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Review Article
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The Potential Use of Fucoidans from Brown Seaweed as a Dietary Supplement

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Introduction

The oceans of the world have always served as a nutrient source, whether from mollusks, fish or vegetation. The world's animal and human populations have always relied upon the sea for nutrition and sustenance. The value of the sea is becoming ever present as soil quality diminishes due to over farming, pesticide use and urban sprawl [1]. In addition, drought is becoming a predominant player in the lower yields offered by land farming [2,3].

Brown seaweed or kelp has been harvested around the world for centuries. It is perhaps best known for its use in Japan and other Asian countries as sea vegetables. In the United States, kelp experienced a general interest in the mid-60's with its inclusion in many household products (e.g. toothpaste, fertilizer, pharmaceutical excipients, thickening agents, etc.). Like any other nutrient source, manufacturing processes have continued to improve both the yield and the quality of the raw compound. One such development for brown seaweed is the identification and isolation of fucoidans [4,5].

Fucoidans are sulphated polysaccharides with a fucose backbone found mainly in brown seaweed and account for more than 40% of the dry weight of the algal cell walls. Fucoidans from seaweeds are heterogenic mixtures of structurally related polysaccharides, with differences in their backbone chains, as well as carbohydrate and non-carbohydrate attachments [4,5]. Their composition varies with the species, the season, the climate and the extraction method used to isolate them.

Potassium alginate, a byproduct of brown seaweed processing, has been used in cosmetics and the pharmaceutical industry for decades as excipients or thickeners [6]. It is just recently that brown seaweed and specifically, fucoidan, have been considered for inclusion in a dietary supplement. There are several excellent review articles on the chemical properties, structure and function of fucoidans in regard to food and pharmaceutical compounds [7-9], the current paper will review the scientific knowledge on brown seaweed and fucoidans as a dietary supplement. The main areas of discussion will cover cardiovascular health, gastro-intestinal health and joint health.

Materials and Methods

The literature selected for this review was obtained through database and Internet search engines and domains. All information was collected from peer-reviewed published literature, technical reports and books. Sources were selected based upon their quality of research and content. Only studies with an appropriate experimental design and valid measurements of presented data were used.

Results

Review of chemical properties and structure of fucoidans

Fucoidans are sulphated polysaccharides with a fucose backbone found mainly in brown seaweed. Isolation of a sulfated fucan (originally called fucoidin) from marine brown (Phaeophyta) algae (Figure 1) was

Figure 1: An example of brown seaweed.

reported in 1913 [10]. Fucoidan is now the name for these compounds according to IUPAC rules, but other names in use include fucan, fucosan and sulfated fucan [11]. Fucoidans are present in all brown algae that have been investigated and account for more than 40% of the dry weight of the algal cell walls. Fucoidans are present in only minor amounts in green algae (Chlorophyta), red algae (Rhodophyta) and golden algae (Xanthophyta) [12]. Sulfated fucans are also found in marine invertebrates (Echinodermata), namely sea urchins and sea cucumbers [8,9].

Fucoidans from seaweeds are heterogenic mixtures of structurally related polysaccharides [12]. Two different types of backbone chains have been described: (1) repeating (1-3) linked alpha-L-fucopyranose residues and (2) alternating (1-3) and (1-4) linked alpha-L-fucopyranose residues. Both chains have carbohydrate (L-fucopyranose, alpha-D-glucuronic acid) and non-carbohydrate substituents (sulfate and acetyl groups). The composition also varies with the season, the climate and the extraction method [12]. The reported molecular weights vary from 13 to 950 kDa [13].

Safety and toxicity of fucoidans

Seaweeds containing fucoidans have been used as foods such as sea

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vegetables for centuries. Those used in Japanese food include kombu (*Saccharina japonica*), wakame (*Undaria pinnatifida*), hijiki (*Sargassum fusiforme*) and mozuku (*Cladosiphon okamuranus*). Fucoidans from two species were tested for mutagenicity. Fucoidan from *Undaria pinnatifida* showed no mutagenicity up to 500 mcL/plate in the Ames test and inhibited the mutagenicity induced by 4-nitro-quinoline-1-oxide. In the bone marrow micronucleus test, the fucoidan did not change the micronucleated polychromatic erythrocyte percentage [14]. Fucoidan from the sporophylls of *Undaria pinnatifida* was tested for gene toxicity in the reverse mutation assay using four strains of *Salmonella typhimurium* as well as *Escherichia coli*, with and without metabolic activation, and did not cause any chromosomal aberrations. The same fucoidan was also administered to ICR mice in doses up to 2000 mg/kg body weight per day without increasing the frequency of micronucleated polychromatic erythrocytes in the bone marrow micronucleus test [15].

Animal toxicological studies demonstrated safety with the exception of an increase in clotting time with high doses. In an acute toxicological test in Sprague-Dawley rats, fucoidan from *Undaria pinnatifida* doses up to 1000 mg/kg body weight per day delivered orally for 28 days did not produce any toxicological changes. Twice that dose produced an increase in plasma ALT [14]. Fucoidan from the sporophylls of *Undaria pinnatifida* was also tested for toxicity in Sprague-Dawley rats. The fucoidan in a dose of 1350 mg/kg for 28 days did not have any toxicological changes [16]. Fucoidan from *Cladosiphon okamuranus* produced no toxicological changes when given to Wistar rats in a dose of 600 mg/kg body weight per day. However, a higher dose of 1,200 mg/kg increased clotting time [17]. The acute and subchronic (6 months) toxicity of fucoidan from *Laminaria japonica* administered orally was investigated in Wistar rats. No significant changes were observed with a dose of 300 mg/kg. However, doses of 900 and 2500 mg/kg increased clotting time [18].

Bioavailability of fucoidans

There is limited information regarding the bioavailability and pharmacokinetics of fucoidans. In general, high molecular weight molecules like fucoidan are not very absorbable. Irhimeh et al. [19] investigated the bioavailability of fucoidan using a monoclonal antibody methodology, similar to previously used with chondroitin sulfate by Barthe [20]. The authors concluded that small quantities of orally administered fucoidan may cross the intestinal wall as whole molecules probably by the process of endocytosis. Fitton provides a thorough review on fucoidan and states that the fate of fucoidan uptake is unknown and that research should be conducted on improving bioavailability [8]. This may be accomplished through nanoparticle technology. In a very eloquent design Huang and Lam constructed chitosan/fucoidan nanoparticles through a simple polyelectrolyte self-assembly method under ultrasonication at room temperature [21]. The objective of their study was to improve the bioavailability of curcumin, known for its water insolubility, but the nanoparticles could be used to improve fucoidan absorbability as well.

Potential health benefits

The use of fucoidans in the dietary supplement industry is relatively new. This review will cover areas related to cardiovascular health, gastro-intestinal health and joint health that can be supported through science and claims substantiation.

Cardiovascular health

Cardiovascular health has been one of the leading causes of death for over 50 years. In most cases, an improvement in diet and exercise can achieve a profound reduction in risk. However, for some individuals there is the need for pharmaceutical intervention. Many of these drugs possess adverse side-effects which at times may be more dangerous than the health condition itself. This generated a large interest in many natural therapies, one of which may be fucoidan supplementation. There are several potential physiological and biochemical processes that may benefit from fucoidan.

Atherosclerosis

Physiological risk factors to cardiovascular health include high blood pressure, elevated serum cholesterol levels and lipoprotein levels, elevated serum glucose levels and elevated fibrinogen levels. Briefly, cardiovascular disease is associated with a narrowing or "hardening" of the coronary arteries known as atherosclerosis. Atherosclerosis develops through the infiltration of fatty deposits into the wall of the artery resulting in plaque formation. Early developments of the condition include the adherence of monocytes and other leukocytes in the blood to the vascular cell wall, followed by their migration to the sub-endothelial space. The primary catalyst for this event is the presence of oxidized lipoprotein particles (ox-LDL) within the wall [22]. The ox-LDL provokes an inflammatory response, in which platelets adhere to the blood vessel walls and monocytes ingest ox-LDL to form foam cells. A lesion or fatty streak develops which is associated with smooth muscle cell proliferation and migration to the outer edge of the arterial wall, forming a fibrous, hard layer.

Fucoidan has demonstrated lipid lowering effects in hyperlipidemic animal models decreasing the concentrations of serum total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), while increasing the concentration of high-density lipoprotein cholesterol (HDL-C) [23]. In an experiment in which the animals were fed a high fat diet for 28 days to establish hyperlipidemia, fucoidan from *L.japonica*, was delivered by gavage in doses of 0.1, 0.2 and 0.4 g/kg for an additional 28 days. All three doses of fucoidan were effective in lowering lipid levels, but the middle dose appeared to have the largest effect. The benefits from fucoidan may have been mediated by an increase in levels of lipid metabolizing enzymes. In cultured adipocytes, fucoidan (from *F. vesiculosus*) induced lipoprotein lipase (LPL) and apolipoprotein C-II (ApoC-II) secretion in a dose- and time-dependent manner. Fucoidan also increased LPL mRNA and LPL protein expression. Further, LPL and ApoC-II secretion induced by fucoidan may be involved in regulating the clearance of plasma triglycerides. The actions of fucoidan were compared to those of heparin, which releases LPL in addition to increasing the intracellular transport and decreasing the degradation of LPL [24].

A rat model which examined the role of C-reactive protein (CRP) in the atherosclerotic plaques, reported that pretreatment of the animals with fucoidan (via injection) inhibited the increased uptake of oxidized low density lipoprotein (OxLDL) caused by CRP. CRP significantly increased OxLDL uptake by air pouch macrophages compared with human serum albumin. Fucoidan (Sigma, 10 mcg/ml), injected into the air pouch in the rat previous to treatment with CRP, inhibited the uptake by 61%. As OxLDL uptake by macrophages contributes to foam cell formation, fucoidan may have a role in helping to prevent atherosclerosis [25].

The binding of fucoidan and other polysaccharides to the main arteries were examined in 10 autopsy cases. Atherosclerotic lesions and non-atherosclerotic areas were analyzed. The percentage of the determined expression of the presence of specific binding sites for

the various probes was the lowest in the carotid and cardiac arteries, and the highest in the pulmonary artery. Pronounced quantitative differences between the normal and atherosclerotic arterial walls were noted for binding of fucoidan in the pulmonic and femoral arteries. The findings suggested that the expression of sugar receptors may be of importance in the development of atherosclerotic lesions in the coronary and carotid arteries [26].

Fucoidan from *Cladosiphon okamuranus* reduced lipid levels in a model of isoproterenol-induced myocardial infarction in rats [27]. The administration of isoproterenol (150 mg/kg, i.p. for 2 days) produced severe myocardial damage, high lipid peroxidation levels and elevated serum lipid levels. Fucoidan reduced the isoproterenol-induced increases in total cholesterol, triglyceride, and LDL-C. It also increased the concentration of HDL-C. Further, fucoidan reduced myocardial damage and peroxidation levels. In addition to the effect on lipid levels, fucoidan ameliorated the increase in serum enzymes (lactate dehydrogenase, creatine phosphokinase, aspartate transaminase and alanine transaminase) caused by "isoproterenol". In addition, it ameliorated the reduction in antioxidant enzymes such as super oxide dismutase and glutathione-S-transferase [27].

Blood clotting and tissue perfusion

Fucoidans from various seaweeds have demonstrated anticoagulant and anti-thrombotic activity in numerous studies. This activity was first reported for fucoidan isolated from *Fucus vesiculosis* in 1957, measured as inhibition of fibrin clot formation and antithrombin activity [28,30]. Current thinking is that fucoidan acts through direct inhibition of thrombin and/or indirect inhibition of thrombin through the activation of thrombin inhibitors (e.g. antithrombin and heparin cofactor II) [13,28]. Studies indicate that the anticoagulant activity of fucoidan may be influenced by the sulfate content and position, molecular weight and sugar composition [28].

Studies of the anticoagulant activity of fucoidans reveal considerable differences among those extracted from various species of seaweeds. In 1987, anticoagulant activities of fucoidans from nine brown seaweed species was tested and compared to the activity of heparin. Fucoidans from all nine species showed some ability to increase activated partial thromboplastin time (aPTT) and thromboplastin time (TT), but none affected antifactor Xa activity. The degree of aPTT and TT activity varied with the source of the fucoidan [29]. A report in 2007 cited anticoagulant activity measured by aPTT in 8 of 9 species of brown algae, with only 5 species displaying antithrombin activity in a platelet aggregation assay. Fucoidans inhibited thrombin effects but not aggregation due to thrombin receptor activating peptide (TRAP) or collagen. The thrombin-related effects were dose related and also differed in activity with the different sources of fucoidan [12].

The antithrombotic effect of fucoidan in vivo was measured using a mouse carotid artery thrombosis model with the injury induced with ferric chloride. A dose of 0.54 mg fucoidan/kg BW, administered intravenously, doubled the occlusion time. When compared to heparin, fucoidan was 2.3 times more effective. As *in vitro* assays tended to show comparatively stronger activity due to heparin, the authors speculated that the antithrombotic mechanism for fucoidan is different from that of heparin and that fucoidan may bind more effectively to heparin cofactor II [30].

The effect of fucoidan on platelet aggregation was explored in baboons administered fucoidan through continuous intravenous infusion (0.5 to 1.0 mg/kg/h). Treatment with fucoidan at the lower dose did not alter platelet aggregation or coagulation profile. However, the higher dose (1.0 mg/kg/h), delivered for 4 hours, resulted in nearly complete inhibition of ex-vivo platelet aggregation in response to thrombin, adenosine diphosphate (ADP) and collagen. This dose also caused an increase in PT from 18 to 65 s. The effects due to fucoidan were rapidly reversed following discontinuation of the agent. Platelet counts, fibrinogen levels, and fibrinogen degradation products remained within the normal ranges [31].

Plasminogen activator inhibitor-1 (PAI-1) is a primary endogenous inhibitor of tissue-type plasminogen activator (t-PA). PAI-1, which is mainly produced by the vascular endothelium, is an inhibitor of fibrinolysis, the physiological process that degrades blood clots. The effect of oversulfated fucoidan (OSF) derivatives on lipopolysaccharide (LPS)-induced release of PAI-1 antigen from cultured human umbilical vein endothelial cells (HUVEC) was studied [32]. Addition of LPS (10 micrograms/ml) enhanced the release of PAI-1 by HUVEC. The increased PAI-1 level was reduced to control level by the simultaneous addition of 10 micrograms/ml of OSF. Interestingly, the suppressive effect of native fucoidan was negligible. The authors also examined the molecular size effect of OSF, using 10-20, 20-40, and 40-60 kDa fragments. The result indicated that these fragments were effective as well as the 100-130 kDa form of OSF, hence suggesting an important role of the degree of sulfation. The suppressive effects of OSF and heparin on LPS-induced PAI-1 release may result from the inhibition of LPS binding to cell surface heparin sulfate proteoglycans (HSPG) [32].

Microvascular control and perfusion

Several experiments with isolated and intact hearts have demonstrated the preventative effect of fucoidan. In isolated rat hearts subject to no-flow ischemia followed by reperfusion, treatment with fucoidan (0.36 mg/mL blood) significantly reduced the leukocyte accumulation in both capillaries and venules ($p<0.05$). In addition, fucoidan significantly reduced the persistence of leukostasis in both capillaries and venules, indicating that it affected a transient adhesion process [33]. In a lamb heart model, fucoidan treatment resulted in better recovery of left ventricular function, coronary blood flow, and myocardial oxygen consumption after cold ischemia, despite a higher circulating white blood cell count [34]. The model used an isolated blood-perfused neonatal lamb heart which underwent 2 hours of cold cardioplegic ischemia with Fucoidan (30 mg/L) added at initial reperfusion. In a rat model, intravenous infusion of fucoidan significantly attenuated myocardial damage induced by ischemia and reperfusion [35]. The model used a 30-min myocardial ischemia followed by a 6 h reperfusion. Intravenous infusion of fucoidan (27 mcg/kg/min from 10 min before to 6 h after reperfusion) significantly attenuated the infarct size expressed as a percentage of the area at risk and as a percentage of the total left ventricular mass compared to those in the control group ($p<0.01$). Fucoidan also significantly decreased the MPO activity to 1/3 of that of the vehicle control group.

The effects of fucoidan on cerebral infarction size and neurological function after middle cerebral artery occlusion and reperfusion was examined in the rat. The animals were subjected to 4 h of occlusion and 24 h of reperfusion. Fucoidan (25 mg/kg) reduced cerebral infarction size by 50% and improved neurological function compared to control animals (both $p<0.05$). In addition, a trend toward decreased cerebral edema was demonstrated [36]. In a model of pulmonary reperfusion injury using rat lungs, fucoidan 20 mg/kg was infused before reperfusion. Fucoidan ameliorated the reperfusion-induced hyperpermeability, measured as a capillary filtration coefficient [37]. The renal vessel of the both rat kidneys were occluded with vascular clamps for 60 min before

reperfusion. Administration of fucoidan (10 mg/kg) by continuous i.v. infusion began before occlusion and continued for 165 minutes.

Treatment with fucoidan returned post ischemic renal blood flow to the initial levels, which was a significant increase compared to control animals [38]. Ischemic pig kidneys were reperfused in an *ex vivo* model with autologous blood with or without fucoidan (100 mg/L). Fucoidan caused a significant decrease in renal blood flow and increased vascular resistance. Histological examination revealed granulocyte emboli in afferent glomerular arteries in five of six fucoidan-treated kidneys and in one of six controls. Previous in vitro studies indicated that higher concentrations of fucoidan, similar to that used in this experiment, large granulocyte aggregates were induced by fucoidan, whereas slightly lower doses of fucoidan prevented l-selectin-dependent homotypic granulocyte adhesion [39]. Ischemia was induced in the cremaster (striated) muscle of mice by occluding the main feeding arteriole for 30 minutes [40]. Blood flow was then restored to allow for 60 minutes of reperfusion. Ischemia/reperfusion induced a rapid and significant increase in leukocyte rolling, adhesion, and emigration. Fucoidan (10 mg/kg, i.v.) given 25 minutes after the beginning of ischemia, completely prevented the increase in leukocyte rolling.

Joint Health

Joint health has been a leading category in the dietary supplement industry for decades. The main ingredient used in most products is glucosamine sulphate with a few other nominal competitors. There has been a modest decline in joint care supplements due to a lack of new candidates.The use of Fucoidan in a dietary supplement may ignite interest from the consumer either as a stand-alone product or within a matrix of ingredients.

Joint damage due to "wear and tear" is associated with a progressive deterioration in articular cartilage, resulting in pain, stiffness and difficulty with physical activities. The joints most likely to be affected are the knees and hips. As the cartilage is worn away, the bone forms spurs, areas of abnormal hardening, and pockets of fluid may accumulate. Pain results from the deformation of the bones and from fluid accumulation in the joints. The pain and inflammation associated with joint damage is associated with the migration of neutrophils to the joint and to the release of inflammatory mediators.

Several animal models of joint damage have demonstrated relief from pain and inflammation following injection of fucoidan. In an arthritis model induced by injecting zymosan into rat knee joints, a fucoidan preparation from *F. vesiculosus* significantly reduced cellular influx. Fucoidan was administered in doses of 15, 30, 50 mg/kg i.p., 1 hour after induction of articular inflammation. The dose of 30 mg/kg also ameliorated the loss in glycosaminoglycans caused by zymosan [41]. Fucoidan (20 mg/kg i.v.) given 20 minutes before the injection of zymozan into the tibio-tarsal joint of mice caused a decrease in inflammatory infiltrate into the joint [42]. In addition to the inhibition of neutrophil migration into the joint, there was a reduction in leukotriene B4 and prostaglandin E2 levels in the joint. The reduction in inflammatory mediators was associated with a reduction in pain in the joint [42]. An intravital video microscope was used to observe leukocyte-endothelial cell interactions in a mouse model of proteoglycan-indiced arthritis. Granulocytes and not lymphocytes were found to be the predominant cells recruited to the inflammed ankle. Injection of fucoidan (10 mg/kg) reduced the leukocyte-endothelial cell interactions and the number of adherant cells declined by approximately 60% [43].

The role of fucoidan in *Staphylococcus aureus*-triggered septic arthritis as explored in mice [44]. Animals treated with fucoidan, or an L-selectin blocking antibody, initially exhibited a less severe septic arthritis compared to control animals. The difference was both clinical and histopathological. However, in the later stages of the disease no significant differences in arthritis were evident compared to controls. High numbers of staphylococci were recovered from the kidneys of selectin-deficient mice, indicating a less efficient clearance of bacteria. The results demonstrated a dual role for selectins in S. aureus-induced arthritis: on the one hand, blockade of these selectins leads to less severe arthritic lesions in the initial stage of the disease; on the other, delayed recruitment of phagocytes decreases the clearance of bacteria.

A study that used a collagen-induced arthritis in mice explored the different effects of high, medium and low molecular weight fucoidans from *Undaria pinnatifida* [45]. The authors reported that the high molecular weight compound (100 kDa) enhanced the severity of the arthritis, increasing the destruction of cartilage, while the low molecular weight compound (1 kDa) had the opposite effect, which was to decrease the severity of the arthritis and the damage to the cartilage.

A small clinical study explored the use of a fucoidan preparation in subjects with osteoarthritis. In this study, 12 subjects were randomized to receive 100 mg or 1000 mg capsules (75 mg or 750 mg fucoidans), orally, for 12 weeks [46]. The test substance contained fucoidans from *F. vesiculosis* (85% w/w), *Macrocystis pyrifera* (10% w/w) and *Laminariajaponica* (5% w/w). The study endpoint was the average comprehensive arthritis test (COAT) score which is comprised of four subscales for pain, stiffness, difficulty with physical activity and overall symptoms severity. After treatment, there was a dose-response improvement in the subjects: the lower dose reduced the average COAT score by 18%, while the larger dose improved the score by 52%. The fucoidan preparation was taken safely without any adverse events attributed to the test product.

Gastrointestinal Health

There is growing interest in gut health due to studies related to gastrointestinal bacteria population dynamics afforded by probiotics. It is important to point out that gut health is a complex environment offering challenges related to acidity, motility and neural control. There are a couple of possible actions that fucoidan may offer for improving gastrointestinal health. These are related to mucosal lining and bacterial population management.

Neutrophil infiltration of intestinal mucosal surfaces is a common feature of many gastric diseases, including ulcerative colitis, Crohn's disease and infectious entercolitis. Fucoidan inhibited neutrophil trans-epithelial migration in the apical-to-basolateral direction as well as the basolateral-to-apical direction, in experiments conducted using cultured monolayers of the intestinal epithelial cells [47].

Inflammatory bowel disease (IBD) is a chronic condition characterized by acute flare-ups accompanied by an influx of leukocytes into the intestinal wall and subsequent release of inflammatory mediators such as TNF-alpha [48]. Leukocyte transmigration occurs in several steps, namely chemoattraction, rolling adhesion, tight adhesion and endothelial transmigration. Leukocyte rolling is mediated by the selectin family of adhesion molecules *in vivo*. The selectin family of adhesion molecules bind to glycoprotein ligands with sulfated and fucosylated carbohydrates. Fucoidan is known to inhibit selectin and has demonstrated the ability to inhibit leukocyte rolling in several different tissues. In a mouse colitis model of IBD, pretreatment with fucoidan (25 mg/kg i.v.) reduced mucosal damage and crypt destruction in the colon

caused by exposure to 5% dextran sodium sulfate (DSS). Fucoidan also reduced the colonic myeloperoxidase (MPO) activity in mice exposed to DSS. *In vivo* microscopy revealed that the dose of fucoidan used in the present study abolished TNF-alpha-induced venular leukocyte rolling and extravascular recruitment. These results demonstrated that fucoidan mediated leukocyte infiltration and tissue damage in experimental colitis. The data support the concept that fucoidan may have a beneficial effect in the treatment of inflammatory bowel disease.

Clostridium difficile is a gram-positive anaerobic spore-forming bacterium that is the most common cause of bacterial diarrhea. The main virulent factors of the bacteria are 2 large exotoxins, toxin A and toxin B. Toxin A causes mucosal disruption, epithelial cell death, inflammation and hemorrhagic enteritis. Leukocyte infiltration is implicated in the resultant release of inflammatory mediators, increase in vascular permeability and intestinal damage. In a model of mouse enteritis induced by Toxin A, there were increases in intestinal fluid volume/length ratios and ileal loop weight/length, as well as disruption of the mucosa. Fucoidan (25 mg/kg) injected via the ocular plexus 5 minutes prior to local challenge with toxin A, significantly prevented the effects of the toxin [49]. Fucoidan also significantly reduced toxin A induced myeloperoxidase (MPO) and adenosine deaminase (ADA) activities. MPO is a microbicidal enzyme present in the granules of neutrophils and its presence has been used as an index of neutrophil infiltration. ADA catalyzes the irreversible deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. ADA is thought to have an important role in acute inflammatory reactions and has been used as a biomarker for inflammation. Reductions in MPO and ADA may both be due to reductions in the infiltration by neutrophils [49].

Intestinal mucosal protection

Two animal studies indicate that fucoidan may reduce the gastric damage caused by non-steroidal anti-inflammatory drugs. In a rat model, aspirin given by gavage (400 mg/kg body weight) caused gastric ulceration, with gastric lesions characterized by disruption of the mucosal layer and increased serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) [50]. Animals were pretreated with fucoidan with a dose of 0.02 g/kg body weight, orally, daily for 2 weeks before the delivery of aspirin had reduced stomach lesions, reduced disruption of the mucosal layer and no increases in transaminases. Aspirin increased the levels of the pro-inflammatory cytokines, interferon (IL)-6 and gamma-interferon and decreased the level of the anti-inflammatory IL-10. Fucoidan reduced the effect of aspirin on IL-6 and IL-10 but had no effect on levels of gamma-interferon. These findings suggest that fucoidan may protect against gastric damage caused by aspirin. In another rat model, gastric damage and an increase in myeloperoxidase (MPO) were induced by indomethacin, 20 mg/kg, via intragastric administration. Fucoidan (Sigma, 25 mg/kg, i.v.) prevented the gastric lesions, the increase in MPO activity and the infiltration of neutrophils. Indomethacin also caused an increase in gastric epithelial expression of iNOS which was positively correlated with gastric damage [51].

There is evidence that fucoidan may have an effect on *Helicobacter pylori*-induced ulcers. Fucoidan (from *Cladosiphonokamuranus*) inhibited *H. pylori* attachment to porcine gastric mucin *in vitro* at pH 2.0 and 4.0. In an *in vivo* model with Mongolian gerbils, fucoidan reduced the gastritis caused by *H. pylori*as well as reducing the prevalence of *H. pylori* in the infected animals. Fucoidan was given in doses of 0.05 and 0.5% in the drinking water, 3 days before inoculation and then throughout the experiment. Six weeks after inoculation, fucoidan had suppressed the gastritis in a dose-dependent manner and the higher dose had reduced colonization of the bacteria by 80%. Timing appeared to be important, as treatment with fucoidan 2 weeks after inoculation of *H. pylori* did not provide any benefit. The authors of the study indicated that fucoidan may help prevent *H. Pylori's* infection [52].

Discussion

The current paper reviews the potential of brown seaweed fucoidan in the dietary supplement industry. There is a solid basis for the basic understanding of fucoidan to suggest potential within the cardiovascular, joint and gastrointestinal health categories. The most striking condition of benefit appears to be cardiovascular health. While heart health is influenced by a multitude of factors and processes, there is considerable evidence showing the possible benefit of fucoidan in the regulation of blood flow, lipid peroxidation and inflammation.

Gastrointestinal health seems to be the second area that may benefit from fucoidan supplementation. There is moderate research showing some positive influence on bacterial health although more work is needed regarding those bacteria known to be of benefit. It is unclear whether fucoidan would work synergistically or separately in this regards. And, joint health is the third and last category that may prove of interest. It seems reasonable from research to date that fucoidan may be helpful for dampening down the inflammatory cascade and the degradative pathways. However, the data is conflicting in some cases which suggest further research is necessary before any final assessment.

In conclusion, fucoidan from brown seaweed appears to be another product of the sea that can be of potential use within the dietary supplement industry. The long use within the Asian countries and the documented safety profile offers some assurance as to safety. While there is limited data from clinical trials of substantial power, it does appear from the data published that fucoidan may be the next new ingredient.

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