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Study of the Structure, Production Methods, and Application of Fucoidan

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Abstract.
Functional foods provide nutrients, but their therapeutic properties are even more important than their nutritional and energy value. The biological diversity of marine flora and fauna makes them a unique source of beneficial chemical compounds.
It covered scientific literture on fucoidan extraction, purification, structure, bioactive profile, and applications published in ScienceDirect (Scopus), Springer Link, MDPI and Google Scholar in 1999–2023.
Fucoidan varies in monosaccharide composition, degree of sulfation, and molecular weight. Microwave extraction provides the highest yield. The biological properties depend on molecular weight, sulfation, and monosaccharide composition. Fucoidan is a safe and promising ingredient for the functional food industry. However, very few publications report fucoidan-based commercial products or results clinical trials.
As a bioactive polysaccharide, fucoidan holds significant promise for the food industry. However, its use is limited by the lack of standardized extraction and purification methods. Therefore, optimizing production parameters and developing standardized purification protocols are the key attention areas within modern biotechnology. Novel approaches will enable fucoidan to become a fully-fledged functional ingredient and expand the range of functional foods.

Keywords. Marine algae, polysaccharides, antioxidant activity, anticoagulant activity, antibacterial properties, anticancer properties

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Структура, получение и применение фукоидана

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Аннотация.
Функциональные продукты обеспечивают организм человека питательными веществами и, помимо питательной и энергетической ценности, обладают терапевтическими свойствами. Морская флора и фауна представляют собой огромное биологическое разнообразие и выступают уникальным источником химических соединений. Цель исследования – оценить структуру, методы экстракции, выделения, очистки и возможности применения фукоидана, полученного из морских водорослей.
Объектами исследования являлись научные публикации, посвященные методам экстракции и очистки фукоидана, изучению его структуры и биологических свойств, а также возможности практического применения. Поиск научной литературы проводился за период 1999–2023 гг. с использованием международных баз данных ScienceDirect (Scopus), Springer Link, MDPI и Google Scholar. При подготовке рукописи проводили отбор публикаций и критический анализ сведений.
В работе систематизированы современные данные о структуре фукоидана, характеризующейся вариативным моносахаридным составом, степенью сульфатирования и молекулярной массой. Представлен критический анализ методов экстракции. Установлено, что наибольший выход полисахарида обеспечивает микроволновая экстракция. Детально рассмотрены биологические свойства фукоидана и показана их зависимость от молекулярной массы, степени сульфатирования и моносахаридного состава. Подчеркнуты безопасность и перспективы применения фукоидана в пищевой промышленности. Отмечено ограниченное количество разработок и коммерческих продуктов на его основе, а также отсутствие клинических испытаний.
Фукоидан представляет собой перспективный для пищевой промышленности биологически активный полисахарид, однако его применение сдерживается недостатком стандартизированных методов экстракции и очистки. В связи с этим приоритетным направлением современной биотехнологии является поиск стратегии оптимизации параметров получения и разработка стандартизированных протоколов очистки. Применение современных подходов позволит сделать фукоидан полноценным пищевым ингредиентом и расширить ассортимент функциональных продуктов питания.

Ключевые слова. Морские водоросли, полисахариды, антиоксидантная активность, антикоагулянтная активность, антибактериальные свойства, противоопухолевые свойства

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Introduction

Eating habits are directly linked to health. Consuming foods that are low in nutrients can weaken the immune system and lead to various health problems while regular nutritional support prevents many diseases [1]. Functional foods provide human body with nutrients [2]. Functional foods are products that, in addition to their nutritional and energy value, possess therapeutic properties. Additional benefits of such products include their safety, affordability, and therapeutic synergy, as well as greater tolerability than in standard medications. The capacity of functional foods to mitigate the risk of chronic diseases is primarily driven by bioactive secondary metabolites of plant or animal origin. Such metabolites exhibit a wide range of biological properties [2, 3].

Marine flora and fauna represent a vast biological diversity. This diversity is a unique source of chemical compounds that are used in the food and agrochemical industries. Green, red, and brown algae produce different metabolites with a wide range of metabolic activity [4].

Most species of brown algae inhabit the littoral and sublittoral zones at depths ranging from 5 to 15 m. They are crucial to marine ecosystems because algae beds serve as natural buffers against waves, providing additional substrate for fish eggs and shelter for marine inhabitants. Algae farms perform the same function. Also, algae are one of the main producers of the world's oxygen [5].

The supply of nutrients to algal thalli is provided by water movement. Its intensity affects the biological state of algae, including such economically important

indicators as growth rate, biomass production, reproductive potential, etc. Gaining insight into aquatic environments reveals the natural growth patterns of algae, paving the way for the sustainable use of their resources [6].

Brown seaweeds, such as *Saccharina latissima, S. hyperborea, Fucus evanescens*, etc., are popular ingredients in the pharmaceutical industry and dietary supplements in nutrition. The reliable therapeutic effects of algal phytochemicals manifest *in vivo* and *in vitro*, rendering them with anticancer, anti-inflammatory, antibacterial, and antiviral activities [4–6].

Recent advances in biopharmaceuticals prompt the investigation of therapeutic agents derived from marine seaweed polysaccharides, particularly sulfated polysaccharides. For instance, fucoidan is currently in the focus of scientific attention. Structurally, fucoidan is a polysaccharide containing L-fucose and phosphate-ester groups found in macroalgal biomass [7]. Fucoidan may possess antioxidant, antitumor, immunomodulatory, and anticoagulant activities [8]. However, scientific and technical literature on its structure, isolation, and therapeutic properties is scattered. Its systematization may provide an insight into the potential applications of fucoidan in the food industry. This review systematizes available data on the structure, sources, extraction methods, and therapeutic profile of this polysaccharide, aiming at highlighting the benefits of its application in nutrition.

The review covers the main sources of fucoidan and their botanical descriptions, as well as methods of fucoidan extraction, purification, and structural modification. It focuses on advanced approaches to studying the structure, extraction, purification, modification, and production of fucoidan. Furthermore, the paper synthesizes recent advancements and promising trends regarding the antioxidant, anticoagulant, antibacterial, antiviral, and anticancer properties of this bioactive compound.

Study objects and methods

The review includes scientific publications on the methods of fucoidan extraction and purification, as well as its structure, bioactive profile, and application prospects. The English-language publications were retrieved from ScienceDirect (Scopus), Springer Link, MDPI, and Google Scholar using the following keywords and phrases: Marine algae, polysaccharides, antioxidant activity, anticoagulant activity, antibacterial properties, anticancer properties. The final pool included research articles or reviews published between 1999 and 2023 that contained descriptions of the main fucoidan sources, preparation methods, structural diversity, and sulfation degree, as well as the bioactivity of its macromolecules and their prospects for functional foods and pharmacy.

Research results and discussion

Structure. Fucoidan is a sulfated polysaccharide. Its composition varies depending on the source. Sulfated L-fucose is the most common fucoidan monosaccharide. Others include galactose, mannose, xylose, glucose, and glucuronic acid [9].

Fucoidan is structurally a branched, heterogeneous molecule. Its heterogeneity is due to its monosaccharide composition, the length of the polysaccharide chain, and the presence of sulfate groups. The branching of the molecule, its sulfation degree (the presence of sulfated groups), and molecular weight depend on the raw material and extraction method. As a rule, fucoidan isolated from macroalgae, e.g., *Ascophyllum nodosum*, consists of α-(1→3)-L-fucose residues or alternating α-(1→3) and α-(1→4) linked L-fucose residues as the main chain with a sulfate group at the C-2 position of α-(1→3)-linked and α-(1→4)-linked L-fucose residues [7–9].

Fucoidans and polysaccharides differ in their composition and structure depending on the source (Table 1). For example, fucoidan extracted from *Fucus evanescen*s and *F. serratus* has a higher content of linked L-fucose residues at α-(1→3) and α-(1→4). Fucoidan extracted from *Sargassum stenophyllus* includes residues of β-(1→6)-D-galactose and β-(1→2)-D-mannose, suggesting that sulfated galactose may serve as an alternative structural basis for fucoidan [7–9]. However, none of these publications provided any information on the quantitative content of fucoidan, which will be estimated later in this review.

The structure of fucoidan correlates with its biological activity. X. Zhang *et al*. [10] studied the anticoagulant properties of fucoidan obtained from nine species of brown algae. The samples demonstrated 2-O-α-D-glucuronic pyranosyl branches in the linear (1→3)-linked poly-α-fucopyranoside chain (eight out of nine species). This structural feature is probably responsible for anticoagulant activity. Conversely, antithrombin activity was observed only in fucoidan obtained from five of these eight species [11]. Thus, studies on the structure of fucoidan provide a deeper understanding of the corelation between its structure and beneficial functions.

The structural composition of native fucoidan obtained from brown seaweed is heterogeneous due to the presence of fucose and other monosaccharides, as well as sulfate groups located at different points [27]. Nuclear magnetic resonance spectroscopy provides limited information on the structure of these compounds. Mass spectrometry is a key method for structural analysis of fucoidan [11, 28–31]. Therefore, deciphering the structure of different forms of fucoidan is an important task for determining its biological activity [32, 33].

The monosaccharide composition and structure of fucoidan depend on the age of the algae. For instant, fucoidan isolated from young seaweed harvested in the Sea of Japan (Russia) contained up to 19–28 mol% mannose and approximately 20 mol% galactose while more mature algae yielded fucoidan dominated by fucose and galactose. The galactose content was 38 mol% [34].

Sources, botanical description, ecology, and content. Marine algae are an important source of bioactive com-

Table 1. Structure of different algal polysaccharides

Таблица 1. Структура полисахаридов, получаемых из разных видов водорослей

Source	Type	Monosaccharides / disaccharide units	Glycosidic bonds	Reference
Chorda filum	S-fucopyranose	Fuc, Glu	Poly-α-(1→3)-fucopyranose, α-(1→2)-linked single units; sulfated at O-4 (mainly) and O-2 positions	[12]
Fucus serratus	S-fucopyranose	Fuc	A backbone composed of alternating α-(1→3)- and α-(1→4)-linked L-fucopyranose residues	[13, 14]
Ascophyllum nodosum	S-fucanes; HMB-cPS; S-laminaran or otherwise modified	Fuc, Xyl, Gal, GlcA, Glc	Alternating α-(1→3)- and α-(1→4)-linked L-fucosyl residues; β-(1→3)- and β-(1→6)-linked glucosyl residues	[15, 16]
Fucus vesiculosus	S-fucanes	Fuc, Xyl, Gal, GlcA	Alternating α-(1→3)- and α-(1→4)-linked L-fucosyl residues	[17]
Fucus evanescens	S-fucopyranose	Fuc, Gal, Xyl	α-(1→3) and α-(1→4) glycosidic bonds	[18]
Sargassum cichorioides	L-fucose	Gal	α-(1→3)-linked L-fucosyl residues	[19]
Sargassum muclurei	L-fucose	Gal	α-(1→3)-L-fucosyls and α-(1→4) linked galactosyl residues	[20]
Turbinaria ornata	L-fucose / galactose	Fuc, Gal	α-(1→3)-L-fucosyls or of β-(1→4) galactosyls and mixed fucosyl-galactosyls	[21]
Turbinaria conoides	SPS	–	–	[22]
Cladosiphon okamuranus	S-fucanes	Fuc, Glc, GlcA	α-(1→3)-linked L-fucosyl residues	[23, 24]
Undaria pinnatifida	S-galactofucanes fucoidan	Gal, Fuc, Xyl, uronic acid	Alternating α-(1→ 3)- and α-(1→4)-linked L-fucosyl residues	[8, 11]
Sargassum fusiforme	S-fucanes	Fuc, Gal, Man, GlcA	(1→2)-α-D-man alternating with (1→4)-β-D-glcA; some (1→4)-β-D-gal	[16]
Ecklonia cava	S-fucanes	Fuc, Rham, Gal, GlcA	α-(1→3)-, α-(1→4)-, and α-(1→6)-linked L-fucosyl residues	[12]
Saccharina japonica	S-galactofucan	Gal, Fuc	Alternating α-(1→3)- and α-(1→4)-linked L-fucosyl residues	[6, 12]
Laminaria japonica	S-galactofucan	Gal, Fuc	Alternating α-(1→3)- and α-(1→4)-linked L-fucosyl residues	[16, 25]
Cladosiphon novae-caledoniae	S-fucoidan	Fuc	–	[26]

pounds due to their vast biodiversity. Table 2 presents some sources of fucoidan, their habitat conditions, and distribution. Macroalgae grown at 10–15 °C are rich in fucoidan (8.00–24.00% d.w.). Cultivating macroalgae at temperatures other than 10–15 °C leads to a decrease in the content of sulfated polysaccharide. Therefore, the fucan content in macroalgal biomass depends on the season, and its accumulation occurs most actively when the water temperature is 15–17 °C. The practical significance of this finding is that macroalgal biomass can be harvested for sulfated polysaccharide during the season when seawater warms to 10–17 °C.

Seasonality presupposes the ambient temperature at which macroalgae grow. It affects not only the fucoidan yield but also its structure and monosaccharide composition. Thus, macroalgae harvested in the spring contain by 1.6% more sulfates than macroalgal biomass harvested in the autumn and summer. Fucoidan contains equal amounts of galactose and fucose [21], although the fucose content decreases when the algae are cultivated at higher temperatures [39]. This is due to the degradation of the thallus during the maturation phase at higher temperatures [40]. Similarly, W. Mak *et al*. [39] reported the fucan content to drop to 5.95% solids by October. The highest fucoidan content was observed in September (13.79% solids). A similar trend was observed in the sulfate content of fucoidan. The fucose content decreased significantly between July and September [39]. Findings are consistent with the empirical data reported by H. R. Fletcher *et al*. [21] and M. Honya *et al*. [40], who showed that the molar ratio of sulfates increased as the algae matured.

Despite the wide variety of marine sources of fucoidan, many remain unexplored [13–16]. *Laminaria*

Table 2. Fucoidan: Sources, habitat conditions, and distribution

Таблица 2. Водоросли – источники фукоидана и их среда обитания

Source	Habitat conditions	Optimal temperature, °C	Content in dry biomass, %	Reference
Fucus vesiculosus	White Sea; Baltic Sea; Barents Sea	10–17	12.00	[13]
Fucus evanescens	Littoral and sublittoral zones	10	8.00	[14]
Fucus serratus	North Atlantic Ocean	10–20	–	[14]
Ascophyllum nodosum	North Atlantic Ocean	5	1.75	[15]
Pelvetia canaliculata	Atlantic coastline of Europe	17	14.00	[35]
Cladosiphon okamuranus	Okinawa, Japan	18–25	2.30	[23]
Sargassum fusiforme	East Asia	25	6.00	[19]
Saccharina latissima	East Asia; France and Russia (cultivated)	15	16.00	[35]
Sargassum horneri	Coast of Japan and Korea	10–15	24.00	[20]
Nemacystus decipiens	Okinawa, Japan	–	12.10	[36]
Padina gymnospora	Atlantic Ocean	–	–	[37]
Saccharina hyperborea	Sublittoral zones; northern part of the Atlantic Ocean	5–10	–	[38]
Fucus serratus	Northern parts of the Atlantic and Pacific Oceans; the Arctic	10–15	13.60	[14]

japonica, Fucus vesiculosus, and *Sargassum horneri* are currently the most promising raw materials with the highest content of fucoidan.

Demand. Fucoidan production is a rapidly developing industry segment that has the potential to influence the global industry. Most algal polysaccharides are used in the food and medical industries. The technological processes for obtaining these polysaccharides are subject to strict control and regulation [41]. The Asian region remains the global leader in fucoidan consumption; in 2017, its regional market intake reached 675 kg, with China and Japan at the forefront of this demand. In 2017, 38.54% of all fucoidan in Asia was consumed in China. The United States is also a major consumer of fucoidan, with a consumption rate of 5,248 kg (36.32%) of global consumption. According to the share of the global market (sales and revenue) of key fucoidan companies, the fucoidan market will grow at an average annual rate of 3.8% in terms of revenue over the next five years. It reached $37 million USD in 2024, compared to $30 million USD in 2019. In recent decades, sulfated fucoidan has attracted great attention from the pharmaceutical and biochemical industries. Fucoidan, alginate, and fucans are used for their anti-inflammatory, anticoagulant, antitumor, and antiviral properties. Their processing costs are reasonable due to easy access to these polysaccharides [42]. The economic value of seaweeds and their derivatives is estimated at approximately $7.4 billion USD [43].

Most companies specializing in fucoidan-based commercial products are located in Asia (Fig. 1, 2). They mostly use *Saccharina japonica* as a source of fucoidan. On the other hand, fucoidan has no medicinal status in Russia or any other country. Despite its extensive range of biological activity, fucoidan has not been approved by the Food and Drug Administration for clinical use [44]. Fucoidan is not the main commercial product obtained from brown seaweed [45], which is one of the factors limiting its production. The mismatch between structural and biological properties, which depend on the species of seaweed, harvest period, and extraction method, is another factor limiting the commercial use of fucoidan. Differences in chemical properties, extraction methods, purification, and production of various forms of fucoidan indicate that fucoidan as a medicinal product does not meet the Good Manufacturing Practice standards established for pharmaceutical products by the World Health Organization (2014). This failure of fucoidan to comply is due to its contamination by other biological polymers and phenols, low bioavailability, and a wide variety of chemical structures.

While fucoidan is still in the process of being approved for clinical use, it has been approved as a safe food product. Several patents feature fucoidans for biomedical purposes. One patent covers the use of fucoidan as a framework for tissue regeneration [45] while another describes the formulation and use of a fucoidan-based product for the treatment of blood-clotting disorders [46]. However, obtaining a patent for a product only protects the inventor's rights and does not give permission for commercial production.

Impurities significantly affect the bioactivity of fucoidans. In accordance with the requirement for clinical use, raw fucoidan must be purified to evaluate its struc-

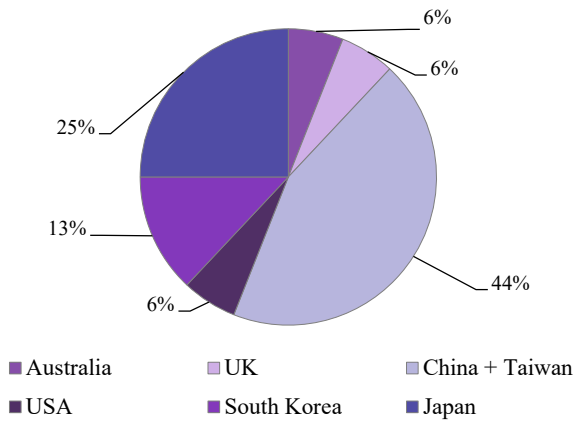

Figure 1. Companies producing fucoidan-based commercial products

Рисунок 1. Компании, производящие коммерческие продукты на основе фукоидана

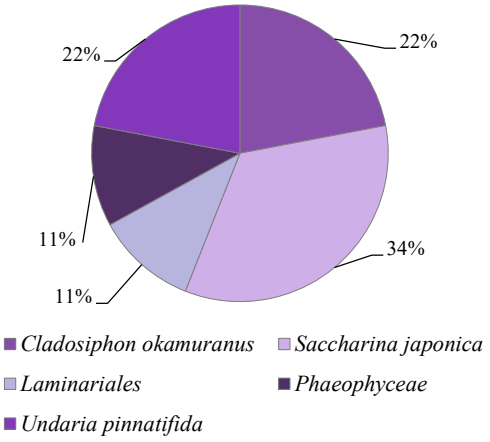

Figure 2. Fucoidan sources in commercial products

Рисунок 2. Источники фукоидана в коммерческих продуктах

ture and bioactivity in its pure form. Purification methods for fucoidans, such as ion exchange chromatography [47], gel permeation chromatography, and biological affinity purification, significantly increase the cost of producing pure fucoidans. The symbiotic relationship between marine algae and marine microbiota is also important. Algal cell walls are typically host to several deeply attached bacterial species [48].

Fucoidan is of great interest as a potential drug candidate due to its anticoagulant, antiviral, and antitumor activities. Several challenges, however, hinder fucoidan from meeting Good Manufacturing Practice regulations, thereby blocking its endorsement by the Food and Drug Administration. These challenges include structural heterogeneity, co-extracted contaminants, and ecology-related issues. Therefore, commercial fucoidan production needs new methods and optimal conditions, which would yield a stable polysaccharide with desirable physicochemical and therapeutic properties. This review, which provides a synthesis of scientific and technical literature, may enable researchers to optimize the parameters and methods for fucoidan extraction and purification.

Table 3. Stages of extraction and purification of polysaccharides

Таблица 3. Стадии экстракции и очистки полисахаридов

Stage	Methods
Harvesting seaweed	Manual method
Preliminary processing	Enzymatic treatment; drying; washing; chemical treatment; grinding
Polysaccharide extraction	Microwave extraction; ultrasonic extraction; acid extraction; hot water extraction; enzymatic extraction
Fucoidan extraction and purification	Fractional precipitation; ion exchange chromatography; membrane filtration; gel chromatography
Establishing fucoidan structure	High-performance liquid chromatography (HPLC); spectrophotometry; nuclear magnetic resonance (NMR); mass spectrometry

Extraction and purification. This review revealed no universal technology capable of producing a heterogeneous polysaccharide from macroalgae. Table 3 presents a theoretical analysis of existing extraction and purification methods. The contemporary phycology involves time-consuming processes that require significant material resources. Their multi-stage nature leads to severe losses of the finished product.

The production of algal fucoidan consists of the following main stages: harvesting of raw materials from the sea; washing them to remove impurities (epiphytes, sand) and excess salts; mechanical (grinding) or chemical (depigmentation) pretreatment; extraction of fucoidan; concentration of polysaccharide extract; purification of the target product (separation methods, chromatography); drying; intermediate storage.

The stages of depigmentation and adsorption of accompanying substances are especially important. Depigmentation involves treating the ground plant material with acetone, methanol, chloroform, ethyl alcohol, or its solution. It removes fat-soluble pigments and lipids [38, 49]. Treating plant-based raw materials (algal biomass) with activated carbon removes aromatic compounds, polyphenolic compounds, and chlorophyll [49]. Other polysaccharides (starch, cellulose, alginate, etc.), which differ structurally from fucoidan, leave the biomass at other processing stages [49–50]. For this purpose, the extract is further treated with acetone and sodium carbonate. As a result, sodium alginate precipitates and can be separated by centrifugation. In addition, the extract is treated with enzyme preparations (amylase, cellulase) to break down starch and cellulose. It is also treated with proteinase K, trypsin, or protease to break down glycopeptides and increase the fucoidan yield [51, 52].

The most common method for isolating fucoidan from macroalgal biomass is thermal extraction with weak acid solutions (hydrochloric acid) and water [14, 53, 54]. Water is heated to 80–90 °C to serve as extractant. Aluminum oxalate or sodium oxalate is then added to the water. These compounds bind the sulfated polysaccharides, resulting in a more efficient extraction [54]. To achieve more complete precipitation of the heterogeneous sulfated polysaccharide, the extraction process is repeated several times. The extracts are then combined and concentrated, after which polysaccharides are precipitated by centrifugation. Table 4 illustrates the methods for extracting fucoidan from macroalgae [20, 21, 55–60].

Microwave extraction yields an extract with the highest fucoidan content (from 16.08 to 18.22% d.w.). The extraction method typically involves adding distilled water to the crushed plant material: 1 g of algae is added to 25 ml of distilled water. The resulting mix is microwaved for 1 min at 120 psi [55–57]. This method has several advantages, including high efficiency and minimal processing time. In addition, it requires no organic solvents and enables a sustainable selective production of sulfated polysaccharides. Avoiding high temperatures and organic or inorganic solvents ensures the preservation of the target polysaccharide's structure [25].

Ultrasonic extraction allows for the production of a sulfated polysaccharide with an intact native structure. However, according to A. K. Patel *et al*. [58], the yield of the target product is low (3.51% d.w.). Ultrasonic extraction induces cavitation through dynamic shock waves directed at the material surface. This procedure disrupts the cell walls of the plant material, thus extracting fucoidan. The method utilizes solutions of hydrochloric acid (0.1 N HCl) and sodium hydroxide (0.1 N NaOH) [61]: it takes place at room temperature for at least 6 h in the presence of 0.1 N HCl (pH 2.0), followed by the neutralization of the supernatant with 0.1 N NaOH [25].

Enzymatic fucoidan extraction demonstrates low efficiency. According to S. Badrinathan *et al*. [20], the yield of the target product is insignificant (6.2% d.w.). Cellulolytic enzymes break down the cell walls of plant materials. Crushed seaweed is mixed with distilled water at a ratio of 1:20 at 25°C. The resulting suspension is adjusted to pH 6.0 with an HCl solution, and 2% cellulolytic enzymes are added. The mix is then incubated at 40 °C for 2 h, then heated to 80 °C and held at this temperature for 60 min. The resulting solution is centrifuged, dialyzed, treated with ethyl alcohol, and dried [62]. The disadvantage of this method is in its multi-stage nature and low yield, attributed to the loss of the target product at each stage.

Extraction with diluted acids is low-effective due the poor solubility of sulfated polysaccharide at low pH. One disadvantage of this method is in its high solvent consumption: 1 kg of plant material requires at least 16 L of 0.1 N HCl. Another disadvantage is that fucoidan undergoes denaturation during the extraction process, which affects its biological activity [25, 63]. Dried algae are soaked in 0.1 N HCl and kept at room temperature for 24 h. The extract is then filtered for the filtrate to be neutralized with a 1 N NaOH solution. Fucoidan is precipitated with 75% ethanol in a 3:1 ratio by volume [63].

Although hot water extraction is inexpensive and easy to use, it is labor-intensive and solvent-demanding. This method relies on the solubility of polysaccharides in water and their ability to precipitate in the presence of alcohols and organic solvents. First, seaweed is finely ground and washed with ethyl alcohol at 80 °C for 60 min. Then, it is treated with distilled water at an extract-to-water ratio of 1:60. Water treatment continues for 7 h at 100 °C. Finally, the supernatant is treated again with ethyl alcohol [60].

In addition to the methods in Table 4, autoclave hydrolysis (AH) with an aqueous hydrochloric acid solution can isolate fucoidan from macroalgae [18, 64]. Combined methods maximize fucoidan yield. Authors isolated fucoidan from *A. nodosum* and *S. hyperborea* by sequentially applying a hydrothermal method in the

Table 4. Methods for extracting fucoidan from macroalgae

Таблица 4. Способы извлечения фукоидана из макроводорослей

Specie	Extraction method	Extraction efficiency / yield, % d.w.	Reference
Ascophyllum nodosum	Microwave extraction	16.08	[55]
Fucus vesiculosus	Microwave extraction	18.20	[56]
	Autoclave hydrolysis	16.50	[56]
	Microwave extraction	18.22	[57]
Nizamuddinia zanardinii	Ultrasound extraction	3.51	[58]
Sargassum ilicifolium	Ultrasonic probe treatment; microwave-assisted extraction; hot water extraction	8.00	[59]
		6.00	
Sargassum myriocystum	Enzymatic extraction	6.20	[20]
Undaria pinnatifuta	Hot water extraction	12.90	[60]
Turbinaria decurrens	Treatment with alcohol and organic solvents (chloroform); sequential extraction with $CaCl_2$, HCl	5.58 (crude)	[21]
		1.28 (purified)	

presence of 0.1 N hydrochloric acid, followed by ultrasonic and thermal treatments [64].

Microwave-assisted extraction (MAE) requires either water or a water-ethanol solution as the extractant [51, 52, 65]. These physical extraction methods help to disrupt the algal cells more thoroughly, thereby increasing the yield of the target product into the extractant [64].

Physical extraction methods by ultrasonication, microwaving, or autoclave hydrolysis shorten the extraction process and reduce the negative impact on the environment since they involve no aggressive chemical agents [58, 64]. However, the processing conditions (time, temperature, pressure) have a significant impact on both the final yield and its structure (monosaccharide composition, degree of sulfation, degree of branching), including the length of the polysaccharide chain (molecular weight) and therapeutic properties [64].

Liquid-phase extraction largely depends on such parameters as temperature and pressure. Exposure to elevated temperatures and pressures breaks the bonds formed by van der Waals interactions and hydrogen bonds, which increases fucoidan yield [56].

The method involving sequential treatment with alcohol and organic solvents (chloroform) requires extraction with calcium chloride and a diluted hydrochloric acid solution. It provides a satisfactory yield of the target product [21].

The scientific and technical analysis of fucoidan extraction from macroalgal biomass (Table 4) may enable scientists to optimize the parameters for isolating the target product and increase its yield.

After fucoidan extraction, the resulting extract contains proteins and other polysaccharides, which are subsequently removed through precipitation and enzymatic treatment [49–52]. Fucoidan purification stage is important as it yields a higher-quality, more therapeutically active product: purified bioactive substances have stronger biological properties than contaminated ones.

The purification process for sulfated polysaccharides should include such stages as fractionation, precipitation, column chromatography (ion-exchange, affinity, and exclusion), and membrane filtration [22, 50, 51]. The fractionation of polysaccharides can be performed either by precipitation (with calcium chloride, ethyl alcohol, or isopropanol) or by column chromatography (ion-exchange chromatography) [51]. Fucoidans with different molecular weights can be separated using membrane separation and gel chromatography [24, 58, 59]. As previously mentioned, algae contain fucoidans with varying molecular weights and degrees of sulfation.

All these methods of fucoidan extraction differ in the number of stages and the equipment used. Currently, no method guarantees fucoidan with a stable structure, sulfation degree, and therapeutic profile. Therefore, further research is needed to screen the technological parameters for extracting a unique polysaccharide from plant-based raw materials, which would yield fucoidan of consistent quality, i.e., with a specific structure, degree of sulfation, and branching. However, our current work may bring researchers closer to this goal.

Bioactivity. Fucoidan is a heterogeneous branched polysaccharide with antioxidant, anticoagulant, anti-inflammatory, immunomodulatory, antimicrobial, and antifungal properties. These effects depend on the extraction method, sulfation, macromolecular branching, and the length of the polysaccharide chain (molecular weight) (Fig. 3) [11, 12, 29, 50, 66–68].

The molecular weight of fucoidan varies widely, from 10,000 to 100,000 Da [11, 12, 50]. Since the bioactivity of the polysaccharide depends on many factors, the results reported in scientific literature also vary. This section synthesizes available information on fucoidan bioactivity

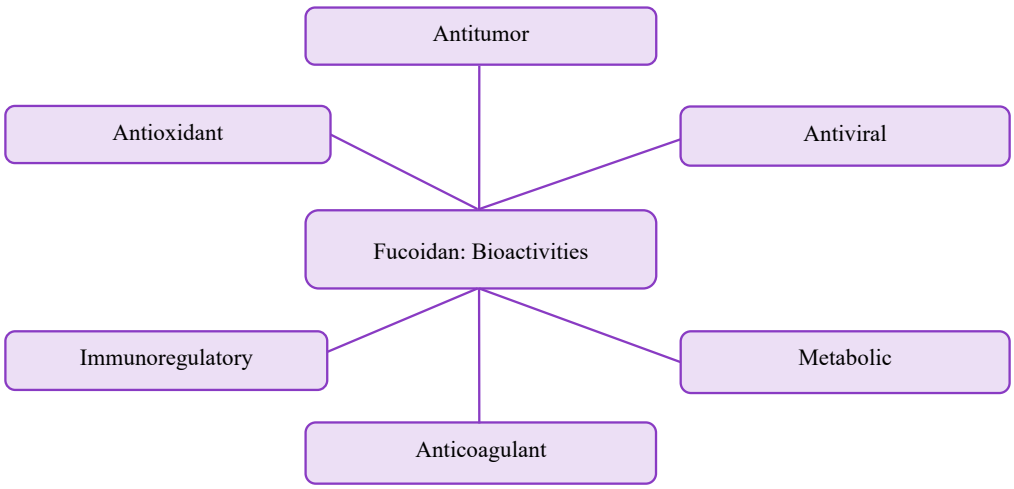

Figure 3. Proapoptotic activity of fucoidan

Рисунок 3. Проапоптотическая активность фукоидана

and the mechanisms underlying its therapeutic profile. Driven by its bioactive properties, fucoidan research is increasingly shifting from fundamental science to practical applications. This nonlinear heterogeneous polysaccharide is a natural, non-toxic substance that rarely causes allergic reactions [29]. Figure 3 presents the main properties of fucoidan in the context of its potential practical applications.

Antioxidant activity. Due to its significant antioxidant activity [7, 13, 31, 69–71], fucoidan is widely recommended by researchers for therapeutic and practical applications. Low-molecular-weight fucoidan is preferable since it possesses stronger antioxidant properties [72–76]. Fucoidan with a short polysaccharide chain binds low-density lipoproteins more readily than native polysaccharide [70]. Lipid concentration depends on the degree of sulfation and the mass fraction of fucose in the polysaccharide [77]. Thus, fucoidans with a high degree of sulfation and a high fucose content possess more pronounced antioxidant properties [7, 9, 77].

While the exact mechanism of fucoidan antioxidant action remains unclear, this polysaccharide is known to be able to neutralise the toxic effects of glutathione, superoxide dismutase, reactive oxygen species, and β-amyloid, as well as reduce their concentrations (Fig. 4) [69–71, 78–82].

All these factors (molecular weight, branching, sulfation, and fucose mass fraction) should be considered synergetically rather than individually as they are directly determined by the source of the fucoidan and the extraction method [75].

Scientific community is still in the early stages of studying the antioxidant properties and mechanisms of action of this unique polysaccharide. To date, science knows no optimal fucoidan extraction and purification method that would facilitate the standardization of its antioxidant potential. Therefore, further research is needed to improve fucoidan extraction technology and to study the mechanisms of free radical scavenging. The results obtained will expand the range of functional foods that slow down oxidation processes and prevent socially significant diseases associated with the accumulation of reactive oxygen species and free radicals.

Antitumor activity. Various types of fucoidan affect the cell cycle of tumor cells, particularly in the G1 phase. K. Mi-Hyoung *et al*. [83] summarized the inhibitory activity mechanisms of fucoidan obtained from *F. esiculosus* in human colon cancer cells. Fucoidan was able to induce the activation of protein kinase B and cell cycle arrest in the G1 phase by increasing the expression of tumor suppressor p21, decreasing cyclin D1/CDK4 and suppressing the expression of cyclin E/CDK2.

Fucoidan isolated from *F. vesiculosus* inhibited the proliferation of human colon cancer cell line HT-29 by reducing the expression of cyclin D1, cyclin E, CDK2, and CDK4 through the involvement of the PI3K/Akt/mTOR/p70S6K1 pathway *in vitro* by western blotting experiments [84]. Fucoidan obtained from *Undaria pinnatifida* inhibited the cell cycle in the G0/G1 phase of prostate cancer cell line PC-3 [85]. Unpurified fucoidan from *F. vesiculosus* blocked the G1 phase of mouse breast cancer cell line 4T1 by reducing β-catenin levels in the nucleus and cytoplasm, thereby reducing c-Myc and cyclin D1 expression (flow cytometry *in vitro*) [86]. Fucoidan from *Cladosiphon okamuranus* could arrest the G0/G1 phase of Huh7 hepatoma cell line by suppressing CXCL12/CXCR4 expression [83]. Fucoidan also blocks other cell cycle phases. For example, fucoidan with a molecular weight of 40 kDa isolated from *C. okamuranus* exhibited anti-proliferative activity against gastric cancer cell line MKN45 and was able to block the S-phase and DNA replication [87].

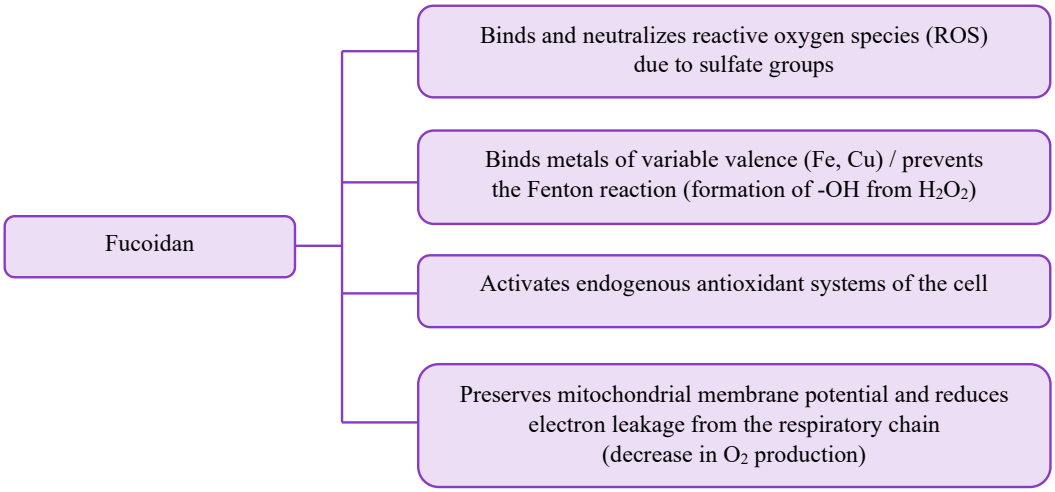

Figure 4. Mechanisms providing fucoidan with antioxidant properties

Рисунок 4. Механизмы, обеспечивающие антиоксидантные свойства фукоидана

Thus, fucoidan obtained from *F. vesiculosus, U. pinnatifida,* and *C. okamuranus* had inhibitory effects on the cell cycle of various tumor cell lines. Among the species studied, the effect of fucoidan from *F. vesiculosus* was found to be the most significant. Although fucoidan arrests the cell cycle in the S phase, its main effect is manifested in the G1 phase through the reduction of cyclin D1, cyclin E, CDK2, and CDK4. Notably, the activation of p21 is not a necessary condition for this effect.

Apoptosis plays a key role in maintaining the homeostasis of a healthy organism, but it can also participate in pathological processes such as cancer [88]. The morphological changes that occur during apoptosis include membrane swelling, chromatin condensation, cell shrinkage, and phagocytosis of apoptotic bodies [89]. Cell apoptosis can occur via either the receptor-mediated pathway (external pathway) or the mitochondrial pathway (internal pathway). The mitochondria are the central translation station for caspase-dependent apoptosis and caspase-independent apoptosis.

Caspase-dependent apoptosis can be initiated by two pathways: activation of death receptors such as DR5 or Fas [90] on the cell surface, which leads to the activation of initiator caspase-8 [91–92] inside cells. These changes ultimately lead to alterations in mitochondrial processes. In turn, these processes cause cytochrome C to be released from the mitochondria into the cell cytosol. In the cell cytosol, cytochrome C is activated by caspase-9 [83]. As in receptor-mediated and mitochondrial mechanisms of caspase-8 and caspase-9 activation, caspase-3 is also activated and participates in the cleavage of poly(ADP-ribose) polymerase. This process ultimately leads to DNA damage and is a marker of apoptosis [84].

If apoptosis occurs via a receptor-mediated mechanism, the activation of caspase-8 can cleave Bid to tBid to activate the mitochondrial pathway in type II cells, so cross-talk between the intrinsic and extrinsic pathways may be mediated by Bid [85]. Thus, sometimes the extrinsic pathway can stimulate the intrinsic pathway of apoptosis.

Binding death receptors with their ligands can also activate NF-kB, PI3K/Akt, and MAPK pathways [91]. The PI3K/Akt and MAPK pathways affect each other. Akt phosphorylation is modulated by p38 [93]. The PI3K/Akt pathway regulates apoptosis by activating caspase-9 [86]. The MAPK family, including ERK, JNK, and p38, can lead to NF-kB activation and cell survival [84–86]. P38 MAPK is mainly associated with apoptosis and differentiation. The ERK1/2 pathway is upstream of GSH and NO or affects the amount of GSH and NO while the JNK pathway depends on the presence of NO in the leukemia cell line HL-60, and GSTs are inhibitors of JNK 74. The MEK1/2-ERK1/2 pathway depends on MEKK1, and ERK1/2 activation affects JNK activity [90, 92].

In addition to mitochondria, the endoplasmic reticulum (ER) also participates in the apoptotic pathway by releasing Ca^{2+} ions into the cytosol. The release of cytochrome from mitochondria facilitates the release of calcium ions, and Bax and Bak affect this process [88]. The process of Ca^{2+} release and subsequent apoptosis is summarized as follows. GRP78 is released from the translocon and depletes ER Ca^{2+}. Then, Ca^{2+} binding to calmodulin activates CaMKII signaling. Finally, CaMKII and JNK induce Fas expression, and CaMKII enhances cytochrome C release and mitochondrial membrane potential loss [91], suggesting that ER stress may mediate both external and internal pathways. In addition, the ER stress signaling pathway may be associated with two cascades, namely PERK\P-eIF2a\CHOP and ATF6 (IRE-1)/XBP-1 [92].

Fucoidan is known to affect apoptotic mechanisms. For example, fucoidan obtained from the commercially available product *C. novae-caledoniae Kylin* induced apoptosis through caspase-independent and mitochondrial pathways. This process resulted in decreased expression of apoptosis inhibitors Bcl-2 and Bcl-xl while increasing the expression of apoptotic markers Bax and Bad, releasing cytochrome C and apoptosis-inducing factor (AIF) and activating the ROS-dependent JNK phosphorylation pathway in the human breast cancer cell line MCF-7 [93–95].

Fucoidan from *C. okamuranus* was reported to induce apoptosis by regulating NF-kB and AP-1 through inhibition of IκBα and JunD phosphorylation [96, 97].

Fucoidan isolated from *F. vesiculosus* raised caspase-3 levels, inducing apoptosis in human colon cancer HT-29 tissues and melanoma cells [98–100]. Fucoidan from *F. vesiculosus* induced apoptosis in the human colon cancer cell line HCT-15 by suppressing Bcl-2, increasing Bax activity, activating caspase-9 and caspase-3, cleaving PARP, activating ERK and p38, and blocking PI3K/Akt pathways [93].

T. Nakamura *et al*. [84] investigated the mechanism of apoptosis induction in the mouse 4T1 breast cancer cell line by unprocessed fucoidan from *F. vesiculosus*. Bcl-2 expression and ERK phosphorylation were significantly reduced, leading to diminished cell survival.

Unprocessed fucoidan from *F. vesiculosus* induced apoptosis in the 4T1 breast cancer cell line in mice by reducing the level of β-catenin in the nucleus and cytoplasm, subsequently reducing the expression of its targets [96].

Fucoidan from *F. vesiculosus* modulated ER stress, leading to decreased GRP78 expression, CaMKII phosphorylation, and high Bax and caspase-12 in the human breast cancer cell line MDA-MB-231. It also induced pro-apoptotic cascade p-eIF2\CHOP while suppressing the survival cascade p-IRE-1/XBP-1s in the human breast cancer cell line MDA-MB-231 and human colon cancer cell line HCT116 to induce apoptosis [96].

Fucoidan from *F. vesiculosus* induced apoptosis in human leukemia cell line HL-60, acute monocytic leukemia cell line THP-1, and human promyelocytic leukemia cell line NB4 by activating MEKK1, ERK1/2, MEK1, and

JNK. The depletion of glutathione and production of NO resulted in Bid cleavage and activation of caspase-8, -9, and -3 [91].

Isolated and purified fucoidan from *F. vesiculosus* was able to induce apoptosis in the human hepatocellular carcinoma cell line HepG2 through the p38 MAPK pathway [100].

Fucoidan obtained from *U. pinnatifida* induced apoptosis in the human hepatocellular carcinoma cell line SMMC-7721 via the AFK-mediated mitochondrial pathway with decreased GSH, accumulation of AFK, increased Bax/Bcl-2 ratio, and activation of caspase-8, -9, and -3 [101].

Fucoidan from *U. pinnatifida* induced apoptosis in the human prostate cancer cell line PC-3 by activating ERK1/2, inactivating PI3K/Akt and p38 MAPK, and suppressing the Wnt/*β*-catenin pathway [101].

Fucoidan from *U. pinnatifida* was reported to induce apoptosis in the human lung cancer cell line A549 by regulating the Bcl-2 family, regulating the MAPK pathway (activating ERK1/2 and suppressing p38), and suppressing the PI3K/Akt pathway [102].

The effects of fucoidan on apoptosis mechanisms are predominantly associated with caspase-dependent apoptosis, the Bcl-2 protein family, the MAPK pathway, the PI3K/Akt pathway, and the Wnt/*β*-catenin pathway. The IAP protein family, ER proteins, and the caspase-independent pathway AIF have a lesser impact on AFK. Fucoidan from various sources can induce apoptosis in a variety of cancer cell lines, including breast, colon, leukemia, hepatocellular carcinoma, prostate, lung, bladder, gastric, and myelodysplastic syndrome/acute myeloid leukemia cell lines. The mechanisms of apoptosis induction involve the activation of various signaling pathways and the modulation of specific proteins associated with apoptosis. However, some experiments *in vitro* demonstrated that fucoidan at cytotoxic concentrations did not affect the growth of tumor cell lines or their mitosis [103].

Ferroptosis is closely related to IR-induced hepatocellular damage. Administration of fucoidan or FER-1 inhibited ferroptosis by removing reactive oxygen species while inhibiting lipid oxidation and iron accumulation whereas these effects were reversible after erastin treatment. Iron accumulation, mitochondrial membrane fission, and reactive oxygen species production associated with ferroptosis were reported to inhibit the entry of nuclear factor erythroid 2-related factor 2 (Nrf2), hemoxygenase-1 (HO-1), and glutathione peroxidase 4 (GPX4) into the nucleus, resulting in decreased protein content. Pre-use of fucoidan facilitated adaptive changes and reduced irreversible cell damage induced by IR or erastin [104].

Fucoidan extracted from *F. vesiculosus* possess reliable anti-inflammatory effect. The related studies featured inflammation induced by lipopolysaccharide (LPS), polyinosin:polycytic acid, Pam2CSK4 (Pam), or tumor necrosis factor alpha (TNF-*α*). The expression of 65 kDa protein (RPE65) and protein (CD59) was verified by western blotting, quantitative polymerase chain reaction (qPCR) (IL6, IL8, MERTK, PIK3CA), and phakocytic activity by microscopic analysis. Fucoidan FV decreased the secretion of proinflammatory cytokines poly I:C IL-6 and IL-8. In addition, FV-fucoidan treatment was able to eliminate the decrease in CD59 in IL-6 and IL-8 expression by RT-PCR, LPS, and TNF-*α* in western blotting [105].

To summarize, heterogeneous sulfated polysaccharides hold great promise for cancer therapy and the functional food industry. However, fucoidan-based anticancer drugs and functional foods require stabilized monomeric composition and sulfation supported by preclinical and clinical molecular trials.

Immunoregulatory activity. Fucoidan is an effective immunomodulator, but this property is still under investigation [106]. According to some studies, the immunomodulatory activity of fucoidan is due to its antitumor and antiviral activities [107, 108]. These biological properties contribute to the modulation of the immune system at the cellular level [109, 110]. On the other hand, fucoidan may owe its immunomodulatory properties to its ability to bind to toll-like receptors, activate chemokines and cytokines, produce interleukin-2 and interleukin-6, stimulate the production of TNF-*α*, and activate the expression of CD40, CD80, and CD86. Fucoidan activates the immune system due to its probiotic activity [47, 109, 111, 112].

The extent to which fucoidan exhibits immunoregulatory activity depends on its structural characteristics, particularly on the number of acetyl and sulfate groups [111]. However, opinions differ, revealing a gap in the study of the relationship between the structure of fucoidan and its immunoregulatory activity. This property is an important area of focus for commercial application of fucoidan.

Antiviral activity. Viruses pose a tremendous threat in this era of rapid social development. Antiviral drugs are largely ineffective, making it a crucial challenge to find new effective but non-toxic antiviral substances. Preparations based on plant-derived polysaccharides were reported to shorten the duration of viral infections and alleviate their symptoms [113]. In addition, sulfated polysaccharides were capable of inhibiting such viruses as herpes simplex, viral diarrhea, influenza, cytomegalovirus, enterovirus, norovirus, HIV-1, hepatitis B, etc. [6, 47, 114, 115] while remaining low-toxic [6].

Fucoidan exerts its antiviral activity by binding to glycoproteins on the viral envelope, thereby preventing the virus from attaching to the host cell. It inhibits the process of viral adsorption by cells, inhibits reverse transcriptase activity, and inactivates the transcription process [6, 115–117]. However, this review fails to cover all the numerous, complex, and diverse mechanisms of fucoidan's antiviral activity [118].

The extent of fucoidan antiviral activity depends on its monosaccharide composition, polysaccharide chain length, degree of sulfation, and degree of branching. Of these parameters, the degree of sulfation has the greatest influence on the biological properties of fucoidan [6, 115]. For instance, fucoidan with a high degree of sulfation exhibited the highest antiviral activity [6]. The sulfate group at the C-4 position was reported to enhance antiviral properties (herpes simplex virus type 1) in the presence of a 1-3-linked glycosidic bond in the fuco-pyranosyl moiety [115].

As a natural substance, fucoidan could be a promising ingredient in next-generation functional foods with antiviral properties. However, developing such products requires a better understanding of fucoidan mechanisms of activity. Our literature search revealed a complete absence of clinical trials of fucoidan against human viruses. Such trials are crucial for confirming the future potential of this polysaccharide. Additionally, we detected a certain lack of information on the optimal molecular weight of fucoidan for antiviral activity. The effect of gastric acidity on fucoidan properties and intestinal penetration remains understudied.

Anticoagulant activity. Anticoagulant therapy is the most common form of treatment for the elderly, and anticoagulant drugs themselves are associated with a number of severe side effects [119]. Thus, searching for natural antithrombotic substances is of great therapeutic relevance [120], and fucoidan could be one of them [121]. This heterogeneous polysaccharide inhibits thrombin formation, slows down factor X synthesis, and inactivates fibrin polymerization [122]. However, these results were obtained using model systems, such as blood plasma and purified coagulation factors. Therefore, this direction requires *in vivo* studies of fucoidan's anticoagulant activity. The anticoagulant activity of fucoidan depends on its structure, including chain length, degree of sulfation, position within the chain, monosaccharide composition, and uronic acid content [109, 121, 123–129]. However, our literature review revealed some inconsistencies, which are summarized in Table 5.

Despite these contradictions, low-molecular-weight fucoidans definitely possess anticoagulant activity. For instance, fucoidans with a molecular weight of ≥ 850 kDa demonstrated no anticoagulant activity [124]. However, this observation was made on a limited number of samples, and further research is needed to establish a more convincing case. Therefore, additional research is required to strengthen the validity of this new knowledge regarding the anticoagulant activity of fucoidan.

Hypothetically, it is not the sulfation degree that affects anticoagulant activity but rather the location of the substituents. For example, H. H. Hsiao *et al*. [128] increased the anticoagulant activity of a natural fucoidan molecule by adding sulfate groups to the fuco-pyranose residues at positions 2 and 3. However, this hypothesis has not yet been confirmed or refuted by other researchers.

While scientific literature provides comprehensive data on the mechanism of fucoidan's anticoagulant activity and its characteristics depending on the molecular structure and composition, the results remain contradicting. Therefore, further scientific research is needed on the effect of molecular weight on anticoagulant activity. We were also unable to find a sufficient number of publications confirming *in vivo* anticoagulant activity with clinical trials. This gap in scientific knowledge remains to be addressed as it may yield a novel anticoagulant drug based on a natural polysaccharide.

Metabolic activity. Metabolic syndrome, also known as Syndrome X, is classified by the World Health Organization as a pathological condition characterized by abdominal obesity, insulin resistance, arterial hypertension, and hyperlipidemia (elevated levels of lipids in the blood). The total economic losses to countries are estimated in trillions as they include healthcare expenditures, loss of productive population, and social support costs [130]. Nutritionists and dietitians recommend incorporating bioactive substances into the diet to treat and prevent this condition. Fucoidan shows great promise in this regard as it alleviates pathological conditions associated with metabolic syndrome, including hyperglycemia, hyperlipidemia, obesity, and hypertension.

In particular, experiments *in vivo* demonstrate that this heterogeneous, non-linear polysaccharide inhibits alpha-glucosidase activity, improves glucose tolerance, and reduces the risk of diabetic retinopathy [38, 131]. For instance, fucoidan was described as a natural bioactive molecule that can prevent and treat non-insulin-dependent diabetes mellitus (type 2) [131–133]. Another benefit of fucoidan is its ability to lower blood pressure. Specifically, experiments on rats with diabetes showed a decrease in blood pressure following fucoidan administration [133].

A few scientific studies suggest that fucoidan may treat diseases associated with lipid metabolism disor-

Table 5. Inconsistencies regarding the anticoagulant activity of fucoidan

Таблица 5. Расхождения в результатах исследований антикоагулянтной активности фукоидана

Parameter	Supporting data	Inconsistencies	Reference
Molecular weight	Active fractions of 50–100 kDa	Some fucoidans with a molecular weight of ≤ 300 kDa have pronounced anticoagulant activity	[109, 124, 125]
High degree of sulfation	Correlates with activity	Some studies do not confirm this correlation	[109, 128]
Low content of uronic acids	Has a beneficial effect on anticoagulant activity	No systematic studies have been conducted	[109]

ders [130, 132, 134, 135]. It slows down lipogenesis and thereby improves lipolysis, suppresses the expression of adipose tissue, and inhibits the production of angiotensin II in blood plasma [130, 135]. As a result, animals' lipid profiles normalize (hyperlipidemia decreases), and macrophage infiltration decreases in adipose tissue. Simultaneously, the concentration of inflammatory cytokines and body weight go down [136, 137].

Fucoidan was reported as an effective prebiotic that stimulates the growth of normal gut flora and normalizes gastrointestinal motility [109, 132, 138]. As fucoidan is a complex polysaccharide, it can stimulate the growth of microorganisms in the intestine. However, because the specific prebiotic mechanisms of fucoidan remain poorly understood, deeper research in this area is required.

The information presented suggests that fucoidan is a unique natural molecule with combined therapeutic effects on metabolism, which contribute to the management of metabolic syndrome. However, information regarding the positive effects of fucoidan on metabolism is limited. This gap prevents a more precise description of its mechanisms of action. Understanding the mechanisms through which fucoidan improves metabolic processes will allow researchers to develop new drugs for treating conditions such as diabetes, hyperlipidemia, obesity, and hypertension.

Fucoidan in the food industry. Safety of fucoidan-based additives. The food industry uses macroalgae: in fact, 85% of all harvested macroalgae are used for this purpose [138]. The most popular microalgae are those grown in aquaculture. In 2019, 34.7 million tons of macroalgae were collected in artificial conditions, compared to only 1.1 million tons harvested in natural conditions [139]. Macroalgae are incorporated into traditional food products, creating foods fortified with macronutrients and bioactive compounds and intended for a broad segment of the population, especially in regions with no coastline [140].

Macroalgae biomass is used to produce agar, iodine, and phlorotannin but not fucoidan. Aquaculture-grown *C. okurana* is the only macroalgae used for industrial-scale fucoidan production [14]. However, fucoidan can be extracted from other macroalgae, e.g., *S. japonica*, *U. pinnatifida*, *F. vesiculosus*, etc. [138]. Sulfated polysaccharide has powerful therapeutic potential. Consequently, fucoidan holds significant potential as a pharmaceutical ingredient or functional food component, although the commercial development of such products remains in the early stages. Future formulations are anticipated to aid in the prevention and management of diverse disorders, particularly metabolic syndrome-associated conditions such as obesity, cardiovascular disease, and diabetes [14, 141].

The contemporary food market knows very few fucoidan-based products [14, 25, 141–147] (Fig. 5), and detailed descriptions of such functional products are virtually absent from scientific literature. Specifically, the only available references feature fucoidan being used in Japan as an ingredient in beverages, dietary supplements, and pills [14]. A. R. Ribeiro *et al.* [142] developed a pasta recipe based on *F. vesiculosus* flour. The flour content was 4–5%. This pasta composition was further fortified with iodine. For pasta with 5% seaweed, the iodine content reached 650–3,650 μg per 100 g of raw pasta. Therefore, seaweed can be used to fortified traditional formulations with fucoidan and iodine [14, 142]. Such foods are recommended for people with hypertension, as well as those with disorders of lipid and glucose metabolism [143, 147]. In such foods, yeast fermentation occurs during the proofing process [145]. Baker's yeast can metabolize galactose, a component of fucoidan. For instance, more gas was produced during proofing in the presence of fucoidan than in control samples [143]. Bread fortified with fucoidan demonstrated antioxidant and anticancer properties (against MCF-7 breast cancer cell line) [25]. Fucoidan can be used in cookie formulations. The functional cookies developed by X. Zhou [147] had a pleasant aroma and flavor while being able to lower blood glucose and promote weight management.

Some scientific publications introduced novel fucoidan-based beverages [148, 149]. One of them featured a functional cocktail drink containing fucoidan, *Triticum spelta*, *Morus australis*, carrots, cruciferous vegetables,

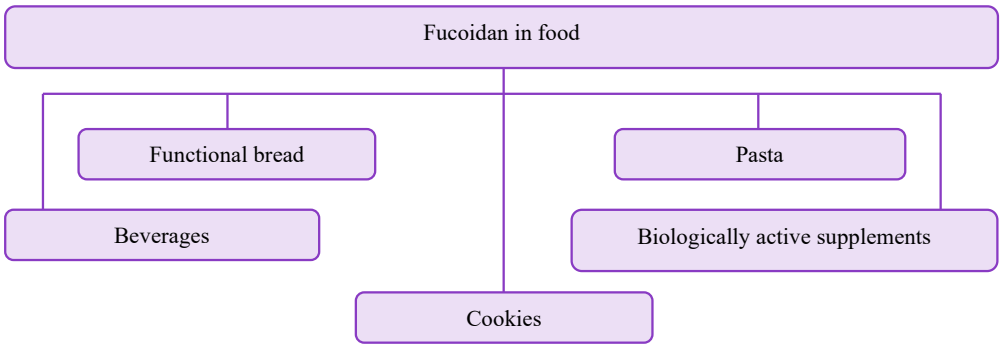

Figure 5. Fucoidan as a functional food ingredient

Рисунок 5. Расхождения в результатах исследований антикоагулянтной активности фукоидана

and fruits (pineapple, guava, noni, and passion fruit). Being able to slow down the progression of colorectal cancer, it can be used in combination with other therapies. The efficacy of this beverage was confirmed *in vitro* and *in vivo* (using a mouse model with tumors). The fucoidan complex demonstrated no side effects. It inhibited cell cycle regulators, the production of proapoptotic proteins, and the disruption of markers that induce the epithelial-mesenchymal transition [148]. Clinical trials of another fucoidan-based herbal beverage also revealed a favorable therapeutic effect. This beverage consisted of water, fucoidan (200 mg), radish seeds, hawthorn seeds, apple juice, green tea powder, broccoli powder, pectin, erythritol, malic acid, citric acid, stevia, sucralose, flavors, and fragrances. It was able to reduce or totally eliminate the bacterial load of *Helicobacter pylori* on the gastric mucosa [149].

Unfortunately, we were unable to find more information about fucoidan as a functional ingredient or the effectiveness of fucoidan-based foods. Nevertheless, the limited information in this study suggests the potential of fucoidan as a bioactive ingredient in functional foods that can normalize gastrointestinal function, promote beneficial intestinal bacteria, enhance human immune status, and improve metabolism [150].

Expanding the polysaccharide-based range of food products is an important challenge because polysaccharides are indispensable for human life. To do that, scientific community, technologists, and food industry engineers need to develop unified technology for producing macroalgae from biomass and purifying fucoidan. This achievement would enable industrial production of a reliable bioactive ingredient. Meeting the demand for fucoidan-based nutrition necessitates increasing either wild seaweed collection or macroalgae cultivation.

Conclusion

This review covered relevant publications and documents on the heterogeneous sulfated polysaccharide fucoidan found in marine algae to organize available information on its structure. This natural molecule possesses a heterogeneous, branched structure and a variable monosaccharide composition, including fucose, galactose, mannose, xylose, and glucuronic acid. Additionally, fucoidan varies in sulfation and molecular weight. The structural features of fucoidan depend on the type of algae, harvest season, water temperature, and extraction method.

The main sources of fucoidan include *Ascophyllum nodosum*, *Fucus vesiculosus*, *Nizamuddinia zanardinii*, *Undaria pinnatifuta*, *Sargassum ilicifolium*, *Sargassum myriocystum*, and *Turbinaria decurrens*. The highest content of heterogeneous polysaccharides (≤ 24% d.w.) was observed at a growth temperature of 10–17 °C, indicating a significant effect of seasonality on fucoidan yield and chemical structure.

The review provides a detailed description of the various methods used to extract and purify fucoidan, including microwave, ultrasonic, enzymatic, hot water, and acid extractions. Microwave extraction was found to provide the highest fucoidan yield (≤ 18.2%) in the shortest amount of time while preserving the native structure of the polysaccharide. However, the lack of a unified technology for producing fucoidan with stable physicochemical properties hinders its application and Good Manufacturing Practice standardization.

Its biological activity depends on molecular weight, sulfation, fucose, and uronic acids. The mechanisms of fucoidan action remain partially understudied or contradictory, highlighting clear avenues for future research.

In the food industry, fucoidan is a promising and safe ingredient for functional foods. However, the list of commercial products fortified with fucoidan is disappointingly short. No publications featured results of clinical trials of novel fucoidan-based foods. Therefore, establishing new strategies to optimize production parameters and develop standardized purification protocols represents a key priority in biotechnology. Novel approaches will make it possible to turn fucoidan into a full-fledged functional ingredient and expand the range of functional foods.

Contributions

D.I. Malkov and S.A. Sukhikh developed the research concept, designed the methodology, analyzed and interpreted the data. S.A. Sukhikh supervised the project. S.A. Sukhikh and N. Barzkar provided the formal analysis. D.I. Malkov, E.V. Kashirskikh, and K.A. Balashova wrote and proofread the review.

Conflict of interest

The authors state that there is no conflict of interest.

Критерии авторства

Д. И. Мальков и С. А. Сухих – концепция исследования, методология, анализ и интерпретация данных. С. А. Сухих – общее руководство проектом. С. А. Сухих и Н. Барзкар – формальный анализ. Д. И. Мальков, Е. В. Каширских и К. А. Балашова – написание и редактирование статьи.

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Авторы заявляют об отсутствии конфликта интересов.

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