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Review

Preparation, Physiological Activity and High-Value Applications of Fucoidan

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Abstract

Fucoidan, a sulfated polysaccharide predominantly derived from brown algae, has garnered significant research interest due to its diverse biological activities and potential biomedical applications. This review systematically examines both established and novel extraction methods for fucoidan. Traditional techniques, including hot water, acid, and alkaline extraction, are summarized, alongside emerging approaches such as enzymatic hydrolysis, ultrasound-assisted, microwave-assisted, and subcritical water extraction, which demonstrate enhanced efficiency and yield. The paper further synthesizes the extensive research on the compound's multifaceted physiological functions, highlighting its immunomodulatory, anti-tumor, antioxidant, anticoagulant, lipid-lowering, and antiviral properties. These findings collectively underscore the critical relationship between fucoidan's structural characteristics—influenced by its monosaccharide composition, molecular weight, and sulfation pattern—and its resultant bioactivities. The conclusion affirms fucoidan's substantial value and broad applicability, particularly within the biomedical sector, for advancing health and therapeutic strategies.

Keywords: fucoidan; preparation method; physiological activity; high-value application

1. Introduction

Polysaccharides are macromolecules composed of numerous monosaccharide units linked by glycosidic bonds, resembling long chains of sugar blocks[1]. Fucoidan, first discovered by Keeling in 1913 [2], is also referred to as fucoidin, fucoidan sulfate, or sulfated fucan. It is primarily found in the cell walls and mucilage of brown algae such as kelp, wakame, and cuttlefish weed. Fucoidans represent a class of fucose-rich, sulfated heteropolysaccharides, generally consisting of a backbone formed by α -linked L-fucopyranose units, variably substituted with groups such as sulfate, acetate, galactose, xylose, mannose, and glucuronic acid. The chemical structures of fucoidans are heterogeneous and species-specific, varying significantly across different types of brown algae. However, most fucoidans commonly feature (1 \rightarrow 3)-linked α -L-fucopyranosyl residues, and in some cases, both (1 \rightarrow 3)- and (1 \rightarrow 4)-linked α -L-fucopyranosyl linkages have been observed [3]. According to the International Union of Pure and Applied Chemistry (IUPAC), the standardized term for this compound is "fucoidan." Fucoidan is predominantly found in brown algae from temperate and cold-water regions, including China, Japan, Korea, Northern Europe, and North America. Variations in algal species and regional growth conditions can lead to differences in fucoidan structure and composition. Sargassum spp. are considered a major source of fucoidan, though it has also been identified in over 70 other brown algal species, including Analipus nodosum, Ascophyllum nodosum, Caulerpa racemosa, Chorda filum, Dictyota dentyalis, Fucus distichus, Hizikia fusiforme, Kemanilla crassifolia, Laminaria hyperborea, Padina gymnospora, Sargassum stenophyllum, and Undaria pinnatifida [4]. The properties and efficacy of fucoidan are closely influenced by the species

of seaweed from which it is extracted, and various factors contribute to its distinct physiological effects, such as immunomodulation, anti-tumor effects, antioxidant activity, and antiviral properties. Interest in marine-derived fucoidan is growing rapidly due to its diverse bioactivities and potential health benefits, and innovative research continues to emerge in fields including pharmaceuticals, the food industry, and cosmetics. Therefore, this review summarizes current preparation methods—including the development of new extraction techniques such as enzyme-assisted, ultrasound-assisted, microwave-assisted, and subcritical water extraction that build on basic methods like hot water extraction, acid extraction, and alkaline extraction—explores the wide range of physiological functions of fucoidan, and highlights its application in high-value products. We hope this work provides valuable insights for future research and product development.

2. Preparation Method of Fucoidan

The extraction of fucoidan aims to maximize yield while preserving its structural integrity. The fundamental extraction workflow is illustrated in Figure 1. Different extraction techniques are suited to different contexts—for instance, certain methods are more appropriate for laboratory-scale research, while others are optimized for industrial-scale production. Therefore, selecting an efficient extraction method should be based on the specific objectives and operational requirements.

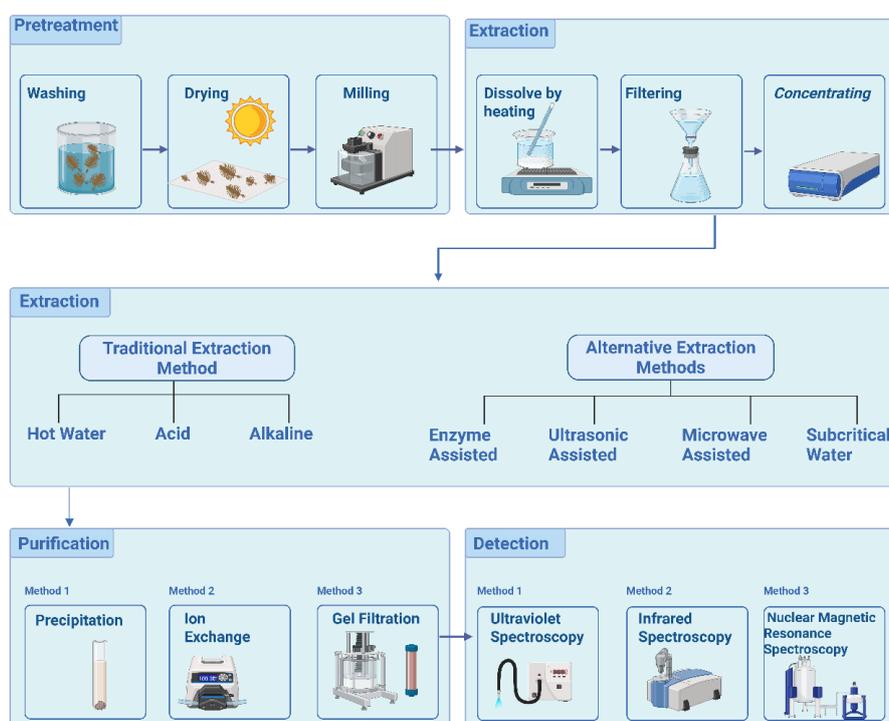


Figure 1. Process flow diagram of fucoidan.

2.1. Traditional Extraction Method

Despite limitations in efficiency and purity, traditional methods (e.g., hot water, acid, alkaline extraction) offer mild and safe operational advantages. These characteristics make them a valuable and often irreplaceable choice for non-demanding purity applications.

Conventional extraction methods for fucoidan demonstrate distinct advantages and limitations in terms of efficiency, product quality, and operational requirements. Hot water extraction operates under mild conditions (60-100°C, neutral pH, 1-8 hours) that effectively preserve the structural integrity and biological activity of polysaccharides, though the extracts typically contain significant co-extracted impurities such as proteins and pigments, necessitating additional purification steps [4,5]. In contrast, acid extraction employing hydrochloric acid at approximately 65°C demonstrates higher efficiency in dissolving fucoidan and yields products with elevated sulfate content; however,

the acidic environment inevitably induces polysaccharide depolymerization, leading to reduced molecular weight and compromised bioactivity. Alkaline extraction utilizing sodium hydroxide solutions (pH 10, 2-10 minutes) effectively disrupts algal cell walls to enhance polysaccharide release, yet the strongly basic conditions demand precise control and immediate neutralization to prevent structural degradation [9]. Each method presents unique value: hot water extraction provides optimal bioactivity preservation, acid extraction maximizes sulfate group retention, while alkaline extraction offers superior processing efficiency. The selection of appropriate methodology depends on the target application requirements, whether prioritizing bioactivity, sulfate content, or production efficiency. Future development should focus on integrating complementary approaches - combining hot water's mild conditions with acid/alkaline efficiency while employing protective additives and assisted technologies to balance yield, purity, and bioactivity for industrial applications.

2.2. Alternative Extraction Method

Recent advancements in green extraction technologies, such as enzyme-, ultrasound-, microwave-, and subcritical water extraction, have significantly improved the efficiency of fucoidan recovery while reducing environmental impact. These improvements pave the way for its broader application across multiple industries [10].

2.2.1. Enzymatic Extraction

Enzyme-assisted extraction (EAE) utilizes specific enzymes to catalyze the breakdown of algal cell walls, thereby facilitating the release of polysaccharide components. This method operates under mild conditions, minimizing structural damage to the polysaccharides and effectively preserving their native conformation and biological activity [11]. As such, it has emerged as the optimal choice for balancing extraction efficiency and activity retention, thus being particularly well-suited for developing high-value-added fucoidan products.

The fucoidan content obtained through EAE varies widely, ranging from 24.7% to 52.1%, and the degree of sulfation is approximately 15% higher than that achieved via hot water extraction [12]. For example, the cellulase assisted extraction method (C-JHCF4) of fucoidan JHCF4 from edible brown algae *Hizikia fusiformes*, which is rich in sulfate groups, has been shown to inhibit cell apoptosis, reduce oxidative stress, and have a protective effect on the liver [13]. It also contributes to the preservation of the C-20 backbone structure of fucoidan. As a promising green extraction technology, EAE is recognized as an ideal method for extracting natural compounds such as fucoidan from seaweed due to its safety, environmental compatibility, and non-toxicity [14]. However, its widespread adoption is currently constrained by high production costs, particularly the expense associated with enzyme preparations. In the future, an integrated strategy of enzyme engineering optimization and biological refining can be used to improve the reusability of enzymes, effectively reducing overall costs and enhancing the economic feasibility of this technology.

2.2.2. Ultrasonic-Assisted Extraction Method

Ultrasound-assisted extraction (UAE) is an efficient and environmentally friendly technique that has demonstrated excellent performance in the extraction of polysaccharides. This method primarily relies on three physical effects induced by ultrasonic waves: cavitation, thermal effects, and mechanical vibration. The underlying principle involves the generation of microbubbles within the liquid medium by high-frequency sound waves. These bubbles undergo rapid formation and collapse, producing localized high temperatures and pressures. This intense physical disruption can break down cell walls or membranes, thereby facilitating the accelerated release of intracellular polysaccharides [15]. Fucoidan is embedded within the complex cell wall matrix of seaweed, where it is intertwined with other components such as cellulose, hemicellulose, and alginate. This structural complexity makes the efficient extraction of fucoidan particularly challenging. As shown in Table 1, the yield of fucoidan extracted from different brown algal species varies significantly when using

ultrasound-assisted methods, highlighting the influence of species-specific factors on extraction efficiency.

Table 1. Fucoidan extracted from brown algae by ultrasonic-assisted extraction method.

Types of algae	Extract the solvent	Solid-liquid ratio(g/ml)	Ultrasonic power (W)	Extraction time (min)	Extraction temperature (°C)	Ultrasonic frequency (k HZ)	Yield of fucoidan (%)	References
Kelp	Distilled water	1:1	200	240	40-65	24	7.9	[16]
Chlorophytum comosum	0.1M HCL	1:10	-	30	30	20	22.95	[17]
Sargassum amansii	90% ethanol	1:50	200	130	70	-	25.8	[18]
Wakame	Distilled water	1:100	1080	-	30	20	31.9	[19]

Ultrasound-assisted extraction (UAE) is an environmentally friendly and efficient method for fucoidan extraction, featuring reduced solvent demand, accelerated extraction rates (shortening time by over half to 30–60 minutes typically), 10%–30% higher yields via optimized parameters, and lower energy/chemical usage [20,21]; however, its high-energy and high-pressure waves may alter fucoidan's structural and chemical characteristics, affecting its inherent properties and biological functions [22]. Combined with data from different algae, UAE parameters vary significantly—solvents include distilled water, 0.1M hydrochloric acid, and 90% ethanol; solid-liquid ratios range from 1:1 to 1:100 (g/ml); ultrasonic power is 200W–1080W; temperatures are 30–70°C; extraction durations are 30–240 minutes—with yields of 7.9%–31.9%, higher yields (25.8%–31.9%) from *Undaria pinnatifida* (high power + large solid-liquid ratio) and *Sargassum amansii* (200W + 90% ethanol + 1:50 solid-liquid ratio), and the lowest yield from *Laminaria japonica* due to its low solid-liquid ratio, while future application can be advanced by combining UAE with other novel extraction technologies to further improve yield and preserve functional integrity.

2.2.3. Microwave-Assisted Extraction

Microwave-assisted extraction (MAE) generates energy that causes charged particles and polar molecules in the solvent to oscillate rapidly, producing localized heating and creating transient high-temperature zones. This thermal effect disrupts the cell walls of seaweed, facilitating the rapid release of intracellular compounds into the solvent. The typical procedure for preparing fucoidan oligosaccharides using microwave-assisted extraction (MAE) is as follows: 1 g of pretreated seaweed and 30 mL of extraction solvent are placed in a dedicated reaction vessel. With magnetic stirring, the microwave reactor rapidly heats the mixture to the target temperature within 2 minutes. Optimal process parameters are reaction at 80°C for 10 minutes; post-extraction, the system is ventilated for 5 minutes to cool and expel fumes [23], building upon this process, integrating oxidative degradation with hydrogen peroxide (1-3%) and catalysis by MCM-41 mesoporous materials (2-10 nm) facilitates efficient production of 500-3000 Da fucoidan oligosaccharides, achieving a sulfate group retention rate of 25-35%—an improvement of 10-20% relative to traditional methods. However, temperature control is critical during extraction, as excessively high temperatures can reduce the yield. When the temperature exceeds 140 °C, the structural integrity of polysaccharides is compromised, resulting in mass loss. For instance, fucoidan has a typical molecular weight of approximately 13 kDa, but at 100 °C, it can reach a molecular weight of up to 240 kDa [24], indicating better structural preservation at lower temperatures. Research indicates that MAE operates under mild conditions, preserving high molecular weight at low temperatures to enhance immunomodulatory activity. Moreover, the

resulting product contains dense sulfate clusters, exhibiting anticoagulant activity. Future research should focus on precision low-temperature degradation and targeted activity enhancement to further boost its anticoagulant and immunomodulatory properties.

2.2.4. Subcritical Water Extraction

Subcritical water extraction (SWE) is an environmentally friendly emerging technology that utilizes water under elevated temperature and pressure conditions to extract compounds that are otherwise insoluble in water under ambient conditions [25]. Subcritical water refers to liquid water maintained above its boiling point but below its critical point by applying high pressure. This technique is commonly applied in processes such as supercritical water oxidation, typically operating at temperatures ranging from 100 °C to 250 °C and pressures between 1 and 8 MPa [26]. SWE offers the significant advantage of eliminating the need for organic solvents, thereby minimizing environmental pollution and health risks. Among the various influencing factors, extraction time and temperature were identified as the two most critical parameters determining the final yield. In a representative application, SWE was employed to extract fucoidan from *Nizamundinia zanardinii*. The optimal extraction conditions were found to be 21 grams of algal biomass per milliliter of water, with extraction carried out at 150 °C for 29 minutes. Under these conditions, the fucoidan yield reached 25.98%, which is significantly higher than the 5.2% yield typically obtained using traditional extraction methods [27].

The high temperature and pressure in SWE may cause polysaccharide structural degradation or modification, compromising their stability and biological activity. Process optimization based on thermodynamic models, alongside clarification of the temperature-time synergistic effect mechanism on polysaccharides' molecular weight distribution and functional group retention, can boost environmental performance, improve extraction efficiency, and preserve biological activity.

3. Physiological Activities of Fucoidan

The molecular size, structure, and biological function of fucoidan sulfate esters in fucoidan may vary due to structural differences [28]. These structural differences give them different physiological functions and demonstrate unique application value in brown algae (as shown in Figure 2).

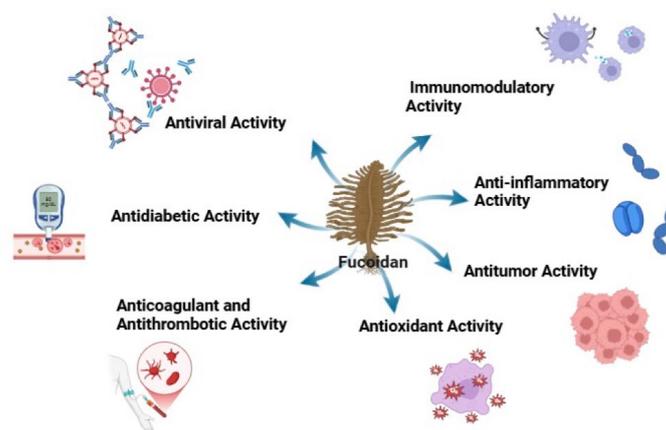


Figure 2. The physiological activities of fucoidan.

3.1. Immune Regulation

Fucoidan is recognized as a potent immunomodulatory compound capable of enhancing the body's immune response. It is particularly effective at activating several key immune cells, including natural killer (NK) cells, macrophages, and T cells [29]. When polysaccharides stimulate macrophages, these immune cells release crucial signaling molecules such as interleukin-6 (IL-6),

tumor necrosis factor-alpha (TNF- α), and nitric oxide (NO), which aid in combating infections, regulating inflammatory responses, and maintaining immune homeostasis.

Fucoidan extracted from Sargassum species has been shown to enhance the activity of immune cells by promoting macrophage phagocytosis and increasing the expression of essential immune signaling molecules, thereby strengthening the body's immunological defense [30]. Similarly, sulfated fucoidan (Fuc Sc) derived from Japanese sea cucumber was evaluated for its immunostimulatory effects using the RAW 264.7 macrophage cell line. The study demonstrated that Fuc Sc activates the NF- κ B signaling pathway via TLR2/4 receptor engagement, significantly increasing the production of immune mediators including NO, TNF- α , IL-6, and IL-10. Moreover, molecular weight was identified as a critical structural parameter influencing the immunoreactivity of Fuc Sc, providing important theoretical insights for the development of efficient immune adjuvants [31]. Another study examined DAP4, a purified fucoidan isolated from the Antarctic brown alga *Durvillaea antarctica*. In vitro assays revealed that DAP4 exhibits significant immunomodulatory activity in the RAW 264.7 cell model: it promotes splenic lymphocyte proliferation, boosts NO production, enhances macrophage phagocytic capacity, and markedly improves NK cell viability [32]. These findings highlight DAP4 as a promising candidate for the development of novel immunoregulatory agents. In summary, fucoidan polysaccharides play a vital role in regulating the human immune system [33]. It not only has considerable potential in treating immune related diseases, but also represents a new direction for precise regulation of immunity by natural products.

3.2. Anti-Inflammatory

Fucoidan isolated from various seaweed species has demonstrated anti-inflammatory properties, primarily by inhibiting lipopolysaccharide (LPS)-induced inflammatory responses. One of its key mechanisms involves protecting I κ B α , an inhibitory protein of NF- κ B, from degradation, thereby suppressing the activation of the NF- κ B signaling pathway and reducing inflammation. For example, Fucoidan purified by column chromatography has been shown to inhibit the production of reactive oxygen species (ROS) triggered by LPS, promote the apoptosis of damaged cells, modulate the NF- κ B pathway in macrophages, and ultimately alleviate inflammatory responses by reducing oxidative stress and supporting cellular clearance mechanisms [34]. Meanwhile, [35] investigated the anti-inflammatory effects of a high molecular weight fucoidan fraction (FE-F3) derived from brown algae, which has a molecular weight range of 110–800 kDa and a sulfate content of 39%. Their findings revealed that FE-F3 effectively modulates inflammatory signaling and inhibits LPS-induced inflammation in endothelial cells. In contrast, low molecular weight fucoidan (LMF) extracted from Sargassum was found to be particularly effective in alleviating skin inflammation caused by fine particulate matter [36]. LMF exhibited protective effects on both the epidermis and dermis, making it a promising candidate for dermatological drug development. Regarding the anti-inflammatory properties of fucoidan, in studies related to spinal cord injury (SCI), Fucoidan, as a multi-targeted synergistic repair agent, exhibits potential in promoting tissue repair and functional recovery. For instance, animal model experiments demonstrated that fucoidan can suppress early inflammatory responses following SCI, enhance myelin regeneration in damaged regions, and support spinal cord function restoration. In vitro studies further revealed that fucoidan promotes the development and maturation of oligodendrocyte precursor cells (OPCs) by activating the PI3K/AKT/mTOR signaling pathway, thereby facilitating remyelination [37]. These findings lay a theoretical foundation for translating spinal cord injury repair from basic research to clinical application. Collectively, these results suggest that fucoidan plays a vital role in tissue repair and inflammation resolution at affected sites. Its broad anti-inflammatory potential positions it as a promising natural candidate for the development of novel therapeutic agents targeting a wide range of inflammation-related diseases.

3.3. Antitumor

Polysaccharides are naturally occurring compounds known for their diverse biological activities, and they are generally characterized by low or negligible toxicity. As such, they hold significant

promise in the prevention and treatment of cancer. Fucoïdan, a sulfated polysaccharide extracted from brown algae, has demonstrated notable anticancer properties in both in vivo and in vitro studies [38]. Fucoïdan polysaccharides exert anticancer effects by inhibiting tumor growth, metastasis, and maintenance through interference with key signaling pathways involved in tumor progression. Table 2 shows the study of different cancer cells with fucoïdan:

Table 2. Research on the Antitumor Effects of Fucoïdan Against Cancer Cells.

Serial number	Research subjects	Laboratory model	Administration route/dosage	Cell cycle arrest	Mechanism of action	Key results	References
1	Human hepato-cellular carcinoma cell line HepG2	In vitro cell experiments	200µg/ml, 24-48h	G0/G1	ROS-mediated oxidative stress and cross-regulation of the PI3K/Akt-JNK/p38 MAPK signaling pathways	Approximately 50% of HepG2 cancer cell proliferation was inhibited by fucoïdan. Upregulating CD24 and downregulating CD44 and Snail expression while targeting the transmembrane glycoprotein EpCAM on cancer stem cells	[39]
2	Mouse breast cancer cell line MDA-MB-231	In vivo cell experiments	400µg/ml, 24-48h	G1 or G2/M	Immunocompetent and anti-tumor macrophages	The cell viability was only approximately 50%.	[40]
3	Human colorectal cancer cell line HT-29	In vitro cell experiments	50-400µg/mL, 24-72h	G2/M	Synergistically regulating the cell cycle and MAPK signaling via the ROS-mitochondrial pathway core axis to induce apoptosis and inhibit cell proliferation	Regulating the PI3K/Akt and MAPK pathways, activating the mitochondrial apoptosis pathway, and inhibiting EMT and MMP activity	[41,42]
4	Human lung cancer cell line A549	In vitro cell experiments	500-1000µg/m, 48h	G0/G1	Triggering apoptosis signaling molecules on cancer cells to induce cancer cell apoptosis	Inducing apoptosis by activating the endogenous mitochondrial pathway along with the caspase-8-activated exogenous pathway	[43]
5	Human gastric cancer cell line AGS	In vitro cell experiments	50µg/mL, 48h	-	-	The percentage of Annexin V-positive cells in AGS cells significantly increased.	[44]

From the above table, fucoidan exhibits both direct antitumor activity and drug delivery system (DDS) potential, serving as a versatile candidate in tumor therapy with “intrinsic efficacy + carrier function”. Its direct antitumor effects have been validated in various tumor cell lines (e.g., HepG2, MDA-MB-231). At 50–1000 $\mu\text{g}/\text{mL}$ for 24–72 hours, it induces G0/G1 or G2/M cell cycle arrest, regulates PI3K/Akt, MAPK and other signaling pathways, activates mitochondrial apoptotic pathways, achieves ~50% tumor cell proliferation inhibition or significant apoptosis induction, and exerts specific effects by targeting cancer stem cell markers (e.g., CD24, Ep CAM). This foundational anti-cancer activity provides the basis for its use in multi-functional drug delivery systems, where it serves as both a therapeutic and a targeting ligand for molecules such as CD44 and Ep CAM [45]. Furthermore, fucoidan enhances the precision and safety of these systems by modulating immune checkpoint pathways and promoting tumor vascular normalization, facilitating synergistic combination therapies [46, 47].

3.4. Antioxidant

To date, more than 50 species of brown algae have been studied globally and shown to possess significant antioxidant properties. Fucoidan's unique sulfated polysaccharide structure and polyhydroxyl groups confer upon it robust free radical scavenging activity and cytoprotective effects. Fucoidan, in particular, plays a protective role against oxidative stress caused by reactive oxygen species (ROS), thereby preventing cellular damage [48].

Studies have demonstrated that low molecular weight fucoidan (FSSQ) derived from the brown seaweed *Sargassum* can suppress oxidative stress and inflammation by inhibiting the MAPK and NF- κ B signaling pathways, as well as NLRP3 inflammasome activation. Concurrently, it activates the Nrf2/HO-1 antioxidant pathway, significantly reducing LPS-induced inflammatory responses in RAW264.7 macrophages and thereby enhancing both cell viability and antioxidant capacity [49]. Further structural analyses using Fourier-transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR) techniques on carrageenan-purified fucoidan have confirmed its potent antioxidant activity [50]. This clarifies its specific chemical structural features—such as the substitution positions and content of sulfate groups—and further confirms that fucoidan, by retaining or enriching key structural motifs with antioxidant functions (e.g., sulfated modifications and specific sugar chain fragments), exhibits robust antioxidant activity. However, when the production of ROS becomes imbalanced with antioxidant clearance capacity—meaning excess ROS accumulates beyond the body's ability to neutralize it—oxidative stress can trigger conditions such as arthritis, neurodegenerative diseases, and cancer. Scientists have long explored strategies to inhibit ROS-mediated oxidative damage, with antioxidants emerging as the core focus. Synthetic antioxidants commonly used in the food industry, such as BHA and BHT, are associated with risks of long-term side effects [51]. In food preservation, fucoidan coatings can replace BHT, thereby extending the shelf life of oils and fats. Thus, fucoidan, as a natural antioxidant, has garnered significant attention. It not only directly scavenges ROS but also activates endogenous antioxidant mechanisms by regulating cellular signaling pathways, thereby shifting from “passive scavenging” to “active defense.” This dual action represents a key mechanism for controlling oxidative stress.

3.5. Anticoagulant

The natural bioactive polysaccharide fucoidan exhibits notable anticoagulant properties. Coagulation is a vital physiological process that prevents excessive bleeding following injury. Fucoidan derived from marine macroalgae has been identified as a promising natural alternative to conventional anticoagulants. Various analytical methods have been employed to assess its anticoagulant activity, among which the activated partial thromboplastin time (APTT) is a widely used indicator for evaluating the functionality of the intrinsic and common coagulation pathways, as well as for monitoring the efficacy of anticoagulant agents. For example, fucoidan extracted from *Chuanjiyu* (broken jade algae) demonstrated a significantly prolonged APTT of 387.8 ± 10.3 seconds, indicating a strong, dose-dependent anticoagulant effect [52]. This activity is closely related to the

specific sulfation pattern and glycosidic linkage positions within the fucoidan molecule. Further mechanistic studies have revealed that fucoidan inhibits the intrinsic coagulation pathway by targeting intrinsic factor Xase, thereby interrupting the clotting cascade at a critical point[53].

Heparin, a well-established sulfated polysaccharide anticoagulant, functions primarily through its interaction with antithrombin III and heparin cofactor II. Fucoidan has shown a similar mechanism of action, with the ability to inhibit thrombin via heparin cofactor II, suggesting strong antithrombotic potential[54]. These findings support the development of fucoidan as a novel natural anticoagulant drug. Ongoing research into the anticoagulant properties of fucoidan may contribute to the development of new therapeutics for the prevention and treatment of thrombosis, abnormal platelet aggregation, and coagulation-related disorders [55].

3.6. Lower Blood Lipids and Lower Blood Sugar

Fucoidan demonstrates significant potential in regulating lipid and glucose metabolism, offering promising applications in managing metabolic disorders. By activating lipoprotein lipase, fucoidan facilitates triglyceride hydrolysis and reduces LDL cholesterol levels [56]. Experimental models confirm its regulatory effects on lipid absorption and metabolism, preventing hepatic fat accumulation and exhibiting notable lipid-lowering effects in high-fat diet-induced hyperlipidemic mice [57,58]. Recent findings further reveal that fucoidan gel reduces intracellular lipid accumulation through LXR- α activation and ABCA1 upregulation [59].

It is projected that by 2045, over 693 million people worldwide will be affected by diabetes [60]. The polysaccharide inhibits α -amylase and α -glucosidase via Sirt-1 pathway modulation while regulating key signaling cascades in glucose metabolism, including cAMP, PI3K/AKT, and JNK/AKT pathways [61,62]. Diabetic models treated with fucoidan (400 mg/kg/day) show significant reductions in fasting blood glucose, glycated hemoglobin, and insulin levels, accompanied by enhanced GLP-1 secretion [63]. The compound also inhibits intestinal glucose absorption through SGLT1 binding and alleviates insulin resistance by reducing ROS production and related signaling pathway activation. Beyond these metabolic benefits, fucoidan counteracts diabetes-induced muscle atrophy by promoting protein synthesis and improving glucose utilization [64].

These complementary mechanisms establish fucoidan as a multifaceted therapeutic candidate for cardiovascular diseases, diabetes, and related metabolic disorders, acting through coordinated modulation of lipid and glucose homeostatic pathways.

3.7. Antiviral

Fucoidan is a natural sulfated polysaccharide extracted from seaweeds. Its unique sulfated structure inhibits viral invasion and replication via multiple mechanisms, thereby exhibiting broad-spectrum antiviral activity—with particular efficacy against enveloped viruses such as HIV, herpes simplex virus type 1 (HSV-1), and herpes simplex virus type 2 (HSV-2), among others. For HSV-1 and HSV-2, fucoidan has been shown to effectively inhibit viral activity at remarkably low concentrations—ranging from 0.48 to 0.89 $\mu\text{g/mL}$ [65], it can block viral binding to host cells, thereby indicating its high efficacy as a natural antiviral agent.. Further studies have confirmed that fucoidan demonstrates strong antiviral effects at low concentrations (9–15 $\mu\text{g/mL}$). Notably, high molecular weight fucoidan (HMW) has been found to be more effective, with a half-maximal inhibitory concentration (IC_{50}) of only 8.3 $\mu\text{g/mL}$, compared to 16 $\mu\text{g/mL}$ for its low molecular weight (LMW) counterpart [66,67]. The antiviral potential of fucoidan against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has also been investigated using both in vitro assays and computational modeling. Results show that fucoidan can interfere with the virus's 3C-like protease (3CL^{pro}) and receptor-binding domain (RBD) of the spike protein, thereby reducing viral replication[68]. Moreover, fucoidan can effectively block the interaction between the SARS-CoV-2 spike protein and human cell receptors, inhibiting viral entry and infectivity. Although these findings suggest that fucoidan may serve as an adjunct strategy in the fight against COVID-19, it remains in the experimental stage and cannot replace current vaccines or approved treatment protocols [69].

Additionally, oral administration of fucoidan derived from *Undaria baicalensis* has been shown to inhibit the systemic spread of avian influenza viruses (e.g., H5N3 and H7N2 subtypes), while simultaneously enhancing immune responses by promoting antibody production and improving host resistance to viral infections [70]. Nevertheless, fucoidan may eventually serve as a complementary therapeutic agent in antiviral treatment strategies, but further research and clinical validation are required.

4. High-Value Applications of Fucoidan

Figure 3 reveals the rich profile of bioactive nutrients in purified fucoidan, which is matched by its wide range of health benefits. With the maturity of raw material supply chains for large-scale production, fucoidan now stands at the forefront of innovative development in pharmaceuticals, functional foods, and cosmetics, showcasing exceptional potential.

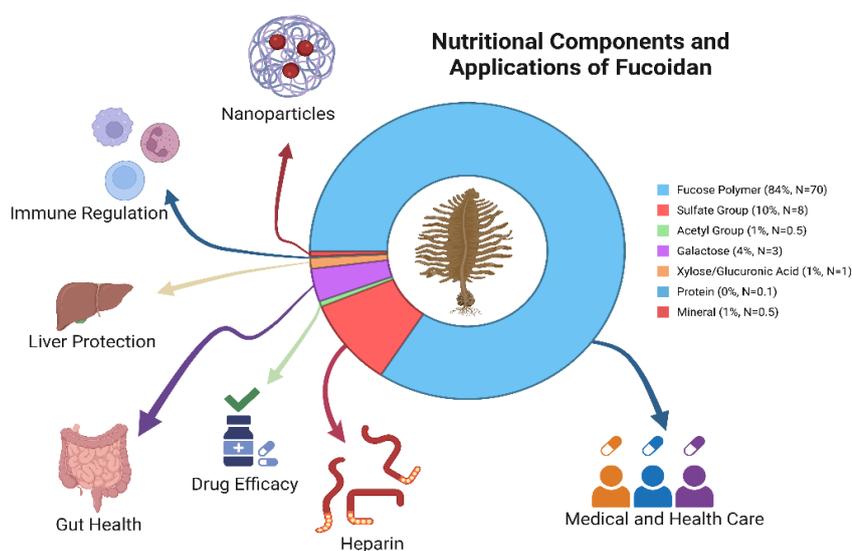


Figure 3. The nutritional components and applications of fucoidan.

4.1. Pharmaceuticals

Fucoidan, a sulfated polysaccharide with diverse physiological activities, holds significant medical potential due to its unique biological properties. Studies confirm its excellent biocompatibility and biodegradability, making it a highly promising material for advanced medical applications, including drug delivery systems and tissue engineering [71].

4.1.1. Drug Carrier

Fucoidan can form polyelectrolyte complexes with proteins, which are widely applicable in drug delivery systems [72]. Due to its excellent biological activity, antibacterial properties, and therapeutic potential, fucoidan has been formulated into powders, tablets, and nanoparticles for oral administration. When fucoidan polysaccharides are encapsulated on the surface of liposomes, they can reduce drug leakage and minimize the burst release effect [73], thereby enhancing liposome stability and improving drug absorption and bioavailability *in vivo*.

Fucoidan-based drug delivery systems can also be developed into nanogels. Owing to its strong water-absorbing capacity and negative surface charge, fucoidan (commercially known as Fucosan) is particularly suitable for hydrogel preparation. It is commonly used in wound dressings and moisturizing medical products to promote wound healing. For example, Rao et al. developed a polyelectrolyte hydrogel composed of chitosan and fucoidan (molecular weight: 46.4 kDa) [74],

which significantly accelerated wound healing in diabetic patients. In addition, nanoparticles formed from fucoidan and peptides can be functionalized with P-selectin to create magnetic resonance imaging (MRI) contrast agents that specifically target inflammatory sites [75], enhancing diagnostic clarity of inflammation-related conditions. These fucoidan-based nanoparticles have also demonstrated the ability to alleviate skin allergies by reducing inflammation and oxidative stress induced by reactive oxygen species (ROS). Furthermore, fucoidan nanoparticles can target tumor tissues by binding to P-selectin expressed on endothelial cells. In glioma models with an intact blood–brain barrier (BBB), these nanoparticles have been shown to cross the BBB via P-selectin-mediated transendothelial transport, enabling targeted delivery to brain tissue [76]. This strategy offers a promising approach for the treatment of central nervous system diseases. In addition, fucoidan has also been used as a carrier for curcumin delivery through soybean-based nanoparticles [77], improving the stability and therapeutic efficiency of curcumin, currently, it has entered Phase II clinical trials for ulcerative colitis, offering a new therapeutic option for chronic inflammatory diseases.

4.1.2. Organizational Engineering

Since its discovery in the 1950s, fucoidan has demonstrated significant medical potential, particularly in reducing bone resorption and promoting bone repair and regeneration. It enhances the activity of bone-forming cells and induces osteogenic differentiation of mesenchymal stem cells by activating key bone development signaling pathways, thereby upregulating osteogenic gene expression [78]. Beyond its osteoinductive properties, fucoidan activates the NRF2 antioxidant pathway, supporting its use in biomimetic tissue engineering [79]. It also exhibits antifibrotic effects in joint health by inhibiting the transformation of synovial fibroblasts into myofibroblasts and restoring normal apoptosis [80]. Additionally, fucoidan helps restore redox homeostasis in intervertebral discs, enhancing tissue stability and mitigating degeneration [81]. These multifaceted activities position fucoidan as a promising alternative biomaterial for bone grafting and regenerative therapies, though systematic clinical investigations remain limited.

These robust biological mechanisms make fucoidan an ideal candidate for developing advanced biomaterials, particularly in the form of 3D-bioprinted scaffolds for complex tissue regeneration. Studies have shown that bioinks composed of fucoidan combined with collagen, chitosan, and other components not only exhibit excellent printability but also effectively support cell survival and proliferation. By co-printing with algae, self-oxygenating scaffolds can be constructed to alleviate tissue hypoxia. Through modification processes, hydrogels with enhanced mechanical properties as well as antioxidant or antibacterial functions can be obtained, making them suitable for various applications such as cardiac repair, cartilage regeneration, and wound healing. These advancements collectively promote the application of fucoidan-based materials in regenerative medicine [71].

4.2. Cosmetic Field

Driven by the rising demand for natural cosmetics, fucoidan has emerged as a promising ingredient with skin regulatory benefits (Figure 4), fueling the industry's shift toward safer, natural, health-focused skincare formulations while offering a comprehensive “prevention-and-repair” strategy against photoaging—laying a solid scientific foundation for advanced skincare products tailored to intense sun exposure, mature skin, and other scenarios.

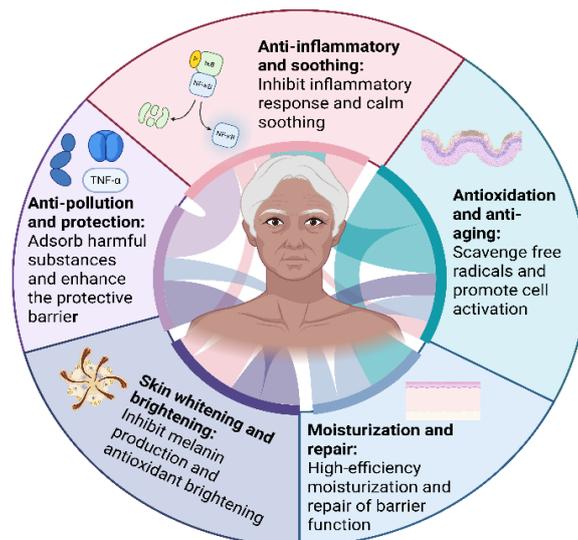


Figure 4. The field of fucoidan in cosmetics.

4.2.1. UV Resistance

Fucoidan demonstrates exceptional efficacy in skin photoprotection, functioning as a natural barrier against UV radiation and environmental stressors [82]. It significantly reduces stinging and burning sensations by specifically inhibiting the activation of TRPV1 and TRPA1 receptors. Studies confirm its potent antioxidant capacity, being 20–50 times more effective than vitamin E, through mechanisms that include scavenging UVB-induced reactive oxygen species (ROS) and inhibiting mitochondrial-mediated apoptosis in keratinocytes—evidenced by downregulation of Caspase-3 and upregulation of Bcl-xL. Specific extracts such as SCOC4 from North Korean seaweed and a 102.67 kDa fucoidan from Sheep’s Seaweed exhibit strong photoprotection even at low concentrations (12.5–50 $\mu\text{g}/\text{mL}$) [83,84]. Additionally, fucoidan derived from carrageenan helps maintain skin barrier integrity and stratum corneum hydration, thereby reducing transepidermal water loss [85]. These multifunctional properties position fucoidan as an ideal “hidden sunscreen” for sensitive skin and provide a molecular basis for developing innovative wearable sun protection products, such as sunscreen patches.

4.2.2. Anti-Aging

Fucoidan effectively delays skin aging through integrated mechanisms that enhance both epidermal barrier function and dermal structural integrity. It significantly improves skin hydration by upregulating tight junction proteins such as claudin-1 and increasing ceramide synthesis by 40%, thereby reducing transepidermal water loss (TEWL). Clinical evidence demonstrates that a 1% carrageenan-derived fucoidan formulation significantly lowered TEWL after three weeks of continuous application [86]. In multi-ingredient systems, when combined with moisturizing agents like ulvan and ectoine, fucoidan enhances the skin’s water-holding capacity by up to 17%, resulting in visibly firmer and more hydrated skin [87]. These findings confirm that fucoidan not only delivers intrinsic anti-aging benefits but also synergistically enhances the efficacy of comprehensive skincare formulations.

4.3. Food Field

Fucoidan, a natural polysaccharide from edible seaweed, is characterized by its unique chemical structure rich in fucose and sulfate. This composition underpins its diverse bioactivities and makes it a promising component for creating value-added health products in the food sector, such as functional foods and preventive health additives.

4.3.1. Immunomodulatory Supplements

Fucoidan is a unique natural polysaccharide that has long been used as a health food ingredient and nutritional supplement to support overall well-being. Naturally present in various seaweed-based foods, fucoidan not only offers physiological benefits but may also exert positive effects on mental health. For example, recent research has shown that fucoidan may help alleviate emotional disorders such as anxiety and depression associated with ulcerative colitis [88]. Fucoidan extracted from Lebanese brown algae has demonstrated inhibitory activity against several human cancer cell lines. In particular, its combination with vitamin C has been found to enhance the suppression of colon cancer cells (HCT-116), promoting apoptosis—or programmed cell death—by increasing the intracellular generation of reactive oxygen species (ROS) [89]. These findings suggest that fucoidan holds promise as a natural dietary supplement for cancer prevention or as an adjuvant in cancer therapy. Moreover, when administered orally as a dietary supplement, fucoidan has been shown to prolong survival in patients with advanced or metastatic cancers. It may also alleviate cancer-related symptoms such as fatigue and inflammation when used alongside conventional treatments [90]. Naturally derived fucoidan, with its multi-targeted action, is of significant importance to immunomodulators; moreover, its bidirectional regulatory activity enables it to both enhance immunity and prevent inflammatory responses.

4.3.2. Gut Healthy Foods

Fucoidan has been shown to improve gastrointestinal health by alleviating constipation, enhancing the structural integrity of the small intestine, promoting intestinal peristalsis, and facilitating the repair of damaged intestinal tissues. As a water-soluble polysaccharide, fucoidan can directly act on the gastrointestinal tract and has been investigated for its potential use in the oral treatment of gastric ulcers. In addition, fucoidan can significantly boost the abundance of beneficial bacteria such as Bifidobacteria and Akkermansia, while inhibiting pathogenic bacteria, fucoidan functions as a prebiotic—meaning it can be metabolized by beneficial gut microbiota to produce health-promoting metabolites [91]. These metabolites, such as short-chain fatty acids (SCFAs), play a key role in maintaining intestinal health and supporting overall metabolic balance. Owing to these properties, fucoidan is considered a valuable component for the development of functional foods aimed at regulating gastrointestinal lipid digestion [92], which is of particular relevance in managing digestive and metabolic disorders. For example, Japan has launched brown algae beverages containing fucoidan, such as “Fucoidan-rich Wakame Tea”, which offer benefits for gut health and more. Fucoidan may be further developed into functional food products or dietary supplements for the prevention and treatment of intestinal conditions such as inflammatory bowel disease (IBD), and may also serve as an adjuvant therapy in cancer treatment strategies.

4.3.3. Edible Packaging Film

Packaging films made from edible ingredients are gaining increasing popularity among consumers due to their safety, biodegradability, and convenience. Large seaweeds are particularly rich in polysaccharides, which can constitute 25% to 60% of their dry weight [93]. These polysaccharides serve as valuable raw materials for the production of bioplastics and are increasingly being incorporated into food packaging applications. For example, a pH-responsive edible composite film was recently developed by forming a Schiff base imine bond between chitosan (CS) and oxidized fucoidan (CS-FU), with cinnamaldehyde (CA) encapsulated as an active ingredient [94], this composite exhibits intelligent reactivity and offers promising potential as an eco-friendly material for fruit preservation and active food packaging, active freshness-preserving films can extend food shelf life, as sulfate groups released by fucoidan disrupt microbial cell membranes. For example, the EU’s BIOPACK project is funding the development of fucoidan-PLA composite films, with the aim of replacing plastic trays for fresh produce in supermarkets. As a biodegradable and environmentally friendly alternative to conventional plastic packaging, such materials offer significant advantages [95].

However, in addition to environmental considerations, ensuring chemical safety is also critical. It is important to prevent the migration of potentially harmful substances into food to ensure consumer safety. Research on fucoidan has evolved from passive applications in packaging to active health interventions, unleashing its transformative potential in medical foods, food waste reduction, and personalized nutrition.

4.4. Animal Health

With its proven bioactivity and natural safety, fucoidan from marine plants shows significant potential in animal nutrition. Studies confirm its role in enhancing immunity and supporting health, making it an ideal supplement for sustainable animal production.

4.4.1. Aquaculture

Aquaculture, as a rapidly expanding global industry, plays a critical role in supplying high-quality animal protein. However, with the growing demand for aquatic products and the continuous intensification of production systems, the industry faces multiple challenges—including how to maintain animal health, optimize growth performance, and reduce environmental impact. *E. maxima*, a species of brown algae, has attracted attention due to its rich content of natural bioactive compounds, including root bark tannins, fucoidan, chlorophyll, polyphenols, carotenoids, and essential vitamins [96]. It can significantly improve fish growth and feed utilization, enhance the digestion and absorption of nutrients[97], thereby boost feed efficiency and weight gain conversion rate. These constituents exhibit strong antioxidant, anti-inflammatory, and immunomodulatory properties, making them highly valuable for improving the health and productivity of aquatic organisms.

4.4.2. Animal Husbandry

Naturally occurring in various marine and plant sources, fucoidan is being explored as a potential alternative to antibiotics and growth-promoting hormones in livestock feed. It not only supports growth and improves meat quality, but also enhances resistance to infectious diseases and even shows potential protective effects against certain cancers. Several commercially available algae-based feed additives have been used in animal husbandry to improve animal health and growth rates. These products help enhance immunity, improve growth performance, and increase disease resistance in poultry. Specifically, fucoidan has been shown to promote healthier growth in both broiler chickens and laying hens, thereby improving farming efficiency and product quality[98]. It can significantly elevate serum IgG and IgM concentrations, enhance macrophage activity, lower the risk of infection by viruses such as avian influenza (H9N2) and Newcastle disease virus (NDV), attenuate the excessive release of inflammatory cytokines (e.g., IL-6 and TNF- α). In addition to poultry, fucoidan supplementation in feed has also shown beneficial effects in ruminants. For example, adding small amounts of fucoidan to lamb feed has been reported to enhance immune resistance, reduce disease incidence, and support overall health and growth [99]. Fucoidan has also been found to increase the activity of antioxidant enzymes in the blood of lambs, aiding in the elimination of harmful substances and improving vitality and physiological resilience. Currently, fucoidan is regarded as a highly promising functional additive for terrestrial livestock production [100]. Fucoidan polysaccharides contribute to healthy animal growth while potentially reducing dependence on conventional drugs. Moving forward, further research is needed to define optimal dosages, application strategies, and long-term effects. Such studies will provide a scientific foundation and technical support for the environmentally sustainable and health-oriented development of modern animal agriculture.

5. Conclusion and Outlook

The global fucoïdan market is projected to exceed USD 1.8 billion by 2025, reflecting the growing prominence of this seaweed-derived sulfated polysaccharide. Characterized by a tunable structure and diverse bioactivities—including immunomodulatory, antioxidant, and systemic regulatory effects—fucoïdan has enabled applications from clinical-stage bone tissue engineering and drug delivery in medicine to prebiotics and edible packaging in the food industry. Evolving research now shifts from isolated mechanisms to a holistic understanding of its health-modulating effects. To fully unlock its potential, future efforts must leverage interdisciplinary technologies to clarify its structure-activity relationships, thereby bridging the gap between laboratory research and commercial application.

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