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Extraction Method of Alginate Polysaccharide, Its Biological Activity and Research on Its Potential in Hypoglycemia, Antioxidation and Immunomulation

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Abstract. Functional active ingredients are key research targets in the food, biomedical, and health sectors, with broad application prospects in the food industry, healthcare, and medicine. Among these, seaweed polysaccharides have drawn significant attention due to their unique properties and application potential. This review summarizes the types, functional characteristics, extraction methods (both conventional and modern, with a comparison of their advantages and disadvantages), as well as the core biological activities and mechanisms of seaweed polysaccharides, based on a comprehensive analysis of domestic and international literature. The results indicate that seaweed polysaccharides exhibit notable functional advantages in food development, pharmaceutical preparations, and health products. Modern extraction techniques outperform conventional methods in terms of extraction efficiency and environmental sustainability. Their anti-inflammatory, antioxidant, hypoglycemic, and immunomodulatory properties show great potential in functional food markets such as diabetes management, immune health, and anti-aging.

Keywords: Algae polysaccharides, Species, Extraction method, Biological activity

1. Introduction

Functional food is mainly a name for foods that can improve physical health or reduce disease in Europe, the United States, and Japan. In our country, the definition of functional food and health food refers to foods that claim to have specific health functions or are intended to supplement vitamins and minerals. That is, it is suitable for consumption by specific groups of people, has the function of regulating the body, is not for the purpose of treating diseases, and does not produce any acute, subacute or chronic harm to the human body. It not only has the energy supply function of traditional food, but also contains a variety of active ingredients that help regulate human physiological functions, such as dietary fiber,probiotics, polyphenols, etc. [1]. With the development of the times, healthy eating has attracted much attention around the world, and food health and functionality have become the general trend of the world food manufacturing industry, and this food category is also widely used in a variety of people. Modern functional foods play an important auxiliary and complementary role in health management, and their core role is to help maintain a healthy state, reduce health risks or assist in improving specific physiological indicators by

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regulating human physiological functions, and they can also assist in regulating metabolism in chronic disease management, such as products containing dietary fiber and plant polyphenols can help control blood sugar, and plant sterols and omega-3 fatty acids can help regulate blood lipids and blood pressure; In addition, the antioxidants contained in functional foods (such as anthocyanins and curcumin) can scavenge free radicals, reduce oxidative stress, and have a positive effect on the prevention of complications of chronic diseases such as diabetes.

Diabetes, as a global health challenge disease, is showing a trend of spreading. According to a study published in The Lancet Public Health, the number of people with diabetes reached 529 million in 2021 and is expected to rise to 1.31 billion by 2050. Based on the data in the Global Diabetes Map released by the International Diabetes Federation (IDF) and the forecast table for the number of people with diabetes in the world and China from 2019 to 2028 generated by prediction models commonly used by industry analysts, the number of people with diabetes in the world and China will continue to grow strongly in the next few years,as shown in Figure 1.The growing diabetic population will drive the demand for functional foods that support blood sugar management. Low-GI foods and beverages have seen a 56% year-on-year increase in search popularity, with significant sales growth. The global diabetes drug market is expected to exceed $145 billion by 2032, with a compound annual growth rate of 6.9%., and in the hypoglycemic and anti-sugar market, the blood sugar control market of medicine and food homologous has shown a rapid growth trend in recent years.

As a class of functional foods of natural origin, its core advantages stem from the inherent natural attributes of this type of food. This paper will systematically discuss the related content of seaweed polysaccharides from three aspects: extraction method, biological activity and mechanism of action, hoping to provide a new theoretical reference for the prevention and management of diabetes and the development of health foods.

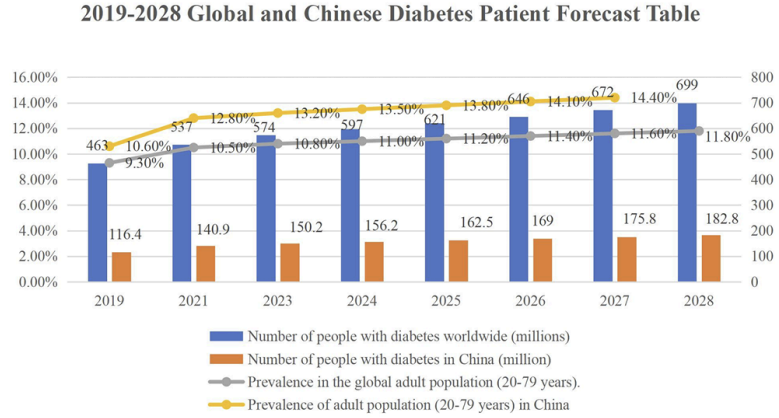

Figure 1. 2019-2028 global and chinese diabetes patient forecast table

2. Types and functions of alginate polysaccharides

2.1. Types of alginate polysaccharides

There are many types of seaweed polysaccharides, mainly divided according to the type of seaweed from which they come (brown algae, red algae, green algae, cyanobacteria). The main species are fucoidan, red algae polysaccharide, chlorophylgoid and cyanopolysaccharide. The most representative of fucoidan is alginate, also known as alginates, which are widely found in the family Fucoididae, and common brown algae such as kelp, wakame, sargassum and other common brown

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algae contain a large amount of alginate in the cell wall and intercellular interstitium. Alginate is a linear polymer formed by the linkage of D-mannuronic acid and L-gurocuronic acid through 1,4-glycosidic bonds. These two monosaccharide units are randomly arranged or segmented in the chain, forming fragments with different structures, and their arrangement order and proportions further affect their properties. It has strong hydrophilicity, gelatination, biocompatibility and adsorption, and can form a thermally irreversible gel with divalent cations (especially Ca^{2+}). Carrageenans, a representative substance of red algae polysaccharides, is widely known in the phylum Carrageenans, which are widely found in the cell walls of common red algae such as unicorn, cauliflower, and carrageenans, and are its important colloidal components. Representative substances of chlorovoidans include sulfated polysaccharides, such as Caulerpa polysaccharide from Fern algae, Ulvan, etc. Chlorophylgide polysaccharides have complex and diverse structures, but many of them have important biological activities are "sulfated polysaccharides". Chlorella sulfated polysaccharides have attracted much attention for their significant biological activities, including antiviral (especially anti-herpesvirus, influenza virus), immunomodulatory, antioxidant, anticoagulant, antitumor and other activities. At present, it is mainly used in health care products, functional foods and pharmaceutical research and development, and its application as a food additive is not as widely as that of fucoidan and carrageenan.

2.2. Functional one

The hypoglycemic function of seaweed polysaccharides is one of its core effects, which is mainly reflected in regulating the activity of glucose metabolism-related enzymes, improving insulin resistance, protecting pancreatic islet β cells, and helping patients control blood sugar levels. When fucoidan acts with the human intestine, it can reduce the postprandial blood sugar peak by delaying the absorption rate of glucose in the intestine - as dietary fiber, it can form a gel-like structure in the intestine, hinder the contact between glucose and the intestinal mucosa, prolong the gastric emptying time, reduce the amount of glucose quickly entering the bloodstream, and then reduce the peak blood sugar [2]. When fucoidan acts on healthy or obese people, it can achieve the effect of regulating blood sugar by reducing the total absorption of glucose by the intestine - for example, after healthy adults eat a drink containing 1.5g of alginate, the maximum blood glucose concentration and total glucose absorption after meals are significantly reduced within 3 hours, and the blood glucose content is also substantially reduced after obese people drink alginate drinks [2]. For example, the relevant experiments in the article "Research on the Purification and Scavenging Activity of Kelp Polysaccharides" showed that WPS-1-1 had superoxide anion radical and hydroxyl radical scavenging activities, with IC_{50} of 0.35mg/mL and 1.0mg/mL, respectively [3]. This study showed that WPS-1-1, a purified component of kelp polysaccharides, can be used as a natural functional free radical scavenger and reflect its efficient antioxidant effect. In addition, fucoidan sulfate is also one of the types of seaweed polysaccharides with excellent antioxidant activity and is widely used in the field of medicine and health care [4]. In 2003, Haikun Xinxi Capsule was approved as a new drug certificate and successfully listed, developed by the team of Zhang Quanbin, a researcher at the Institute of Oceanography of the Chinese Academy of Sciences, mainly for the treatment of chronic renal failure.

2.3. Functional two

Meanwhile, the anti-inflammatory properties give trehade polysaccharides deeper development potential in medicine, health products, food, cosmetics and other fields. It mainly plays an anti-

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inflammatory effect by regulating inflammation-related signaling pathways, such as inhibiting the NF-κB signaling pathway (core pathway), regulating MAPK signaling pathway sugars (such as fucoidan can inhibit the phosphorylation of key kinases in the MAPK pathway, block the transmission of inflammatory signals from the outside of the cell to the nucleus, and reduce the production of TNF-α, IL-1β and other factors [5]). The study in "The Anti-Inflammatory Effect of Low Molecular Weight Fucoidan from in Lipopolysaccharide-Stimulated RAW 264.7 Macrophages via Inhibiting NF-κB/MAPK Signaling Pathways" clearly states that In lipopolysaccharide-stimulated RAW 264.7 macrophages, fucoidan sulfate can dose-dependently reduce the phosphorylation levels of p38, ERK, and JNK in the MAPK signaling pathway, while inhibiting the activation of NF-κB signaling pathway, and the relationship between its anti-inflammatory mechanism and phosphorylation inhibition of the MAPK pathway is elaborated [5]. A study published in Materials Science & Engineering C showed that low sulfate-based content of κ/β-carrageenan oligosaccharides could stimulate the secretion of anti-inflammatory factors IL-10 and TGF-β2 in M1 RAW264.7 macrophages, reduce the secretion of pro-inflammatory factors IL-6 and TNF-α, and accelerate the transformation of M1 macrophages into M2 phenotypes, indicating the anti-inflammatory effect of carrageenan oligosaccharides [6]. The product can effectively inhibit the reproduction of bacteria, reduce the inflammation and exudation of skin tissue, relieve the symptoms of redness, swelling, pain and other symptoms caused by damage to the barrier, and promote wound healing. It is correlated with the anti-inflammatory effect of carrageenan oligosaccharides. Under normal physiological conditions, agar oligosaccharides stimulate the secretion of immune-enhancing factors such as IFN-γ [7] to maintain the stability of the body's immune function, which is equivalent to "icing on the cake". These research results clearly confirm the positive role of seahade polysaccharides in the benefits of Jiankang, and their future development has unlimited potential.

3. Extraction method of alginate polysaccharide

3.1. Traditional extraction process

Seaweed polysaccharides are polysaccharides, and there are many extraction and preparation methods, with different advantages and disadvantages, and the common traditional extraction methods include water extraction, acid-base extraction, and alcohol extraction [8]. Hot water extraction is one of the commonly used traditional methods for polysaccharide extraction [9], while seaweed polysaccharides are easily soluble in water, and the traditional water extraction method is widely used in the extraction of seaweed polysaccharides. The water extraction method involves the separation of the plasma wall of cells with the assistance of heat, and the infiltration of aqueous solvents into the cells to dissolve polysaccharides [8]. The optimal extraction conditions of different plants are different, and the extraction rates of polysaccharides under different solid-liquid ratios, temperatures, and times are also different [9]. Wang Xian et al. showed that the optimal extraction process of seaweed polysaccharides by hot water method was 55°C, solid-liquid ratio 1∶32, and extraction time of 90min [8]. The advantages of water extraction are low cost, easy operation, and suitable for large-scale industrial use, but it is inefficient and time-consuming, and often requires optimization of other extraction methods [9]. The acid-base extraction method promotes the expansion and rupture of algal cells through the action of acid-alkali solution, resulting in the release of polysaccharides [10]. Wang Zhirong et al. showed that citric acid extracted kelp polysaccharides with the best effect, and the optimal process was: time 2h, liquid-to-solid ratio 25/1, temperature 100°C, pH 2.0, and yield of 12.95% [9]. However, the acid-base method can easily destroy the structure and activity of polysaccharides, and complex purification treatment is required after

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extraction, which is difficult to operate [8,11]. The alcohol extraction method precipitates polysaccharides by dehydration of alcohol solvents, which has a high yield and small activity loss, but is expensive and complicated to operate [12]. A study by Chengdu University showed that the best conditions for the extraction of kelp polysaccharides from alcohols were 5 times concentrated after water extraction, and 95% ethanol with a 4.5-fold volume fraction was added, with a yield of 10.49% [13]. In general, traditional methods have shortcomings in extraction efficiency, activity retention, cost, and environmental protection, making it difficult to fully meet the needs of high-purity and high-activity extraction, and still need to be further optimized, such as combining new technologies such as enzymatic hydrolysis and ultrasonic assistance.

3.2. Modern extraction method

It is the limitations of traditional extraction methods of seaweed polysaccharides that have prompted researchers to explore more efficient, gentle and accurate extraction technologies, and have given birth to emerging extraction methods such as ultrasound-assisted extraction, enzymatic hydrolysis extraction, and microwave-assisted extraction. Ultrasound-assisted extraction is a non-thermal extraction technique that induces pressure changes and cavitation through sound waves, disrupting cell walls and enhancing solvent contact with target compounds [14]. Wang Yongliang et al. showed that the extraction rate of isocladosis sulfate polysaccharide reached 48.14% when the ultrasonic time was 20 min, the power was 150 W, and the solid-liquid ratio was 1:90, which was significantly better than that of hot water extraction [15]. The advantages of ultrasound-assisted extraction are atmospheric pressure, low temperature, and high efficiency, but the price of equipment is high, such as ultrasonic extraction instruments, which are as high as 8,800 yuan [7]. Enzymatic hydrolysis uses specific enzymes to hydrolyze the outer wall of algae cells, increase permeability, and release polysaccharides. Zhang Feng et al. used xylanase to extract coral algae polysaccharides, and the optimal process after optimization was 0.8% xylanase addition, enzymatic hydrolysis temperature 50°C, and enzymatic hydrolysis time of 3h, with the highest yield [16]. The enzymatic hydrolysis extraction method is carried out under mild conditions, which can effectively protect the structure and activity of heat-sensitive substances [17]. However, the activity of enzymes is greatly affected by temperature, pH, etc., and the price of enzymes is high, making them difficult to recycle. In recent years, new extraction technologies such as ultrasound, enzymatic hydrolysis, and microwave have improved the extraction efficiency of seaweed polysaccharides and optimized the process, significantly improved the yield, shortened the extraction time, reduced the use of organic solvents, and avoided the damage of polysaccharide structure by high temperature or chemical reagents. As shown in Table 1.

Table 1. Extraction method of alginate polysaccharide

Extraction method	Type	Advantages	Disadvantage	Applicable Scenarios
Water extraction method	Traditional	Low cost, easy to operate, suitable for large-scale industrial use.	The efficiency is low and time-consuming, often requiring optimization through alternative extraction methods.	Large-scale industrial production in cost-sensitive scenarios.

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Table 1. (continued)

Acid-base extraction method	Traditional	The extraction efficiency is relatively high.	The structure and activity of polysaccharides are easily compromised, requiring complex purification processes after extraction, which poses significant operational challenges.	Extraction of specific types of seaweed polysaccharides.
Soxhlet extraction method	Traditional	The yield rate is relatively high, and the activity loss is minimal.	The cost is relatively high.	Scenarios with high demands for polysaccharide activity.
Ultrasound-assisted extraction	Modern	Constant pressure, low temperature,high efficiency.	The price of the equipment is relatively high (for example, the price of the ultrasonic extraction instrument reaches 8,800 yuan), and the operation is complex.	Laboratories and small-scale production scenarios that require high extraction efficiency.
Enzymatic extraction method	Modern	Usually conducted under mild conditions, it effectively protects the structure and activity of heat-sensitive substances.	The activity of enzymes is significantly influenced by factors such as temperature and pH, and the high cost of enzymes makes them difficult to recycle.	The extraction of high-value seaweed polysaccharides, in scenarios where the preservation of activity is of utmost importance.

4. Bioactivity and mechanism of action of alginate polysaccharides

4.1. Antioxidant activity and mechanism of action

The significant antioxidant activity of seahade polysaccharides has attracted much attention in many research and development fields. Oxidative stress is an imbalance between oxidants and antioxidants, manifested by excessive production of reactive oxygen species (free radicals, hydrogen peroxide, etc.), or the inability of the antioxidant system (e.g., antioxidant enzymes, vitamin C/E, etc.) to effectively remove these reactive oxygen species, leading to cell damage, which in turn leads to aging, cardiovascular disease, neurodegenerative diseases, etc. [18]. Like other natural antioxidants, trehado polysaccharides can exert their antioxidant effects by scavenging reactive oxygen species, inhibiting oxidative reactions, or enhancing the body's antioxidant function [19]. The fucoidan SFF-PS-F5 isolated from fermented hijiki (Sargassum fusiforme) can effectively protect oxidative stressed Vero cells and reduce cell damage in vitro. In vivo, it can improve the survival rate of H_2O_2-stimulated zebrafish and reduce cell death. The mechanism is to inhibit oxidative stress by regulating the Nrf2 signaling pathway, upregulating the expression of superoxide dismutase (SOD) and catalase (CAT), and enhancing the ability to scavenge reactive oxygen species [20]. Other studies have also shown that Sargasso fucoidan SF-F can improve the viability of Chang hepatocytes treated with ethanol and significantly improve the survival rate of zebrafish. SF-F exerts antioxidant effects by inhibiting lipid peroxidation because its molecular structure contains active groups such as hydroxyl groups and sulfate groups, which can bind to reactive oxygen species and remove them, reduce the occurrence of lipid peroxidation, and protect cells from oxidative damage [21]. The results showed that seaweed polysaccharides showed significant antioxidant potential in improving cell damage caused by oxidative stress and reducing lipid peroxidation.

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4.2. Anti-diabetic and mechanism of action

The hypoglycemic ability of seaweed polysaccharides provides important support for its health value, especially in the context of the continuous growth of the global population of diabetes and hyperglycemia, the role of seaweed polysaccharides in blood sugar regulation has attracted widespread attention. Trehaidan can slow down the digestion and absorption of carbohydrates by inhibiting digestive enzyme activity, and lower postprandial blood sugar. Shi Shuo et al. found that crude polysaccharide (EGP) and its purified components EGP-1, EGP-2 and EGP-3 could effectively inhibit the activities of α-amylase and α-glucosidase in a dose-dependent manner. The IC50 of EGP-3 for α-amylase was 2.15 mg/mL, and the IC50 value for α-glucosidase was 0.62 mg/mL, and the hypoglycemic effect was the best [22]. Li Can et al. found that the four graded alcohol precipitation components of wakame fucoidan, UPP-45, UPP-55, UPP-65, and UPP-75 all had hypoglycemic activity, among which UPP-65 had the highest inhibition rate of α-amylase, with an IC50 value of 0.008 mg/mL [23]. Trehade polysaccharides can also regulate blood sugar levels by enhancing insulin sensitivity and promoting insulin secretion. Studies have shown that kelp polysaccharides can significantly reduce fasting blood glucose levels and increase serum insulin levels in mice with type 2 diabetes, indicating its promoting effect on the secretory function of pancreatic islet cells [24]. In addition, in the study of Liu Qianyang et al., the polysaccharide can significantly reduce fasting blood glucose and the area under the blood glucose curve in diabetic mice in the dose range of 200-400 mg/kg, improve pancreatic islet function, and increase serum insulin content [25]. These studies provide a theoretical basis and new research direction for the development of seaweed polysaccharide-related hypoglycemic functional health products.As shown inTable 2.

Table 2. Hypoglycemic cases

Seaweed species	Polysaccharide name/component	Hypoglycemic effect	Mechanism of action
Qiongzhi Qilin vegetable	Crude polysaccharide (EGP) and purified components EGP-1, EGP-2, EGP-3	EGP-3 inhibits α-amylase IC_{50}: 2.15 mg/mL; Inhibition of α-glucosidase IC_{50}: 0.62 mg/m	Inhibition of digestive enzyme activity: By inhibiting the activity of α-amylase and α-glucosidase, it delays the digestion and absorption of carbohydrates, thereby reducing postprandial blood sugar, and the effect is dose-dependent.
Wakame	Fucoidan grading component UPP-65	Inhibition of α-amylase IC_{50}: 0.008 mg/mL (highest inhibition rate mentioned in this article)	Inhibition of digestive enzyme activity: effectively inhibits α-amylase activity, prevents the decomposition of starch into glucose, and slows down its absorption.
Kelp	Kelp polysaccharides	Significantly reduced fasting blood glucose levels and increased serum insulin levels in mice with type 2 diabetes.	Regulates insulin function: Regulates blood sugar levels by enhancing insulin sensitivity and promoting insulin secretion, improving pancreatic islet cell function.
Moss	Moss is rich in sugar	At a dose of 200-400 mg/kg, it can significantly reduce fasting blood glucose and the area under the glycemic curve in diabetic mice, and increase serum insulin content.	Regulate insulin function: Improve pancreatic islet function and promote insulin secretion, thereby comprehensively regulating fasting and postprandial blood sugar levels.

4.3. Immune regulation and its mechanism

The regulatory role of seaweed polysaccharides in the immune system is worth paying attention to. The immune system is the body's defense system that destroys pathogens and diseased cells [26]. Immune imbalances can lead to immunocompromised, allergic reactions, or autoimmune diseases.

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Trehado regulates immune function by activating immune cells (such as macrophages and lymphocytes), promoting cytokine secretion, and modulating immune signaling pathways. It was found that high molecular weight fucoidan sulfate FPS1M could significantly induce the transformation of macrophages to M1 phenotype and promote apoptosis of colon cancer cells. FPS1M promotes macrophage glycolysis and regulates macrophage phenotypic differentiation to M1 phenotypic by activating the TLR4-mediated PI3K-AKT-mTOR-PPARγ signaling axis, thereby improving the tumor microenvironment [27]. Li Yizhen et al. showed that Artemisia polysaccharides can effectively promote the proliferation of RAW264.7 in mouse macrophages and significantly induce cells to secrete cytokines such as NO, IL-1β, TNF-α, and IL-6, which play an immunomodulatory role [28]. In addition, the immunomodulatory effects of seaweed polysaccharides are also manifested in anti-inflammatory aspects, with excessive or persistent inflammation causing damage, while seaweed polysaccharides have anti-inflammatory effects. In studies of acute radiation enteritis, fucoidan significantly reduced the incidence of radiation enteritis and improved the patient's symptom and functional status [29]. These studies suggest that seaweed polysaccharides have unique advantages in the prevention and intervention of immune-related diseases.

5. Conclusion

Seaweed polysaccharides, a class of natural polymeric compounds extracted from marine algae, are primarily categorized into four types: brown, red, green, and blue algae polysaccharides. Extraction techniques have evolved from traditional water-based and acid-alkali methods to modern assisted approaches including ultrasonic, enzymatic, and microwave extraction, significantly improving efficiency and precision. Studies have demonstrated that seaweed polysaccharides exhibit multiple biological activities such as anti-inflammatory, antioxidant, hypoglycemic, and immunomodulatory effects. With advancements in green extraction technologies and the standardization of raw materials, seaweed polysaccharides are expected to play a significant role in functional food markets including diabetes management, immune health, and anti-aging.

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