p<0.05$.

Table 5. Effects of mozuku or fucoidan on excretion of neutral sterols and bile acids.

	Feces weight[a] (g/day)	Neutral sterols (mg/day)	Bile acids (mg/day)
Mozuku	1.63±0.07[a]	53.9±2.89	64.9±2.7
Fucoidan	1.31±0.10[a]	49.0±2.11	56.3±4.8
Guar gum	1.11±0.08[b]	57.8±5.21	65.0±6.1
Cellulose	1.24±0.07[b]	49.8±3.69	59.6±4.4

Feces weight is dry weight. [a,b] Significant difference at $p<0.05$.

@ FUCOIDAN TESTING, PAGE 01

Pre-Marketing Fucoidan Testing

Objective:

Hokugan Co. Ltd., 3-6-1 Minatomachi, Naha, Okinawa, Japan 900-0001 has conducted a safety evaluation of Fucoidan which is extracted from Mozuku, one type of sea kelp. Even though there are animal test research studies that indicate the safety and produces no harmful side effects taking Fucoidan, our test reconfirms the safety and non-toxicity of our products "Algaia tablets " which are made with Fucoidan ingredient. Fucoidan is extracted from Cladspiphon okamuranus - "Okinawa Mozuku" and nemacystus deceiphiens - "Itomuzuku" and is used in dietary supplements and cosmetic products in Japan.

Safety Testing Methodology:

The test was conducted for 90 days monitoring 21 people who are range in age of 20 to 60 years old taking 6 tablets per day (each tablet contains 30 mg of Fucoidan). The health conditions of each person was evaluated before the test and then evaluated again after 30, 60 days and at 90 days.

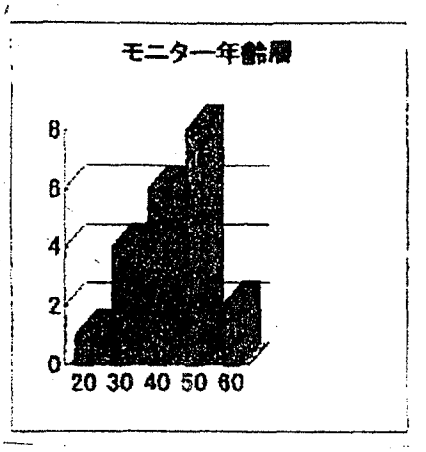
Result:

There are no conditions indicated by any of the test subjects that Fucoidan effected their health condition; bad fever, diarrhea and or vomiting by taking Fucoidan tablets ("Algaia"). Over all, the test result indicates Fucoidan is safe and produces no harmful side effects. Several people indicated that their stomach became a little warm. According to the research documented in the past, this symptom develops as "the intestines react to the effect of the fiber found in Fucoidan" therefore, it will solve this kind of condition by adjusting (decreasing) the number of tablets taken.

Translation of Fucoidan Test Report Provided by Hokugan Co., Ltd.

FUCOIDAN TESTING, PAGE 02

The Test Result from Algaia Tablets



Participant Data

Age	No.
20	1
30	4
40	6
50	8
60	2

Male 1, Female 20

Survey questions before this test.

Average Height	151.3 Kg.	
Average Weight	58.0 cm	
Constipation		4
Purchasing Health Foods		9
Eating between Meals every days		8
Eating between Meals sometimes		9
No. Snacks at all.		4

Effect on constipation condition

	Good	Normal	Poor
before	17	0	4
30 days	19	1	1
60 days	17	3	1
90 days	14	7	0

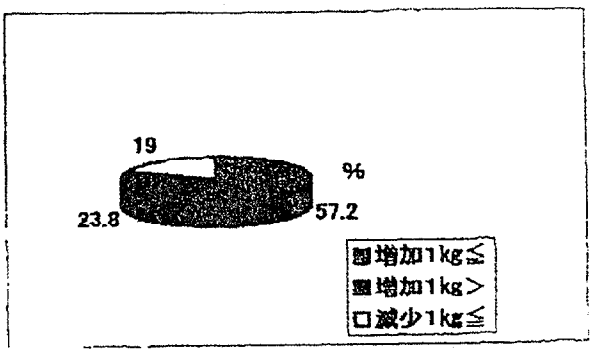
Effect on weight condition

	Weight Increases	No Change in Weight	Weight Decrease
*30 days	11	9	1
*60 days	12	6	3
*90 days	15	2	4

Average Weight Increase at 30 days, 1.18 kg; at 60 days, 1.30 kg; at 90 days, 0.97 kg.
Average Weight Decrease at 30 days, 1.0 kg; at 60 days, 4.3 kg; at 90 days, 0.33 kg

Summary of Weight Increases or Decreases for the group:

Average Increase in Weight over 1 kg.
5 Participants 23.80 %
Average Increase in Weight under 1 kg.
12 Participants 57.10%
Average Decrease in weight under 1 kg.
4 Participants 19 %

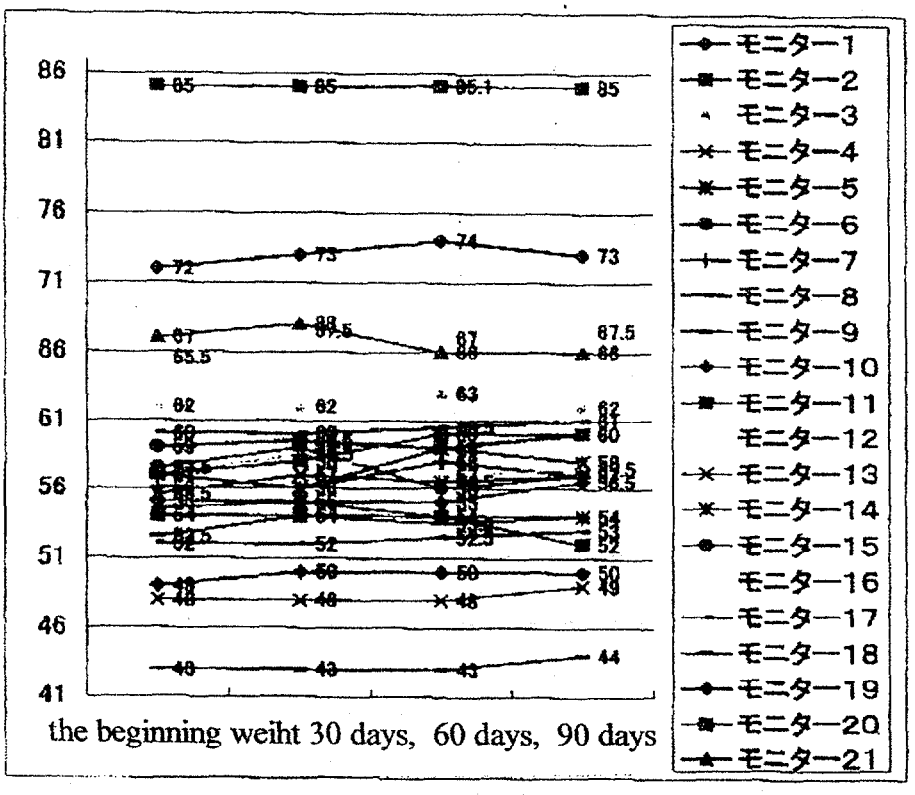


the beginning FUCOIDAN TESTING, PAGE 03

Participants weight 30 days, 60 days, 90 days

モニター番号	初期体重	30日後	60日後	90日後
1	72	73	74	73
2	54	54	54	52
3	62	62	63	62
4	55.5	57	56.5	57
5	57	56	59	58
6	59	59.5	59	60
7	56	56	58	57
8	60	60	60.5	61
9	43	43	43	44
10	55	55	55	56.5
11	85	85	85.1	85
12	65.5	67.5	67	67.5
13	48	48	48	49
14	54.5	55	54	54
15	57.5	59	56	57
16	57	58.5	57	57.5
17	52	52	52.5	53
18	52.5	54	53.5	54
19	49	50	50	50
20	57	58	60	60
21	67	68	66	66

Participants



アルガイア錠剤モニターの個別体重変化グラフ

The Graph of Participants Weight Changes taking Algaia Tablets

History of Mozuku

There are many different type of sea kelp and seaweeds that have been harvested from the ocean and consumed as food souses in Japan for generations. Okinawa Mozuku (cladosiphone okamurnus) are types of brown sea kelp and has been consumed by people in this region as a every day food source since ancient times. Particularly in the islands of Okinawa, farming and harvesting of Okinawa Mozuku commercially began in full-scale since 1978 (see attached photograph) as a daily food supply. This Fucoidan used in food sources and dietary supplements in Japan are extracted from Okinawa Mozuku which contains polysaccharides and has enormous health benefit. There are no reports that indicates any toxicity of Fucoidan raw materials or other sea kelp in the food history in Japan.

The Fucoidan extraction process, we don't use Rather, we use that are approved and commonly used by the food industry. Therefore, there are no indications or traces of toxicity after the extraction process is completed. Sea kelp, in general, does not contain heavy metals such as arsenic, cadmium, lead and tin. Any traces are insignificant and are much lower than that allowed under the Japanese government's food and health standards. Okinawa Mozuku seeds are planted at an ocean depth of approximately Mozuku is highly susceptible to environmental pollution and Mozuku requires the best and cleanest ocean water for its survival and commercial harvesting.

The Health Products and the Cosmetic Products which contains Fucoidan and the List of Japanese Companies:

A. Health food and dietary supplement manufactures using Fucoidan as an ingredient:

(1) Hokugan Company
(2) Okinawa Fermentation chemical
(3) Takara Sake K.K.
(4) Morishita Jintan K.K.
(5) Fancel
(6) Marui Trade K.K.
(7) Nagase Sangyo

B. Cosmetic companies using Fucoidan in their cosmetic products:

(1) Jintan Fine Chemical
(2) Yakult K.K.
(3) Kao K.K.
(4) Takara Sake Brewing Co.

C. Pet Food Market. Takara Sake Brewing Co.

Translation of Fucoidan History Provided by Hokugan Co., Ltd.

D. Commercial Fish-farming and fish hatchery: Takara Sake Brewing Co.

E. Introduction of health food products in the Japanese market using Fucoidan as an ingredient:

Year	Product Name	Product Description	Manufacture's Name
1997	Apoidan U	Health drink	Takara Sake Brewing Co,
1998	Apoidan U	Dietary Supplement tablet	Takara Sake Brewing Co.
1999	Mansaiju	Health Drink	Fancel K.K.
	Manzaiju	Dietary Supplement Tablet	Fancel K.K.
	Algaia	Health Drink	Hokugan K.K.
	Algaia	Dietary Supplement	Hokugan K.K.
	Jintan Fucoidan plus 3	Health Drink	Morishita Jintan K.K.
2000	Fucoidan grain	Dietary Supplement Tablet	Okinawa Fermenting Chemical
	Aqua Museum	Health Drink	Hokugan K.K.
	BM Royal	Dietary Supplement Tablet	Nagase Sangyo