



# MARINE ALGINATE OLIGOSACCHARIDES – A PROMISING BIOMATERIAL: CURRENT USE AND FUTURE PERSPECTIVES IN FOOD INDUSTRY AND PHARMACEUTICAL APPLICATIONS

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**Abstract.** Alginate oligosaccharides (AOS) have been known as a natural material with a wide variety of biological activities, and used for a long time. The evidence of using AOS to confer health benefits have been documented. The isolation and characterization of the properties, biological activity as well as the applications of AOS in various fields have been studied recently. In present work, we provide the recent research of AOS, particularly focusing on the applications in food and medicinal industry. This review also describes some experimental models, application and discuss the functional and biological mechanisms of AOS. In conclusion, AOS promotes beneficial effects on the immuno-metabolic response to various infectious diseases as well as it is promising as a biomaterial for functional foods and medicinal drugs development.

**Keywords:** alginate, alginate oligosaccharide, biological activity, marine drug, molecular mechanism.

**Classification numbers:** 1.2.1; 1.3.2; 1.5.4

## 1. INTRODUCTION

Marine algae are recognized as a rich source of alginate, a polysaccharide with high biodiversity serving numerous biological applications. It has been known that alginates are produced from two sources, algae and bacteria [1]. However, according to Goh *et al.* (2012), alginates isolated from bacterial sources such as *Azotobacter* (*Azotobacter vinelandii*) and *Pseudomonas* species are usually not economically viable for commercial applications and confined to small-scale research studies [1, 2]. Therefore, commercial alginates are currently extracted and derived mainly from the brown algae [1, 2]. The global marine algae population has been known as the growing importance sector in industrial food-related production, which

plays a major role in providing protein, polysaccharides, and biomaterials for the increasing demand of human health, especially for pharmaceutical application. It is responsible for approximately 40 – 50 % of the photosynthesis each year that occurs on earth [3]. According to Rodriguez-Jasso *et al.* (2011), brown algae are the second most abundant group comprising about 2,000 species [4]. Some species, such as *Ascophyllum* spp., *Fucus* spp., *Laminaria* spp., *Sargassum* spp., and *Turbinaria* spp. are the most commonly used in industrial production [4, 5]. With abundant raw resources and high reserves for alginate production, this opens up a new opportunity for agriculture to develop towards a higher value. However, this is also a challenge in the planning of raw material areas and synchronous post-harvest technologies to ensure sustainable development. Alginates are quite abundant in nature since they occur as a structural component in marine brown algae (*Phaeophyceae*), comprising up to 40% of the dry matter [5]. Therefore, it is important to understand the mechanisms of action in the biological systems and also figure out the high value of the use of alginates for the sustainable development of marine resources.

Alginate oligosaccharides (AOS) depolymerized by different methods from polymers show various pharmacological activities [5]. The production and application of AOS have been extensively studied by a number of authors. Alginate from marine brown algae has been used for a wide range of commercial application [3, 5]. Marine algal seaweeds are often regarded as an underutilized bioresource; many have been long and widely used as a source of food, industrial raw materials, and in therapeutic and botanical applications. Moreover, seaweeds and seaweed-derived products have been used as amendments in crop production systems due to the presence of a number of plant growth-stimulating compounds for many decades. As the estimation, the total wholesale value of dried brown algae worldwide collected in the wild or cultivated is about \$300 million and continuously increasing. Moreover, AOS produced from alginate by depolymerizing the polysaccharide using alginate lyase showed non-toxic, non-immunogenic characteristics and its exert numerous biological activities such as antitumor, antioxidant, antiviral, immunomodulatory effects, and neuroprotective activity [3, 5].

In this review, we discuss the biological functions of AOS, which focuses on the mechanisms of action. The potential value of AOS and its derivatives in three major sectors including agriculture, food and pharmaceutical application will also be summarized. In addition, the future perspectives of research and application of AOS will be considered.

## 2. PRODUCTION OF ALGINATE OLIGOSACCHARIDE

### 2.1. Extraction of sodium alginate from algae

Sodium alginate is a natural polysaccharide product, which is mainly isolated from seaweeds. Alginate consists of  $\beta$ -D-mannuronate (M) and  $\alpha$ -L-guluronate (G) as monomeric units. Common algae (*Phaeophyceae*) species that are commercially important include *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, *Eclonia maxima*, *Lessonia nigrescens*, *Durvillea antarctica*, *Sargassum* sp., *Macrocystis pyrifera* and etc. [1, 5].

Several previous authors have developed the method to obtain sodium alginate from natural sources as brown seaweeds and showed the differences in the manufacturing process [4, 5]. A schematic of the alginate extraction procedure is represented in Figure 1. Alginate extraction process from seaweeds includes several steps, which usually starts with treating the dried raw material using diluted mineral acid. The purpose of this extraction process is to remove the

counterions by proton exchange using mineral acid. After further purification, in the presence of calcium carbonate, the obtained alginic acid (both soluble and insoluble) is solubilized by alkali into water-soluble sodium salt and then next transformed back into acid or its expected salt. Sodium alginate is then precipitated directly by alcohol, calcium chloride or a mineral acid. The product is dried and milled. Finally, the product will be identified by the functional properties (structural, physicochemical properties and functions) and quality using different analytical techniques. The commercial alginate differs in molecular weight, composition, and the ratio of M-block and G-block, which is responsible for their physicochemical properties as well as the biological activities. Also, alginate obtained from different sources show differences in their components and properties.

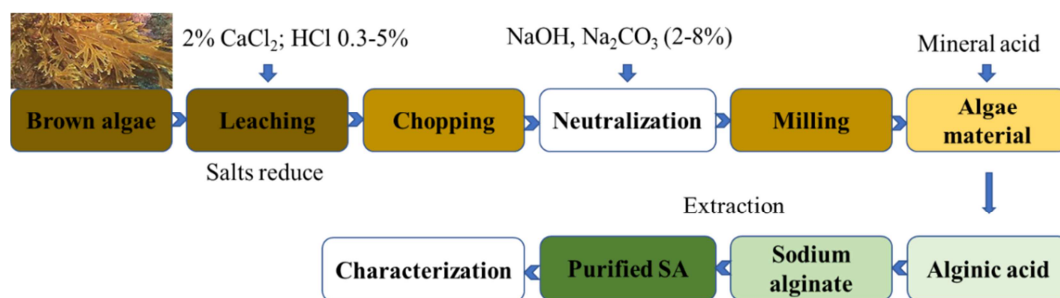


Figure 1. Schematic of sodium alginate extraction procedure from brown algae.

## 2.2. Production of AOS by enzymatic hydrolysis

Alginate oligosaccharides (AOS) are generated from alginates, is a natural acidic unbranched polysaccharide, extracted from marine brown algae. AOS contain  $\alpha$ -L-guluronate (G) and  $\beta$ -D-mannuronate (M) (Figure 2). AOS could produce using different degradation methods including enzymatic degradation, acid hydrolysis, and oxidative degradation. Enzymatic hydrolysis method to produce AOS from SA has attracted more interest in recent studies based on a number of advantages such as easy for reaction conditions process, excellent in gel properties, and specific products accessible for purification [6].

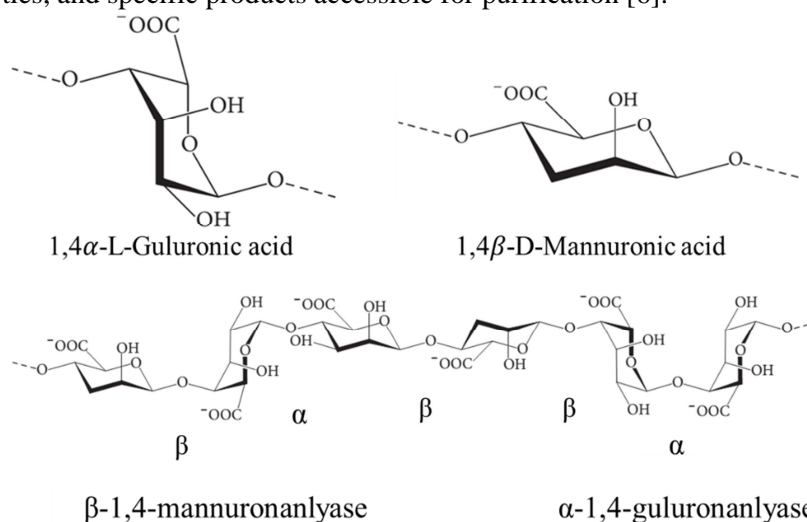


Figure 2. The structure of alginate: monomers; chain conformation and profile of degradation position and mode of action of enzymes on marine carbohydrates.

Table 1. List of alginate lyases have been used for AOS production.

Enzyme	Source	The optimal temp. (°C) and pH	Reference
Algb	<i>Vibrio</i> sp. W13	30/8.0	[6]
AlyA	<i>Pseudoalteromonas atlantica</i> AR06	40/7.4	[7]
Aly5	<i>Flammeovirga</i> sp. MY04	40/6.0	[8]
AlySY08	<i>Vibrio</i> sp. SY08	40/7.6	[9]
Cel32	<i>Cellulophaga</i> sp. NJ-1	50/8.0	[10]
FlAlyA	<i>Flavobacterium</i> sp. UMI-01	55/7.7	[11]
Aly-SJ02	<i>Pseudoalteromonas</i> sp. SM0524	50/8.5	[12]
AlyL2-CM	<i>Agarivorans</i> sp. L11	35/7.0	[13]
AlyL2-FL		45/8.6	
AlyAL-28	<i>Vibrio harveyi</i> AL-28	35/7.8	[14]
AlyATCC	<i>Vibrio alginolyticus</i> ATCC17749	35/8.2	
AkAly28; AkAly33	<i>Aplysia kurodai</i> (sea hare)	40/6.7	[15]
HZJ216	<i>Pseudomonas</i> sp. HZJ 216	30/7.0	[16]
A1-IV; Atu3025; Alg17c	<i>Sphingomonas</i> sp. strain A1; <i>Agrobacterium tumefaciens</i> ; <i>Saccharophagus degradans</i>	37/7.5~8.5 30/7.3 40/6.0	[17]
FlAlyA; FlAlyB; FlAlyC; FlAlex	<i>Flavobacterium</i> sp. UMI-01	50/7.8	[18]
AlyA1	<i>Zobellia galactanivorans</i>	30/7.0	[19]
AlyL1	<i>Agarivorans</i> sp. L11	40/8.6	[20]
MJ3-Arg236Ala	<i>Sphingomonas</i> sp. MJ-3	50/6.5	[21]
A1m	<i>Agarivorans</i> sp. JAM-A1m	30/9.0	[22]
Aly510-64	<i>Vibrio</i> sp. 510-64	26/6.5	[23]
NO272	<i>Alteromonas</i> sp. strain No. 272	25/7.5~8.0	[24]
AlyYKW-34	<i>Vibrio</i> sp. YKW-34	40/7.0	[25]
AlgMsp	<i>Microbulbifer</i> sp. 6532A	50/8.0	[26]
-	<i>Paenibacillus</i> sp. S29	50/8.7	[27]

Alginate lyases (ALs) were a key tool for oligosaccharide preparation and energy bioconversion. Alginate lyases have either endo- or exo-degradation activity with the corresponding substrate specificity [5, 28]. Up to date, numerous alginate lyases have been elucidated. Alginate lyases have been isolated from various sources such as marine bacteria, soil microorganisms, and fungi or even *Chlorella* virus [1, 5, 28]. Several hundred kinds of ALs from various sources have been isolated, characterized and utilized [8]. ALs are classified into three groups base on their substrate specificity due to their amino acid sequences. The first type is specific toward PolyG block (EC4.2.2.11 also known as  $\alpha$ -1,4-gulonanyase), the second type is specific toward PolyM block (EC4.2.2.3 also known as  $\beta$ -1,4-mannuronanyase), and the third type is a combination of PolyG and PolyM blocks [28, 6]. Those alginates specific to G or M blocks are called monofunctional ALs, while those specific to PolyM-G blocks are called bifunctional ALs [7]. There are some bacteria that can only secrete one kind of alginate lyase, and there are also bacteria that can secrete both. As shown in Table 1, there are many studies that have characterized and evaluated the ability of many alginate lyases for the AOS production.

Han *et al.* (2016) reported the characterization and module truncation of Aly5, an alginate

lyase obtained from the polysaccharide-degrading bacterium, *Flammeovirga* sp. Strain MY04 [8]. The authors have described the enzymatic properties and catalytic mechanisms of a guluronate lyase for AOS production. In another study, Zhu *et al.* (2016) showed that a new alginate lyase with high activity (24,083 U/mg) had already been purified from a newly isolated marine strain, *Cellulophaga* sp. NJ-1 [10]. The research stated that it is completely hydrolyzed sodium alginate into oligosaccharides of low degrees of polymerization, which have been promised a power tool for the production of AOS from sodium alginate. While Kurakake *et al.* (2017) described that an alginate lyase was isolated from soil bacteria, *Paenibacillus* sp. S29 [27]. The study showed that both M and G blocks of alginate were degraded efficiently, however, polyM was the more susceptible substrate for this lyase. Thus, these alginate lyases differed from each other in substrate specificities, properties (the optimum pH, temperature, and salt concentration) as well as degradation products. Therefore, the selection and use of suitable enzymes for high specificity and facilitating the final purification of products should be considered for production conditions, which is crucial to reduce cost and improve the quality of AOS.

### 3. POTENTIAL APPLICATIONS

#### 3.1. Applications in agriculture

Table 2. Some applications of alginate oligosaccharides in crops development.

Name/ ingredients	Plants/models	Functions/Mechanism	Reference
AOS	Rice ( <i>Oryza sativa</i> L.)	Enhance root development; AOS induced the expression of the auxin-related gene; accelerate auxin biosynthesis and transport, and reduced indole-3-acetic acid (IAA) oxidase activity also induced calcium signaling generation in rice roots.	[29]
Alginate-derived oligosaccharides	Tomato ( <i>Lycopersicon esculentum</i> Miller)	Anti-drought stress by the reduction of the electrolyte leakage and the concentration of malondialdehyde (MDA); enhancement of the contents of free proline, total soluble sugars (TSS), and abscisic acid (ABA); also, increasing the activities of catalase (CAT), superoxide dismutase (SOD), peroxidase (POD), and phenylalanine ammonia-lyase (PAL).	[30]
AOS	Wheat ( <i>Triticum aestivum</i> L.)	Induced root development as well as promoted the generation of nitric oxide (NO) in the root system;	[31]
AOS	Wheat ( <i>Triticum aestivum</i> L.)	Anti-drought stress; AOS up-regulated genes involved in ABA signal pathways, such as late embryogenesis abundant protein 1 gene (LEA1), psbA gene, Sucrose non-fermenting 1-related protein kinase 2 gene (SnRK2) and Pyrroline-5-Carboxylate Synthetase gene (P5CS)	[32]

Seaweeds have long been and widely used as sources of organic matter and fertilizer nutrients to increase plant growth and yield for centuries. Numerous commercial seaweed

extracts are available for use in agriculture and horticulture. Many previous studies have reviewed the beneficial effects of seaweed extracts on plants, such as early seed germination and establishment, improved crop performance and yield, elevated resistance to biotic and abiotic and enhanced postharvest shelf-life of perishable products. Zhang *et al.* (2014) demonstrated that AOS promoted root formation and growth in rice (*Oryza sativa* L.) [29]. Zhang *et al.* (2013) reported that AOS induced root development as well as promoted the generation of nitric oxide (NO) in the root system [31]. Furthermore, Liu *et al.* (2013) reported that AOS, which prepared from degradation of alginate enhanced *Triticum aestivum* L. tolerance to drought stress [32].

Based on these observations, AOS and their derived products can be considered as a great biofertilizer, bioproducts for replacement of chemical reagents in sustainable agricultural development.

### 3.2. Applications in food industry

Alginates have been used as a natural food additive, while sodium alginate has wide application and potential role in the food industry. Several alginates have been applied in the food industry, which mainly are sodium alginate (SA), potassium alginate (PA), ammonium alginate (AA) and propylene glycol alginate (PGA) [33]. Several examples of the application of alginate and its derived have been shown in Table 3 [34]. Specifically, SA is used to gel in the presence of calcium, as a shear-thinning thickener in the absence of calcium, to stabilize emulsions or foams and to form films. As an example, SA was widely used as a thickener in sauces, syrups, and toppings for ice cream. Sodium alginate was added to reduces the formation of ice crystals during freezing, giving a smooth result, great taste and favorable anti-melting properties for final products [35]. In addition, in many types of product with water-in-oil emulsions such as mayonnaise and salad dressings thickened, the addition of SA is helping to improve the stability [35]. On the other hands, in modernist cuisine, SA is often combined with calcium salts as a good mouth-feel [35].

Table 3. The use of alginate-derived as salt in food industries.

Code	Main ingredient	Functions
E400	Alginic acid	Emulsifier, formulation aid, stabilizer, thickener
E401	Sodium alginate	Texturizer, stabilizer, thickener, formulation aid, firming agent, flavor adjuvant, emulsifier, surface active agent
E403	Ammonium alginate	Stabilizer, thickener, humectant
E404	Calcium alginate	Stabilizer, thickener
E405	Propylene glycol alginate	Emulsifier, flavoring adjuvant, formulation aid, stabilizer, surfactant, thickener

(Adapted from Szekalska *et al.*, 2016) [34]

According to Rastall (2010), oligosaccharides are recently attracting increasing interest as prebiotic functional food ingredients [36]. Functional oligosaccharides have been regarded as a keen constituent in prebiotics such as sweeteners, fiber, humectants, etc. [37]. Wang *et al.* (2006) investigated the *in vivo* prebiotic potential properties of AOS on bacterial growth [38]. The authors found that AOS promoted the growth of *Bifidobacterium bifidum* ATCC 29521 and

*Bifidobacterium longum* SMU 27001 significantly higher in comparison with fructooligosaccharides (FOS).

In muscle processed foods especially in meat products, SA can effectively reduce the cooking loss also improve the texture properties, reduce the cost of production as well as for the improvement of product quality. Alginate and other hydrocolloids have been used to reduce or replace fat without affecting sensory and textural properties of final products. Several examples of using SA and AOS were shown in Table 4. Moreno *et al.* (2008) found that using SA in combination with microbial transglutaminase increased binding ability of restructured fish muscle [39]. While Raeisi *et al.* (2016) suggested the application of SA coating solutions containing nisin, cinnamon, and rosemary as natural preservatives for the microbial quality in chicken meats [40]. In addition, Ma *et al.* (2015) and Zhang *et al.* (2017) showed similarity in cryoprotective effects of two saccharides including trehalose and AOS during chilled storage of peeled shrimp (*Litopenaeus vannamei*) [41, 42]. The results suggested that might promising an excellent way to use AOS as additives replacer in seafood to maintain quality during storage. Earlier, Maitena *et al.* (2004) and Nishizawa *et al.* (2016) investigated the role AOS in conjugation to control Maillard reaction and improve solubility and stability of carp myosin [43, 44].

Nowadays, based on the concept that food can function as a drug, it, therefore, is promising a higher value for food industries to explore the functions of alginate-derived as diet intervention or functional foods. Recently, AOS has received much attention because of their unique properties. There is a great deal of studying of biological functions and evaluated effects of AOS in food and health. Previously, Falkeborg *et al.* (2014) evaluated the antioxidant properties of alginate oligosaccharides, which were prepared by enzymatic depolymerization [45]. The results revealed that AOS was able to completely (100 %) inhibit lipid oxidation in linoleic acid emulsions, superior to ascorbic acid that only 89 % inhibition. These results show that AOS is an excellent natural antioxidant, which may be beneficial biomaterials for many applications in the food industry.

Table 4. Some applications of alginate-derived in food.

Name/ ingredients	Food products	Functions	Reference
Sodium alginate	Restructured fish muscle processed	Emulsifier, enhanced the gelification	[39]
Sodium alginate	Chicken meats	Coating solution; inhibits microbial growth and extend the shelf life during refrigeration	[40]
AOS	Frozen shrimp	Cryoprotection; reduced thawing and cooking losses, maintained texture, myofibrillar protein content in frozen shrimp.	[41, 42]
AOS	Salmon fish myofibrillar protein	Controlled Maillard reaction in drying stage	[43]
AOS	Carp myosin	Improved solubility and stability of carp myosin	[44]

### 3.3. Pharmaceutical and biomedical applications

Table 5. Biological activities and pharmaceutical applications of AOS.

Name/ Compound	Biological activity and applications	Mechanism of functions	Study models and reference
AOS	Enhances LDL uptake	Increased LDLR expression and intracellular uptake of LDL by hepatocytes; enhanced nuclear translocation and mRNA levels of SREBP-2 and PCSK9	HepG2 cells [46]
AOS-derived	Inhibits neuro-inflammation and microglial phagocytosis	Inhibited nitric oxide (NO) and prostaglandin E2 (PGE2) production, highly expressed inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and secretion of proinflammatory cytokines; attenuated the LPS-activated overexpression of toll-like receptor 4 (TLR4) and nuclear factor (NF)- $\kappa$ B	BV2 microglia cells [47]
OligoG (AOS)	Cystic fibrosis (CF), treatment of chronic obstructive pulmonary disease(COPD), improvement of antibacterial and antifungal therapy, antifungal activity	Modulation of mucus viscosity by induction alterations in mucin surface charge, formation porosity of the mucin networks in cystic fibrosis sputum; eradication bacterial and fungal lung infections by modification of biofilm structure together with growth inhibition, improvement the efficiency of conventional antibiotics against multidrug resistant bacteria or fungi	Pathogens [48]; healthy human and in CF patients [49]
SA oligosaccharides	Antihypertensive	Due to the reduction in cardiovascular and renal damage; through reducing salt absorption and a direct action on vascular vessels.	Dahl salt-sensitive (Dahl S) rats [50, 51]
AOS	Prevents acute doxorubicin cardiotoxicity	Suppressing oxidative stress and endoplasmic reticulum-mediated apoptosis	Adult male C57BL/6 mice [51]
Guluronate oligosaccharide	Immunomodulatory activity	Induced NO production and inducible nitric oxide synthase (iNOS) expression, and stimulated ROS and TNF- $\alpha$ production.	RAW264.7 cells [53]
AOS	Probiotic and prebiotic activity	Stimulation cecal and fecal microflora	Pathogens; Wistar rats [38]
Alginate-derived oligosaccharide (ADOs)	Protection against pathogens	Antibacterial activity	Pathogens such as <i>B. subtilis</i> (AS 11731), <i>E. coli</i> (ATCC 12069) [38, 54]
ADOs	Anti-tumor activities	Modulation of the host-mediated immune defense reaction is suggested	tsFT210 cells; Kunming mice [55]



Recently, marine products have been the most important of natural materials used in therapeutic applications against numerous human diseases. Especially, alginate and its derived isolated from marine source have been shown to notably diverse pharmacological activities [4]. In fact, alginates are used in wound healing [1], to stimulate the immune system, and promote the potential for anti-obesity through weight reduction [3, 5]. In addition, the reduction of glycemic index through reduced intestinal absorption also increases satiety. Alginate also reduces mucosal aggregation as well as modulation of gut microbiota. Recently, AOS and their derivatives have gained more interest in the pharmaceutical and medicinal applications. Several studies have evidenced the physiological effects and the biological activities of AOS (Table 5). Yang *et al.* (2015) used HepG2 cells as a model to study about low-density lipoprotein (LDL) uptake, and the results have shown that alginate oligosaccharide enhances LDL uptake via regulation of low-density lipoprotein receptor (LDLR), SREBP-2 and PCSK9 expression [46]. While Zhou *et al.* (2015) found that alginate-derived oligosaccharide has a positive effect on neuroinflammation and promotes microglial phagocytosis of  $\beta$ -amyloid [47].

In another research, Pritchard *et al.* (2016) described a new class of safe oligosaccharide (OligoG), with the highly purified content (> 85 %) of guluronic acid. It currently is being evaluated as a treatment for chronic respiratory diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) [48]. Furthermore, Guo *et al.* (2016) found that AOS decreased the expression of Caspase-12, C/EBP homologous protein (CHOP) and Bax while up-regulating the expression of anti-apoptotic protein Bcl-2, which are markers for endoplasmic reticulum-mediated apoptosis [51]. Taken together, these results demonstrated that AOS is a promising compound that prevents acute DOX cardiotoxicity via inhibition of oxidative stress and endoplasmic reticulum-mediated apoptosis [51]. Therefore, with the unique properties of AOS and their derivatives, they might be beneficial biomedicine in many diseases.

## 4. FUTURE PERSPECTIVES

### 4.1. As a potential functional food for anti-obesity and other metabolic diseases

Obesity is serious health problem worldwide, which increases the risk of other different chronic diseases. Numerous factors, such as poor diets, physical activity, and alcohol, could induce obesity. In 2014, about 40 % of adults were overweight, and 13 % were obese worldwide (WHO, 2016). Obesity is a common metabolic disease, has now become a major global health challenge due to its increasing prevalence, and the associated health risk. Since 1991, the functional food concept was first introduced in Japan; several oligosaccharides were classified as “foods for specified health use” (FOSHU). Nowadays, the increasing health consciousness of modern consumers has enhanced the demand for specific types of dietary carbohydrates. On the other hand, recent studies have discussed a variety of drugs from marine sources that promote anti-obesity effects such as Fucoxanthin from brown algae. In addition, a number of previous studies showed that the positive effect on anti-obesity of diets contains extracts from brown seaweeds [56]. Those studies found that the diets supplemented with the extracts from seaweeds have an inhibitory effect on lipogenesis in adipocytes, decrease in total cholesterol and triacylglycerol levels as well as blood glucose and insulin levels and especially in reducing the body weight [56]. Since AOS and their derivatives are water-soluble, non-toxic and no side-effect, they may be beneficial biomaterials in various metabolic disorders such as obesity and diabetes. It has been known that the important function of alginate in food is a dietary fiber, however, other functions of alginate and their derived such prebiotic and prevent the metabolic disease still poorly understood. Furthermore, its mechanism of roles needs to be explored via

multi-omics approach.

#### 4.2. As a promising cancer drug

Cancer, a serious medical challenge requiring a proper therapeutic approach with fewer side effects. Recently, marine algae have been exploited for potential anticancer agents, although the use of polysaccharides as antitumor therapies is under intense debate. Numerous the polysaccharides found in marine creatures have been evaluated for their anticancer properties, and some have been widely conducted *in vitro*, and *in vivo*, however, research is still in its infancy. With the rapid development of next-generation sequencing (NGS), liquid chromatography–tandem mass spectrometry (LC×MS/MS) and multi-omics approach, it has been much easier and faster to identify more toxins and predictive functions with bioinformatics pipelines, which pave the way for novel drugs development [57].

#### 4.3. As promising neurological diseases target treatment

Nowadays, neurological diseases and metabolic disorder are a big concern for human well-being. Based on the observation of Zhou *et al.* (2015), AOS and their derived products promoted the inhibitory effect on neuroinflammation and a positive effect on microglial phagocytosis of  $\beta$ -amyloid [47]. These results suggest a potential value of AOS and their derivatives might be a nutraceutical or therapeutic agent for neurodegenerative diseases, especially in Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), a fatal neurodegenerative disease.

### 5. CONCLUSIONS

This review provides a detailed and updated description of the protective effects of AOS on various diseases and its beneficial application for agricultural production, foods and drugs development. It was evident that AOS with the potential use not only in agricultural production, in the food industry and especially in medical applications, therefore it will be a valuable biomaterial and will add up new and higher values for marine resources to next-generation sustainable. Furthermore, the fourth industrial revolution is creating a new opportunity to figure out the mechanisms of action based on next generation sequencing, multi-omics approach such metabolomics, proteomics, transcriptomics, etc. Although several studies performed *in vivo* have demonstrated the biological activities of AOS in different pathways, the related studies of AOS applied to clinical treatment for serious diseases in human are limited. Future prospects, therefore, more clinical studies should be conducted to assess the effects of AOS in this field.

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