REVIEW ARTICLE

Brown Algae as Medicine, From Food

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Abstract

For millennia, humans have been consuming seaweeds as vegetables and using them as traditional medicines. In modern times, extracted fractions have been found to contain compounds with useful properties as additives to foods and other products and with beneficial bioactivities in a wide variety of disease states. Some of these extracted compounds—the fucose-containing, sulfated polysaccharides known collectively as *fucoidans*—have demonstrated particularly potent activities in preclinical investigations. Reported bioactivities include antitumor, immunomodulatory, anti-angiogenesis, antioxidant, antiviral, antithrombotic/anticoagulant, and anti-inflammatory effects. This article reviews the most promising of these potentially medicinal bioactivities, providing citations to the original investigations.

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If you have ever been scuba diving in the ocean, you have likely had the experience of flying through a kelp forest and felt the long seaweed fronds swirling around your body as you glide through them. Even though the kelp might momentarily encircle an arm or a leg, it will never cling or entangle for long, thanks to the lubricating properties of the slimy mucilage that coats the plant's surface. *Slime*, broadly defined, is a common theme in nature, produced by diverse organisms throughout the animal, plant, and fungi kingdoms. Think of the Hagfish's suddenly expelled secretions that confuse, gag, and sometimes suffocate would-be predators; the incredibly gooey sap of the prickly pear cactus; and the shiny, viscid, beautifully-colored caps of the woodland mushrooms known as *waxy caps*.

Chemically, these natural slimes are diverse, consisting of many different varieties of polysaccharides and/or proteins—glycoproteins when chemically combined. The mucilage found in kelp, as well as other brown algae and sea cucumbers, is distinguished by its component sulfated polysaccharides, which are large, branching chains of sulfated sugars. As its backbone, one variety of these sulfated polysaccharides mainly comprises the sugar fucose, although it also contains some mannose, galactose, xylose, glucose, and other sugar moieties. As a group, these large, fucose-backboned molecules and their smaller oligosaccharide derivatives are known as *fucoidans,* and they are of special interest because they have been shown to possess a large variety of biological activities of potential benefit to human health.

Uses of Fucoidans

Past and Future

Brown algae species have long been consumed by humans as food. In Asian cuisine, they are prepared whole as vegetable dishes. Examples include (1) *mozuku—Cladosiphon okamuranus*; (2) kelp—*Saccharina japonica*, also known as *Laminaria japonica* and with other common names—*kunbu*, *kombu*, *dashima*, *kombu dashi*, and *haidai*; (3) wakame—*Undaria pinnatifida*; (4) *hijiki—Sargassum fusiforme*, as well as others. These sea vegetables are especially rich in certain nutrients while low in calories and fat.

For example, 20 g contains significant amounts of vitamin K (16.5% daily value [DV]), folic acid (9% DV), calcium (3% DV), iron (3% DV), magnesium (6% DV), iodine (>100% DV), cystine (4% DV), tryptophan (3% DV), and many other vitamins, minerals, and amino acids in the 1% to 3% DV range. The same serving contains about 9 calories (<1% DV), and nearly zero fat.[1]

Extracts from multiple species containing Carrageenans, another kind of sulfated polysaccharide like fucoidans, are used as gelling, thickening, and clarifying agents in foods such as ice cream, salad dressings, and beer.

Some brown algae are also used in traditional medicines; for example, species of kelp (kunbu) and *Sargassum* (*hai zao*) are commonly found in traditional Chinese medicine, used to treat such afflictions as scrofula (tuberculous lymphadenitis), goiter, tumor, edema, and testicular pain, and swelling. The fact that brown algae are an excellent source of iodine certainly lends credence—from the perspective of modern medicine at least—to their use in treating goiter.[2]

But evidence is accumulating from preclinical in vitro and animal studies that fucoidans may indeed possess a plethora of health-promoting bioactivities. Since the first reported biochemical isolation of *fucoidin*, as it was then spelled, in 1913,[3] over 1800 papers related to fucoidan have been reported in the scientific literature, with the largest increase in publications occurring within the past 10 years.[4] Some of the reported activities are highlighted in the text that follows.

Anticoagulant and Antithrombotic Activities

In 1957, Springer and colleagues first reported the inhibition of fibrin-clot formation or antithrombotic activity of fucoidans isolated from *Fucus vesiculosus*.[5] Since then, this heparin-like anticoagulant activity of fucoidans from many different species of brown algae has been widely studied and characterized, although not yet completely understood. A number of investigations have suggested that more than one mechanism may be involved, including direct inhibition of thrombin and indirect inhibition through activation of thrombin inhibitors such as antithrombin and heparin cofactor II.[6-9]

The anticoagulant potencies of fucoidans correlate with their structural features, such that greater activity is associated with greater (1) fucose content, (2) sulfate content, (3) sulfate-to-total-sugar-residue ratio (>1), and (4) higher molecular weight.[10-14] Development of fucoidan products for medical use will need to take into consideration these observed variations in bioactivities depending on the structure of different fucoidans.

No firm recommendations can currently be made regarding clinical use of either brown algae or fucoidans in persons requiring anticoagulation. Individuals who consume these products need close clinical monitoring, as is discussed in the Safety section of this article.

Antitumor Activities

Studies investigating sulfated polysaccharide fractions from several species of brown algae from the genera *Sargassum*, *Laminaria*, *Fucus*, *Undaria*, and others have demonstrated remarkable antitumor bioactivities, including on sarcoma-180 cells implanted into mice and L-1210 leukemia in mice[15-17] and on growth of lung- and skin-cancer cells.[18]

Immune Modulation. This activity of fucoidans appears to involve increased production of macrophage-mediated, immune-response signals,[19-21] such as IL-2, IL-12, and IFN-γ.[18,19] These immune-response signaling molecules, known as cytokines, lead to enhanced cytolytic activity by natural killer (NK) cells.

Apoptosis. Another action of so-triggered cytokines may be extrinsic inducement of proteolytic caspases within cancer cells, leading to apoptosis or cell death. Multiple studies have demonstrated induction of apoptosis by fucoidans in various cancer-cell lines, including melanoma cells,[18] colon cancer cells,[22] MCF-7 human breast cancer cells,[23] and HS-Sultan human lymphoma cells.[24]

Inhibition of Angiogenesis. In studies examining effects on the function of human umbilical-vein endothelial cells, fucoidans isolated from brown algae caused inhibition of cell proliferation, cell migration, tube formation, and vascular-network formation, suggesting significant antiangiogenic activity.[25] Interestingly, this effect is weakened, and then lost, with a reduced molecular weight of derivative fucoidans (<30 kDa),[26] analogous to the observations for the anticoagulant activities of fucoidans as mentioned above.

Again, clinical use must await further refinement in scientists' understanding of these bioactivities and in refinement and standardization of fucoidan preparations.

Immunomodulatory Activity

Fucoidans' effects on the immune system are multiple and complex. Depending on the situation, they may exhibit either proinflammatory or anti-inflammatory activities. For example, in a recent in vivo study[27] using lipopolysaccharides-induced (LPS-induced) inflammation in RAW264.7 cells, fucoidans with low molecular weights displayed potent anti-inflammatory effects in macrophages, apparently through attenuation of specific cytokines such as IL-1β, IL-1, and TNF-α and through the degradation of protein-kinase intracellular-signaling molecules, such as mitogen-activated protein kinases. The same study suggested that these fucoidans might block nitric oxide (NO) as well as the expression of reactive oxygen species (ROS), which subsequently inhibits the iNOS and COX-2 expression induced by LPS.

However, fucoidan from *Fucus vesiculosus* induced iNOS in RAW264.7 macrophage cells, leading to enhanced production of nitric oxide.[28,29] Similarly, while some cytokines were inhibited in the study involving LPS-induced inflammation, the production of other cytokines was

enhanced in other situations, such as mentioned above in the section on antitumor effects (ie, fucoidan-induced enhancement of the cytolytic activity of NK cells).

It is far from clear how to incorporate these immunomodulatory effects in clinical practice.

Activity Against Infectious Pathogens

Multiple studies have indicated antiviral activity for fucoidans, including activity against (1) avian influenza A (H5N1) in vitro,[30] (2) HSV-1 in vitro,[31] (3) Newcastle disease virus in vitro,[32] (4) hepatitis C virus in a small clinical trial,[33] and (5) HIV in vitro,[34] as well as others. Some limited evidence also exists for antibacterial activity in vitro[35] and prebiotic activity in vitro.[36]

Further study in clinical trials is required before any antiviral, antibacterial, or prebiotic use can be recommended. The only human data available is for suppression of hepatitis C virus, summarized in Table 1 of this article.

Safety: A Question of Quantity

Seaweeds have served as food for coastal civilizations for thousands of years, which generally argues in favor of their likely health and nutritional values and seems reasonable in light of their favorable nutritional profile. At least one extract of kelp—*L japonica*, GRN No. 123—has been approved under the Food and Drug Administration's (FDA's) GRAS (Generally Regarded as Safe) provision.

Fucoidans derived from all species tested have lacked toxicity in vitro and in vivo.[37] However, two main areas of potential toxicity must be discussed. First, for individuals taking anticoagulants for underlying medical conditions, therapeutic anticoagulation ranges may be exceeded or levels may become unpredictable when taking fucoidans in addition to usual medications. Close monitoring of laboratory and clinical-bleeding parameters, with attention to the fucoidan-consumption pattern and dosages, is advised.

One study examined the effects of fucoidan extracted from *L japonica* on the clotting time in rats and found no adverse effects at a dosage of 300 mg/kg body weight but also found a significant increase in clotting time when the dose was increased to above 900 mg/kg.[38] Whether this dosage range applies in humans needs to be tested in clinical trials before explicit recommendations can be made regarding optimal fucoidan starting dosages in individuals taking anticoagulants.

Second, if large amounts of seaweed or their fucoidan extracts are consumed regularly, some theoretical concern exists regarding potential exposure to elevated levels of iodine and trace minerals such as mercury and arsenic. It is likely that concentrations of these minerals will vary depending on the water conditions in which the algae are growing.

The guidelines of the World Health Organization (WHO) and the US Environmental Protection Agency (EPA) agree that the safe upper limit for arsenic in drinking water should be 10 mcg/L, implying a range of acceptable chronic exposures. Similarly for mercury, the EPA gives its reference dose of 0.1 mcg methylmercury/kg body weight per day as an estimate of an acceptable chronic exposure in humans, likely to be without an appreciable risk of deleterious effects during a lifetime. Other agencies, including the WHO, propose somewhat higher limits (2-3× higher).

Iodine is required for human health, with a recommended daily allowance that varies throughout the life cycle, from 90 mcg daily in children to 290 mcg daily in lactating women. Most iodine-sufficient diets are in the range of 1000 mcg per day. Iodine toxicity is rare and generally only occurs at very high doses in the range of many grams. An exception to this can occur in individuals who are significantly iodine deficient, in whom too-rapid repletion can lead to hyperthyroidism.

With these figures in mind, comparisons can be made to known values for these substances in seaweed products. For example, one study of the total arsenic and mercury content of fucoidans reported levels in the range of 2 to 3 mcg/g and 0.1 to 0.2 mcg/g, respectively.[39] These levels fall well within the above guidelines as long as the dosage of these fucoidans is limited to the range of several grams; typical supplement capsules contain less than 1 g of fucoidans. Iodine content in brown seaweed is variable, ranging from 500 to 8000 mcg/g of dried brown algae, a rich source but not at the toxic level.[40]

The potential for drug interactions exists. Some of the specific theoretical interactions mentioned in the literature include those with potassium supplements, potassium sparing diuretics, ACE inhibitors, and digoxin, leading to abnormal potassium levels. Potassium levels should be monitored in patients taking any of these agents concomitantly.

In individuals taking anticoagulants, the potential exists for further increases in bleeding times with use of fucoidans. Appropriate monitoring of clinical and laboratory indicators (prothrombin time, INR, activated partial thromboplastin time, and thrombin time), with adjustments in dosages of both anticoagulant medications and fucoidans, is recommended.

Therefore, a reasonable consumption of seaweed as a food should be considered safe. In small quantities, fucoidan extracts are also likely safe, keeping in mind the above considerations.

Dosage and Drug Interactions

Uncertainty exists regarding dosages in part due to variations in fucoidan structures.[41,42] To allow accurate dosage recommendations, future preclinical investigations and clinical trials are needed to clarify specific relationships between fucoidan structural conformations and functions. However, as mentioned above in the Safety section, this broad range of possible doses is well below the toxicity level with regard to excessive heavy metals; therefore, empirical treatment with careful clinical monitoring is reasonable.

Table 1. Example Dosages From Preclinical Trials

Activity		Fucoidan Dose Used	Approximate Equivalent Dose for 60-Kg Human[a]
HCV Suppression (in humans)[b]		830 mg/d	~830 mg/d
Toxicity (in rats)[c]	**No toxicity observed**	300 mg/kg/d	~2900 mg/d
	Toxicity observed	≥900 mg/kg/d	~8800 mg/d

Abbreviations: HCV = hepatitis c virus.

[a]Reagan-Shaw S et al, using conversion formula: rat dose/kg × km rat/km human (6/37) × 60 kg = total human dose.[43]
[b]Mori N et al.[33]
[c]Li N et al.[38]

Table 1 demonstrates that the extracts are available in a variety of forms. For example, some capsules contain 600 mg of the dried juice of otherwise unprocessed *L japonica*, reportedly containing 35% fucoidan, or around 200 mg. Other more processed forms such as capsules or dose-packed powders contain more purified fucoidan: 212.5 mg and 100 mg per dose, respectively. In the Natural Medicines Comprehensive Database,[44] a typical dosage of 500 to 650 mg of ground *Laminaria* is mentioned. No firm dosage recommendations can be made for any specific conditions due to lack of adequate preclinical and clinical trials. Table 1 is provided as a point of reference, not as a treatment guideline.

Discussion

Well-known in Asian cuisine but also reported in the anthropologic literature from other prehistoric cultures, including Native American nations,[45,46] seaweed has long been included in the human diet. With such a long ethnobotanical history, it is intuitively logical that seaweed is nutritious. In recent years, a growing body of scientific investigation points to many bioactivities potentially beneficial to human health. Of particular interest is the group of compounds derived from brown algae known as fucoidans. Clinical trials are needed to delineate specific uses within specific disease states fully. However, it is safe to consider that consumption of brown algae as a food is generally healthful; it is rich in minerals, protein, calcium, iron, iodine, and vitamins while low in calories and fat. Furthermore, it is likely that the use of extracts containing fucoidans can have an adjunctive role in preventing and/or treating certain medical conditions. Given the accelerating pace of fucoidan research in the past 5 to 10 years, the author hopes that definitive clinical trials will be completed that will help to identify and refine these potential uses of brown algae as medicine, from food.

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