

Fucoidan Tsushin News Letter vol.5 Jun. 2011

The pioneer of mozuku sea algae foods Marine Products Kimuraya Co., Ltd.

“Relieving effect by fucoidan on side-effects caused by anticancer agents”

Articles published in an international
academic journal.

Marine Products Kimuraya Co., Ltd.
Senior Staff Researcher of R&D Division
Dr. of Science

Minoru Funakoshi

Graduated Kyushu University Faculty of Science in 1994.

Completed Kyushu University, Graduate School of Medical Sciences, Faculty of Medical Sciences in 2000 and obtained Doctor of Science in 2000.

In 2004, studied in USA (Yale University) the Program of “Postdoctoral Fellowship for Research Abroad” of “Japan Society for the Promotion of Science” .

Dec. 2010, joined Marine Products Kimuraya Co., Ltd. A specialist of molecular biology science, centrally genetics.

Currently conducting research on the taste-change of drinking by addition of fucoidan and relevance of fucoidan to the immune function.

Also researching various types of sea algae and their constituents that have not yet been commercialized.

Hobby is “kitchen-gardening” , with a special focus on cultivating unfamiliar vegetables he sampled in the USA.

Additional hobbies include enjoying the great pleasure of opening a paperback book and working on a farm in his spare time.

Looking for a bride candidate who enjoys Nature and Agriculture.

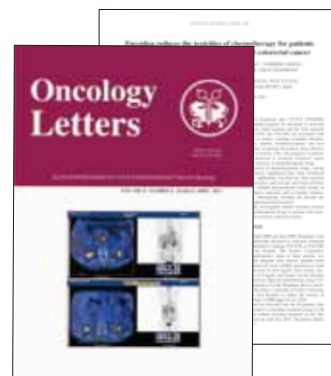


“Relieving effect by fucoidan on side-effects caused by anticancer agents”

Articles published in an international academic journal.

We examined the influence of high polymer mozuku fucoidan against advanced/recurrent colorectal cancer in joint research with Tottori University Faculty of Medicine and Marine Products Kimuraya Co., Ltd.

The results of this research were published in the international academic journal on cancer, “Oncology Letters”



International Academic journal
“Oncology Letters” Vol. 2,
March/April 2011

We applied/obtained numerous patents on fucoidan.

Marine Products Kimuraya Co., Ltd. who are producing high polymer fucoidan have been carrying out leading edge research of function of fucoidan.

Through our joint research with Shimane University, Tottori University Faculty of Medicine, Faculty of Agriculture Department of Veterinary Medicine, Faculty of Technology and others, we have made various discoveries that confirm the usefulness of fucoidan, such as antibacterial activity against O-157, maintenance activity of health, anticancer activity.

Among various discoveries of functions about fucoidan, we have already obtained 3 patents, namely, “Effects of mozuku fucoidan on inhibition of proliferation of stomach cancer cell” (Patent No. 4589900,) which was the result of joint research with Shimane University; “Suppression effect of mozuku fucoidan on side-effects of anticancer agents” (Patent No. 4034146), which is the result of joint research with Shimane University; and “Preventive effect of mozuku fucoidan on thrombosis” (Patent No. 4428486); which is the result of joint research with Tottori University.

In total, we have applied for 18 patents, including PCT International application (including US Patents).

Some of them are “Effect linking to prevent gout”, “Effect to improve environment inside intestines”, “Acceleration effect regeneration of cartilage”.

From 2005 to today (April 2011), Marine Products Kimuraya Co., Ltd. has been promoting 22 joint research studies on the functionalities of fucoidan with Tottori University Faculty of Medicine, Faculty of Agriculture Department of Veterinary Medicine, Faculty of Technology.

Proved the suppressant effect of fucoidan on side-effects of anticancer agents in the experiment.

Among fucoidan's many useful functions, the most remarkable one is its action to suppress side-effects of anticancer agents.

Anticancer agents are effective therapy options to combat cancer, by killing and inhibiting proliferation of cancer cells.

However, anticancer agents also kill normal cells, causing some patients to suffer from such side-effects as fatigue, nausea, vomiting, loss of appetite and others.

This not only imposes serious burdens on patients' bodies, it also often forces the administration of drugs to be suspended, due to such strong side-effects.

In 2002, Marine Products Kimuraya Co., Ltd. conducted experiments on the suppressant effect of high polymer fucoidan on side-effects of anticancer agents together with Shimane University.

We mixed cultured human stomach cancer cells in a test tube with normal cells, and added "5-Fluorouracil (5-FU) only" which is mostly used for stomach cancer therapy and "5-FU added fucoidan", and observed the status of cells in each case.

In the 5-FU only cases, cancer cells, as well as some normal cells, were killed; meanwhile in the 5-FU was added high polymer fucoidan cases, cancer cells were killed while normal cells were not, thus keeping the effects of anticancer agents to kill cancer cells, while dramatically reducing the causes of harmful side-effect. (Fig. 1)

Based on this discovery, in 2007, Marine Products Kimuraya Co., Ltd. obtained the patent "Suppressant agents of side-effects of anticancer agents".

Implemented clinical tests of influence on the anticancer chemotherapy, first time in the world

Furthermore, since 2008, we started first in the world joint clinical tests, to research the suppressant effect of high polymer mozuku fucoidan on side-effects of anticancer chemotherapy.

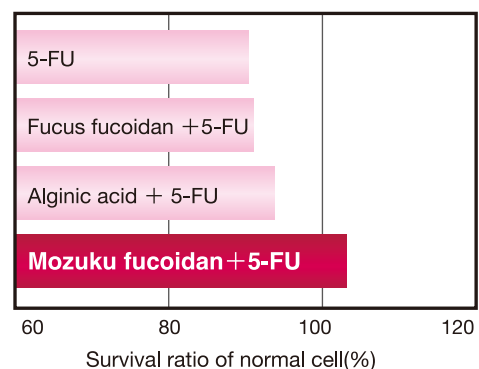
In these clinical tests, we are comparing and examining the relieving effects of side-effects, of anticancer chemotherapy, and the influence on cycles of prescription of anticancer agents.

Now an article about the physiological activity of fucoidan, including earlier mentioned

contents, was published in the international cancer research journal "Oncology Letters" Vol. 2. Mar.-Apr. 2011. (Refer to below column)

Marine Products Kimuraya Co., Ltd. also applied this research achievement for patent

[Fig. 1] Survival ratio of normal cell in case of addition of 5-FU and fucoidan



on “Suppressant agents of side-effects of anticancer agents” together with Tottori University. (PCT/JP2010/052641)

Marine Products Kimuraya Co., Ltd. will conduct additional medical research, through clinical tests and action tests, in order to make use of the effectiveness of fucoidan for the prevention and therapy of all diseases, including such relieving effect of side-effects caused by anticancer agents.

Reducing effect by fucoidan on side-effects of anticancer therapy for advanced/recurrent colorectal cancer patients

Our articles about the physiological activity of fucoidan, which we jointly researched with Tottori University, was published in the international academic journal of cancer research “Oncology Letters”, Vol. 2, March/April 2011.

This study reported that the effects of fucoidan to reduce side-effects caused by anticancer drugs were verified by clinical tests for colon cancer patients.

Nowadays, when administering medical treatment against advanced and recurrent cancer, it is common practice to use multiple anticancer drugs, such as FOLFOX ①, or FOLFIRI ②.

This treatment provides high therapeutic efficacy, however at the same time, induces various intense side-effects including fatigue.

On the other hand, through the basic research being used on human cultivated cells ③, it was confirmed that fucoidan has “the efficacy to protect normal cells from being killed by anticancer drugs”.

This fact shows that fucoidan has the possibility to suppress side-effects during anticancer drugs therapy.

We then conducted clinical tests on actual cancer patients to examine whether fucoidan has effects to suppress side-effects caused by anticancer drugs ④.

We have administered anticancer drug therapy on 20 colon cancer patients, for 6 months.

We divided the patients into two groups.

10 patients were administered fucoidan, and 10 patients were not administered fucoidan.

The administration subject patients started ingesting fucoidan every day from the date



Our joint research partner Tottori University
Faculty of Medicine
(Yonago-shi, Tottori)

of start of anticancer therapy As a result, the administered group's average cycle of prescription of anticancer drugs ⑤ was 19.9, while the non-administered group's was 10.8.

It was clear that the administered group's cycle was more.

As for the side-effects shown during therapy period, 6 patients showed the sense of fatigue of Grade 2 ⑥ among 10 non-administered fucoidan subjects, while only one patient showed the sense of fatigue among the 10 administered fucoidan subjects. Statistically we confirmed that the sense of fatigue of administered fucoidan patients was clearly reduced.

Thereafter, therapy continued for 15 months, and 2 fucoidan administered patients died and 4 fucoidan non-administered patients died. (Fig. 2)

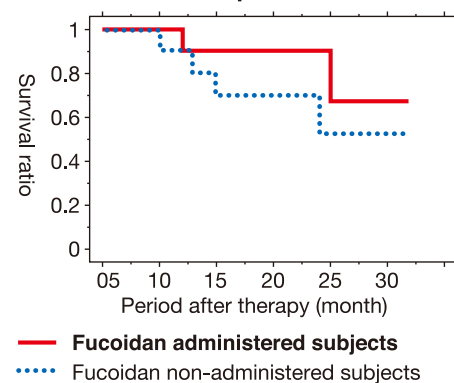
Namely fucoidan administered subject showed a higher survival ratio than fucoidan non-administered subjects.

We must conduct more research to confirm this significant difference.

From the above examination, we confirmed that fucoidan has “suppression effects of the sense of fatigue of colon cancer patients under anticancer therapy” and “to be able to increase cycle of prescribed therapy of anticancer drugs”.

The fucoidan used in the clinical test was High polymer fucoidan, made by Marine Products Kimuraya, which was extracted from Okinawa mozuku.

[Fig. 2]Transition of survival ratio of fucoidan administered patients and non-administered patients



Glossary

① **FOLFOX** : One of the ways to prescribe anticancer drugs.

2 kinds of anticancer drugs, Oxaliplatin and 5-Fluorouracil, and Leucovorin which activates activity of 5-Fluorouracil are administered at the same time.

② **FOLFIRI** : One of the ways to prescribe anticancer drugs.

2 kinds of anticancer drugs, irinotecan and 5-Fluorouracil, and Leucovorin which activates activity of 5-Fluorouracil are administered at the same time.

③ **Cultivated cell** : Artificially cultivated cell in vitro. Used frequently in areas of basic research, especially molecular biology, biochemistry and cell biology.

④ **Clinical test** : Tests in order to ensure safety and efficacy, administering drugs and medicines, using medical equipment for patients and healthy persons.

This test is done after enough basic researches and animal clinical tests.

Previously both patients and healthy persons who will receive the tests should receive enough explanation, and their privacy issues are well respected.

⑤ **Cycle of prescription of anticancer drugs** : According to the prescription of FOLFOX or FOLFIRI, anticancer drugs and medicines are administered by intravenous injection drip, the subjects are followed up in the two weeks course.

This is called one cycle.

In case severe or continuous toxicity appeared, density of drug and medicine is decreased or start of the next cycle is broken off.

⑥ **Grade 2** : Showing degree of adverse event.

“The adverse event” means of undesired event occurred in the user of the medicines.

The Degrees of Symptoms are unified by National Cancer Institute in USA as “Common Terminology Criteria for Adverse Events”.

There are 6 levels according to severity from Grade 0 (Normal) to Grade 5 (Death due to adverse event).

Grade 2 is defined as “moderate adverse event” and minimum level of treatment, or local treatment, or non-invasive therapy (treatment which doesn’t disrupt normal situation of the body).



Marine Products Kimuraya Co., Ltd.
Technical advisor
Prof. Emeritus of Tottori University

Takeshi KASAGI

Usefulness of fucoidan attracts international attention such as reducing effects of side-effects of anticancer therapy

I turned from Doctor of Engineering to a researcher of physiology

Firstly I talk about my odd and unique career.

During my University and Graduate School days, I worked for the Faculty of Technology, engaged in design and development of semiconductor devices. This was a world of energy conversion and information interchange in substance. Be awakened by an occasion, I became interested in how a substance was transported and how information was delivered in a living organism and in its cells. After I completed my master's course of Graduate School, I achieved my expectation to work as an assistant of physiological course of the Faculty of Medicine, Tottori University, in Tottori Prefecture, where I came from.

In research on how a taste substance was detected by the tongue and sweetness is expressed, I was fascinated by the specific character of gymnemic acid, which is a main constituent "Gymnema sylvestre", a plant in India.

I thought to apply this to the absorption activity of sugar in the small intestine and confirmed its effectiveness by the ingestion in animal tests and human clinical tests. In the wake of this, I achieved various material developments for health food, repeating the development and test of food material substances which influence

digestion and absorption of sugar in the small intestine.

Around the time of my retirement of Tottori University, I had chance to meet Marine Products Kimuraya Co., Ltd. where I started research on fucoidan.

At Marine Products Kimuraya Co., Ltd, I successfully advanced my research on “Improvement action of inside of intestines” for healthy adults, and such safety tests as “Excessive ingestion test and Long term ingestion test”, “Reducing action of density of actaldehyde/ethanol while drinking.”

Fucoidan reduces side-effects symptoms by anticancer agents

Today, I am most interested in “Suppressant effect of side-effects by fucoidan for the advanced/recurrent colorectal cancer patients”, which was confirmed by joint research with Tottori University Faculty of Medicine.

I think I can say, the experiment results which Marine Products Kimuraya Co., Ltd. accumulated at culture cell level were examined at the clinical test level.

In this experiment, they divided 20 patients of the advanced/recurrent colorectal cancer into 2 groups of 10. One group was administered fucoidan and the other group was non-administered.

On the first day of anticancer therapy, the administration group started ingesting fucoidan every day. They were followed-up.

This anticancer therapy is a combination prescription of multiple anticancer agents, such as FOLFOX and FOLFIRI, strengthens anticancer action, and is very effective; however it induces various side-effects and imposes burden to patients' bodies, therefore it has been a problem.

But in this experiment, such side-effects as fatigue, nausea, vomiting, loss of appetite which are being induced during therapy were confirmed to be suppressed in the group of administration of fucoidan.

In addition, the average number of cycles to prescribe anticancer agents for the group of administration became about 2 times of the non-administration group.

I suppose anticancer therapy could be carried on, increasing number of cycles to prescribe anticancer agents because the side-effect symptoms of patients were relieved by administration of fucoidan.

Normally, when the number of cycles is increased, the side-effects also increase, making it difficult to continue the therapy, and the colon cancer tends to become more advanced.

However, if further research is conducted on anticancer therapy combined with administration of fucoidan, I expect we can get more interesting achievements.

Further development of research for health of many people is expected.

In 2005, Marine Products Kimuraya Co., Ltd. and Tottori University Faculty of Medicine started joint research on the functionality of fucoidan and have done clinical

tests using fucoidan over many years.

One of our research achievements has been an administration test of fucoidan against the advanced/recurrent colorectal cancer patients.

Through this research we confirmed the reducing action of side-effects of anticancer therapy, and an increase in the number of cycles of prescription of anticancer agents.

This result was published in the international cancer research journal "Oncology Letters" Vol. 2. Mar.-Apr. 2011.

I am very pleased to have published the articles because the results of our research will now come to the public's attention.

Fucoidan extracted from mozuku which has such many activities is considered to be a substance which mozuku produces to protect themselves.

I would like to accumulate more research for the sake of protecting the health of many people, piling up examinations from various aspects about fucoidan's action for the body, which have been verified this time at Tottori University.

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