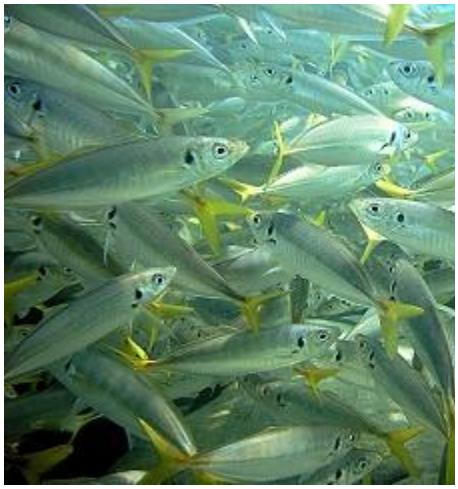

U-Fucoidan Research

Fucoidan is a polysacharride which makes up about 4% of the total dry weight of brown seaweed. One of its main elements include sulfuric esterified L-fucose, and traces of galactose, xylose, and glucuronic acid.

U-Fucoidan (U-Fn) is a bio-available form of Fucoidan.

Mineral properties of Fucoidan were discovered a long time ago, but it was a problem making them available for humans. When extracted, Fucoidan itself does not work. That is why japanese research and development of U-Fucoidan products (dietary supplements, which naturally deliver Fucoidan's qualities) became a unique substance. U-Fucoidan is a complex of Fucose, Glycose, Laminaran and Alginic acids. Sulfated polysaccharides of brown seaweed with natural presence of those elements are acceptable by human gastrointestinal tract, that do not have toxicity limits and can be consumed with benefits to ones health.

Extensive research has been ongoing for the benefits of seaweed. In particular, the Takara Shuzo's Biomedical Research Laboratories and the Research Institute for Glycotechnology Advancement worked together to find more about this unique substance U-fucoidan. In order to study its chemical structure, they also used a specific technique called pyridlamination.

Even though fucoidan has been characterized with the ability to reduce cholesterol levels, and to act as both an anti-contraceptive and an anti-tumor agent, not enough research has been conducted to have a definitive consensus. One thing for certain is that these two groups have confirmed that fucoidan does cause certain types of growing cancer cells to self-destruct, a phenomenon called apoptosis. This is different from necrosis, where cells are destroyed because of external stimuli such as physical damage or toxic substances. Programmed into the natural makeup of cells, is this apoptosis mechanism. For cells to self-destruct, this mechanism is triggered and the cell's DNA is rendered useless through the activation of the deoxyribonuclease found within the cell itself.

This phenomenon has been observed in human acute promyelocytic leukemia cells (HL-60 cell line), human stomach cancer cells (AGS cell line), human colon cancer cells (HCT-116 cell line), and cancer cells of the descending colon (SW-480 cell line/WiDr cell line). Interestingly, these cancer cells were destroyed without affecting normal cells. More research is still underway on this unique phenomenon.

FUCOIDAN

Clinical studies have shown that FUCOIDAN can:

- Decrease cholesterol levels resulting from the way that enzymes breakdown fatty acids in the liver
- Diabetes control by slowing down the release of glucose into the blood
- Lower blood pressure
- Improve liver function
- Improve immunity from increasing the production of immune cells or natural killer cells (NK cells)
- Reduce stomach disorders
- Skin rejuvenation by increasing the production of integrin, a protein that helps in skin repair and firmness
- Increase cell regeneration
- Relieve allergies because of the increase of NK

cells
- Arthritis relief by promoting the production of fibronetin which plays an important part in keeping joints flexible and lubricated
- Herpes remedy because of fucoidan's antiviral properties
- Stop formation of cancer cells through a process called apoptosis (cell self-destructing)

U-Fucoidan Causes Cancer Cells to Self-Destruct

Japanese researchers discovered that a polysaccharide known as Fucoidan, found in kombu and other types of brown seaweed (wakame, mozuku, and hijiki), causes various types of established cancer cell lines to self-destruct.

What is U-Fucoidan?

About 4 percent of the total dry weight of many types of brown seaweed consists of a polysaccharide known as Fucoidan. Fucoidan is a sulfated polysaccharide that possesses a complex structure. Its chief components include a sulfuric esterified L-fucose, and the trace elements of galactose, xylose, and glucuronic acid.

Working cooperatively, Takara Shuzo's Biomedical Research Laboratories and the Research Institute for Glycotechnology Advancement were able to confirm the presence of two different types of Fucoidan molecules in brown seaweed.

The first type, bearing the name F-Fucoidan, consists mainly of sulfated fucose. The second type bears the name U-Fucoidan, and approximately 20 percent of it consists of glucuronic acid.

Researchers were able to use a technique known as pyridlamination to shed light on the chemical structure of U-Fucoidan.

The biological activity of Fucoidan

Numerous accounts have ascribed to Fucoidan properties such as the ability to act as an anti-contraceptive, to reduce cholesterol levels, and to act as an anti-tumor agent. However, a definitive consensus concerning the precise nature of Fucoidan has still not been reached.

The Biomedical Research Laboratories of Takara Shuzo and the Research Institute for Glycotechnology Advancement have focused their attention on the anti-tumor properties of Fucoidan, and have managed to confirm that this substance causes certain types of rapidly growing cancer cells to self-destruct.

Examples of cancer cell strains where this self-destruct phenomenon was observed include human acute promyelocytic leukemia cells (HL-60 cell line), human stomach cancer cells (AGS cell line), human colon cancer cells (HCT-116 cell line), and cancer cells of the descending colon (SW-480 cell line/WiDr cell line). Moreover, this self-destruction was observed to take place without affecting normal cells. Currently, efforts are underway to clarify the precise mechanism by which this phenomenon occurs.

Some of the reasons which have until recently prevented the formation of a definitive scientific consensus concerning the precise nature of Fucoidan include the fact that it possesses an extremely complex structure, as well as the difficulty of obtaining pure samples of Fucoidan.

The mechanism through which cancer cells self-destruct

In the presence of certain substances, as well as under other unusual environmental conditions, cells may self-destruct and disappear altogether. This self-destruct phenomenon is known as *apoptosis*. It should be distinguished from *necrosis*, which is the death of cells directly brought about by external stimuli such as poisonous substances or physical damage to the cell.

Properly speaking, apoptosis is brought about by a mechanism that is programmed into the natural makeup of cells. Organisms activate this mechanism when necessary. Once the apoptosis mechanism has been triggered, the genetic blueprint of the cell (DNA) is rendered useless, through activation of the deoxyribonuclease found within the cell itself. Apoptosis thus can be described as a natural means through which living organisms manage to eliminate harmful cells from their systems.

The significance of this discovery and future prospects

From ancient times (dating from the Jomon era, approximately before the 2nd Century BC onwards), brown seaweed has been a mainstay of the traditional Japanese diet. It is precisely these seaweeds that contain the U-Fucoidan that trigger the apoptosis mechanism described above.

The inhabitants of Okinawa, Japan enjoy some of the highest life expectancies in Japan. Okinawans happen to have one of the highest per capita consumption rates of kombu -- 1 gram per person per day. It is noteworthy that the cancer death rate in Okinawa is the lowest of all the prefectures in Japan.

The average per capita consumption rate of kombu in Japan is approximately 0.5 grams per day. Such a serving of kombu would include roughly 5 mg of U-Fucoidan. *In vivo* experiments are currently underway to determine the effects of U-Fucoidan within living organisms. If it is confirmed that U-Fucoidan can help bring about apoptosis solely in cancer cells that are multiplying at uncontrolled rates, we would then have within our reach the long-dreamed-of cancer drug -- one that does its job without causing adverse side effects.

Studies on various supplements and natural medicine topics, including fucoidan, and their practical interpretation by Ray Sahelian, M.D.

Fucoidan and tumors

The Role of NK cells in Antitumor Activity of Dietary Fucoidan from Undaria pinnatifida Sporophylls (Mekabu).

Planta Med. 2006 Oct 20; Department of Pathology, School of Allied Health Sciences, Kitasato University, Kitasato Kanagawa, Japan.

Fucoidan from Mekabu (sporophyll of undaria pinnatifida), a dietary alga, exerts antitumor activity possibly through enhancing the immune response. The present report describes the effects of dietary Mekabu fucoidan on the tumor growth of

mouse A20 leukemia cells and on T cell-mediated immune responses in T cell receptor transgenic (DO-11 - 10 - Tg) mice. The animals were fed with a diet containing 1 % Mekabu fucoidan (0.034 +/- 0.003 g/mouse/day) for 10 days and subcutaneously (S. C.) inoculated with A20 leukemia cells. Thereafter, the mice were fed with the diet containing fucoidan for 40 days. Mekabu fucoidan inhibited tumors by 65 %. We studied how the killer activities of T cell-mediated and natural killer (NK) cells are augmented in DO-11 - 10 mice fed with Mekabu fucoidan. Thus, these findings suggested that Mekabu fucoidan mediates tumor destruction through Th1 cell and NK cell responses.

Fucoidan against HIV virus

Defensive effects of a fucoidan from brown alga Undaria pinnatifida against herpes simplex virus infection.

Int Immunopharmacol. 2008 January. Hayashi K, Nakano T, Hashimoto M, Kanekiyo K, Hayashi T. Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan.

Fucoidan, a sulfated polysaccharide isolated from an edible brown alga Undaria pinnatifida, was previously shown to be a potent inhibitor of the in vitro replication of herpes simplex virus type 1 (HSV-1). HSV-1 is a member of herpes viruses that cause infections ranging from trivial mucosal ulcers to life-threatening disorders in immune compromised hosts. In the present study, the effects of fucoidan were examined on in vivo viral replication and the host's immune defense system. Oral administration of the fucoidan protected mice from infection with HSV-1 as judged from the survival rate and lesion scores. Phagocytic activity of macrophages and B cell blastogenesis in vitro were significantly stimulated by the fucoidan. Oral administration of the fucoidan produced the augmentation of NK activity in HSV-1-infected immunosuppressed mice. The production of neutralizing antibodies in the mice inoculated with HSV-1 was significantly promoted during the oral administration of the fucoidan for 3 weeks. These results suggest that oral intake of the fucoidan might take the protective effects through direct inhibition of viral replication and stimulation of both innate and adaptive immune defense functions.

Fucoidan protects against radiation damage

Radioprotective effects of fucoidan on bone marrow cells: improvement of the cell survival and immunoreactivity.

J Vet Sci. 2008 December. College of Veterinary Medicine, Cheju National University, Jeju 690-756, Korea.

Fucoidan is a sulfated polysaccharide purified from brown algae including Fucus vesiculosus and has a variety of biological effects including mobilization of hematopoietic progenitor cells. Recently, we demonstrated that fucoidan stimulates the antigen-presenting functions of dendritic cells. In this study, we investigated the radioprotective effects of fucoidan on bone marrow cells (BMCs), which are the main cellular reservoir for the hematopoietic and immune system. To evaluate the effects of fucoidan, we assayed cell viability and immune responses. In a viability assay, fucoidan significantly increased the viability of BMCs. Based on the results of flow cytometric analysis, the increased viability of fucoidan-treated BMCs was attributed to the inhibition of radiation-induced apoptosis. Furthermore, fucoidan altered the production of immune-related

cytokines from BMCs and increased the capability of BMCs to induce proliferation of allogeneic splenocytes. Taken together, our study demonstrated that fucoidan has radioprotective effects on BMCs with respect to cell viability and immunoreactivity.

Fucoidan side effect and toxicity

Toxicological evaluation of fucoidan extracted from Laminaria japonica in Wistar rats.

Food Chem Toxicol. 2005 Mar;43(3):421-6.

Investigating the toxicity of fucoidan. In this study, the acute and subchronic (6 months) toxicity of varying levels of fucoidan extracted from Laminaria japonica was investigated in Wistar rats after oral administration. The results showed that no significant toxicological changes were observed when 300 mg/kg body weight per day fucoidan was administered to rats. But when the dose was increased to 900 and 2500 mg/kg body weight per day, the clotting time was significantly prolonged. Besides this, no other signs of toxicity were observed. Based on these results, it can be concluded that the no side effect level of fucoidan from L. japonica is 300 mg/kg body weight per day.

Fucoidan and allergy

Fucoidan prevents C epsilon germline transcription and NFkappaB p52 translocation for IgE production in B cells.

Biochem Biophys Res Commun. 2006 Nov 24;350(3):501-7. Hiroshima Prefectural Institute of Industrial Science and Technology, Higashi-Hiroshima, Japan.

Fucoidan, a dietary fiber contained in seaweed, reduces the increase of antigen-specific IgE in mice exposed to ovalbumin. In this study, we investigated the effect of fucoidan on IgE production and intracellular events in B cells in vitro. Fucoidan inhibited the production of IgE and C epsilon germline transcription in murine B cells induced by IL-4 (100 ng/ml) and anti-CD40 antibodies (10 microg/ml), whereas it stimulated cell proliferation. A significant effect of fucoidan on IgE production was observed when B cells were stimulated with a higher dose (5 microg/ml) of anti-CD40 antibodies, but not when stimulated with lower doses (1.25, 2.5 microg/ml), regardless of the IL-4 concentrations. Moreover, nuclear translocation of NFkappaB p52, but neither that of NFkappaB p65, nor the phosphorylation of JAK1 and STAT6 was reduced by fucoidan. These results suggest that fucoidan inhibited IgE production by preventing the NFkappaB p52-mediated pathways activated by CD40.

Fucoidan tumor and cancer effect

Immunomodulating activity of arabinogalactan and fucoidan in vitro.

J Med Food. 2005 Winter;8(4):446-53.

Department of Biotechnology & Bioproducts Research Center, Yonsei University, Seoul, South Korea.

Many polysaccharides obtained from natural sources are considered to be biological response modifiers and have been shown to enhance various immune responses. Here, we investigated the immunomodulating effects of arabinogalactan and fucoidan in vitro. Mouse spleen lymphocytes became cytotoxic to tumor cells after culture with arabinogalactan and fucoidan at concentrations of 10-100 microg/mL. These data suggest that arabinogalactan

and fucoidan are activators of lymphocytes and macrophages. This property may contribute to their effectiveness in the immunoprevention of cancer.

Fucoidan as anticoagulant

Use of sulfated fucans as anticoagulant and antithrombotic agents: future perspectives.
Curr Pharm Des. 2004;10(9):967-81.
Sulfated alpha-L-fucans from brown algae (also known as fucoidan) have complex and heterogeneous structures but recent studies revealed the occurrence of ordered repeat units in the sulfated fucans from several species. Even in these cases, the presence of highly branched portions and the complex distributions of sulfate and acetyl groups highlight the heterogeneity of algal fucans. Another source of sulfated alpha-L-fucans (and their parental compounds sulfated alpha-L-galactans and fucosylated chondroitin sulfate) is marine invertebrates. The invertebrate polysaccharides have simple, ordered structures, which differ in the specific patterns of sulfation and/or position of the glycosidic linkages within their repeating units. The algal and invertebrate sulfated fucans have potent anticoagulant activity, mediated by antithrombin and/or heparin cofactor II. As most of the studies were carried out with algal fucans it was not easy to trace a structure versus activity relationship. This aspect was clarified as studies were extended to invertebrate polysaccharides. These definitively established that regular, linear sulfated alpha-L-fucans and sulfated alpha-L-galactans express anticoagulant activity, which is not simply a function of charge density, but depends critically on the pattern of sulfation and monosaccharide composition. Sulfated alpha-L-fucans and fucosylated chondroitin sulfate also express antithrombotic activity when tested on in vivo models of venous and arterial thrombosis in experimental animals. These polysaccharides constitute potential therapeutic compounds as alternative to heparin and may help to design structure-based drugs with specific activity on each type of thrombosis episode and few side effects. They can also serve as research reagents to investigate and distinguish among a variety of interrelated events, such as coagulation, bleeding, thrombosis and platelet aggregation.

Anticoagulant activity of fucoidan from brown algae Fucus evanescens of the Okhotsk Sea.
Bull Exp Biol Med. 2003 Nov;136(5):471-3.
In vitro and in vivo experiments showed that anticoagulant activity of sulfated polysaccharide from Fucus evanescens (brown algae of the Okhotsk Sea) was similar to that of heparin. Anticoagulant properties of fucoidan are determined by thrombin inhibition mediated via plasma antithrombin III.

Immunostimulating and anticoagulating activity of fucoidan from brown algae Fucus evanescens of Okhotskoe sea
Antibiot Khimioter. 2003;48(4):11-3.
Fucoidan --nontoxic sulfated polysaccharide was isolated from brown algae Fucus evanescens in Okhotskoe Sea. Chemical analysis of the compound was performed, it was shown that fucoidan is freely soluble in water and acid solutions. Immunotropic and anticoagulating properties of the compound were evaluated in comparison with heparin. It was demonstrated that fucoidan in wide

range of doses stimulated phagocytic and bactericidic activity at leucocytes of mice peritoneal exudate. Heparin on the contrary demonstrated depressive effect on these functions at high dose. It was shown that fucoidan has dose-dependent anticoagulating activity in vitro and in vivo comparable with heparin activity. The results of investigation demonstrated possibility of fucoidan application as immunomodulating and anticoagulating agent of plant origin.

Fucoidan and oxalate kidney stone

Renal peroxidative changes mediated by oxalate: the protective role of fucoidan. Life Sci. 2006 Oct 4;79(19):1789-95. Epub 2006 Jun 16. Department of Medical Biochemistry, Dr ALM Post Graduate Institute of Basic Medical Sciences, University of Madras, Taramani Campus, Chennai, India.

Oxalate, one of the major constituents of renal stones is known to induce free radicals which damage the renal membrane. Damaged epithelia might act as nidi for stone formation aggravating calcium oxalate precipitation during hyperoxaluria. In the present study, the beneficial effects of fucoidan on oxalate-induced free radical injury were investigated. Male Wistar rats were divided into four groups. Hyperoxaluria was induced in two groups by administration of 0.75% ethylene glycol in drinking water for 28 days and one of them was treated with fucoidan from Fucus vesiculosus at a dose of 5 mg/kg b.wt subcutaneously commencing from the 8th day of induction. A control and drug control (fucoidan alone) was also included in the study. The extent of renal injury in hyperoxaluria was evident from the increased activities of alkaline phosphatase, gamma-glutamyl transferase, beta-glucuronidase, N-acetyl-beta-D-glucosaminidase in urine. There was a positive correlation between plasma malondialdehyde levels and renal membrane damage indicating a striking relation between free radical formation and cellular injury. Increased protein carbonyl and decreased thiols further exemplified the oxidative milieu prevailing during hyperoxaluria. Decreased renal membrane ATPases accentuated the renal membrane damage induced by oxalate. Renal microscopic analysis showed abnormal findings in histology as an evidence of oxalate damage. The above biochemical and histopathological discrepancies were abrogated with fucoidan administration, indicating its protective role in oxalate mediated peroxidative injury.