Recent Advances on Bioactivity of Seaweed Polysaccharides

Junwen Wang,^a Xueyan Li,^a and Chaoyan Zhang^{*,a,b,c,d}

^a Department of Marine Bio-Pharmacology, College of Food Science and Technology, Shanghai Ocean University, Shanghai 201306, China

^b National Freshwater Aquatic Products Processing Technology R&D Center (Shanghai), Shanghai 201306, China

^c Shanghai Aquatic Products Processing and Storage Engineering Technology Research Center, Shanghai 201306, China

^d Laboratory of Storage and Preservation Quality and Safety Risk Assessment of Aquatic Products of the Ministry of Agriculture (Shanghai), Shanghai 201306, China

Email: chzhang@shou.edu.cn (C. Z.)

Abstract Seaweed polysaccharide is an important active substance in seaweed with good gel property, stability, and film-forming properties. It possesses various biological activities such as anti-virus, anti-tumor, immune regulation, anti-oxidation, and is widely used in food, health care and cosmetics. This article reviews recent advances on biological activities of seaweed polysaccharides, with a view to better development and utilization of seaweed polysaccharides, and promoting the sustainable and healthy development of the seaweed polysaccharide industry.

Keywords seaweed polysaccharide, bioactivities, applications

Introduction

Marine life accounts for about 80% of the earth's biological resources and grows in a special environment with high pressure, high salt, low oxygen and low nutrition.^[1] According to the origin, marine life is divided into three categories: seaweed, marine microorganisms and marine animals.^[2] Compared to marine animals and microorganisms, algae has attracted much attention in the fields of pharmacology and biochemistry in the past decade. Seaweed is a good source of carotenoids, vitamins, minerals, phenols, sulfated polysaccharides, peptides and proteins.^[3] These compounds have a variety of biological activities, including antioxidant,^[4] anti-tumor,^[5] anti-viral,^[6] anti-allergic^[7] and anti-microbial,^[8,9] etc. Due to the bioactivities, seaweed extracts have been studied as important ingredients in food and feed products. According to ancient Chinese medical literature, seaweed can be used as a therapeutic agent.^[10,11] For modern research, seaweed consumption also contributes to human health, such as the regulation of intestinal flora.^[12,13] This article reviews current bioactivities of seaweed polysaccharides with a view to providing references for further development and utilization of seaweed polysaccharides.

Structure of Seaweed Polysaccharide

Seaweed polysaccharide is a class of high molecular weight natural compound with complex chemical structures.^[14] According to their sources, they can be divided into red algae polysaccharides, green algae polysaccharides, and brown algae polysaccharides. In recent years, the research on brown algae polysaccharide is the most, and the red algae polysaccharide is the second. Macie *et al.*^[15] isolated and purified a red sulfated polysaccharide from *Gracilaria birdiae*. Structural analysis showed that the polysaccharide was mainly composed of galactose, and the sulfate group was linked to the C-6 position (Figure 1). Barros *et al.*^[16] obtained a polysaccharide gel permeation chromatography (GPC) with a molecular

Figure 1 The structure of the galactan from species of marine red algae.^[15]

weight of 250 kDa from red algae *Gracilaria caudata*, which is mainly composed of galactose.

It is well known that brown algae produces different polysaccharides, such as alginates, fucoidans, and laminarans. Fucoidan and laminarans are main water-soluble polysaccharides of brown algae, and high molecular alginic acid is an alkali-soluble polysaccharide. Fucoan can be divided into three categories: fucoidan, xylose glucuronide, and glycogalactan (Figure 2a). Fucoidan is a branched-chain polysaccharide sulfate, and its main component is L-fucose 4-sulfate. Fucoidan is composed of fucose, uronic acid, galactose, xylose and sulfated fucose. Xylose glucuronide is mainly poly- β -(1,4)-D-mannuronic acid and 3-O-D-xylosyl-L-fucose-4-sulfate or occasional uronic acid. Glycogalactan is composed of a linear chain of (1,4)-D-galactose on C5 with L-fucosyl-3-sulfate or

occasionally uronic acid. Laminaran is a water-soluble polysaccharide containing 20–25 glucose units, which are composed of (1,3)- β -D-glucans with β (1,6) branching (Figure 2b).^[17] There are two types of laminaran chains (M or G) and their reducing ends are different. The M chain ends at a mannitol residue and the G chain ends at a glucose residue. Laminaran has a molecular weight of about 5000 Da. Alginic acid or alginate is the common name for a class of linear polysaccharides that contain 1,4-linked β -D-mannuronic acid and α -L-gulose in an irregular, block order along the chain (Figure 3).

Figure 2 Structural unit of polysaccharides from brown algae (a) fucoidan; (b) laminaran.^[18]

Figure 3 Monomeric compounds present in alginic acid. (a) β -D-mannuronic acid; (b) α -L-guluronic acid.^[18]

Antioxidant Effect of Seaweed Polysaccharide

In recent years, more and more research has been focused on the anti-oxidation of seaweed polysaccharides. Currently, hydroxyl radicals, superoxide radicals, peroxy-radicals and NO radicals are generally considered as reactive oxygen species (ROS). Due to different oxygen metabolism pathways, including overstimulation of NAD (P) H via cytokine/xanthine oxidase and mitochondrial electronic pathways, ROS is continuously produced in organisms.^[19-21] The production of intracellular ROS often creates an imbalance between oxidant generation and antioxidant system, which ultimately leads to oxidative stress in the body.^[22] However, long-term use of synthetic antioxidants has side effects such as blood coagulation.^[23] At present, the development of effective antioxidants from natural resources such as land and sea is the focus of current research. In recent decades, seaweed polysaccharides extracted from

seaweed have received considerable attention.

Some research shows that crude polysaccharides from spore leaves of *Undaria pinnatifida* can significantly increase the thymus and spleen indexes of oxidatively injured mice, promote lymphocyte proliferation, enhance the killing power of NK cells and the ability of antibody secretion.^[24] Feng *et al.*^[25] studied on the monosaccharide composition and antioxidant activity of *Ulva lactuca*, *Saccharina japonica*, *Undaria pinnatifida*, and *Porphyra*. The results showed that the ability of *Undaria pinnatifida* polysaccharide for removal of 2,2-diphenyl-1-picrylhydrazyl was significantly higher than the other three seaweed polysaccharides. *Ulva*, *Undaria* and *Saccharina* have strong scavenging activities for hydroxy free radicals, while *Porphyra* polysaccharides have poor scavenging ability for hydroxy free radicals. The activity of scavenging activity of *Ulva* and *Undaria* on superoxide anion is stronger than that of *Saccharina* and *Porphyra*. Ma *et al.*^[26] studied the free radical scavenging ability and lipid peroxidation inhibition ability of crude polysaccharides from *Betaphycus gelatiniae*, *Ulva*, *Sargassum polycystum*, *Padina australis* and *Caulerpa Sertularioides*. The results showed that the polysaccharides of *Padina* and *Sargassum polycystum* had strong reducing power and they had strong scavenging activities against superoxide anion and hydroxyl radical. Zhao *et al.*^[27] analyzed the composition of seaweed polysaccharides such as *Sargassum thunbergii*, *Hizikia fusiforme*, *Saccharina* and *Porphyra yezoensis*. The results showed that *Sargassum thunbergii* and *Hizikia fusiforme* showed good antioxidant activity. Different seaweed polysaccharides have different antioxidant capacities. Seaweed with strong antioxidant capacity can be selected for further research.

Antiviral Effect of Seaweed Polysaccharides

In recent years, infectious diseases caused by emerging viruses have caused huge threats, and we are committed to the research and development of antiviral drugs.^[28] Although the number of antiviral drugs approved for clinical use has been increasing, the treatment of infectious diseases is still problematic due to insufficient drug efficacy and high cost. Therefore, there is an urgent need to develop new antiviral drugs. Some polysaccharides isolated from seaweed have antiviral and immunomodulatory activities and are suitable for developing antiviral agents.^[29] Although the life cycle of a virus varies greatly between species, there are six basic stages of the life cycle of a virus: attachment, penetration, unshelling, replication, assembly, and release. It has been reported that marine polysaccharides, especially polysaccharides in seaweeds, have a unique structure and play a role in killing various viruses by interfering with different stages of the viral infection process (Figure 4).^[30] It has resulted in widespread interest in drug development and antiviral drug development.^[31]

Zhang *et al.*^[32] used *in vitro* cell culture methods to study the antiviral activity of seven seaweed polysaccharides in the South China Sea. The results showed that these seven seaweed polysaccharides showed certain antiviral activity against herpes simplex virus 1 (HSV-1) and Coxsackie B group 3 virus (Cox B3). Among them, *Ulva lactuca* polysaccharide and *Grateloupia filicina* polysaccharide can significantly inhibit HSV-1 virus, IC₅₀ is about 3.90 μ g/mL, and the selection index (SI) can reach 363.0 and 296.4, respectively. *Ulva lactuca* polysaccharides and *G. divaricatum* Martens polysaccharides can significantly inhibit Cox B3 virus, with IC₅₀ of 1.95 and 7.81 μ g/mL, and SI of 1025.6 and 212.0, respectively. Zou *et al.*^[33] studied the antiviral biological activity of *Eucheuma muricatum* polysaccharides. The results showed that *Eucheuma muricatum* polysaccharides inhibited viral infection by directly

Figure 4 The process of viral infection and the antiviral phase of seaweed polysaccharides.^[30]

inactivating HSV-2 and inhibiting the virus from adsorbing on cell membranes. At the same time, *Eucheuma muricatum* polysaccharides could down-regulate the amount of viral RNA transcription, but had no effect on viral DNA copy number.

Anti-tumor Effect of Seaweed Polysaccharide

The anti-tumor activity of polysaccharides is closely related to its immune regulation function. Polysaccharide can inhibit or kill tumor cells by enhancing the body's immune function. Wu *et al.*^[34] studied the anti-inflammatory and anti-tumor activities of two large-scale seaweed polysaccharides using *Gracilaria chouae* and *Gracilaria lemaneiformis*. The results showed that the polysaccharides of *Gracilaria chouae* inhibited tumor cell autophagy by inhibiting the function of lysosomes in tumor cells, causing cell metabolism disorders and further apoptosis. *Gracilaria chouae* polysaccharide achieves anti-cancer effect by inhibiting autophagy and promoting apoptosis. The polysaccharides of *Gracilaria chouae* and *Gracilaria lemaneiformis* have anti-inflammatory activity *in vitro*. *Gracilaria lemaneiformis* can relieve intestinal inflammation and protect the intestinal tract, and it is expected to be developed as an intestinal health product and an anti-inflammatory drug for functional food and biomedical fields. Zhang *et al.*^[35] studied the anti-tumor activity of *Saccharina* polysaccharides using *Saccharina* as a raw material. The results showed that the tumor inhibition rates of the mice in the low-dose group, the medium-dose group, the high-dose group, and the positive control group were 5.0%, 22.3%, 27.9%, and 50.3%, respectively. The tumor control rates of the positive control group were significantly higher than those of the other three groups. The tumor inhibition rate of the high-dose group was significantly higher than that of the low-dose and middle-dose middle-dose groups, and the tumor-suppression rate of the middle-dose group was significantly higher than that of the low-dose group. Therefore, *Saccharina* sulfate polysaccharide has a significant anti-tumor effect.

Brain and Kidney Protective Activity of Seaweed Polysaccharides

Alzheimer's disease (AD) is commonly known as Alzheimer's disease and is a degenerative disease of the central nervous system. The pathogenesis of AD is the lack of choline through the impulsive transmission of nerves, excessive phosphorylation of tau protein, excessive apoptosis, β -amyloid protein (A β) deposition, genetic factors and genetic susceptibility, Intestinal flora imbalance.^[36] It is known that traditional Chinese medicine polysaccharides have a good inhibitory effect on AD, such as Resveratrol,^[37] Fallopia multiflora,^[38] Rhodiola rosea L,^[39] Astragaloside A,^[40] Centella asiatica,^[41] Icariin.^[42] In recent years, more and more

researchers have found that seaweed polysaccharides can delay the onset of AD.^[43] Sulfate groups exist in seaweed polysaccharides, and sulfated polysaccharides have inhibitory effects on the activities of acetylcholinesterase, butyrylcholinesterase, and β -secretase, so that the fibrils of A β protein disappear, and it can be used as a nutraceutical to treat AD.^[44] Tang *et al.*^[45] studied the intervention effects of *Sargassum fusiforme* polysaccharide on the behavior of AD rat model. Compared with the normal control group, the learning and memory ability of the model group was significantly reduced. Compared with the model group, the treatment groups of 0.8 and 1.6 g/kg *Sargassum fusiforme* polysaccharide extract can improve the learning and memory ability and have a certain dose dependence. It can be seen that *Sargassum fusiformis* improves the learning and memory ability of AD rats.

The formation of kidney stone is the main result of CaO_x salt supersaturation in renal tubule fluid.^[46] The stone formation process involves nucleation, growth and aggregation of crystals. When urine supersaturation exceeds metastable state, oxalate and calcium ions begin to form spontaneous crystal nucleation.^[47] Sulfated polysaccharides in seaweeds have a large number of negatively charged groups such as sulfate, carboxyl, and hydroxyl groups. These anions have a strong ability to interact with calcium ions.^[48] These anions increase the concentration of soluble Ca²⁺ in the supernatant and reduce the degree of supersaturation of the renal fluid, thereby inhibiting the nucleation of CaO_x crystals (Figure 5).^[49] Veena *et al.*^[50] found that Fucoidan, extracted from *Fucus*, reduced the content of major components of kidney stones, such as calcium, oxalate, uric acid, and phosphorus in urine.

Figure 5 The sequential schematic for the inhibitory mechanism of seaweed polysaccharides at each step of CaOx stone formation.^[48]

Regulation of Intestinal Flora by Seaweed Polysaccharides

In our daily diet, only small amounts of nutrients such as starch and monosaccharides (glucose, sucrose and lactose) can be processed directly by enzymes encoded by our genome.^[51] Many complex carbohydrates in the gastrointestinal tract pass through fermentation and become food for symbiotic bacteria. Utilizing and processing complex carbohydrates is essential for the intestinal flora, as it relies primarily on indigestible fiber and polysaccharides as energy sources.^[52] After a long time, the co-evolution between the intestinal flora

and the host and intestinal microorganisms has developed a variety of foraging glycan.

Marine polysaccharides in the diet are not absorbed and cannot be processed by stomach and intestinal enzymes. Once in the lower digestive tract, they are degraded and fermented by specific microorganisms in the gut. The degradation of marine polysaccharides produces a large amount of oligosaccharides, which can be absorbed and exert a therapeutic effect. Fermentation of marine polysaccharides and their oligosaccharides can produce short chain fatty acid and other metabolites. SCFA is easily absorbed and may have a positive systemic physiological effect on the host. During the fermentation process, the composition of the gut microbiota changed because marine polysaccharides and their oligosaccharides stimulated the growth or activity of only a limited number of local bacteria (for example, *Bifidobacterium* and *Lactobacillus*) (Figure 6). Song *et al.*^[54] studied the effect of sea cucumber polysaccharides on the intestinal flora of experimental mice induced by antibiotics. When the concentration of polysaccharides extracted from sea cucumber was 1.92 mg/mL, the intestinal flora of mice in the normal control group was dominated by beneficial bacteria (*Lactobacillus* and *Clostridium*). After the intervention of antibiotics, the content of the two bacteria decreased significantly, and the pathogenic *Porphyromonas* was detected. After treatment with sea cucumber polysaccharide, the content of beneficial bacteria recovered and the content bacteria decreased.

Figure 6 Gut microbiota degradation of marine polysaccharides and its effects on intestinal ecology.^[53]

Conclusion

The active components and functions of seaweed polysaccharides have begun to be valued by food, medical, marine and nutrition scholars, but the analysis of the composition and structure of seaweed polysaccharides needs to be further studied. The specific function of polysaccharide components also requires the improvement of separation and purification technology of seaweed polysaccharides. Therefore, the study of seaweed polysaccharides will be a systematic project with great research value and broad application prospect.

Conflict of Interest

The authors declare no conflict of interest.

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