Brown Marine Algae

A Survey of Therapeutic Potentials

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Seaweeds or marine algae have long made up a key part of the Asian diet and are also consumed in other parts of the world, such as in Ireland and Wales. Seaweed has often been used as a food for people who are sick and has been credited with health-giving properties.[1] Today, seaweed supplements for human use are usually considered to be sources of iodine or minerals but may offer other therapeutic benefits.

Marine Algae as Food

Marine algae are classified as brown, red, or green algae.[2] Examples from all of these categories are edible and are shown in Table 1. This article concentrates on brown seaweeds, in particular the commonly eaten Japanese *wakame* or *Undaria pinnatifida*.

Japanese and Korean populations are the biggest consumers in the world of seaweed products. Most of the brown seaweed intake in the daily diet is of *Undaria*, commonly known as wakame and *mekabu* and of *Laminaria* species commonly known as *kombu*.[1,2] Both are used dried in condiment and soup bases or eaten fresh in salads, rolls, or stews, or with rice.

It is thought that the overall content of certain traditional Asian diets contributes to the low incidence of cancer,[3] particularly breast cancer.[4] It is apparent that the unique levels of seaweed intake contribute to the variance in the levels of breast cancer.[5,6] There is a ninefold lower incidence of breast cancer in the Japanese population and an even lower incidence in the Korean population compared to the incidence in the West.[4,5,7]

The relative longevity and health of Okinawan Japanese populations has been attributed in part to dietary algae in studies.[8] These studies compared Okinawan descendants who were living in Brazil with Okinawans. The former have a higher risk of developing cardiovascular and other diseases. For a dietary intervention study, 3g of decosahexaenoic acid, 5g of seaweed (wakame) powder, and 50 mg of isoflavonoids from soybean (*Glycine soja*) were given daily to immigrants, at high risk for developing diseases, in Brazil for 10 weeks. This combination reduced blood pressure and cholesterol levels, suppressed the urinary markers of bone resorption, and attenuated a tendency toward diabetes.

Contents of Algae and Algal Extracts

Brown algae consist mainly of water (90 percent) in the native state. Polysaccharides are major components and comprise alginates, cellulose, and sulfated polysaccharides such as fucoidans and laminarins. Other components include proteins, free mannitol, minerals such as iodine and arsenic (inorganic and organic), polyphenols, peptides, fatty compounds, and various pigments.[1] Alginates, probably the most widely used of the algal extracts, are composed of block copolymers of mannuronic and guluronic acid sugars and have been adopted by the food industry as thickening agents and by the pharmaceutical industry as binders, gelling agents, and wound absorbents.

Possible Therapeutic Role of Sulfated Polyanions

Fucoidans are found only in brown algae. They consist of long branched chains of sugars and include a substantial amount of fucose. The type of fucoidan, its sulfation, molecular weight, and conformation of sugar residues varies with the species of seaweed.[1,9,10] Thus, the fucoidan from *Fucus vesiculosis* contains 90 percent fucose,[11] whereas the major fucoidan in *Undaria* contains a roughly equal balance of fucose and galactose.[12,13]

When purified, the fucan fractions from Korean *Undaria* and *Laminaria* comprised respectively 12.75 and 4.76 percent of the total dry weight of the algae.[12] The fucose composition (as a percent of total sugars) of the fucoidans isolated from the *Undaria* and *Laminaria* was 57.11 percent and 80.43 percent respectively. It should be noted that while the bulk of the fucoidans in seaweeds are of high molecular weight, there is a small percentage of smaller fucoidan-type molecules that are sometimes complexed with proteins.[11,13]

Fucoidans are considered to have similarities to the (much smaller) mammalian molecule heparin sulfate.[14,15] As such, they compete for heparin sulfate-type receptors such as those used for viral entry into cells.[16,17] Thus, fucoidans are highly effective antiviral agents.[14,15] In addition, they inhibit leukocyte movement into tissues,[18] modulate metastasis,[19] have heparin-like anticoagulant qualities in vitro,[20] anticomplement activity in vitro and in vivo,[21,22] and antilipidemic activity in vivo.[13]

Other biologic activities related to the heparin-like nature of fucoidans include stimulating hematopoietic progenitor cell mobilization[23,24] and inhibiting smooth-muscle proliferation.[25]

Most of the effects noted above were observed when using intravenous fucoidans in animal models. However, in vivo bio-

logic effects after *Undaria* ingestion indicate that there is uptake of active components, via the gut; for example, ingestion of water extracts of *Undaria* by mice with carcinogen induced tumors markedly suppresses tumor development.[6,26] Hiebert[27] has found that oral heparin is absorbed and found at approximately 1 percent in plasma in rats. There is a pronounced endothelial uptake of oral heparin and, thus, oral heparins have marked biologic effects despite the low plasma levels. It is possible that fucoidans behave similarly.

Use of Algae in Traditional Medicines

Chinese and Kampo (Japanese) medicine both use dried thallus (stem and spore areas) of brown seaweeds *(Laminaria*, *Undaria*, or *Ecklonia* species). These are used to "eliminate phlegm and move water" and are also recognized sources of iodine.[28]

They are recommended for treating cancer in Chinese and Ayuverdic medicinal texts.[28,29]

In Korea, new mothers are given a diet that is rich in seaweed for the first month after birth because this diet is believed to provide many health benefits for mothers and their children.[30]

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Brown algal preparations have been used as detoxifying agents.[31,32] The iodine and other elements in the seaweeds inhibit absorption of similar radioactive elements by the body. In addition, there is some chelation of contaminants such as Strontium 90 by alginates in seaweeds. More recently, it has been demonstrated that *Undaria* ingestion assists in eliminating dioxins in rats.[33]

Feeding on beach-cast seaweeds or seaweed-treated pasture is known to improve health and increase disease resistance in sheep and cattle.[34,35] Seaweed and other natural polysaccharides also alter the bacterial spectrum of the gut, indicating a possible mechanism for these observed effects.[34,36]

Antiviral Effects

Brown seaweeds, including the commonly eaten *Undaria*, have inhibitory effects on herpes viruses. Herpes viruses are important human pathogens and include *Herpes simplex* (HSVI), genital herpes (HSVII), Varicella/chicken pox/shingles, cytomegalovirus, Epstein-Barr virus (EBV), herpes 6, 7 (Roseola, post-transplant infections), and herpes 8 (associated with Kaposi's sarcoma). In Japan, where ingestion of brown seaweed in the diet averages 2–3 g per day with a high of 12 g calculated as dry weight,[37] there is a lower rate of reactivation of HSVI,[38] and the lowest levels of HSVII compared to other countries.[39]

Acyclovir (ACV) and its derivatives comprise the most common drug group used against herpes infections. These pharmaceuticals inhibit viral DNA polymerase, thereby preventing viral replication. ACV-resistant viral strains are prevalent in 5 percent of all HSV infections in immunocompromised patients.[40] Alternatives that do not give rise to drug resistance would be invaluable.

Ingestion of *Undaria* led to inhibition of reactivation of herpes and amelioration of active infections in a patient study.[41] In this study, one patient with an ACV-resistant HSV II recurrent infection experienced no symptoms for 3 months while taking an *Undaria* supplement.

In vitro, *Undaria* extracts and purified galactofucan sulfate from *Undaria* had inhibitory effects on forty different clinical strains of HSVI and HSVII, of which half were ACV-resistant.[42] The mechanism of inhibition was via blocking the receptor on the cell surface that is normally used by the viruses to enter cells.[43] In other studies, *Undaria* extracts have also inhibited EBV, HSV, and human immunodeficiency virus (HIV).[44–48] *Undaria* extracts were also shown to have additive effects with the antiretroviral drug zidovudine in an animal model.[49]

In the studies by Ohigashi et al.[44] and Hudson et al.,[46] organic solvent–soluble fractions of *Undaria* were demonstrated to have antiviral properties. However, most research attention has been directed toward the antiviral effects of anionic polysaccharides (which are water soluble).[14,15,42,43,48]

The mechanism of viral inhibition by large anionic molecules (by inhibiting viral entry to cells) does not generate resistant strains to the same degree as acyclovir-type drugs[15] (which inhibit viral replication) and the inhibition covers a wide spectrum of viral strains.[14,15] If viral inhibitory polyanions, such as those found in brown seaweeds, can supplement conventional therapies, the total amount of other drugs required and the emergence of resistant strains may be reduced.

Anticancer Effects

The lower incidence of breast cancer in the Japanese and Korean populations[4,5,7] has intrigued researchers. Researchers have found that dietary brown algae and their extracts inhibit carcinogen-induced breast cancers, lung metastases, and leukemia in animal models.[6,22,26,44,48–51] Similarly, tests on the seaweed extracts in bacterial systems revealed that the extracts had a profound antimutagenic quality.[52,53]

Most recently Funahashi et al.[6,26] have shown that wakame extracts (as wakame soaked in animals' drinking water) have a potent inhibitory effect on the progression of mouse mammary tumors. Similar extracts produced an equally profound apoptotic effect on breast cancer cells in vitro while the extracts were nontoxic to ordinary breast cells.

Table 1. The Marine Algae

Classes of marine algae	Examples of edible seaweed	Latin binomials
Brown	*Wakame*; *mekabu* Kelp or *kombu*	*Undaria pinnatifida* *Laminaria* species
Red	*Nori* (Japan) or Laver bread (Wales)	*Porphyra* species
Green	Sea lettuce	*Ulva* and *Enteromorpha* species

From the animal model experiments, when *Undaria* or other brown seaweed was included in the animals' diets, it is very clear that there is a direct anticancer effect of ingestion although the active components have not been determined. Over the years, it has variously been attributed to iodine,[54,55] tryptophan,[56] fucoidans,[50] or vitamins.[6]

The Viral Connection with Breast Cancer

There has been a recent revival in research on viral connections with breast cancer.[4,57–59] Human homologues of mouse mammary tumor virus, papilloma viruses, and herpes viruses, chiefly EBV, are implicated. The lower rates of herpes in seaweed-eating populations may be a cofactor in the observed lower rates of breast cancer. Seaweed ingestion, which is already thought to be connected with reduced rates of breast cancer,[5] may, perhaps, elicit these protective effects via inhibition of herpes viruses.

Effects on Immunity and Inflammation

Stimulation of T-cell multiplication in vitro by algal extracts[59,41] may account for in vivo observations by other researchers, including increased monocytes in cattle who were fed seaweed-extract sprayed grasses.[35] The extensive gut lymph tissue would contact seaweeds passing through the gut. Specialized T cells in gut lymphatic tissue are important in achieving a rapid response to pathogens, in particular, to viruses such as HSV I[61,62] and may also modulate intestinal lipid metabolism.[63]

Inflammatory disorders, such as psoriasis and some types of colitis, are characterized by an excessive presence of leukocytes and may be ameliorated by seaweed ingestion. Algal-derived fucoidans inhibit the passage of leucocytes into tissues by receptor blocking. These fucoidans are being investigated clinically for their potential to prevent destruction of postischemic heart muscle by invading leucocytes.[18]

Effects on Plasma Cholesterol and Hypertension

Many foods are known to reduce cholesterol levels and brown algae fall into this category. *Undaria* ingestion results in lower cholesterol levels in rats.[64] This effect on lipid processing seems to be the result of stimulation of liver enzymes.[65] *Undaria* fucogalactan fractions were shown to reduce lipid clearance times dramatically when introduced intravenously.[13] The fucoidan component may block the macrophage scavenger receptor that is involved in low-density lipoprotein uptake.[66]

Undaria contains substantial amounts of laminine and similar tetrapeptides, which have been shown to have angiotensin-converting enzyme inhibitory qualities both in vitro and in vivo.[67] Ingesting 3.6 g per day of *Undaria* (wakame) for 4 weeks resulted in a 14 mm Hg drop in systolic blood pressure in Asian patients who had hypertension.[68] Relying on ion exchange properties, rather than laminine, a Swedish clinical study found that ingesting potassium-loaded seaweed fibers countered hypertension sucessfully.[69]

Mineral Contents

Mineral concentrations vary according to the growth environment and age of marine algae. Iodine or trace-element requirement is currently the most common reason for seaweed supplementation. The maximum tolerated dose of 1000 µg of iodine per day (according to the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives) can be reached with only small amounts of some kelps[1] and should be assessed carefully by practitioners. Arsenic is considered to be toxic in the form of the inorganic salt when it consumed in excess of 2 µg per kg body weight per day.[70] Arsenic is also an essential trace element with a recommended minimum intake of 12–50 µg per day.[71]

In broad terms, annual growth algae such as *Undaria* contain the lowest amounts of minerals and can, therefore, be consumed in larger quantities. For example, Tasmanian *Undaria* contains 53 µg per g of iodine and 0.96 µg per g of arsenic.*

Conclusions

Brown algae as either food or in supplement form may provide useful additional therapy for treating herpetic viral infections and some cancers. Other benefits include mild antihypertensive- and cholesterol-reducing effects. Used with caution, so as not to exceed the maximum iodine or arsenic intakes, these algae also provide valuable mineral supplementation.

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References

1. Chapman VJ, Chapman DJ. Seaweeds and Their Uses, 3rd edition. London: Chapman and Hall, 1980.

2. Guiry MD, Nic Dhonncha E. Algae Base. Online document at: www.algaebase.org 2001.

3. Kanke Y, Itoi Y, Iwasaki M. Effects of human diets of two different Japanese populations on cancer incidence in rat hepatic drug metabolising and antioxidant enzyme systems. Nutr Cancer 1996;26:63–71.

4. Lawson JS, Tran D, Rawlinson WD. From Bittner to Barr: A viral, diet and hormone breast cancer aetiology hypothesis. Breast Cancer Res 2001;3:81–85.

5. Teas J. The dietary intake of *Laminaria*, a brown seaweed, and breast cancer prevention. Nutr Cancer 1983;4(3):217–222.

6. Funahashi H, Imai T, Mase T, et al. Seaweed prevents breast cancer? Jpn J Cancer Res 2001;92(5):483–487.

7. Adami HO, Signorello LB, Trichpoulos D. Towards an understanding of breast cancer etiology. Cancer Biol Semin 1998;183:255–262.

8. Yamori Y, Miura A, Taira K. Implications from and for food cultures for cardiovascular diseases: Japanese food, particularly Okinawan diets. Asia Pac J Clin Nutr 2001;10(2):144–145.

9. Black WAP, Dewar ET, Woodward FN. Laboratory-scale isolation of fucoidan from brown marine algae: Manufacture of algal chemicals. IV. J. Sci Food Agric 1952;3:122–129.

10. Larsen B. Fucoidan. In. Hellebust JA, Craigie JS, eds. Handbook of Phycological Methods: Physiological and Biological Methods. New York: Cambridge University Press:152–156.

11. Nishino T, Nishioka C, Ura H, Nagumo T. Isolation and partial characterization of a novel amino sugar-containing fucan sulfate from commercial *Fucus vesiculosus* fucoidan. Carbohydr Res 1994;255:213–224.

12. Koo JG, Jo KS, Do JR, Woo SJ. Isolation and purification of fucoidans from *Laminaria religiosa* and *Undaria pinnatifida* in Korea. J Korean Fish Soc 1995;28(2):227–236.

13. Mori H, Kamei H, Nishide E and Nisizawa K. Sugar constituents of some sulphated polysaccharides from the sporophylls of wakame and their biological activities. In: Hoppe HA, Levring T, eds. Marine Algae in Pharmaceutical Science, vol. 2. New York & Berlin: Walter de Gruyter, 1982:109–121.

14. Schaeffer DJ, Krylov VS. Anti HIV activity of extracts and compounds from algae and cyanobacteria: Ecotoxicology and environmental safety 2000;45:208–227.

15. Witvrouw M, de Clercq E. Sulfated polysaccharides extracted from sea algae as potential anti-viral drugs. Gen Pharmacol 1997;29:497–511.

16. Ibrahim J, Griffin P, Coombe DR, Rider CC, James W. Cell-surface heparin sulfate facilitates human immunodeficiency virus Type 1 entry into some cell lines but not primary lymphocytes. Vir Res 1999;60:159–169.

17. Campadelli-Fiume G, Cocchi F, Menotti L, Lopez M. The novel receptors that mediate the entry of herpes simplex viruses and animal alpha herpes viruses into cells. Rev Med Virol 2000;10(5):305–319.

18. Ritter LS, Copeland JG, McDonagh PF. Fucoidan reduces the coronary microvascular leukocyte accumulation early in reperfusion. Ann Thorac Surg 1998;66:2063–2071.

19. Coombe DR, Parish CR, Ramshaw IA, Snowden JM. Analysis of the inhibition of tumour metastasis by sulphated polysaccharides. Int J Cancer 1987;39:82–88.

20. Church FC, Meade JB, Treanor RE, Whinna HC. Antithrombin activity of fucoidan: The interaction of fucoidan with heparin cofactor II, antithrombin III, and thrombin. J. Biol. Chem 1989;264:3618–3623.

21. Blondin C, Fischer E, Boisson-Vidal C, Kazatchkine MD, Jozefonvicz J. Inhibition of complement activation by natural sulfated polysaccharides (fucans) from brown seaweed. Mol Immunol 1994;31:247–253.

22. Itoh H, Noda H, Amano H, Ito H. Immunological analysis of inhibition of lung metastases by fucoidan (GIV-A) prepared from brown seaweed *Sargassum thunbergii*. Anticancer Res 1995;15(5B):1937–1947.

23. Frenette PS, Weiss L. Sulfated glycans induce rapid hematopoietic progenitor cell mobilisation: Evidence for selectin dependent and independent mechanisms. Blood 2000;96(7):2460–2468.

24. Sweeney EA, Lortat-Jacob H, Priestley GV, Nakamoto B, Papayannopoulou T. Sulfated polysaccharides increase plasma levels of SDF-1 in monkeys and mice: Involvement in mobilization of stem/progenitor cells. Blood 2002;99(1):44–51.

25. Logeart D, Prigent-Richard S, Jozefonvicz J, Letourneur D. Fucans, sulfated polysaccharides extracted from brown seaweeds, inhibit vascular smooth muscle cell proliferation: I. Comparison with heparin for antiproliferative activity, binding and internalization. Eur J Cell Biol 1997;74(4):376–384.

26. Funahashi H, Imai T, Tanaka Y, et al. Wakame seaweed suppresses the proliferation of 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in rats. Jpn J Cancer Res. 1999;90:922–927.

27. Hiebert LM. Oral heparins. Clin Lab 2002;48:111–116.

28. Yubin Ji, Guangmei Z. Pharmacological Action and Application of Available Antitumor Composition of Traditional Chinese Medicine. Heilongjiang, China: Heilongjiang Science and Technology Press, 1998.

29. Hoppe HA, Levring T, Tanka Y, eds. Marine Algae in Pharmaceutical Science. Berlin & New York: Walter de Gruyter, 1979.

30. Moon S, Kim J. Iodine content of human milk and dietary iodine intake of Korean lactating mothers. Int J Food Sci Nutr 1999;50:165–171.

31. Gong YF, Huang ZJ, Qiang MY, Lan FX, et al. Suppression of radioactive strontium absorption by sodium alginate in animals and human subjects. Biomed Environ Sci 1991;4:273–282.

32. Shandala NK. Alimentary methods for decreasing the radiation load of the body with cesium and strontium radionuclides [in Russian]. Gig Sanit 1993;10:51–54.

33. Morita K, Nakano T. Seaweed accelerates the excretion of dioxin stored in rats. J Agric Food Chem 2002;13;50:910–917.

34. Orpin CG, Greenwood Y, Hall FJ, Paterson IW. The rumen microbiology of seaweed digestion in Orkney sheep. J Appl Bacteriol 1985;58:585–596.

35. Saker KE, Allen VG, Fontenot JP, Bagley CP, Ivy RL, Evans RR, Wester DB. Tasco-Forage: II. Monocyte immune cell response and performance of beef steers grazing tall fescue treated with a seaweed extract. J Anim Sci 2001;79:1022–1031.

36. Wyatt GM, Bayliss CE, Holcroft JD. A change in human faecal flora in response to inclusion of gum arabic in the diet. Br J Nutr 1986;55:261–266.

37. Yamauchi H, Takahashi K, Mashiko M, Saitoh J, Yamamura Y. Intake of different chemical species of dietary arsenic by the Japanese and their blood and urinary arsenic levels. Appl Organomet Chem 1992;6:383–388.

38. Okinaga S. Shedding of *Herpes simplex* virus type 1 into tears and saliva in healthy Japanese adults. Kurume Med J 2000;47:273–277.

39. Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and -sociological patterns of *Herpes simplex* virus infection in the world. Scand J Infect Dis Suppt 1990;69:19–36.

40. Field HJ. *Herpes simplex* virus antiviral drug resistance—current trends and future prospects. J Clin Virol 2001;21:261–269.

41. Cooper R, Dragar C, Elliot K, Fitton JH, Godwin J, Thompson K. GFS, a preparation of Tasmanian *Undaria pinnatifida* is associated with healing and inhibition of reactivation of herpes. BMC Complement Altern Med 2002;2:11.

42. Thompson KD, Fitton JH. Anti-viral activity of Tasmanian seaweed extracts against clinical strains of *Herpes simplex* virus (HSV). [abstr.] 18th Annual Clinical Virology Symposium, Florida, April 28– May 1, 2002.

43. Thompson KD, Fitton JH. The mode of action of two Tasmanian seaweed extracts against *Herpes simplex* virus (HSV) [abstr.] 27th International Herpes Virus Workshop, Cairns, July 20–26, 2002.

44. Ohigashi H, Sakai Y, Yamaguchi K, Umezaki I, Koshimizu K. Possible anti-tumor promoting properties of marine algae and in vivo activity of *wakame* seaweed extract. Biosci Biotechnol Biochem 1992;56:994–995.

45. Muto S, Niimura K, Oohara M, Oguchi Y, et al. Polysaccharides and antiviral drugs containing the same as active ingredient. U.S. patent number 5,089,481.

46. Hudson JB, Kim JH, Lee MK, DeWreede RE, Hong YK. Antiviral compounds in extracts of Korean seaweeds: Evidence for multiple activities. J. Appl Phycol 1999;10:427–434.

47. Hoshino T, Hayashi T, Hayashi K, Hamada J, Lee JB, Sankawa U. An anti virally active sulphated polysaccharide form *Sargassum horneri*. Biol Pharm Bull 1998;21:730–734.

48. Luscher-Mattli M. Polyanions—a lost chance in the fight against HIV and other virus diseases? Antiviral Chem Chemother 2000;11:249–259.

49. Furusawa E, Furusawa S, Chou SC. Antileukemic activity of Viva-Natural, a dietary seaweed extract, on Rauscher murine leukemia in comparison with anti-HIV agents, azidothymidine, dextran sulfate and pentosan polysulfate. Cancer Lett 1991;56(3):197–205.
50. Teas J, Harbison ML, Gelman RS. Dietary seaweed (*Laminaria*) and mammary carcinogenesis in rats. Cancer Res 1984;44:2758–2761.
51. Riou D, Colliec-Jouault S, Pinczon du Sel D, Bosch S, et al. Anti-tumor and anti-proliferative effects of a fucan extracted from ascophyllum nodosum against a non–small-cell bronchopulmonary carcinoma line. Anticancer Res 1996;16(3A):1213–1218.
52. Reddy BS, Sharma C, Mathews L. Effect of Japanese seaweed (*Laminaria angustata*) extracts on the mutagenicity of 7,12-dimethylbenz[a]anthracene, a breast carcinogen, and of 3,2'-dimethyl-4-aminobiphenyl, a colon and breast carcinogen. Mutat Res 1984;127:113–118.
53. Okai Y, Higashi-Okai K, Nakamura S. Identification of heterogenous antimutagenic activities in the extract of edible brown seaweeds, *Laminaria japonica* (*mekabu*) and *Undaria pinnatifida* (*wakame*) by the umu gene expression system in *Salmonella typhimurium* (TA1535/pSK1002). Mutat Res 1993;303:63–70.
54. Venturi S, Donati FM, Venturi A, Venturi M, Grossi L, Guidi A. Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. Adv Clin Path 2000;4:117.
55. Cann SA, van Netten JP, van Netten C. Hypothesis: Iodine, selenium and the development of breast cancer. Cancer Causes Control 2000;11:121–127.
56. Takahashi N, Ojika M, Dogasaki C, Nishizawa M, et al. Substance isolated from the kelp rhizoid identified as L-tryptophan shows high inhibition of breast cancer. Gan To Kagaku Ryoho, 2000;27:251–255.
57. Yasui Y, Potter JD, Stanford JL, Rossing MA, Winget MD, Bronner M, Daling J. Breast cancer risk and "delayed" primary Epstein-Barr virus infection. Cancer Epidemiol Biomarkers Prev 2001;10:9–11.
58. Bonnet M, Guinebretiere JM, Kremmer E, Grunewald V, Benhamou E, Contesso G, Joab I. Detection of Epstein-Barr virus in invasive breast cancers. J Natl Cancer Inst 1999;18;91:1376–1381.
59. Subramanian C, Cotter M, Robertson, ES. The Epstein-Barr virus nuclear antigen EBNA3C interacts with the human metastatic suppressor nm23-H1: A molecular link to cancer metastasis. Nature Med 2001;7:350–355.
60. Shan BE, Yoshida Y, Kuroda E, Yamashita U. Immunomodulating activity of seaweed extract on human lymphocytes in vitro. Int J Immunopharmacol 1999;21:59–70.
61. Sciammas R, Kodukula P, Tang Q, Hendricks RL, Bluestone JA. T cell receptor-gamma/delta cells protect mice from *Herpes simplex* virus type 1-induced lethal encephalitis. J Exp Med 1997;185:1969–1975.
62. Selin LK, Santolucito PA, Pinto AK, Szomolanyi-Tsuda E, Welsh RM. Innate immunity to viruses: Control of vaccinia virus infection by gamma delta T cells. J Immunol 2001;166:6784–6794.
63. Fahrer AM, Konigshofer Y, Kerr EM, Ghandour G, Mack DH, Davis MM, Chien Y-H. Attributes of gamma delta intraepithelial lymphocytes as suggested by their transcriptional profile. Proc Natl Acad Sci USA 2001;98:10261–10266.
64. Iritani N, Nogi J. Effect of spinach and *wakame* on cholesterol turnover in the rat. Atherosclerosis 1972;15:87–92.
65. Murata M, Ishihara K, Saito H. Hepatic fatty acid oxidation enzyme activities are stimulated in rats fed the brown seaweed, *Undaria pinnatifida* (*wakame*). J Nutr 1999;129:146–151.
66. Yokota T, Ehlin-Henriksson B, Hansson GK. Scavenger receptors mediate adhesion of activated B lymphocytes. Exp Cell Res 1988;239:1:16–22.
67. Suetsana K, Nakano T. Identification of an antihypertensive peptide from peptic digest of *wakame* (*Undaria pinnatifida*). J Nutr Biochem 2000;11:450–454.
68. Nakano T, Hidaka H, Uchida J, Nakajima K, Hata Y. Hypotensive effects of *wakame*. J Jpn Soc Clin Nutr 1998;20:92.
69. Krotkiewski M, Aurell M, Holm G, Grimby G, Szczepanik J. Effects of a sodium–potassium ion-exchanging seaweed preparation in mild hypertension. Am J Hypertens 1991;4(6):483–488.
70. Mohri T, Hisanaga A, Ishinishi N. Arsenic intake and excretion by Japanese adults: A 7-day duplicate diet study. Food Chem Toxicol 1990;28(7):521–529.
71. Uthus EO, Seaborn CD. Deliberations and evaluations of the approaches, endpoints and paradigms for dietary recommendations of the other trace elements. J Nutr Sci 1996;126(9[suppl.]):2452S–2459S.

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