Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Fucoidan

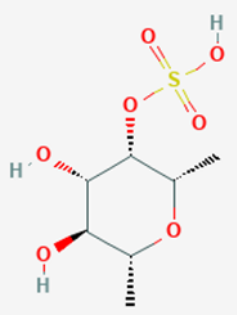
Evidence Summary

May reduce immune cell mediated inflammation and oxidative stress, but has very low oral bioavailability. May exert beneficial effects through modulation of the intestine/microbiome.

Neuroprotective Benefit: Can protect against onset of inflammatory and oxidative damage by mitigating immune cell activation in animal models. Unlikely to significantly benefit after onset of neurological damage.

Aging and related health concerns: May help regulate glucose homeostasis, have anti-thrombotic effects, and improve tolerability of chemotherapy, but benefits are limited by poor oral bioavailability.

Safety: Well-tolerated with no adverse events in clinical trials, even at high doses. Possible risk for increased bleeding when used in combination with blood thinners.

Availability: OTC as supplements and in the diet from brown seaweed.	**Dose**: Clinically beneficial dose not established.	**Chemical formula:** $C_7H_{14}O_7S$ **MW**: Varies  Source: PubChem
Half-life: Varies with preparation (~1-3 hours in rats)	**BBB**: Not penetrant	
Clinical trials: Diabetes/obesity (n=25, n=30), Cancer adjunct to chemotherapy (n=20, n=54) osteoarthritis (n=12, n=122, anti-viral (n=12, n=15), flu vaccine adjuvant (n=70)	**Observational studies**: Diets rich in fucoidan associated with increased lifespan and lower cancer incidence.	

What is it? Fucoidans are polysaccharides that are a component of the cell wall of brown algae (seaweed). Fucoidan fractions extracted from algae contain a mixture of polysaccharides of different molecular weights, and crude extracts may contain large amounts of non-fucoidan components [1]. Fucoidan contains a backbone of sulfated fucans, and its structure depends on the species of algae and harvest conditions [2]. The sulfate groups are critical for the bioactivity of fucoidan. ***In vitro*, fucoidan shows potent anti-cancer and anti-thrombotic activities, however, these findings have generally not translated to clinically meaningful benefits in clinical trials due to low oral bioavailability**. High molecular weight fucoidans have high bioactivity, but are not bioavailable, and the more bioavailable low molecular weight fucoidans tend to have lower bioactivity. The modest **benefits appear to be indirect, due to modulation of the intestinal environment where it is a good source of fiber** and acts as a microbiota-assessible carbohydrate, rather than the direct activities seen in cell culture studies [3]. Consequently, benefits may depend on an intestinal environment/microbiome that is capable of utilizing the fucoidan. Most clinical studies with evidence of benefits, albeit minor ones, were conducted in Japan, where fucoidan rich seaweed is a normal part of the diet, thus people there may already have microbiome more conducive to extracting benefits from fucoidan.

Neuroprotective Benefit: Can protect against onset of inflammatory and oxidative damage by mitigating immune cell activation in animal models. Unlikely to significantly benefit after onset of neurological damage.

Types of evidence:

- 2 clinical trials for seaweed extract for cognitive function (n=60, n=59)
- Numerous laboratory studies (various fucoidan formulations)

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

No studies have directly tested the specific effects of fucoidan supplementation, however, there have been a couple of placebo-controlled clinical trials examining the effects of brown seaweed extract supplementation on cognitive function. One study testing fermented extract from *Laminaria japonica* in healthy elderly Japanese adults (Treatment: n=28, age 72.35 ± 5.54; Placebo: n=32, age 74.57 ± 5.69) found that 6 weeks of supplementation (1.5 g/day) led to improvements on tests for cognitive function and memory [K-MMSE, numerical memory test (working memory), Raven's test (visual and spatial reasoning), iconic memory test (visual spatial memory)] relative to placebo [4]. Another study tested post-prandial cognitive function following consumption of a hot water extract derived from *Ascophyllum nodosum* and *Fucus vesiculosus* (InSea2® 500 mg, equivalent to 10 g dried seaweed) in healthy adults (Treatment n=30, age 33.1±14.6; Placebo n=29, age 37.9 ±16.9) and found improvements in accuracy on digit vigilance and choice reaction time tests [5]. The fermented extract was characterized for GABA content (mean 54.5± 0.071 mg/g), while the hot water extract was characterized for polyphenol content (>20%). These studies suggest that **brown seaweed contains compounds that can at least temporarily improve some aspects of cognitive function**, however, the fucoidan content of these preparations was not characterized, thus it is **not clear if any of these effects can be attributed to fucoidan.**

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Due to its high molecular weight and low bioavailability, orally supplemented fucoidan is not expected to be brain penetrant [6]. However, the **neuroprotective effects described in preclinical studies are largely indirect** and primarily involve the ability of fucoidan to promote a neuroprotective environment

through the **reduction of inflammatory and oxidative stressors**. Fucoidan appears to be most effective when used as a preventative, to mitigate tissue damaging immune cell infiltration and activation.

Alzheimer's disease: Potential benefit for prevention (preclinical)

Different preparations of fucoidan have been found to protect against Aβ induced cytotoxicity in cell culture and *C. elegans*, and mitigate scopolamine, ethanol, sodium nitrate, D-galactose, or A□40 induced cognitive impairment in rodents [7; 8; 9; 10; 11; 12]. The neuroprotective effects were generally seen when fucoidan was administered prior to or shortly after exposure to the cell stressor, and were associated with reduced production of reactive oxygen species (ROS). Fucoidan treatment was also associated with less caspase activation and apoptosis. Fucoidans are similar in structure to glycosaminoglycans, which are known to regulate oxidative stress induced apoptosis. The properties most important for neuroprotective activity have not been fully characterized, but likely include the **degree of sulfation, molecular weight, and sugar composition**. One study comparing fucoidans with different chemical compositions derived from *Fucus vesiculosus* or *Undaria pinnatifida* found that the sample with the highest polyphenol content, lowest carbohydrates, lowest sulfate content, and highest molecular weight showed the lowest neuroprotection against Aβ in PC12 cells [7]. Some of the fucoidans (Molecular weight MW 33-56 kDa, sulfates 23-31%) enhanced neurite outgrowth, which has also been seen with bioactive polysaccharides from other species. In rat cognitive impairment models, a fucoidan isolated from *Sargassum fusiforme*, SFPS65A, with a sulfate content of 17.5% was protective, while a related isolate, SFPS65B, with a lower sulfate content of 2.7% was not neuroprotective [10].

Parkinson's disease: Potential benefit for prevention (preclinical)

Fucoidan pretreatment has been found to be protective in models of MPTP, 6-OHDA, or rotenone mediated dopaminergic neurotoxicity [13; 14; 15; 16; 17]. Fucoidan can reduce toxin induced behavioral deficits, mitochondrial dysfunction, and dopamine neuron cell death. The protective effects primarily involve the inhibition of microglial activation, and a reduction in levels of oxidative stress (ROS, protein carbonylation, lipid peroxidation). In these studies benefits were seen with fucoidan derived from *Laminaria japonica* from Qingdao, China (48% total sugar, 28% fucose, 29% sulfate, fucose: galactose 1:0.24, MW 7kDa), a 198 kDa L-fucose-4-sulfate fucoidan from the China National Institute for Control of Pharm and Biological products (16121901), and a fucoidan from *Turbinaria decurrens* collected in Yervadi, India (carbohydrate 59.62%, sulfate 26.52%, and uronic acid 6.3%, MW 234 kDa). Since the protective effects appear to stem largely from preventing the induction of pathological processes associated with the onset of neuronal damage, it is not clear whether fucoidan would benefit as a treatment for patients with established disease.

Stroke/Traumatic Brain Injury: Potential benefit (preclinical)

Fucoidan pretreatment has been found to be protective in rodent models of cerebral ischemia (stroke) [18; 19; 20; 21], LPS-induced neuroinflammation [22; 23], intracerebral hemorrhage [24], and traumatic brain injury [25]. The vast majority of these studies used a fucoidan preparation supplied by Sigma which is derived from *Fucus vesiculosus* and contains 44% fucose and 26% sulfate [26]. Fucoidan treated animals had reduced neurological deficit scores, reduced infarct/lesion volumes, decreased cell death near the lesion, reduced pro-inflammatory cytokines (IL-1β, IL-6, TNFα, MPO), and reduced oxidative stress markers (8-OHdG, 4-HNE, MDA). Effects were typically dose dependent, with lower doses (typically under 50 mg/kg) failing to show benefits. The **neuroprotective effects may also be contingent on time of administration**, as fucoidan was protective in a model of traumatic brain injury when given from 0-4 hours after injury, but failed to protect against neurological deficits when given 6 hours after injury [25]. In this study, the protective effects were attributed to the induction of Sirt3. The time window effect may relate to its mechanism of action in inhibiting the entry of activated immune cells into the brain by blocking P-selectin mediated interactions, which can mitigate the damage. Therefore, fucoidan would not be expected to have a significant effect once immune cells have entered, and damage has occurred.

APOE4 interactions: Unknown

Aging and related health concerns: May help regulate glucose homeostasis, have anti-thrombotic effects, and improve tolerability of chemotherapy, but benefits are limited by poor oral bioavailability.

Types of evidence:

- 17 clinical trials (Obesity n=25, n=72; Type 2 diabetes n=30; Advanced Cancer n=20, n=20, n=20, n=54 ; Osteoarthritis n=12, n=122; Hair loss n=94; Hepatitis C n=15; HTLV-1 associated myelopathy n=13; Healthy elderly getting flu vaccine n=70; Healthy volunteers for skin anti-inflammatory n=20, anti-thrombosis n=33, anti-clotting activities, safety n=20)
- Observational studies for seaweed consumption with lifespan, disease incidence, cancer risk
- Numerous laboratory studies (various fucoidan formulations)

As a class, bioactive polysaccharides, such as fucoidan, tend to show hypoglycemic, anti-inflammatory, antioxidant, anti-microbial, and anti-cancer properties [27]. Fucoidan has been tested in a variety of clinical trials, however, each trial used a different formulation of fucoidan, and there is no clear evidence

that any of these formulations are optimized for a given indication. **It is possible that a specific formulation is necessary to achieve clinical benefit, however, structure-activity analyses have not been incorporated into the clinical trials conducted thus far.** The discrepancies between preclinical and clinical efficacy appears to be related to the poor bioavailability of the oral fucoidan supplements used in clinical trials, suggesting that fucoidan could be a viable therapeutic if a more bioavailable formulation could be developed.

Lifespan: Unclear

The high percentage of centenarians in Okinawa, Japan has been primarily attributed to the 'Okinawa diet', which is rich in vital nutrients, but low in calories [28]. Fucoidan rich seaweed is a staple of the Okinawa diet, however, it is not clear how much fucoidan intake contributes to lifespan, if at all.

Diabetes: Potential benefit

Fucoidan has been shown to alter glucose metabolism, insulin secretion and resistance, and inhibit nephropathy in rodent models of diabetes. The results from small clinical trials suggest that the effect sizes are likely to be more modest in humans, and may be dependent on the baseline patient characteristics. Furthermore, due to low bioavailability, the **effects may be largely mediated through modulation of the intestinal environment** by influencing glucose absorption, reducing levels of gut inflammation, and altering the microbiome.

In mouse models of obesity and Type 2 diabetes (db/db) fucoidan treatment could improve glucose homeostasis and increase serum adiponectin [29; 30]. One study using 500 mg/kg low molecular weight fucoidan (from *Undaria pinnatifida*, Bion Co. Ltd) for 6 weeks saw a reduction in blood lipids and body weight [29]. The effects on glucose and lipid levels involved the regulation of AMPK, which is an enzyme involved in energy homeostasis. Another study using fucoidan from *S. hemiphyllum* (300 mg/kg harvested from Penghu Taiwan in December 2014, MW 0.8kDa, 33% sulfate) for 6 weeks led to improvements in hepatic glucose metabolism, and improved metabolism in adipose tissue (increased insulin receptor (IRS-1) and PPARγ), but had no effect on overall body weight [30]. Fucoidan (from *Fucus Vesiculosus*, Sigma) treatment was also able to attenuate renal fibrosis and inflammation in a rat model of diabetic nephropathy by reducing expression of TGF-β1 and NF-kB [31]. In a mouse model of streptozotocin-induced diabetes, fucoidan (from *Sargassum fusiforme*, China) altered the microbiome and decreased the abundance of diabetes-associated intestinal bacteria, which may have contributed to its therapeutic effects [32].

One small RCT (n= 30, average age 59) suggests that fucoidan **may help regulate glucose metabolism in a subset of Type 2 diabetic patients by affecting the intestinal environment** [33]. Fucoidan is a water-soluble dietary fiber, and was found to promote productive bowel movements. In a subset of patients without insulin resistance (based on HOMA), 24 weeks of fucoidan treatment led to decreases in glycolated hemoglobin (HbA1c from 6.73 ± 1.00 to 6.59 ± 1.00%, $P < 0.05$) and plasma glucagon-like peptide-1 (GLP-1 from 6.42 ± 3.52 to 4.93 ± 1.88 pmol/L, $P < 0.05$). However, the effects may be dependent upon the baseline characteristics of the patients since similar benefits were not seen in non-diabetic obese adults in other clinical trials. In one RCT (n=25, average age 44), fucoidan treatment (500 mg/day F-fucoidan from Green Foods, Swanson Health) for 3 months led to a minor increase in insulin levels and insulin resistance (based on HOMA) [34]. Meanwhile, a separate RCT (n= 72, average age 47.5 years) found that fucoidan (500 mg/day from *Fucus Vesiculosus*, Maritech Synergy) for 3 months had no significant effects on insulin resistance (HOMA) or any other measures of cardiometabolism relative to placebo [35].

Based on preclinical studies the beneficial effects may have been mediated by changes to the microbiome, although it has not been studied in any of the clinical trials thus far. It should be noted that the trials took place in Mexico [34], New Zealand [35], and Japan [33]. **Benefits were only seen in the trial in Japan.** Seaweed consumption, including fucoidan containing brown algae, is highest in Japan. Therefore, the Japanese may already have higher levels of intestinal bacteria that can utilize fucoidan, and be more likely to benefit.

Cardiovascular: Potential benefit

Preclinical studies suggest that fucoidan has anti-atherosclerotic and anti-thrombotic properties, however, clinical studies suggest that the **oral bioavailability of currently used fucoidan preparations may be too low to exert clinically meaningful cardiovascular benefits** in most people [36].

Hypertension: Nitric oxide (NO) generated by endothelial nitric oxide synthase (eNOS) regulates vascular tone and blood pressure, and decreased levels can lead to vascular dysfunction. Fucoidan (from *Undaria pinnatifida* MW 54 kDa) activated eNOS to increase NO production by 1.4-fold in cell culture, and reduced blood pressure (systolic by 18.4%, diastolic by 19.7%, mean by 16.3%; $P<0.01$) in hypertensive rats [37]. The anti-hypertensive effects were maintained for at least one week after discontinuation of fucoidan treatment, and were accompanied by a 1.4-fold reduction in aortic wall media thickness, and a 2.1-fold decrease in aortic wall cell proliferation. Fucoidan treatment (500 mg/day of F-fucoidan from Green Foods, Swanson Health; 95% sulfated esters of fucose) for 3 months reduced diastolic blood pressure (67.8±13.8 vs. 71.7±12.2 mmHg; $P<0.05$) in non-diabetic obese adults (n=25, average age 44)

in a placebo-controlled RCT [34]. Since effects on blood pressure have not been noted in other clinical trials, it is not clear if these effects are dependent on the baseline characteristics of the patient population and/or the formulation of fucoidan.

Atherosclerosis: Fucoidan supplementation has been shown to partially alleviate lipid dysregulation and atherosclerosis induced by high fat diet in ApoE deficient mice [38; 39]. In one study, supplementing a high fat diet with 5% fucoidan (from *Cladosiphon okamuranus* Tokida; Oriental Bio Co., Ltd), reduced the high-fat diet induced increase in total cholesterol (by 28.9%) and triglycerides (by 35.6%) [38]. There was also a decrease in the thickness of lipid plaques, lipid peroxidation (oxidative stress), and foamy macrophage accumulation in the aortas of these mice. Gene expression analysis indicated that these effects may stem from changes in genes regulating lipid metabolism and energy homeostasis, including PPARa and Srebf1. A separate study using fucoidan from *S. japonica* (MW 8kDa, 36.85% sulfate) for 11 weeks found that the treatment decreased triglycerides and oxidized LDL, and reduced vascular inflammation [39]. Fucoidan treatment stabilized the atherosclerotic lesions by preventing the development of foamy macrophages and the migration of smooth muscle cells in the aorta.

The **changes in blood lipids may stem from its actions in the intestine**. Fucoidan (4.05 g/day for 2 weeks) was found to decrease total cholesterol and LDL serum levels in a safety study in healthy volunteers, which was attributed to its ability to prevent cholesterol absorption in the intestine as a water-soluble dietary fiber [40].

Fucoidan may exert its direct protective effects by reducing vascular inflammation and oxidative stress by inhibiting migration and adhesion of immune cells to the vascular endothelium through P-selectin, as well as by preventing adverse vessel wall remodeling [36]. **Fucoidan is currently being developed as an imaging tool to identify vulnerable atherosclerotic plaques.** Radiolabeled fucoidan has been shown to act as a ligand for P-selectin on activated platelets to identify cardiovascular plaques in animal models, and 99mTc-Fucoidan SPECT is being tested in a clinical trial (NCT03422055).

Heart Disease: Fucoidan (25 mg/kg/day) delivered via an intraperitonially implanted osmotic pump for 21 days immediately following induction of heart injury in an experimental autoimmune myocarditis rat model inhibited the extravasation of inflammatory immune cells into the myocardium, resulting in less damage (myocarditis), and improved heart function (left ventricular ejection fraction) [41]. Fucoidan treatment for 28 days (500 mg/kg Hi-Q Oligo-fucoidans from *Sargassum hemiphyllum*, Hi-Q Marine Biotech) in aged mice (2 years old) was able to improve ventricular rhythms, and age-related declines in GSK3β, CREB, and IRS-1 [42]. Fucoidan also influenced metabolic pathways, including the TCA cycle,

glycolysis, and steroid hormone biosynthesis. These studies suggest that fucoidan may have cardioprotective activity by reducing inflammation and regulating metabolism.

Thrombosis: *In vitro*, fucoidan acts similar to heparin, however, ***in vivo*** **its antithrombotic properties are stronger than its anti-coagulant properties**, so it has a lower hemorrhagic risk than heparin [36]. Cell culture studies indicate that fucoidan can inhibit thrombin generation and induced platelet aggregation. In clinical studies the anti-clotting activity was found to be very low in humans due to low bioavailability. In healthy volunteers (n=20, average age 24.5) fucoidan (3 g capsule from Tasmanian *Undaria pinnatifida*, 20% sulfate, Marinova Pty.) for 12 days partially increased thromboplastin time and antithrombin-III, but changes were still within reference values [43]. **Oral fucoidan is poorly absorbed, and was not found at detectable levels in the blood**, which accounts for the discrepancies between *in vitro* and *in vivo* studies. In healthy volunteers (n=33, average age 24.5) fucoidan (from *Laminaria japonica* from Hakodate, Japan) treatment for 5 weeks shortened lysis time of thrombosis in a blood test, and increased secretion of the platelet aggregation inhibitor prostacyclin [44]. Based on an associated mouse study, the effect appears to be indirectly mediated via the intestine. Dietary fucoidan was found to induce H_2O_2 production in the intestinal epithelial cells, which in turn released H_2O_2 into the blood and served to modulate eicosanoid production in platelets.

Osteoarthritis: No clinical benefit

Fucoidan has been tested in two RCT for mild to moderate osteoarthritis (of the knee), but failed to show significant benefits relative to placebo. In a pilot study (n=12, average age ~60) testing 100 or 1000 mg of Maritech extract containing *Fucus vesiculosis* (85% w/w), *Macrocystis pyrifera* (10% w/w) and *Laminaria japonica* (5% w/w) plus vitamin B6, zinc and manganese (Marinova Pty. Ltd, Australia) for 12 weeks, the average comprehensive arthritis test (COAT) score was reduced by 18% for the 100 mg dose and by 52% for the 1000 mg dose, but had no effect on serum levels of an inflammation marker (TNFα) [45]. However, in a larger trial using 300 mg of the *Fucus vesiculosis* (85% w/w) extract (Marinova), reduction of COAT score was similar to placebo (30.6% vs 29%) [46]. It is not clear why the formulation was altered between trials, and it is possible that the combination with vitamins and minerals, as would be found in whole seaweed, is necessary for benefit. However, **lack of change in serum markers of inflammation** in either trial suggests that the bioavailability of these preparations may be too low to exert physiologically meaningful effects.

Cancer: Potential benefit as adjunct therapy

Observational studies indicate that daily intake of seaweed (30 g fresh or 2 g dried) is associated with overall reduced disease risk [47], and some types of cancer, including breast cancer [48]. However, there is no clear evidence that this association is mediated by the anti-cancer effects of fucoidan.

The anti-cancer properties of fucoidan have been extensively studied in preclinical models, however, there have only been a few small clinical trials testing fucoidan supplementation in cancer patients, and the benefits have been minimal. Bioactive polysaccharides are attractive anti-tumor agents because they typically do not act on tumor cells directly, but rather, induce changes in the host's immune system tumor microenvironment that reduces the viability of tumor cells [49]. Since the polysaccharides themselves are not directly cytotoxic, they do not pose a risk to the viability of healthy host cells. Fucoidan shows anti-tumor effects against a variety of cell cancer lines in cell culture and xenograft models, though the anti-cancer effects are highly dependent on sulfate content. In cancer cell lines, fucoidan can induce apoptosis primarily through inhibition of P13K/Akt or ERK1/2 signaling [2]. Due to the low bioavailability, its anti-cancer potency *in vivo* is greatly diminished, and has primarily been tested for its ability to be used as an adjunct to traditional anti-cancer therapies.

The clinical trials conducted thus far suggest that fucoidan may be beneficial for cancer patients receiving chemotherapy in terms of **reducing side effects/improving tolerability of the chemotherapy**. In advanced colorectal cancer patients (n=20, average age 70) undergoing chemotherapy (FOLFOX or FOLFIRI), fucoidan (4.05 g/day in 150 ml from *Cladosiphon okamuranus* [Okinawamozuku], Marine Products Kimuraya Co., Ltd.) for 6 months reduced chemotherapy-associated fatigue (incidence 10% with fucoidan vs. 60% in controls) [50]. The fucoidan treated patients were able to tolerate more cycles of chemotherapy (19.9 vs 10.8, P<0.016), and this resulted in a trend toward longer survival in this cohort. Critically, a separate open-label trial in breast cancer patients (n=20) found that fucoidan treatment (500 mg 2x daily Maritech extract from *Undaria pinnatifida*, Marinova) had no significant effects on the pharmacokinetics of the chemotherapeutic agents letrozole, tamoxifen, or their active metabolites [51], suggesting that fucoidan does not negatively interfere with the efficacy of the chemotherapeutics. In an open-label trial in advanced cancer patients with metastases (n=20), fucoidan (4 g/day in 400 ml extracted from Cladosiphon novae-caledoniae kylin [Mozuku], Power Fucoidan, Daiichi Sangyo) for at least 4 weeks was associated with a stabilization of quality of life scores and a reduction of proinflammatory cytokines (1L-1β, IL-6, TNFα). The reduction in IL-1β within the first two weeks was a prognostic factor for survival (Hazard ratio, HR: 0.08, 95% CI 0.007 to 0.588, P = 0.01) [52]. A double-blind, controlled RCT in metastatic colorectal cancer patients undergoing chemotherapy (n=54) found that fucoidan (4 g powder, MW 0.8 kDa, from *Sargassum hemiphyllum*, Hi-Q Marine Biotech) for 6

months improved the disease control rate (92.8% vs 69.2%, P = 0.026), but had no significant effects on overall response rate or survival [53].

These studies suggest that fucoidan supplementation is not harmful, and may improve treatment tolerability or survival in some cancer patients, but has minimal to no direct anti-cancer potency.

Anti-viral: Unclear clinical benefit

Polysaccharides play important roles in immune modulation, and glucans are known to enhance the effects of anti-microbial agents. Many bioactive polysaccharides, including fucoidans, have been shown to have anti-microbial properties. Fucoidan (6g daily from Kanehide Bio Co., Japan) was tested in in an open-label trial in patients with Human T-lymphotropic virus type 1 (HTLV-1) associated myelopathy/tropical spastic paraparesis (HAM/TSP) (n=13) for 6-13 months [54]. *In vitro*, fucoidan has been shown to inhibit cell-to-cell transmission of HTLV-1, **as fucoidan can prevent the viral attachment to cells**. Since this process is mediated by interactions of sulfated polysaccharides, the **antiviral activity of fucoidan is dependent on the degree of sulfation** [55]. Fucoidan treatment led to a 42.4% decrease in HTLV-1 pro-viral load, but had no effect on host immune cell frequencies or responses [54]. In an open-label trial testing fucoidan capsules (0.83g/day containing fucoidan from *Cladosiphon okamuranus* Tokida cultivated in Okinawa, Japan. 83% fucoidan content, 72% carbohydrates, 24% uronic acids, 8% sulfate, MW 21 kDa) in patients with chronic Hepatitis C (n=15) for 12 months, patients experienced a decrease in HCV replicon levels, and liver enzyme levels (serum alanine aminotransferase), but there was **no clinically detectable improvement** [56].

Skin aging: Potential minor benefit

Fucoidans have been incorporated into skin care products due to their anti-inflammatory and antioxidant properties. In hairless mice, topically applied fucoidan was shown to be protective against UVB induced skin photoaging by reducing neutrophil recruitment and associated inflammatory cytokine production (IL-1β) and oxidative stress induction [57]. In a company sponsored clinical study (n=20) in Australia, topically applied 3% w/w fucoidan cream (*Undaria pinnatifida* extract with 8% fucoidan [27.4% sulfate] or *Fucus vesiculosus* extract with 60% fucoidan [10.1% sulfate], 30% polyphenol from Marinova) was effective at **reducing erythema and transepithelial water loss after UV exposure** compared to placebo [1]. Use of the *F. vesiculosus* extract for 60 days also led to trends for reduced skin spots (in 50% of participants), increased skin brightness (in 65%), and improved wrinkles (in 45%). *In vitro* studies indicate that the extract can increase Sirt1 expression and has antioxidant properties, which may contribute to its protective effects. Another company sponsored placebo-controlled RCT

(n=94, average age 41) in Korea found that 400 mg of fucoidan containing capsules (MK-R7: Complex of 150 mg *Cistanche tubulosa* extract and 50 mg *Laminaria japonica* including echinacoside glycosides and fucoidan, Misuba RTech) increased hair density (23.29 n/cm^2 ± 24.26 vs 10.35 n/cm^2 ± 20.08, $p < 0.05$) and hair diameter (0.018 mm ± 0.015 vs 0.003 mm ± 0.013, $p < 0.05$) in people with mild to moderate patterned hair loss [58]. However, these effects appear to have marginally reached statistical significance, and it is unclear if the improvements are clinically meaningful.

Immunosenescence: Potential benefit

The ability to mount an effective immune response to a pathogen declines with age due to the rise of senescent immune cells. Consequently, elderly people tend to produce weaker responses to viral antigens in vaccines, and thus have reduced immunity. Adjuvants are often added to vaccines to boost immune responses in the elderly. In a placebo-controlled RCT in elderly adults in Japan (n=70, average age 87, 91% female), treatment with 300 mg of Mekabu fucoidan (derived from *Undaria pinnatifida,* Riken) for 4 weeks prior to receiving the flu vaccine **increased antibody titers for all 3 flu strains in the vaccine** [59]. The antibody titers were maintained for over 20 weeks after vaccination. Fucoidan treated patients also experienced a transient increase in natural killer (NK) cell activity, suggesting that fucoidan can help reverse some of the signs of aging-associated immunosenescence.

Mesenchymal Stem Cell (MSC) enhancement: Potential benefit (preclinical)

While the low bioavailability of fucoidan may limit its protective effects *in vivo*, pre-treatment of MSCs with fucoidan may enhance the protective and pro-angiogenic effects of MSC therapy. Fucoidan treated MSCs have been shown to be beneficial in a variety of preclinical models. Fucoidan (from Sigma) treatment enhanced cell survival, reduced oxidative stress, improved neovascularization, and enhanced functional recovery in a mouse model of hind limb ischemia [60; 61]. Fucoidan (from *Fucus vesiculosus*, Sigma) was also able to reverse cell senescence in MSCs exposed to p-cresol, which involved the regulation of FAK-Akt-TWIST signaling [62].

Safety: Well-tolerated with no adverse events in clinical trials, even at high doses. Possible risk for increased bleeding when used in combination with blood thinners.

Types of evidence:

- 17 clinical trials (various formulations of fucoidan)
- observational studies on fucoidan-rich seaweed consumption
- Numerous laboratory studies

Fucoidan intake, even at high doses, has been shown to be safe in clinical studies. Up to 4.05 g per day of fucoidan (in 150 ml from *Cladosiphon okamuranus* [Okinawamozuku], Marine Products Kimuraya Co., Ltd) has been tested in healthy volunteers for 2 weeks [40] and in cancer patients for 6 months [50] with no evidence of adverse effects. In all clinical trials, fucoidan use was **well-tolerated, not associated with an increase in adverse events**, did not induce significant changes on blood tests or vital signs, and exhibited no evidence of cytotoxicity. As a rich source of water-soluble fiber, fucoidan can promote bowel movements, and in one study a subset of patients (4/13) developed diarrhea that resolved upon discontinuation of fucoidan [54]. Due to its anti-clotting activity, although generally weak *in vivo*, it has **drug interactions with blood thinners**, such as warfarin (MSKCC). It is possible that the low incidence of adverse events is related to the low oral bioavailability, determined to be less than 0.6% in humans in a pharmacokinetic study [63], and that preparations with higher bioavailability may be associated with more side effects.

Although fucoidan has not been tested as a supplement in clinical trials longer than 1-year, long-term intake of fucoidan rich brown algae is associated with health benefits (i.e. Okinawa diet). In Japan, the daily intake of fucoidan from brown algae and other dietary sources is estimated to be about 400 mg/capita [44].

Sources and dosing:

Fucoidan is derived from brown algae and sold OTC as a supplement. The biological activity of the fucoidan can vary greatly depending on a variety of factors including: the species of brown seaweed from which it was obtained, the location the seaweed was grown, the time of year the seaweed was harvested, the method of extraction, the sugar content of the fucan backbone, and the level of branching of the backbone [2]. **The fucoidan content in brown seaweed is maximal in late autumn and early winter**, which is also the time when it has the highest degree of sulfation [64]. The most **important aspects for bioactivity appear to be the molecular weight and the degree of sulfation**. High molecular

weight fucoidans with high levels of sulfates tend to have the most bioactivity *in vitro*, however, low molecular weight fucoidans have much greater bioavailability *in vivo* [2]. In many of the commonly used extraction methods, particularly acidic hydrolysis, branching and sulfates are eliminated, which reduces the bioactivity. Extraction via gamma irradiation or enzymatic degradation is better at preserving the bioactive sulfate groups. **The optimal form of fucoidan for therapeutic use has not been established**, and is likely to vary for different disease indications based on the properties necessary for therapeutic benefit [65]. It is anticipated that in order to be a viable therapy, a low molecular weight formulation will need to be developed which contains a high proportion of the bioactive sulfate groups.

Due to the low bioavailability noted in various fucoidan preparations in clinical trials, there is **no clear evidence that currently available preparations of fucoidan supplements can elicit the types of benefits seen in preclinical studies**. Therefore, incorporating fucoidan rich brown seaweed, such as Kombu (*Saccharina japonica*), Wakame (*Undaria pinnatifida*), Hijiki (*Sargassum fusiforme*), Nori (*Pyropia tenera*), and Mozuku (*Nemacystus decipiens*), into the diet is likely the best currently available source of fucoidan. Brown seaweed is also rich in various minerals and other compounds with purported antioxidant and anti-inflammatory properties, which may act to increase the bioavailability of fucoidan and/or act synergistically. However, seaweed is rich in iodine, so very high consumption may increase the risk for thyroid cancer.

Research underway:

According to Clinicaltrials.gov, there are two active clinical trials for fucoidan. One is using radiolabeled fucoidan as an imaging agent for cardiovascular plaques (NCT03422055), and the other is testing the effect of fucoidan supplementation on quality of life in patients with non-small cell lung cancer undergoing chemotherapy (NCT03130829). The latter trial is sponsored by Hi-Q Marine Biotech.

More research is needed to determine the optimal structural properties and formulation of fucoidan for therapeutic use, and the development of more bioavailable formualtions.

Search terms:

Pubmed, Google: Fucoidan +

- Alzheimer's disease, Parkinson's disease, stroke, neurodegeneration, aging, lifespan, cardiovascular, cancer, diabetes, clinical trials, safety, bioavaialability

Websites visited for Fucoidan:

- Clinicaltrials.gov
- Drugs.com
- PubChem
- Memorial Sloan Kettering Cancer Center

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