Macroalgal Fucoidan Extracts: A New Opportunity for Marine Cosmetics

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ABSTRACT: *This article explores the bioactivity and historical applications of macroalgae with a particular focus on fucoidans, as well as outlines the research underlining their growing use in nutraceuticals and discusses their potential in novel cosmetic formulations.*

Macroalgae and macroalgal blends have been included in cosmetic formulations for decades. Used as emollients, skin conditioning agents and viscosity-controlling ingredients, macroalgal products have benefited from their inherent stability, physical and bioactive properties, and natural marine source. In the development of spa products particularly, macroalgae have played a major role, whether as seaweed wraps, pastes of milled macroalgae, or in Irish hot seaweed detox baths.[1]

In addition to their cosmetic role, macroalgae have long provided mankind with sources of food and medicine. Their extracts such as agar and carrageenan have been used for nutritional and nutraceutical benefits and have provided the impetus for their inclusion in successful cosmetic formulations.

This article explores the bioactivity and historical applications of macroalgae with a particular focus on fucoidans—sulfated polysaccharides currently emerging as popular nutraceutical ingredients. The article will outline the research underlining the growing nutraceutical use of fucoidans and discuss the potential for these natural ingredients to be used in the development of novel cosmetic formulations.

A Natural Diversity

Macroalgae make an excellent food supplement, being nutrient and micronutrient dense, with protein yields exceeding 30% in some cases. Macroalgae also contain all the essential amino acids, omega-3 lipids and soluble fiber,[2] as well as a wide variety of bioactives including lipid-modulating, blood pressure lowering and glucose metabolism-modifying compounds.[3]

> Fucoidan fractions, alginates and phloroglucinols isolated from marine algae have enzyme inhibitory properties.

Oral ingestion of seaweed was a popular Victorian remedy for weight loss and considered to be an effective topical treatment for scrofula or mycobacterium infection of the skin, in addition to arthritis, sprains and bruises, and as embrocations for the "limbs of rickety children."[4] Such recommendations can be traced back through the ages to Gerard's *On the History of Plants*[5] published in 1633 and further back to ancient texts such as that by the Greek, Pliny the elder,[6] who wrote:

> *But it is the phycos thalassion, or sea-weed, more particularly, that is so excellent a remedy for the gout … . Used before it becomes dry, it is efficacious as a topical application not only for gout, but for all diseases of the joints … .*

There are several traditional Chinese medicines that include macroalgae such as "concoction of the Jade flask," which includes *Ecklonia* and *Sargassum* and is used to treat goitre (iodine deficiency).[7] Today, in the Western market, there are traditional nutraceuticals available such as kelp granules, and there is also an increasing number of novel products containing either whole macroalgae or fucoidan extracts. The preparations can help to maintain skin health in a number of ways, including the supplementation of essential micronutrients.[3]

The term *macroalgae* refers to a diverse family of marine plants. These can be divided into three main groups classified as *Phaeophyta* (brown), *Rhodophyta* (red) and *Chlorophyta* (green). Readers may be familiar with the very long brown seaweeds such as *Macrocystis* that make up kelp forests, in addition to the smaller, commonly eaten red seaweed *Porphyra* (Nori) or green seaweed *Ulva* (sea lettuce). The bioactivity of macroalgae is equally as diverse and includes anti-viral properties, lipid-lowering activity, heavy metal and organic toxin elimination, enzyme inhibition, growth factor modulation and even anti-cancer activity.[8]

The active components of macroalgae are varied as well, including bioactive carbohydrates such as fucoidan and laminarin, pigments such as polyphloroglucinols and fucoxanthin,[9–12] and minerals, including iodine. Many of these are generally known to have antioxidant qualities and contribute to the antioxidant nature of aqueous and nonaqueous extracts. Glutathione, an antioxidant sometimes used as an orally delivered skin whitening agent, is a constituent of all macroalgae with some species containing as much as 3,082 mg/100g.[13]

Additionally, omega-3 fatty acids such as stearidonic acid and hexadecatetraenoic acid are found in edible marine algae such as *Undaria pinnatifida* and *Ulva*, contributing up to 40% of the plants' total fatty acid content.[14] Fucoidan fractions, alginates and phloroglucinols isolated from marine algae have enzyme inhibitory properties against hyaluronidase, heparanases, phospholipase A2, tyrosine kinase and collagenase expression.[15–19] Also, profound anti-viral activity against coated viruses such as herpes and HIV is exhibited by the sulfated polysaccharides found in macroalgae.[20,21]

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Supplementing

The most common use of whole macroalgae in the current nutraceutical market is as iodine supplements. Iodine is essential for formation of thyroxine (T_4) and triiodothyronine (T_3), hormones essential for regulating the metabolic rate, body heat, and energy.[22] It is important for manufacturers to consider the iodine levels in products since concentrations vary widely in the various species, from relatively low levels in *Porphyra* and *Undaria* (up to 50 mcg/g), to extremely high levels (1,000s of micrograms/g) in some of the kelps.[23]

The upper limit for intake is 300 mcg/day, and the upper limit for toxicity is 1,000 mcg/day. There are also instances where high iodine levels are desirable: the non-radioactive iodine in macroalgae inhibit radioactive iodine uptake, and the polysaccharide components assist in the chelation and elimination of radioisotopes.[24] Sodium alginate from *Sargassum* reduced strontium absorption when added to bread at 6% level, while alginate syrup has a more rapid action.[25]

While iodine is an important and often neglected essential trace element, the benefits of ingesting macroalgae extend to general detoxification. Dioxins are common organic toxins that can accumulate in tissues. Ingestion of *Porphyra* has been shown to increase the rate of excretion of dioxins in animal experiments.[26] This detoxification activity via oral ingestion of whole macroalgae is boosted by the additional micronutrient and immunomodulating effects of the bioactive carbohydrates, pigments and omega-3 lipids found in the plants. Whole *Undaria* macroalgal supplements have been shown to lessen the effects of herpes infections,[27] and ingestion of macroalgae as a regular part of the diet appears to have many health benefits including inhibition of cancer[28] and a lower incidence of allergic rhinitis.[29]

Fucoidans

Fucoidan or *fucan* is a generic term for a class of bioactive carbohydrates found only in brown marine macroalgae and echinoderms. These polysaccharides have a high-fucose polymer backbone; are usually highly branched—in algae, whereas echinoderm fucoidans contain linear structures; and are both sulfated and acetylated.

Extraction methods for fucoidan vary in the literature but it is possible to produce high molecular weight materials that can be fractionated in a controlled fashion to produce lower molecular weight derivatives. Levels of sulfation and acetylation also can be controlled that will enable creation of new substances with increased efficacy. Pure fucoidan extracts are generally off-white or brown soluble powders with no strong odor or taste (see **Figure 1**).

Figure 1. Fucoidan extracted from Tasmanian **Undaria pinnatifida**

Fucoidans are sometimes considered to be plant homologues of the mammalian compound heparin. While the sugar backbone structure of heparin is different, it also is highly sulfated. Both fucoidans and heparins exhibit an effect on the coagulation cascade[30,31] and share other common bioactivities such as the potentiation of growth factor activity.[32] The two families of polysaccharide, however, are different. For example, both fucoidan and heparin exhibit anti-proliferative effects on vascular smooth muscle but the activity is via subtly different mechanisms.[33]

Each brown macroalgae contains its own specific fucoidan.[34] The molecules tend to vary in their natural sugar composition, molecular weight and levels of sulfation. Comparative studies on fucoidans from different sources recently were carried out, illustrating subtle but important targets for activity.[35]

Fucoidans can both inhibit and promote enzymes. A marked example of inhibition is that of phospholipase A2 (PLA2) in snake venoms.[36] Snake venom PLA2 is a toxin that causes muscle necrosis in the snake's prey. The mammalian homologue PLA2 is an important part of the eicosanoid cascade and is partly responsible for the regulation of prostaglandin production. The latter are inflammatory mediators important in many conditions, from atherosclerosis to neural degenerative diseases.[37]

Bioactivity in Fucoidans

Marinova has designed a solvent-free coldwater process to extract fucoidan and is currently developing extracts from a range of brown macroalgae species sourced from Tasmania, Australia; Nova Scotia, Canada; The Kingdom of Tonga; and Patagonia, South America. Traditionally the extraction of fucoidan has relied on ethanol precipitation and high temperatures, resulting in extracts with unpredictable molecular weights and solvent residue; however, the new process yields extracts with defined molecular weight ranges and high levels of purity. The company's research, described later, has focused on a range of indications and has demonstrated that, much like heparin, fucoidans have relevance to an array of diverse applications.

The company's initial research, in partnership with the University of Chicago, investigated the antiherpetic activity of fucoidans. A small clinical trial involving 17 patients demonstrated the significant efficacy of Tasmanian *Undaria* fucoidan in the inhibition of both normal and acyclovir-resistant strains of HSV-1 and HSV-2.[27]

In recent unpublished experiments, fucoidan extracts were assessed for α-glucosidase activity. The action of α-glucosidase inhibitors is to delay carbohydrate absorption, reducing the post-prandial increase in blood glucose, making them a suitable treatment for noninsulin dependent diabetes mellitus.[38] *Undaria* and *Fucus vesiculosus* fucoidans were shown to be particularly efficacious by inhibiting the activity of α-glucosidase by 50% at a concentration of less than 20 μg/mL, in comparison with luteolin, which inhibited α-glucosidase activity at approximately 18 μg/mL.

Fucoidans were shown to exhibit excellent immunomodulating activity, having a modulatory role on various biomarkers affecting the inflammatory and immune response. Fucoidans have also been demonstrated, in animal trials, to inhibit the development of tumors.[39,40] In some instances, immunological effects appear to be governed by molecular weight. Mice fed on a high molecular weight fucoidan (2-3x10^5) from *Cladosiphon okamuranus*, at a level of 5% in the diet, exhibited increased T cells while lower molecular weight fucoidans from the same source had no effect.[41]

This variability of activity led the company to further investigate the uptake of fucoidan into the blood serum after oral ingestion. Although it was unknown whether absorption or uptake by the gut lymphatic system occurred, evidence that other high molecular weight sulfated polysaccharides, such as chondroitin sulfate, are absorbed whole in small amounts in the small intestine[42] led researchers to postulate that serum uptake of fucoidan would occur similarly. In a clinical study, a low but significant serum uptake of a high molecular weight *Undaria*-derived fucoidan was measured using a novel antibody technique.[43]

To summarize the methods used, healthy human volunteers of either sex, aged 20–46 years (average 29), were divided into three groups. The first (n = 6) ingested 3g of guar gum as placebo. The second (n = 6) ingested 3g of whole *Undaria* containing 10% fucoidan w/w and the third group (n = 40) ingested 3g of 75% fucoidan w/w daily for 12 days.

Figure 2 illustrates the relative amounts of free fucoidan in the serum for each group. The effect was only significant when 75% fucoidan was ingested, although the increase could also be seen in the "whole *Undaria*" group (see **Figure 2**). In addition, the researchers were able to demonstrate a small but measurable increase in fucoidan or its breakdown products in urine.

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This study confirmed that systemic effects can be attributed to serum uptake, even from a high molecular weight fucoidan. The company has recently developed a low molecular weight standardized fucoidan from Nova Scotian *Fucus vesiculosus* to hopefully maximize this uptake. In a follow-up clinical study by the company, the effects of orally ingested *Undaria* fucoidan on stem cells was investigated.

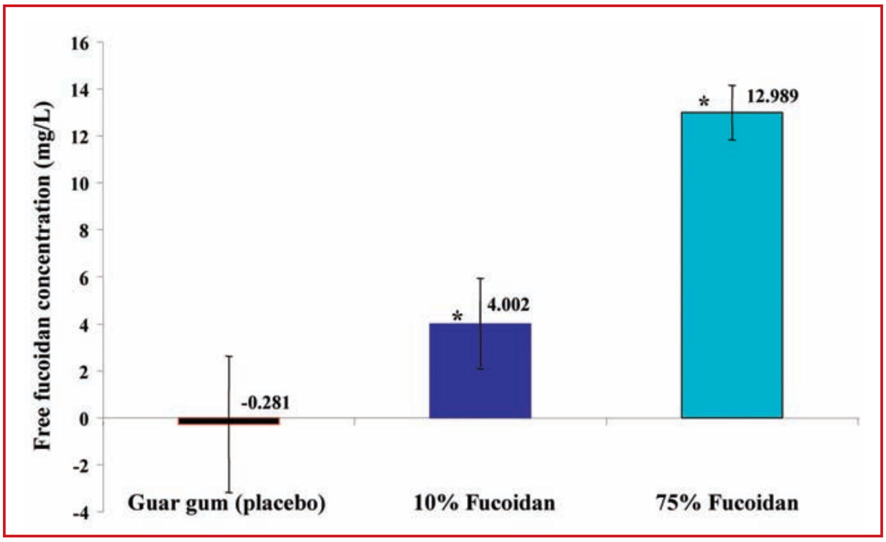

Figure 2. Concentration of free fucoidan in blood plasma (median) at 4, 8, and 12 days for each group (placebo, 10% fucoidan w/w, and 75% fucoidan w/w); ± 95% confidence intervals; * p-value < 0.05 (ANOVA).

Previous research has shown that intravenous fucoidan has a pronounced and extended mobilizing effect on a class of stem cells that circulates in the blood. These cells are called haemapoietic stem cells (HPCs) and they give rise to immune cells and potentially other cell types in the body. A sticky receptor on the stem cells called CXCR4 helps the cells to settle wherever they are required by adhering to the chemokine stromal derived factor-1 (SDF-1).

After ingestion of *Undaria* fucoidan, a profound increase in the sticky receptor CXCR4 occurred on the cells, in addition

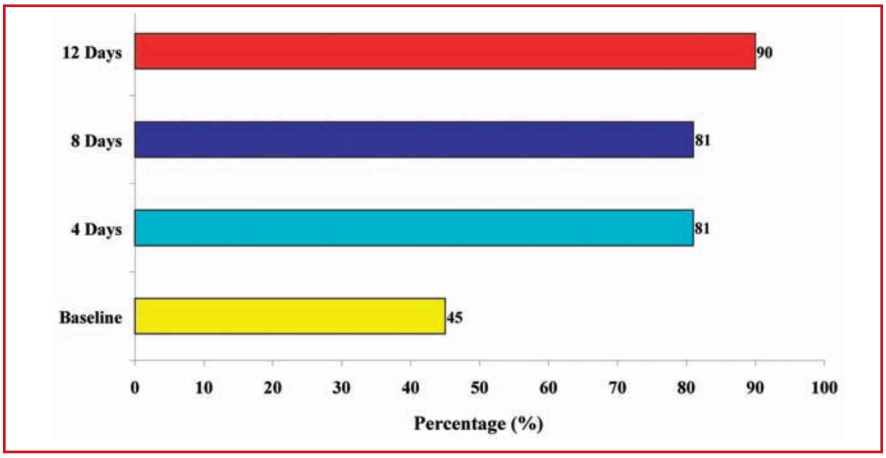

Figure 3. Serum uptake of fucoidan

to a significant increase in the total numbers of HPCs. This was accompanied by healthy changes in cholesterol levels, and an increase in the immune regulating cytokine interferon gamma.[44]

Stem cells are a popular topic in health today. Stem cell technology is creating advances in regenerative therapies in which damaged or diseased organs are given a new lease on life with infused stem cells. The significant effects of orally ingested fucoidan suggest potential for rejuvenation nutraceuticals designed to give the body a boost of immune function.

Fucoidans in Nutraceuticals

With a growing body of related research undertaken by private companies and research institutes in Japan, Korea and the United States, fucoidans are attracting increasing interest from nutraceutical formulators. Increasingly touted as the active component of edible seaweeds such as *Laminaria japonica (kombu)* and *Undaria pinnatifida (wakame)*, fucoidans can be used in formulations ranging from beverages to tablets. Like their colloidal cousins, alginates and carrageenans, fucoidans are relatively stable molecules.

In Korea, products such as Fucowell, a fucoidan-containing beverage, are increasing in popularity and in the United States, fucoidans are being integrated into immune-boosting and anti-inflammatory formulations as well as in nutritional beverages and functional foods such as those produced by Takara in Japan, or Mannatech in the United States.

With the development of low molecular weight fucoidans, Marinova will be initiating a set of clinical studies in 2007 specifically focused on investigating the immunomodulatory and anti-inflammatory properties of fucoidans, currently of interest to nutraceutical developers. The trials will aim to underline the relevance of fucoidans as complements to other ingredients such as glucosamine.

Fucoidans as Novel Cosmetic Ingredients

Throughout the past 20 years there has been a growing body of in vitro research focused on the bioactive properties of fucoidans. Many of these studies have focused on the potential for fucoidan as a cosmetic or cosmeceutical ingredient. The key focus of this research has been on the inhibitory effects of topically applied fucoidan on aging and photo-damaged skin. Relevant research papers have focused on the following activities:

1. Increasing dermal fibroblast numbers and matrix production;[45]
2. Inhibition of matrix metalloproteases (collagenase) and the serine protease elastase;[45]
3. Contraction of fibroblast-populated collagen gels, increasing integrin expression on fibroblasts;[46]
4. Increased skin thickness and elasticity in clinical trials;[47]
5. Modulation of growth factor activity;[31]
6. Inhibition of inflammation;[48] and
7. Inhibition of tyrosinase.[49]

Fucoidan acts to enhance dermal fibroblast proliferation and deposition of collagen and other matrix factors.[45] Matrix metalloproteases, which modulate connective tissue breakdown, are inhibited by low molecular weight fucoidan due to increased association with their inhibitors. In addition, the serine protease leukocyte elastase was inhibited, which protected elastic fiber network in human skin cultures.[46] *Undaria*-derived fucoidan inhibited the enzyme hyaluronidase,[15] as did a smaller *Sargassum*-derived fucoidan.[27] Tyrosinase also is inhibited by fucoidan fractions, indicating potential for inclusion as a whitening agent.[49]

Fujimura initially demonstrated that a fucoidan extract of *Fucus vesiculosus* (up to 30,000 MW) promoted fibroblast-populated collagen gel contraction and that the promotion of the gel contraction was due to the increased expression of integrin alpha2beta1 on the surface of the fibroblasts.[46]

A clinical study followed in which a gel formulation with 1% of the fucoidan was applied topically to human cheek skin twice daily for five weeks. A significant decrease in skin thickness measured by B-mode ultrasound was elicited, as was a significant improvement in elasticity measured with a Cutometer as compared with controls.[47] It appears that the activity in skin is in part modulated by growth factor potentiation. Heparin, the mammalian analogue for fucoidan, is an essential cofactor for particular growth factor activities, including that of fibroblast growth factor.

Marinova observed, in an unpublished study, that crude fucoidan isolated from *Undaria* also was able to potentiate fibroblast growth factor activity in vitro, at concentration levels similar to heparin. Transforming growth factor beta (TGF beta) is an important regulator of wound healing. O'Leary et al demonstrated that concentrations >1mg/mL of fucoidan were able to modulate the activity of inhibitory effects of TGFb1 in a tissue culture model, increasing the migrating of cells into wounded defects, reaching normal levels at 10mg/mL.[32] These results using a relatively unrefined fraction of fucoidan indicate a promising future for research into both cosmetic applications and pharmaceutical applications such as wound healing.

Fucoidan is also an effective inhibitor of CXCR4 and inhibits the accumulation of eosinophils in models of allergic skin inflammation.[48] Topical heparin is useful as a treatment in burns,[50] where modulation of the CXCR4 interaction may result in superior healing.[51] Fucoidan has potential as a topical and oral anti-inflammatory choice for cosmetic aftersun, allergic skin condition-soothing products, or speciality postsurgical products to inhibit eosinophilia. Fucoidan has greater stability than heparin, and is a plant product, conferring certain advantages.[52]

No data is available to date on the penetration of fucan fractions into the skin. Heparin, however, is formulated into topical lotions for the treatment of bruises where it acts as a fibrinolytic agent. It has demonstrable penetration,[53] which could potentially be mimicked by similar formulations using fucoidan fractions of comparable molecular weight.

Toxicity is always a consideration for any nutraceutical or cosmetic ingredient. Fucoidans can be considered to be a dietary fiber and are nontoxic in cell culture. There were no toxicological changes observed in rats given up to 300mg/kg orally of fucoidan from *Laminaria japonica*; anticoagulant effects were observed at doses of 900 to 2,500mg/kg, but no other signs of toxicity were noted.[54] Marinova has undertaken a safety trial in cancer patients in Australia and demonstrated that ingestion of up to 6g per day of *Undaria* containing 10% w/v fucoidan has no observable side effects. This study is currently unpublished.

Formulating with Fucoidan

Fucoidans are, in essence, natural aqueous extracts of marine macroalgae. A number of these extracts are already INCI listed and available for use in cosmetic products, as outlined in the **Table 1**.

As natural marine products, these extracts are ideal for inclusion in cosmetics. But how easy are they to formulate? Fucoidans are effectively water-soluble and create relatively nonviscous solutions in water or dilute salt solutions. Thus, in contrast to alginates or agar, they will not add significant body to formulations. Generally, fucoidans are heavily sulfated and thus anionic, which should be taken into account during formulation. Since they can be formulated in many different molecular weights and from several different source macroalgae, it is difficult to give an indicator for viscosity. In one example, viscosity of a high molecular weight *Undaria* derived fucoidan ranged from ~4.5cP in a 1% solution, to ~40cP in a 5% solution. Bioactivity for fucoidan may occur in 1mg/mL range, indicating formulation concentrations at around 0.1%–1% level, depending on other factors such as molecular weight.

The use of fucoidan also sits well with the recent trend for "beauty from within" nutraceutical formulations and provides the opportunity to offer a cosmetic solution from a systemic, as a well as a topical approach.

Table 1. INCI listing of macroalgal fucoidan extract functions

Macroalgal Species	CAS Number	INCI Listing Functions
Laminaria japonica	223751-72-2	Skin protecting
Ascophyllum nodosum	84775-78-0	Skin conditioning
Fucus vesiculosus	84696-13-9	Soothing, smoothing, emollient, skin conditioning
Undaria pinnatifida	223751-81-3	Skin protecting
Durvillea antarctica	223749-87-9	Skin protecting
Macrocystis pyrifera	---	Viscosity controlling

Conclusion

Fucoidans are interesting nutraceutical ingredients with significant potential for topical cosmetic formulations. Purified fractions can be easily incorporated into creams and lotions, providing cosmetic antiaging benefits such as inhibition of matrix enzymes and anti-inflammatory activity, in addition to increasing numbers of dermal fibroblasts and collagen tightness. As nutraceutical ingredients they offer unique opportunities in immunomodulation and rejuvenation.

Sourced from some of the most pristine waters in the world, fucoidans combine excellent bioactivity, physical protective properties and a natural organic source, thus bringing together the best elements of both science and marketability.

While macroalgae remain a staple of the spa industry, fucoidan-rich macroalgal extracts have a growing role to play in the nutraceutical market and strong potential for commercial success in cosmetics.

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