Preface

Why can't we overcome cancer despite science being advanced?

Many 'anticancer drugs' were developed by scientific knowledge, but it has been difficult to solve problems of harmful and unexpected adverse effects, for which combination of several anticancer drugs was clinically devised or new drugs, such as molecular targeting drugs which target specific molecules to treat diseases, were developed, but fundamental solution has not been achieved.

Under such circumstances, approach by scientifically re-discovering effectiveness of natural materials is attracting attention and expected to shed new light on anticancer action. Okinawa mozuku (seaweed)-derived polysaccharide, fucoidan, introduced in this book is expected to have high affinity for the body. I believe that this functional substance produces innovation in 'health creation' with regard to cancer prevention and treatment.

Hiroyuki Abe, Doctor of Medicine

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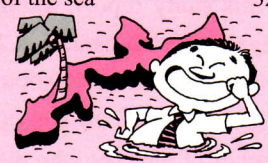


(Illustration / Satoru Yamamoto)

1 "Cancer" is a common disease---Anyone can have cancer.

In Japan, persons who died of "cancer", "heart disease", or "stroke", which are known as the most common causes of death, account for approximately 60% of all deaths. Since 1980, cancer has been the most common cause of death in Japan; one of 3 persons died of cancer. On the other hand, the most frequent cause of death in the world (6.2 billion persons) is infectious disease, comprising 1/4 of all deaths. However, "cancer" and "heart disease" show the highest and second highest percentages in advanced countries.

In December 2008, the International Cancer Research Institute, which belongs to the World Health Organization (WHO), announced that cancer would be the most common cause of death throughout the world in 2010, exceeding the heart disease-related deaths. According to this study report, the number of patients who were diagnosed with cancer in 2008 throughout the world is estimated to be 12,400,000. It is expected that this count will increase to 26,400,000 before 2030, and that the number of patients who die of cancer will increase from

7,600,000 in 2008 to 17,000,000. In males, lung cancer is the most frequent cause of death.

In females, breast cancer shows the highest percentage. The number of patients who die of cancer is high in males than in females.

According to WHO, the reasons for this include the rapid aging of society in many countries, an increase in the proportion of smokers, a higher proportion of smokers in males, and the introduction of European/American lifestyle-related factors, such as high-fat diet and lack of exercise, in developing countries.

Thus, cancer is currently a common disease. However, most healthy persons do not believe that they will have cancer.

As you know, cancer does not suddenly develop, differing from infection. It exists with the host over a long period. In our bodies, a large number of "cancer cells" appear night and day, while we are not aware of their presence. However, many persons lead healthy lives without the onset of cancer, while other diagnosed with cancer can live by medical treatment. What is the turning point?

2 Immunity protects the human body against "cancer cells".

In our bodies, a large number of "cancer cells" appear and disappear night and day, while we are not aware of their presence. These cancer cells are eliminated via the immune system. It has been shown that approximately 60 trillion cells comprise the human body, and that genetic damage/destruction related to specific factors result in a mutation. A gene, as a cellular design, has car accelerator- and brake-like functions, regulating cellular proliferation. For the normal tissue production of cells necessary for the human body, the cell count is closely regulated so that only a specific number of cells are produced. However, a mutation affects accelerator/brake control, leading to a higher production of cells than needed or the creation of cells differing in their features from normal cells. This is considered to be a "cancer cell". However, cancer does not develop immediately after a single gene mutates, and results from abnormalities in several genes over a long period.

The immune system protects the body against such a process. A large number of "cancer cells" are routinely produced. It was hypothesized that, despite this, the onset of cancer is not frequent because these cells are eliminated via the immune system.

Recently, the development of cancer has gradually been clarified. Factors such as ultraviolet light, smoking, alcohol consumption, food-derived harmful substances, stress, viruses, and exhaust gas may promote cellular canceration. It is also known that the anticancer immunity decreases with age. Approximately 70% of patients with cancer are 65 years old or older. In many cases, cancer is detected after cancer cells appearing at a young age have grown. The number of cancer patients may increase with the rapid aging of society. Therefore, we cannot distinguish persons who tend to develop cancer from cancer-free persons. Furthermore, recent cancer cells do not target the human society in comparison with previous cells. Anyone may be a "cancer candidate", and the probability of cancer development increases with age.

3 Physiological effects of phytochemicals

In the field of medicine, phytochemicals have recently been emphasized. Phytochemicals, which are also termed vegetable nutrients, refer to vegetable-derived compounds that may be important to prevent disorders and maintain a healthy state. Many studies have reported their physiological effects including the improvement of the immune function, activity against bacteria/viruses, anti-inflammatory actions, and inhibitory effects on cancer/cardiovascular diseases. Other actions may also be discovered. In particular, the role of phytochemicals as vegetable anticancer substances is emphasized in the field of medicine. The limitations of anticancer drugs regarding side effects have not been overcome. With this background, recent studies have investigated the functions of phytochemicals. As side effects of anticancer drugs are harmful for cancer-related morbid conditions, the necessity of developing safer anticancer substances has been suggested.

Anticancer drugs that directly target cancer cells have been demonstrated to negatively act on normal cells in the body. This was an unexpected result.

Currently, there are treatment options such as molecule- and cell-targeting therapies, which were developed to avoid such adverse effects. They were devised so that agents exhibited curative effects by inhibiting harmful cell functions, improving the efficacy and safety without damaging normal cells.

In such a situation, phytochemicals have been investigated as compounds that inactivate/destroy cancer cells via an action mechanism differing from that of anticancer drugs.

In my clinic, patients' body constitutions are evaluated using genetic diagnosis to select more effective prophylactic/treatment methods. A strategy to consume phytochemical-containing functional health foods, including Cladosiphon okamuranus-derived fucoidan, has also been introduced. A study regarding the anticancer actions of vegetable-derived food components confirmed that this substance induced apoptosis.

4 Apoptosis induction to eliminate "cancer cells"

◆Cladosiphon okamuranus contains 90% fucoidan.

A large amount of fucoidan is contained in viscous substances such as tangle weed and wakame/mozuku seaweed. I employed Cladosiphon okamuranus-derived fucoidan, because fucoidan comprises 90% of polysaccharides contained in Cladosiphon okamuranus. In Japan, the anticancer effects of fucoidan were reported at a meeting held by the Japanese Society of Cancer in 1996. Fucoidan, as a food component, was found to induce apoptosis. This was an epoch-making finding.

Apoptosis refers to cellular programmed death in genes. It is regarded as "cellular suicide". Apoptosis is induced not only in cancer cells but also in normal cells. In mutant cells related to various factors such as canceration and infection, apoptosis induction may lead to cancer reduction/disappearance. Apoptosis, as a homeostatic function, is an important cellular activity essential for life. Employing this as a key word, physicians and

investigators are engaged in cancer treatment/ research.

In this report, fucoidan contained in tangle weed was used. However, tangle weed polysaccharides contain a large amount of alginate. It is difficult to isolate and purify fucoidan alone with respect to cost-performance.

For this reason, I investigated Cladosiphon okamuranus-derived fucoidan. I was informed that its isolation/purification had been successfully achieved, suggesting the possibility of its widespread use. Simultaneously, various experiments were carried out to examine its efficacy, effective dose, and action mechanism. I will introduce a summary of the results.

I utilized fucoidan based on the results of an experiment regarding its "apoptosis induction activity". In addition, it was speculated that no side effect affecting cancer-related morbids condition would appear.

5 Science of Okinawa mozuku-derived fucoidan: Basic study

◆ Fucoidan specifically kills cancer cells

In the first experiment, the influences of fucoidan on normal and cancer cells were investigated. Two dishes containing 10,000 colorectal cancer cells or normal cells were prepared, and fucoidan dissolved in distilled water was added to each dish at 1 g/L.

The cancer cell count was reduced to about half after 24 hours and few cells were observed at 60 hours. In contrast, no change was noted in the normal cells. Fucoidan damaged only cancer cells, while having no influence on normal cells.

◆ The morality increases with the concentration

The fucoidan concentration was then investigated. Several dishes containing normal human lymphocytes (PBL) or human tumor cell line Molt4 (acute lymphoblastic leukemia cells) were prepared. Fucoidan solution was added to the dishes at various concentrations, and the survival rate of the cells was compared (**Fig. 1**).

As shown in **Fig. 2**, the normal cells proliferated

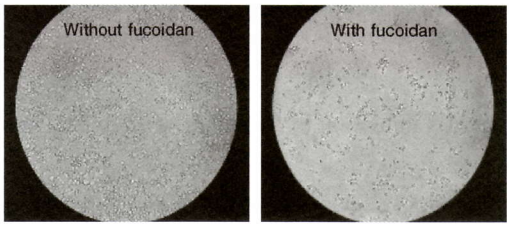


Fig. 1 The addition of fucoidan (1,500 mg/ml) markedly inhibited cancer cell proliferation (right picture).

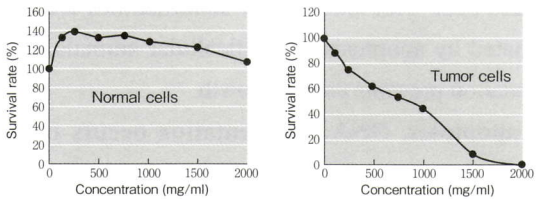


Fig. 2 The survival rate of cancer cells was markedly reduced compared to that of normal cells as the fucoidan concentration increased.

and the survival rate exceeded 100%, whereas that of the cancer cells decreased reaching close to 0% as the fucoidan concentration increased.

These findings revealed that Okinawa mozuku-derived fucoidan specifically recognizes and kills cancer cells.

6 Apoptosis induction by fucoidan: Basic study

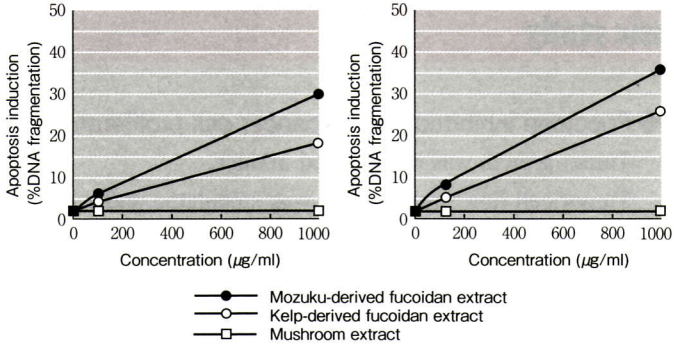
Apoptosis induction by fucoidan was confirmed in this experiment.

As described above, apoptosis represents a natural cell death process. Although cancer cell apoptosis has not been completely elucidated, it is known that cancerous cells and cells with intracellular abnormalities are mostly eliminated by apoptosis in multicellular animals, and its continuation prevents cancer growth.

In apoptosis, DNA fragmentation occurs in cells. Fucoidan-induced apoptosis was measured in cancer cell lines NOS4 (human cultured ovarian cancer cells) and HL60 (promyelocytic leukemia cell line).

Okinawa mozuku-derived fucoidan induced DNA fragmentation in about 30% and nearly 40% of NOS4 and HL60 cells, respectively (**Fig. 3**).

Similar experiments were performed using kelp-derived fucoidan and Agaricus for comparison, and the Okinawa mozuku-derived fucoidan-induced apoptosis rate was significantly higher.



Apoptosis induction in cultured human ovarian cell line (MOS4)

Apoptosis induction in promyelocytic leukemia cell line (HL60)

Fig. 3 Comparison of apoptosis induction in 2 cell lines

Interestingly, Agaricus did not induce apoptosis, despite its reputation for an anticancer effect.

It was suggested that the mechanism of the effect of fucoidan is different from that of the anticancer effect of Agaricus.

7 Possibility of immunoactivation: Basic study

◆ Fucoidan inhibited mouse cancer cell proliferation

Tumor growth was investigated in mice.

Tumor cell line Sarcoma 180 was inoculated under the dorsal skin in 20 male nude mice aged 4 weeks, and the animals were divided into 2 groups (10 animals each). Fucoidan extract was orally administered once daily for 21 days to one group (fucoidan group) while distilled water was administered to the other (distilled water group), and the tumor diameter was measured weekly to estimate the tumor weight.

Tumor cell proliferation was significantly inhibited after day 14 in the fucoidan group. The tumor weight was about 1/3 of that in the distilled water group, and cancer disappeared in 6 animals and the size was reduced to 1/10-1/2 of that in the distilled water group in the other animals (**Fig. 4**).

◆ Fucoidan activates immunocompetence

To further investigate the effectiveness of fucoidan against cancer cells, immunoactivation by fucoidan was investigated. Immune function may be activated during

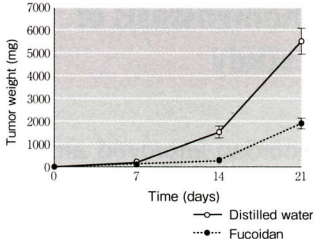


Fig. 4 Inhibitory effect of fucoidan on tumor cell proliferation

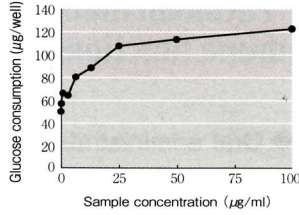


Fig. 5 Macrophages were activated and the glucose consumption increased as with the fucoidan concentration.

the cancer-resolution process.

There are various methods to investigate immunoactivation. Macrophages were investigated in this experiment. Macrophages are a type of leukocytes with amoeba-like appearance present in the circulation and are involved in immunity. These cells phagocytose (uptake and digest) bacteria and viruses which entered the body and dead cells, and consume blood glucose for their activity.

This glucose consumption was investigated in this experiment. The glucose consumption increased with the fucoidan concentration (**Fig. 5**).

8 Fucoidan maintains homeostasis of immune function: Basic study

◆ Oral administration of fucoidan improved atopic dermatitis

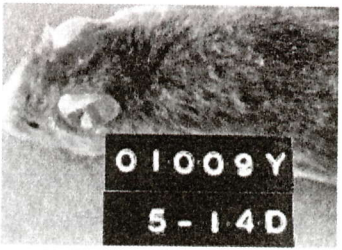
In addition to macrophages, complex and diverse factors, such as white blood cells, granulocytes, lymphocytes, interferon, and interleukins, are involved in biological immune function, which was partially investigated in the above experiment. Based on the results, the effect on allergy was investigated in mice.

Excess immunocompetence induces autoimmune diseases, such as allergic diseases and rheumatism. For example, atopic dermatitis may be aggravated if fucoidan one-sidedly increases immunocompetence, but some positive effect on allergic reactions, which are abnormal or excessive immune reactions, may be observed if fucoidan acts toward recovery of immune function or maintenance of homeostasis.

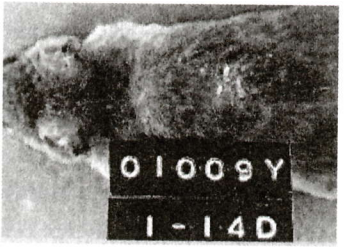
To investigate the above, an experiment using a mouse atopic dermatitis model was performed.

In the mice used, dermatitis aggravates to keratinization of the skin and epilation when left untreated.

One group of the model mice was orally administered



Fucoidan was administered



Control

Fig. 6 Fucoidan was administered to the mouse atopic dermatitis model to confirm the anti-allergic effect of fucoidan. A marked effect was noted as seen in the upper picture.

fucoidan extract daily and the other with distilled water. The 2 groups were observed for 2 weeks, and marked improvement was noted in the fucoidan group.

Figure 6 shows typical cases of the 2 groups. Improvement with time was observed in the fucoidan-treated mice.

9 Two cases in which the efficacy of fucoidan was suggested (Clinical cases)

Phytochemicals are derived from vegetables, fungi such as mushroom, and seaweed. I devised a human diurnal biorhythm-associated time-difference administration method based on chronopharmacology, employing 3 phytochemicals with different anticancer action mechanisms (Cladosiphon okamuranus-derived fucoidan, autumn turmeric, and Agaricus). More potent clinical effects were achieved. However, initially, fucoidan alone was used.

At that time, our findings suggested that fucoidan reduces the tumor size, inducing dormancy of cancer cells.

I will introduce two cases, which support the clinical application of fucoidan.

[Case 1] Gradual decrease in the level of a tumor marker in a patient with recurrent liver cancer (third relapse)

In 1995, Patient R with liver cancer underwent partial resection of the right liver at a university hospital located in Tokyo. After 6 months, examination revealed relapse. Additional partial right hepatectomy was performed. Concerning the medical history, a primary disease, hepatitis C, progressed to liver cirrhosis, leading to liver cancer. Three years after surgery (in autumn), follow-up examination also confirmed relapse.

Patient R consulted my clinic. The condition was progressive.

At this point, an animal experiment of fucoidan had started based on its anticancer actions confirmed in petri dishes. I informed Patient R that fucoidan promoted cell apoptosis, and that the risk of severe side effects was very low. However, the development of fucoidan was in the phase of sample extraction for experiments. Concerning its use, I explained that we should wait for a while.

However, Patient R said, "I wish to take fucoidan for experiments".

Considering the patient's condition at this point, it was impossible to wait until the completion of mass plant production. I requested the manufacturer to provide fucoidan for experiments.

In mid-December, the consumption of fucoidan at 3 g/day was initiated. Simultaneously, Krestin powder (extracted/prepared from Trametes versicolor; this preparation improves the immune response, inhibiting cancer tissue proliferation.) and vitamin preparations were prescribed.

On the initial consultation, the level of a tumor marker, AFP (a protein as a marker of liver cancer), was 126, markedly higher than the reference value (20 or less). After 4 weeks of fucoidan consumption, the level was increased to 132. This was possibly associated with irregular diet related to new-year events. Six weeks after the start of consumption, the AFP level was slightly decreased to 105.

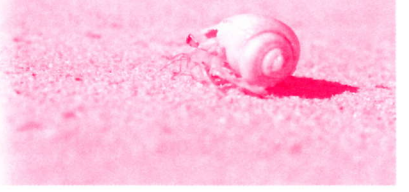
At this point, a fucoidan extraction/manufacturing system was almost completed, and activated. Therefore, Krestin powder and vitamin preparations were discontinued, and fucoidan alone was administered.

Continuous fucoidan consumption decreased the AFP level to 98, 88, 76, and 50 in late February, March, late April, and June, respectively.

Based on this finding, I was convinced of the effects of fucoidan. The data suggested that fucoidan inhibited cancer tissue proliferation, arresting disease progression.

Furthermore, it was significant for Patient R to achieve an improvement in a social life. Nonstressful cancer inhibition and the absence of side effects at an increased dose were consistent with the results of an experiment using petri dishes.

The influence of an extracted component on the physical condition must be carefully investigated even if it is derived from a food. In the present case, a fucoidan extract inhibited cancer growth without affecting the patient's physical condition during treatment, improving the quality of life (QOL) and facilitating physical conditioning with cancer coexistence.



[Case 2] Improvement in the QOL related to the disappearance of bone metastasis-associated pain and tumor reduction

In 1992, Patient S underwent radical surgery for right breast cancer at a university hospital located in Tokyo, showing a favorable course. However, in 1998, the patient consulted the hospital with pain involving the lumbar to bilateral legs. Detailed examination revealed cancer metastases to the bilateral femurs and pelvis. The patient was admitted.

For treatment, combination therapy with 3 anticancer agents, cisplatin, adriamycin, and 5FU, was administered. However, side effects appeared immediately after the start of this therapy, and alopecia gradually involved the whole body.

Patient S became anxious, hearing that relapse was detected in most patients with transient metastatic bone tumor reduction related to anticancer agents or radiotherapy. The patient consulted my clinic to receive alternative therapy.

At this point, the patient's condition was difficult to

treat using alternative therapy. However, fucoidan does not cause any side effect, differing from anticancer agents. I considered that a long period was required to improve the condition. However, the efficacy appeared 1 month after the start of fucoidan consumption.

On the initial consultation, the patient complained of severe pain of the bilateral legs and lumbar region. However, pain markedly subsided after 6 weeks of fucoidan consumption, suggesting metastatic bone tumor reduction.

After 4-month consumption, diagnostic imaging procedures confirmed slight cancer retraction.

In the present case, the relief of cancer-related pain markedly improved the patient's QOL, suggesting its importance. For cancer treatment, the host's physical strength to coexist with cancer is necessary as an absolute condition. In this sense, fucoidan may also be useful for cancer treatment.

10 Early detection/treatment

Advances in medicine have facilitated survival from cancer. Although many issues remain to be clarified, it has been indicated that early detection/treatment exhibited the most potent effects. Treatment prior to an advanced stage markedly improves the probability at which cancer is cured. In accordance with the staging of cancer, the grade of cancer progression can be classified, and site-related conditions such as gastric/breast cancers and 5-year survival rates are presented. Three major standard therapies for cancer, surgery, chemotherapy (treatment with anticancer agents), and radiotherapy, contribute to a high survival rate when administered in the early stage.

However, in most cases, cancer gradually enlarges before detection, as described above. The number of patients in whom early detection/treatment are possible is limited. In some cases, treatment is difficult at the time of detection. Furthermore, despite treatment-related recovery, cancer often develops again in another site.

From this background, immunotherapy (immunocytotherapy) has recently been emphasized as

"fourth cancer therapy". As cancer treatment with the 3 conventional therapies is limited, immunotherapy has also been introduced as a high-level advanced medical procedure at university hospitals in Japan over the past few years.

In my clinic, immunocytotherapy has been employed in addition to the 3 major standard therapies. This therapy attacks cancer cells by improving the functions of immunocytes, which essentially exist in the human body. It is not stressful, contributing to cure. Internationally, data were scientifically analyzed, and the mechanism was clarified. How does immunity function?

Immunity refers to a system via which pathogens and cancer cells are recognized as foreign bodies (non-self), and eliminated. Pathogens such as viruses and parasite, as well as "cancer cells", as described above, may be eliminated. They are distinguished from normal cells/tissues. On the other hand, pathogens may antagonize the immune system via adaptation/evolution for survival in vivo. Therefore, the immune system has very complex mechanisms. Early detection/treatment before cancer is advanced is important.

11 Organizational strength of immunity protects the body from cancer and infection

Active players in the immune system are leukocytes. Leukocytes are cellular components of blood, and there are 3 types; granulocytes, lymphocytes, and monocytes, playing different roles. These cells eliminate foreign bodies which entered the body, tumors, and cells which completed their roles.

Monocytes migrate by amoeboid movement, incorporate foreign bodies, such as bacteria, and digest them with intracellular enzymes (phagocytosis). These cells are also considered to migrate to extravascular tissues and lumens, become macrophages and dendritic cells, and phagocytose foreign bodies in tissues. These are called 'phagocytes', and seeds of cancer are mostly phagocytosed by phagocytes.

Lymphocytes called natural killer (NK) and killer T cells play the central role, attacking tumor cells. It has recently been clarified that macrophages and dendritic cells regulate these cells. Dendritic cells have

several to several tens times greater ability to regulate. Dendritic cells are immunocytes named based on their branch-like processes (dendrites). These cells recognize the characteristics (antigens) of foreign bodies by phagocytosis and make lymphocytes remember the characteristics, through which lymphocytes become capable to attack only foreign bodies. The precursor of these cells, monocytes, plays an important role in beginning immune reactions.

Therapeutic methods to increase the cancer-curative effect by increasing isolated monocytes and returning these to the body or activating NK and killer T cells have been developed by Japanese researchers. This approach is called cellular immunotherapy. Since actions of immune system cells are utilized, the body is less distressed compared to the 3 major cancer therapies described above.

However, at present, only a few medical institutions can perform this therapy. On the other hand, it has been clarified that immunocompetence can be increased by regular diets.

12 Strengthening of immunocompetence by regular diets: Major immune system in the intestine

◆ Fucoidan acts in the intestine

Food is digested in the digestive organs including the stomach and intestine and nutrients are absorbed, but it has recently been shown that food ingestion enhances the action of the immune system, not just merely supplying nutrients. Okinawa mozuku-derived fucoidan is positioned as a food which activates intestinal immunity. Briefly, Okinawa mozuku-derived fucoidan is a type of food fibers classified as a high-molecular-weight polysaccharide with a maximum molecular weight of 500,000. Since only about 10% may be absorbed from the intestine because of the high molecular weight, fucoidan was previously considered to be a non-digestible food of no importance.

However, high-molecular-weight polysaccharides have been shown to have diverse and important actions with the advances in studies on the immune system, and now it is called 'the 6th nutrient' following carbohydrates, protein, lipids, vitamins, and minerals. About 60% of all lymphocytes in the body are present in the intestine.

The small intestinal wall is composed by mucosa and its structure is suitable for digestion and absorption. The villi, small mucosal processes, cover the wall and form folds, in which many waiting sites of lymphocytes called 'Peyer's patches' and capillary blood vessels are present, and the largest immune systems consisting of small intestinal epithelial cells/lymphocytes indigenous to the intestine and lamina propria mucosae/lymphocytes indigenous to the mucosa are also formed. It has been clarified that intestinal stimulation by non-nutrient food components is important, in addition to the necessity of a sufficient amount of protein, minerals, and vitamins. Non-digestible polysaccharides, such as Okinawa mozuku-derived fucoidan, stimulate the immune system after being captured as intruders during passing through the intestine, and activate leukocyte actions starting from dendritic cells.

As these actions of the immune system were clarified, health foods have become upgraded from the cancer therapy viewpoint. Ingestion of immunoactivating foods in regular diets is important for disease prevention and treatment.

13 Inseparable relationship between human life and fruits of the sea

After some time had passed since the discovery of specific function of fucoidan, Okinawa mozuku, flourishing in the blue sea of Okinawa, finally became a candidate for 'mother material' of fucoidan in 1998 because very pure fucoidan powder can be produced without using organic solvent, such as ethanol, due to a low level of alginic acid, the slimy component of seaweed.

Although fucoidan was discovered in seaweed and its outstanding function was demonstrated by science, fucoidan was created by the sea. Considering that the first life on the earth born in the sea had continued until today, I think it grateful and the most fortunate fate that we, who enjoy convenience while losing vitality and life force, are saved by nature's bounty, even though it is inevitable.