2024 • Vol. 2, No. 1 • pp. 22-34
Trends in Pharmaceutical Biotechnology (TPB)

Trends in Pharmaceutical Biotechnology (TPB)
Print ISSN: 3006-0516 Online ISSN: 3006-0354

Biomedical Applications of Alginate Oligosaccharides: Exploring Their Therapeutic Potential and Modification Techniques

Mokhles Mohammed[1,*], **Haider Nasser Jabber**[2], and **Fatima Mohammed Abdul Jabbar**[3]

[1] *Department of Pharmacy, Medical Sciences, University of Iran, Iran*
[2] *College of Pharmacy, Basra University, Basrah 61004, Iraq.*
[3] *College of Pharmacy, Al-Zahraa University for Women, Karbala 56001, Iraq.*
[*] *Corresponding author name: Mokhles Mohammed, Email:mokhles.mohammed@yahoo.com*

Access this article online

REVIEW ARTICLE
Received: 28.01.2024 **Revised:** 25.03.2024
Accepted: 10.04.2024 **DOI:** 10.57238/tpb.2024.152722.1011

OPEN ACCESS

ABSTRACT

Thorough research has been conducted on marine algae, with a specific emphasis on their potential health advantages. Scientists have discovered and separated many constituents from marine algae that have the potential to be used in medicine. One example is alginate oligosaccharides, which are small polysaccharides with low molecular weight that are present in the cell walls of brown algae. These chemicals have many health benefits, such as reducing inflammation, fighting against microorganisms, preventing oxidative damage, inhibiting tumour growth, and modulating the immune system. Due to their little toxicity, lack of immunogenicity, and capacity to degrade naturally, they are very well-suited for use in biomedical applications. Alginate oligosaccharides have the ability to undergo chemical or biochemical changes in order to enhance their biological activity and potential for use in medicinal applications. This study provides a succinct summary of the attributes of alginate oligosaccharides, the techniques used to modify them, and highlights their significant health-enhancing benefits.

Keywords: Alginate oligosaccharides, Marine algae, Biomedicine

1 Introduction

Brown algae constitute a substantial group of multicellular algae and are a crucial part of the marine ecosystem [1]. These biologically diverse organisms encompass thousands of species, predominantly occupying the intertidal and subtidal zones of rocky shores [2]. They thrive from coastal estuaries to deep-sea areas, characterized by rapid growth, unique structures, high adaptability, and extensive distribution. Their ecological importance is partly due to their contributions to marine biomass and carbon cycling. Brown algae serve as food and habitats for numerous other organisms, fostering the overall health of the marine biosphere [3]. Economically, brown algae are significant, particularly in Asian countries, where they are consumed as food. They are also used as natural feed or fertilizer because of their high mineral and trace element content and are a source of biological products like alginates, mannitol, and iodine [4,5]. Brown algae hold immense potential as a source of unique functional components not found in terrestrial plants.

Recently, valuable compounds extracted from brown algae, such as alginates, fucoidan, and laminaran, have been investigated for their applications in nutrition and drug development [6,7]. Alginate is a linear acidic polysaccharide commonly found in the cell walls of brown algae [8]. It is made up of hexuronic acid residues, specifically M and α G, linked exclusively by $1 \rightarrow 4$ glycosidic bonds. Its properties of chelation, gelation, and hydrophilicity have led to its extensive use in the food, cosmetic, and biomedical industries [9]. Increasing evidence shows that alginate, when used as a therapeutic adjuvant, drug carrier, wound healing material, and biological scaffold, can enhance antitumor immune efficacy in ovarian cancer, melanoma, liver cancer, and breast cancer [10]. However, the direct therapeutic use of alginate in biomedical applications has been significantly hindered by its macromolecular structure, poor solubility, and low bioavailability [11]. Alginate can be chemically or enzymatically digested to produce

AOS, which have lower molecular weights and viscosity. AOS exhibit improved solubility and bioavailability. Consequently, there is considerable interest in AOS due to their enhanced pharmacological activities and beneficial effects in biomedicine [12].

This paper provides an overview of the structure, biological activities, and modification patterns of AOS. It also explores recent advancements in using AOS for treating chronic and degenerative diseases, modulating human gut microbiota, and enhancing the efficacy of traditional drugs as therapeutic adjuvants or drug carriers.

2 AOS Structure

As a degradation product of alginate, AOS are a mixture of linear oligomers composed M and G (Figure 1) in varying ratios and DP [13]. The overall composition and distribution of these two uronic acids along the oligomer chain differ significantly depending on the algae species, affecting the properties of AOS. Typically, three types of oligomer blocks (with $2 \leq \mathrm{DP} \leq 25$) are obtained: M, G, and mixed MG blocks, depending on the source and degradation methods used. In terms of structure, the monomeric units M and G are epimers at C-5 due to the different orientation of the carboxyl group at this position [14]. The molecular formula of M or G units is C6H10O7, and the conversion relationships of AOS Mr and the DP can be described as shown in Eq. (1):

$$Mr = DP \cdot Mr(C6H10O7) - (DP - 1) \cdot Mr(H2O) \quad (1)$$

When the atomic weights of carbon, hydrogen, and oxygen, and the molecular weight of H2O are substituted into the formula, the DP can be calculated using Eq. (2):

$$DP = (Mr - 18)/176 \quad (2)$$

The epimerization at C-5 leads to significant differences in spatial structure and physicochemical properties of their oligomers. The equatorial configuration of the β-1,4-glycosidic bond results in a stretched chain conformation of poly M, while the axial linkage of the α-1,4-glycosidic bond tends to form helices in poly G [15]. Generally, poly G with axial linkage is more rigid compared to poly M, which involves equatorial linkage.

3 Production of AOS

Currently, three primary methods are utilized for the production of AOS: AH, OD, and ED. Each method has its own advantages and limitations. In AH of alginate, the main characteristic is the random cleavage along the polysaccharide chains, resulting in AOS fragments with unmodified hexuronic acid residues at both ends. Consequently, AOS obtained by acid hydrolysis can retain the inherent structure of alginate. AH is commonly employed to produce various AOS with different degrees of polymerization due to its cost-effectiveness, ease of control, simplicity, and availability. However, AOS with a molecular weight below 4000 can only be obtained through acid hydrolysis under high temperature and pressure conditions. Furthermore, a significant number of inorganic salts is produced during the final neutralization stage of acid hydrolysis. The use of AH has been constrained by equipment corrosion, high energy consumption, and the generation of residual waste pollution. Another chem-

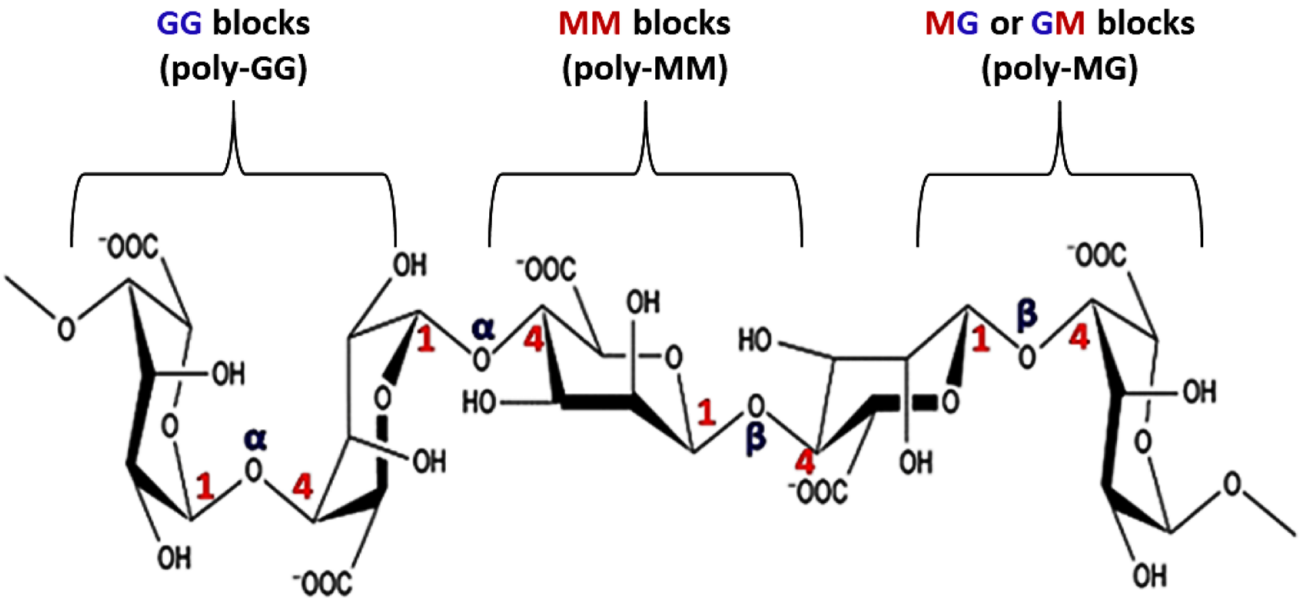

Fig. 1. Alginate's chemical structure.

ical degradation method is OD, which offers higher reaction efficiency and yield compared to AH. H2O2, an easily degradable reagent that produces only water as an oxidation by-product, has been widely used to produce functional AOS with high purity and quality. AOS residues undergo easy ring-opening at the reducing end to form carboxyl groups during OD. This additional carboxyl radical could induce novel bioactivities of oxidative AOS. Zhou et al. reported that GOS-OD, but not GOS produced by acid hydrolysis or enzymatic digestion, significantly reduced the LPS-stimulated overproduction of NO in RAW 264.7 cells [16]. The presence of the additional carboxyl group may play a crucial role in the NO-inhibitory and subsequent anti-inflammatory effect of GOS-OD. Enzymatic digestion appears to be the most promising method for producing AOS due to its significant advantages, including site-specific cleavage reactions, mild reaction conditions, efficient reaction rates, and high yields. Alginate lyases are crucial enzymes that catalyze the degradation of alginate. They cleave the O-C4 bond to uronic acid residues via a β-elimination reaction, resulting in the formation of the 4,5-unsaturated hexuronic acid residue at the non-reducing terminus. This unsaturated terminal structure with a C4–C5 double bond can be detected at 230 nm. Unsaturated AOS exhibit various novel bioactivities such as antioxidant, anti-tumor, neuroprotective, and immuno-stimulation [17].

In comparison with saturated AOS, unsaturated AOS demonstrated efficient anti-obesity effects in HFD-fed mice by activating the AMPK signaling pathway. Despite the numerous advantages and promising applications of enzymatic digestion of alginate, most studies are still at the laboratory level. There is a high demand for the discovery and development of novel enzymes with high yield, activity, and stability to achieve industrial production of AOS [18].

4 AOS Modification

Various approaches, such as vanadylation, sulfation, selenylation, or oxidation, have recently been employed to modify the backbone of AOS, aiming to enhance their physicochemical and biological properties. For instance, VAOS exhibits higher antioxidant activity than unmodified AOS in hydroxyl and DPPH radical scavenging systems [19]. Additionally, VAOS has shown strong antiproliferative effects against the human hepatoma cell line BEL-7402 and could significantly inhibit tumor progression in NSCLC [20]. VAOS was synthesized by slowly adding vanadium (IV) oxide sulfate hydrate into the AOS solution under constant stirring and pH 12 throughout the process. The vanadium content of VAOS could reach about 3.0%. FT-IR spectral analysis revealed changes in the absorption peaks of various functional groups of the oligosaccharide chain such as C-O-C, C=O, and C-O upon the introduction of vanadyl groups. A similar infrared shift has also been observed in FT-IR spectra of vanadyl (IV)/ CSA complex.

Although the precise structure of VAOS is yet to be determined, based on available data, it is suggested that VAOS is a new type of coordination compound rather than a covalent compound. Previous reports, as indicated by FT-IR spectra in this study, suggest a hypothetical structure of VAOS involving coordination through the hydroxyl oxygen of the carboxylate group and the glycosidic oxygen of G or M moieties [21]. Both the C-O-C and the O-C-O groups occupy two coordination positions. This proposed coordination structure may significantly contribute to improving the bioavailability of vanadium and the bioactivity of AOS. However, further investigation is needed to establish the definite structure-function relationship of VAOS. In a recent study on selenium-containing alginate oligosaccharides [22], the modification of AOS involved two reaction steps: In the sulfonation step, Poly M and SO3-Py were each suspended in dimethyl methanamide, and then the two solutions were mixed and reacted to obtain S-PM; whereas in the selenylation step, sulfur in S-PM was partially replaced by Se by reacting with Na2SeO3 in the presence of excess BaCl2 in 5% HNO3 at 60 °C for 8 hours. Based on the FT-IR spectra of PM, S-PM, and Se-PM, specific absorption peaks of S-O and C-O-S were detected only in S-PM and Se-PM, confirming the successful sulfation substitution.

Moreover, the spectrum of Se-PM resembled that of S-PM, indicating their similar carbon-skeleton structure. Additionally, the measured S content in Se-PM decreased to about 60% of that in S-PM, suggesting that some sulfur bound was replaced by selenium. Therefore, it was speculated that selenium might be in the form of -SeO3 covalently bound to sites originally occupied by sulfur. As a novel covalent compound, Se-PM combines the benefits of selenium and AOS, demonstrating various bioactivities including antioxidation, anti-inflammation, and neuroprotection, which are superior to those of selenium itself or selenium-free oligosaccharides [23]. The resulting low molecular weight Se-PM showed enhanced neuroimmunoregulatory activity in LPS-induced BV2 microglia, likely due to the covalent structure formed during the replacement process. This structure could attenuate the secretion of NO and PGE2, as well as the expression of iNOS and COX-2, depending on the treatment dose. A distinct type of S-MOS was synthesized by treating mannuronate oligomers with ClSO3H in formamide. Analysis using 13C- NMR indicated that sulfate modification of mannuronate takes place at the hydroxyl groups of C-2 and partially at C-3 with varying degrees of substitution.

5 Relationship between the Structure and Function of AOS

The size, composition, and structure of AOS can vary depending on the algal species, degradation patterns, and

modification methods [22,24,25]. Structural characteristics of AOS, such as degrees of polymerization, the ratio of G/M, residue structure, and spatial conformation, play a crucial role in the biological functions of AOS. AOS with a DP5 (pentamer composed of randomly arranged G and M) obtained through enzymatic digestion, rather than AOS with DP2, DP3, or DP4, showed significant inhibitory effects on the growth of osteosarcoma cells in vitro [26]. Unsaturated guluronate oligomers (DP3–DP6) notably enhanced the bacterial phagocytosis of macrophages, with GOS DP5 (the guluronate pentamer) showing the maximum enhancement among all measured oligomers [27].

These studies indicate that AOS with different DP, even when derived through the same degradation patterns, exhibit distinct biological activities. Interestingly, AOS with anti-obesity effects tend to have a lower average DP, typically no more than 4 as reported in several studies [18,28].

Xu et al. found that unsaturated GOS prepared through enzymatic digestion exhibited a macrophage-activating effect in mouse immune response, while GOS prepared by other methods or MOS showed very low or no such effects [29]. Several studies have demonstrated the potential of guluronate-rich alginate OligoG CF-5/20 (containing >85% G residues) as an effective treatment in chronic respiratory disease [30]. OligoG could directly interact with mucin, reducing its linearization and flexibility, thereby effectively detaching CF mucus [31]. On the contrary, MOS plays crucial roles in the treatment of human melanoma and AD. MOS produced by M-specific alginate lyase strongly inhibits anchorage-independent colony formation of human melanoma cells compared to polymannuronate and GOS [32], suggesting MOS as a potential drug candidate for synergistic tumor therapy. Recently, two studies demonstrated that MOS (DP2-DP11) could significantly inhibit the aggregation of Aβ oligomer and Aβ fibril formation, although their MOS samples were prepared using different methods [33]. These findings indicate that the mannuronate component and appropriate DP may play crucial roles in alleviating AD. Moreover, the G/M ratio can determine the spatial conformation of AOS and influence their gelation, mechanical properties, and biological activity. As discussed in section 2.1, G blocks tend to adopt a helical conformation, while M blocks have a relatively straight chain-like conformation due to their different linkages at C-1 and C-4. Alginate with a higher proportion of M residues was found to have higher tensile strength and elongation percentage compared to alginate dominated by G blocks [34]. It's widely recognized that alginates containing G-blocks can form strong hydrogels in the presence of divalent cations such as calcium, following the so-called egg-box model [35].

However, several studies also suggest that such cooperative ionotropic gelation occurs only when the length of the G blocks involved in the dimerization exceeds a certain threshold. For instance, it has been demonstrated that 3 and 8 ± 2 contiguous G residues are necessary to form stable junction zones for Sr2+- and Ca2+-induced gelation, respectively [36]. Therefore, AOS with a low G/M ratio and DP might not establish stable crosslinking conformations even in the presence of divalent cations, maintaining high water solubility, which is beneficial for their in vivo delivery. Conversely, AOS with higher DP and G/M ratio may retain gel-forming properties similar to alginate, making them potential candidates as drug carriers. G blocks typically contribute to stiffer, brittle, and mechanically stable gels. In contrast, M blocks lead to softer and more elastic gels [37].

As a potential drug carrier, MOS were incorporated into an alginate-based drug delivery system, improving the mechanical properties and antifungal activity of the entire delivery system [38]. The flexible conformation of MOS may facilitate penetration into bacterial cells, leading to better antimicrobial effects compared to GOS, which usually forms stiff chains [39].

AOS produced by enzymatic digestion typically have an unsaturated structure at the non-reducing end, whereas AOS obtained through oxidative degradation are always opened at the reducing end to form carboxyl groups. These unsaturated and oxidative terminal structures are crucial factors that determine the biological function of AOS. UMOS, primarily composed of mannuronic acids (M/G ratio = 2.12), demonstrate remarkable anti-obesity effects by inhibiting triglyceride accumulation and enhancing intestinal microflora [40]. Similarly, UAOS also showed significant anti-obesity effects [18]. Furthermore, this anti-obesity effect was solely associated with the unsaturated structure, irrespective of the composition of G or M. MOS obtained from enzymatic digestion and oxidative degradation showed similar inhibition of Aβ oligomer aggregation. However, the underlying molecular mechanisms of these two types of MOS in the treatment of AD were distinct, despite having very similar DP and G/M ratios. The unsaturated MOS enhanced autophagy to facilitate the clearance of APP and Aβ in AD cell models [33], whereas the oxidative MOS reconstituted gut microbiota and improved anti-neuroinflammatory responses to inhibit AD progression [25]. These studies suggest that the molecular mechanisms of AOS are significantly influenced by different terminal structures. This also indicates a direct correlation between the structural characteristics of AOS and their biological activities. Molecular size, G/M ratio, and terminal structure are key factors in determining the biological functions and mechanisms of action of AOS. To obtain AOS products with stable structure and specific functions, several important factors need consideration:

1. The source of alginate: The G/M ratio, content, and arrangement of alginate vary depending on algal species and their respective environments. For instance, alginate extracted from Laminaria japonica with an M/G ratio of 1.86 Guo et al. was degraded by alginate lyase from Pseudomonas sp [24]. HZJ 216

for 6 hours at 30 °C, resulting in AOS with DP 2 to 6. However, when the source of alginate was changed to another brown seaweed, Laminaria sp., with an M/G ratio of 2.28, AOS products mainly consisted of oligomers of DP 2 and 3 under the exact same degradation conditions. Thus, having a consistent alginate source is crucial for obtaining uniform AOS [41].

2. Production technology: The techniques used for production significantly impact the structural properties and biological functions of AOS products. For instance, the type of alginate lyase plays a vital role in determining the final product in enzymatic methods. An alginate lyase capable of specifically producing AOS with DP 5 to 7 has been reported [42]. Recently, two mannuronate-specific alginate lyases were discovered in a marine bacterium, Formosa algae, and the human gut microbe Bacteroides cellulosilyticus [32]. These alginate lyases can be utilized to produce specific AOS variants. Developing and standardizing efficient and stable production technology is crucial to ensure the quality, yield, and variety of AOS products.

3. Purification and characterization methods: Typically, AOS are mixtures of oligomers with varying DP, G/M ratios, and sequences. Therefore, it's essential to develop purification and analytical methods for the qualification and quantification of AOS. Currently, FT-IR and NMR spectroscopy are commonly used to obtain precise and essential information about AOS structure [22]. HPLC, MS, and related techniques are employed for the purification and characterization of AOS [43].

6 Prospective Biomedical Applications for AOS

6.1 Cancer treatment

Cancer remains a significant global public health concern. Over the past few decades, many natural compounds exhibiting anti-cancer properties have been identified. AOS and their derivatives, originating from marine algae, demonstrate diverse anti-cancer effects (Table 1). Han et al. demonstrated that AOS can inhibit the growth of prostate cancer cells by modulating the Hippo/YAP pathway. AOS influence regulatory processes in prostate cancer cells involving different transcription factors and effectors. Initially, AOS activate the Hippo signaling pathway, which negatively regulates YAP activity through phosphorylation cascade. Treatment with AOS resulted in decreased expression of the oncogene YAP and increased levels of phosphorylated YAP protein in prostate cancer cells.

Recruitment of both the coactivator YAP and c-Jun (a component of the transcription factor activator protein-1, which includes c-Jun, JunB, and JunD) to the upstream response region of the sialyltransferase ST6Gal-1 promoter was significantly inhibited in the absence of YAP. Consequently, reduced levels of ST6Gal-1, a molecule crucial for the growth, migration, and invasion of prostate cancer cells, were observed at various stages of transcription, translation, and sialylation in cultured cells and a xenograft mouse model. Ultimately, the growth of human prostate cancer cells was inhibited at a non-cytotoxic concentration of AOS (0.5 mg/ml for cell lines; 2.5 mg/kg for mouse models) by suppressing the Hippo/YAP/c-Jun pathway and sialylation through the downregulation of ST6Gal-1 gene expression [44]. In a clinical study, AOS showed significant suppression of aneurysm recurrence following EVAR [45]. Over a 2-year period of AOS treatment (oral administration, 10 mg/day), the size of remaining aneurysms decreased significantly compared to the control group. The occurrence of EVAR-related adverse effects like back and chest pain, pulse-less legs, persistent cough, and wound infection was also reduced. The trial indicated that AOS with DP 3 to 6 effectively decreased aneurysm recurrence post-EVAR. AOS, as a bioactive compound, could influence related signaling pathways such as the expression of miR-29b and toll-like receptor signaling. Their findings showed that miR-29b expression levels in patients with aortic aneurysms significantly decreased after AOS treatment. As a result, it influenced the TLR signaling pathway, involving various downstream factors such as MAPK, NF-κB, IL-1 β, and IL-6. They concluded that AOS can inhibit aneurysm regeneration by reducing the levels of TLR4, NF-κB, IL-1β, and IL-6 through the inhibition of miR-29b. Myeloma, also referred to as plasma cell tumor, is a malignant tumor originating from plasma cells in the bone marrow. A notable characteristic of myeloma cells is the high expression of the cell surface heparin Sdc-1 [46]. HGF binds to Sdc-1, enhancing downstream HGF signaling, which stimulates angiogenesis, cell migration, and tumor growth [47]. Inhibiting the interaction between HGF and Sdc-1 can effectively suppress tumor cell proliferation. Arlov et al. discovered that sulfated AOS could directly attach to HGF, preventing its interaction with Sdc-1 [48]. When appropriate sizes of sulfated AOS were used, the sulfated AOS-bound HGF was released from the surface of myeloma cells. Conversely, no release of HGF was observed when treated with non-sulfated AOS. A recent study demonstrated that VAOS, a newly modified coordination compound, effectively inhibits NSCLC both in cell cultures and mouse models with tumor cell transplants [20]. Further investigation confirmed that VAOS (12.5, 25, 50 μM) induces apoptosis in NSCLC cells by AKT, thereby increasing intracellular ROS levels. Phosphorus colorimetric analysis revealed that VAOS significantly inhibits the dephosphorylation activity of PTEN, an upstream regulator of AKT belonging to the PTPases. Moreover, ectopic overexpression of PTEN reduced VAOS-induced apoptosis. In vivo, treatment with VAOS (intraperitoneal injection, 30 mg/kg for 2 weeks) led to hyperactivation of AKT by significantly reducing the phosphatase activity of PTEN, resulting in ROS accumulation and apoptosis of NSCLC cells.

Table 1. Actions of AOS against tumors.

Anti-tumor mechanism	Cell line and Cancer style	Ref.
Reduction of HGF-induced angiogenesis	Human myeloma RPMI-8226 cells	[48]
Inhibition of colony development and cell proliferation	Human melanoma cells SK-MEL-5, SK-MEL-28, and RPMI-7951	[26]
	Human bone cancer cell MG-63	[32]
	Human aneurysm	[44]
	Human prostate cancer cells DU145 and PC-3	[45]
	Human myeloma RPMI-8226 cells	[48]
Cell apoptosis induction	Human non-small cell lung cancer cells A549 and LTEP-a-2	[20]

6.2 *Anti-microbial activities*

Microbial infections are a major cause of human diseases. The ability of pathogens to form biofilms and the resulting increase in drug resistance make them a formidable challenge [49]. AOS have shown significant potential in treating infections caused by common opportunistic pathogens such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Candida species [50]. Powell et al. reported that OligoG CF-5/20 significantly reduced the biomass, thickness, and density of Pseudomonas aeruginosa biofilms both during early formation and after establishment [51]. They found that OligoG CF-5/20 not only inhibited biofilm growth but also disrupted the structure of established biofilms. The compound rapidly diffused throughout the biofilm, causing it to collapse from within by disrupting the extracellular polysaccharide matrix and DNA-Ca2+-DNA bridges, which are crucial for biofilm formation and maturation [52].

Additionally, combining OligoG CF-5/20 with antibiotics enhanced antibiotic efficacy. Recently, Stokniene et al. reported that artificial bi-functional compounds of OligoG CF-5/20 and polymyxins exhibited prolonged antimicrobial and antibiofilm activities against multidrug-resistant Gram-negative bacteria, compared to the parent antibiotic, while reducing its toxicity to humans. OligoG CF-5/20 demonstrated a strong inhibitory effect on infections caused by Candida albicans by reducing its growth, mycelium formation, and invasion. Additionally, pretreatment with OligoG significantly decreased the gene expression and protein production of a key phospholipase, which is a major virulence factor, in C. albicans ATCC 90028 cells [53].

6.3 *Anti-inflammation*

Repeated administration of anticancer medications often leads to gastrointestinal inflammation, resulting in various side effects. To mitigate pharmacotherapy-induced intestinal disruption, several agents like probiotics, selenium, volatile oils, and prebiotics have been explored [49]. However, these attempts have shown limited success. There is an urgent need for novel bioactive compounds to aid in the recovery from inflammation following cancer therapy. Research has demonstrated that AOS can effectively reduce inflammation induced by busulfan, a medication used in chronic myeloid leukemia patients [50]. Additionally, AOS enhances the integrity and migratory ability of IPEC-J2 cells (a porcine small intestinal cell line) [51]. The underlying molecular mechanisms are diverse and extensive, involving the regulation of AOS on cellular transcriptome and subsequent responses of various intestinal cell types. SiRNA experiments conducted in IPEC-J2 cells confirmed that AOS exert their function by interacting with mannose receptors on the cell surface, leading to significant remodeling of transcriptomes in different types of small intestine cells. The study identified 184 active and differently expressed genes, including several transcription factors and related cofactors. Ultimately, administration of AOS (oral gavage, 10 mg/kg for 2 weeks) restored the developmental timeline of various types of small intestinal cells (enterocytes, goblet cells, Paneth cells, tuft cells) disrupted by busulfan, along with their functions related to microvilli organization, cell junctions, antibacterial humoral response, and more. Furthermore, improvements in the plasma metabolome further confirmed that AOS could restore small intestinal function in individuals undergoing anticancer chemotherapy.

Furthermore, FMT from mice treated with AOS proved to be an effective strategy for reducing small intestine mucositis by reshaping gut microbiota and enhancing blood metabolome on a multi-omics level [52]. Another study demonstrated that AOS reduced TNF-α-induced inflammatory damage by lowering the concentrations of pro-inflammatory cytokines (IL-6 and TNF-α) and the apoptosis rate mediated by TNFR1 in TNF-α-treated IPEC-J2 cells [53]. Se-PM, a modified AOS derivative, significantly reduced the inflammatory response in LPS-activated murine macrophage RAW264.7 cells, as well as primary microglia and astrocytes, by inhibiting the activation of the NF-κB and MAPK signaling pathways [54]. The cytotoxicity of Se-PM was assessed using the CCK-8 assay, revealing no cytotoxic effects on primary glial cells at concentrations up to 0.8 mg/ml. Se-PM treatment notably decreased the phosphorylation of the NF-κB inhibitor (IκB-α), Akt, p38, ERK, and JNK. This resulted in reduced phosphory-

lation and nuclear translocation of transcription factors, particularly p65, leading to a significant decrease in the expression of downstream target genes iNOS and COX-2. As a result, the production of pro-inflammatory mediators such as ROS, NO, PGE2, and the secretion of cytokines including TNF-α, IL-1β, and IL-6 decreased in cells treated with Se-PM. Se-PM effectively inhibited the inflammatory response in various types of LPS-activated cells. Additionally, Se-PM significantly reduced pro-inflammatory cytokine production induced by carrageenan and suppressed LPS-triggered activation of microglia and astrocytes in different mouse models. Se-PM may obstruct the interaction between LPS and receptors on the surface of LPS-stimulated RAW264.7 cells.

These findings enhance the understanding of Se-PM's potential health benefits in mitigating prolonged and excessive inflammation associated with degenerative diseases such as cancer, cardiovascular diseases, type 2 diabetes, and arthritis.

6.4 Anti-obesity

Obesity, a metabolic disorder marked by excessive body fat accumulation, is linked to numerous diseases, including hypertension, hyperlipidemia, diabetes, and even cancer. It has become a significant threat to human health. Beyond the general advice of maintaining a proper diet and regular exercise, various strategies have been suggested to combat obesity, such as using functional food supplements with anti-obesity properties. AOS, a naturally-derived food additive with multiple beneficial effects, might be a potential candidate for obesity treatment. Li et al. explored the anti-obesity effects of UAOS derived from the enzymatic degradation of Laminaria japonica in a HFD mouse model [18]. Their findings revealed that UAOS exhibited stronger anti-obesity effects compared to acid-hydrolyzed SAOS, as evidenced by greater reductions in body and liver weights, adipose tissue mass, and serum and liver lipid contents. Other studies have similarly demonstrated the superior biological activity of UAOS [55]. UAOS significantly increased the phosphorylation of both AMPKα and ACC in adipocytes, indicating that UAOS functions as an anti-obesity agent through AMPK signaling. In another investigation, it was noted that AOS treatment resulted in a reduction in adipocyte size and improvement in lipid metabolism, including a decrease in TG and LDL-C levels, along with the inhibition of lipogenesis gene expression. AOS alleviated HFD-induced metabolic disorders and inflammation by modulating gut microbial communities, leading to the release of microbiota-dependent SCFAs and a reduction in endotoxin levels. AOS treatment restored the HFD-disturbed gut microbiota by increasing the abundance of specific beneficial gut microbes, such as Akkermansia muciniphila, Lactobacillus reuteri, and Lactobacillus gasseri. These findings indicate that the inhibitory effect of AOS on obesity is closely associated with its regulation of intestinal microorganisms.

6.5 Anti-oxidation

Oxidative stress signifies an imbalance between the production of ROS and the body's natural antioxidant defenses. Disruptions in the normal redox state of cells can result in the formation of peroxides and free radicals, which damage proteins, lipids, and DNA. This stress can cause cell dysfunction and apoptosis by interfering with cellular signaling mechanisms. In humans, oxidative stress is believed to be linked to the onset and progression of various degenerative diseases, particularly atherosclerosis. Research has demonstrated that AOS treatment can significantly boost the activity of antioxidant enzymes and the levels of free radical scavengers, such as SOD, CAT, and GSH, in HUVECs [54]. AOS treatment also decreased H2O2-induced ROS accumulation, the production of MDA—a final product of lipid peroxidation—and the secretion of ET-1, a signaling molecule that stimulates ROS and superoxide generation. Furthermore, AOS protected HUVECs from oxidative stress-induced apoptosis by regulating the expression of genes involved in the caspase-mediated apoptosis pathway and the integrin-α/FAK/PI3K pathway. These studies indicated that AOS can safeguard endothelial cells through their potent antioxidant and anti-apoptotic properties, presenting a promising therapeutic approach for the prevention and treatment of atherosclerosis.

6.6 Drug carrier

Park et al. proposed the use of AOS as a drug carrier in oral sustained release formulations, considering the challenges of alginate hydrogels' in vivo degradation [56]. They conducted in vitro simulations to mimic the oral drug passage from the stomach to the intestine by controlling the pH of the reaction solution. AOS obtained through enzymatic digestion formed spherical gels containing lysosomes, demonstrated by liquid dropping tests, effectively protecting the lysosomes from degradation or hydrolysis under acidic conditions (pH 1.2). Subsequently, the gel dissolved, releasing the encapsulated lysosomes at near-neutral pH (pH 6.8), while maintaining the morphological integrity and antimicrobial activity of lysosomes. Hence, they suggested that AOS hold potential as an oral delivery system for drugs, proteins, and lysosomes for treating metabolic diseases. Furthermore, AOS showed promise in alleviating enterotoxigenic E. coli-induced intestinal mucosal damage in weaned pigs and improving intestinal morphology and growth [57].

The studies above suggest that AOS may have dual roles, acting both as drug carriers and as promoters of intestinal microecology. In another investigation, AOS with high M content were utilized as matrices for drug delivery to enhance the antifungal activity of POS [38]. They employed the freeze-thaw technique to fabricate AOS gels. This process involves solvent crystallization during freezing, resulting in the compression of AOS chains' space and

increased interactions between them, facilitating their connection and hydrogel formation upon thawing. Through this method, conventional antifungal drugs were incorporated into AOS at appropriate concentrations and proportions to achieve optimal mucoadhesive properties and prolonged drug release. Ultimately, it was demonstrated that mucoadhesive films containing POS, based on AOS for buccal delivery, exhibited larger zones of inhibition and reduced the growth of all tested Candida spp. Generally, AOS exhibit improved water solubility and bioavailability owing to their shorter chain length. While AOS differ from alginate in molecular size, they still retain the ability to form effective gels similar to alginate by adjusting AOS size, proportion, concentration, and employing appropriate preparation techniques. These investigations have demonstrated that AOS-based gels also possess good mucoadhesive and swelling properties, along with a prolonged drug release effect, all of which are crucial for a drug carrier [56]. Additionally, AOS offer extra benefits such as antimicrobial effects, enhancement of drug efficacy, and triggering physiological and pathophysiological stress responses. Hence, AOS represent a natural and emerging type of drug carrier with dual therapeutic effects, holding significant potential for diverse applications and warranting further research and development [50].

6.7 Alzheimer's disease therapies

AD is a progressive neurodegenerative condition characterized by the accumulation of Aβ plaques and the hyperphosphorylation of tau protein, leading to NFTs, neuronal loss, and glial cell activation [55]. Aβ peptides are produced from APP through sequential cleavage by BACE and γ-secretases [58]. Recent studies have highlighted the significant role of AOS in the pathogenesis of AD with various mechanisms of action. Bi et al. investigated the effects of two different types of AOS, MOS (derived from enzymatic digestion) and Se-PM (modified with Se), in the treatment of AD. Both MOS and Se-PM demonstrated significant inhibition of Aβ1–42 oligomer aggregation, considered the most neurotoxic form, and reduced the expression of Aβ1–42, APP, and BACE1 in N2a-sw cells [33]. Moreover, MOS and Se-PM reduced ROS production and oxidative stress levels. These findings suggest that the presence of Se and unsaturated double bonds in AOS may play a crucial role in their biological activity. Furthermore, MOS was found to activate autophagy by suppressing the mTOR signaling pathway, facilitating the clearance of intracellular APP and Aβ accumulation in AD cell models, while Se-PM attenuated cell apoptosis and improved cell survival in N2a-sw cells by reducing cytochrome c expression and enhancing mitochondrial membrane potential. Research has shown that GV-971, a type of MOS derived from oxidative degradation, functions in the treatment of AD by acting on the gut-brain axis [25]. GV-971 improves cognitive functions by reshaping gut microbiota, reducing the production of abnormal metabolites, particularly phenylalanine and isoleucine, preventing the infiltration of peripheral immune cells into the brain, suppressing neuroinflammation, and reducing brain Aβ deposition and tau hyperphosphorylation. Results from a phase 3 clinical trial indicated that GV-971 significantly reversed cognitive impairment in patients with mild to moderate AD. Furthermore, GV-971 has been shown to penetrate the blood-brain barrier and directly bind to multiple subregions of Aβ, inhibiting the formation of Aβ fibrils and destabilizing Aβ aggregates into non-toxic monomers. Understanding the action mechanism of GV-971 undoubtedly offers a crucial scientific foundation for comprehensively exploring gut microbiota targeting as a novel treatment approach for AD. It also provides a detailed experimental groundwork for the research and development of similar drugs as a new therapeutic pathway for AD. Currently, GV-971 has been launched in China and FDA-approved for ongoing international Phase 3 clinical trials.

7 Commercialization and Safety of AOS

Evaluating the biosafety of AOS is crucial for their potential biomedical applications. None of the AOS variants (-ED, -AH, and -OD) showed any cytotoxic effects on RAW264.7 cells at a concentration of 1 mg/ml according to WST-8 assay [29]. AOS at a concentration of 1 mg/ml did not induce toxicity in endothelial cells isolated from human aneurysms [45]. Zhao et al. demonstrated that AOS treatment at various doses (0.05, 0.1, 0.2, 0.4, and 0.8 mg/ml) exhibited no cytotoxicity on HUVECs [59]. Moreover, Ogawa et al. found no obvious cell toxicity or mutagenicity of AOS in mice after 31 days of oral administration at a dosage of 600 mg/mouse/day [60]. Clinical studies including a double-blind, randomized, placebo-controlled phase I study (NCT00970346) assessing the in vivo safety and tolerability of inhaled OligoG CF-5/20 in healthy volunteers, and a multicenter, randomized, placebo-controlled, crossover phase II study (NCT01465529) evaluating the safety, tolerability, and preliminary efficacy of OligoG CF-5/20 in subjects with CF chronically colonized with Pseudomonas aeruginosa, have been completed. Currently, OligoG CF-5/20 is undergoing phase IIb/III clinical trials in patients with CF. In a recently completed phase III trial (NCT02293915), GV-971 (administered at 900 mg twice a day for 24 weeks) met the primary endpoint with statistical significance ($p < 0.001$). There were no serious adverse events observed, and the incidence rate was similar between the GV-971 and placebo groups [25]. GV-971, a low-molecular-weight mannuronic acid oligomer, has now been formulated into sodium oligomannate capsules and successfully launched in the Chinese market. Overall, these studies collectively indicate that AOS doses exhibit no apparent toxicity or side effects across different cell lines, mouse models, and human patients, suggesting the safety of AOS for use as food supplements, drug carriers, or pharmaceutical ingredients. However, future biomedical applications of AOS still re-

quire extensive research on their metabolism and safety, considering their diverse composition, variable structure, and various modification styles. Commercialization is an effective strategy to enable widespread application of AOS products. Currently, there are only a limited number of commercially available biomedical products based on AOS. GV-971-related products have been launched in the Chinese market after over 20 years of research and development. GV-971 is the first new Alzheimer's drug to receive regulatory approval globally since 2003. This notable and successful case serves as significant inspiration and provides valuable practical experience for the future development of AOS-based drugs. Additionally, the drug candidate Oligo G CF-5/20 has demonstrated safety. AlgiPharma, a pharmaceutical company, is developing its product line, having successfully completed five clinical trials (NCT00970346; NCT01465529; NCT01991028; NCT02157922; NCT02453789), including a drug deposition study in CF patients. Multiple formulations for inhalation, oral, and topical administration targeting respiratory diseases and microbial infections are expected to be available in the near future.

8 Conclusion

In summary, the physicochemical and biochemical characteristics of AOS, including their small molecular size, low viscosity, high water solubility, and intestinal absorption, render them suitable for formulation into various dosage forms for different routes of administration, such as inhalation, intraperitoneal injection (i.p.), and oral gavage. AOS can exert their unique biological functions through three modes: as extracellular signaling molecules that induce host biological reactions, as prebiotics that stimulate and improve interactions between symbiotic microbiota and host metabolism, and as drug adjuvants or carriers to enhance drug efficacy. The structure and properties of final AOS products are determined by different sources of raw materials, preparation methods, and modification styles, which influence their beneficial functions and specific effects. AOS doses vary depending on their applications, such as 0–1 mg/ml for cell line treatments, 2.5–500 mg/kg/day or 5 mg/mouse for xenograft mouse models treatments, and 0.2–10% when used as drug carriers or antimicrobials. Current challenges in AOS research include: 1) Most studies remain confined to the laboratory, with only a few progressing to human clinical trials; 2) Industrial-scale production of AOS is still not realized.

Particularly, the low yield and hydrolysis efficiency of current alginate lyases are major constraints for industrial production of enzymatically digested AOS; 3) The production cost of AOS is prohibitively high, resulting in expensive drugs based on AOS, especially those not covered by medical insurance, thus increasing the economic burden on patients. Despite these obstacles, AOS possess significant research importance, development potential, and wide-ranging application prospects due to their strong structural adaptability, high bioavailability, and diverse beneficial effects.

Therefore, investing more efforts in exploring their potential applications is warranted. In future research, emphasis should be placed on the following areas: 1) Conducting more clinical trials involving humans to provide comprehensive experimental evidence, thereby enhancing the reliability and credibility of AOS products. 2) Developing more efficient manufacturing technologies to increase the production rate and yield of AOS. One approach is to identify stable and efficient alginate lyases through large-scale screening and identification of alginate lyase-producing microbes, cloning and expression of alginate lyase-encoding genes, purification and characterization of enzymes with high catalytic activity and optimizing the enzymatic hydrolysis process. 3) Furthermore, advanced multidisciplinary techniques should be developed to modify and characterize AOS, elucidating their underlying structure-function relationship. We believe that through collaborative efforts of researchers, the emergence and success of AOS-based drugs will be realized in the near future.

Abbreviation

Abbreviation	Definition
M	β-D-mannuronic acid
G	α-L-guluronic acid
AOS	alginate oligosaccharides
DP	degrees of polymerization
Mr	relative molecular weight
AH	acid hydrolysis
OD	oxidative degradation
ED	enzymatic digestion
H2O2	Hydrogen peroxide
GOS	guluronate oligosaccharides
GOS-OD	guluronate oligosaccharide prepared by oxidative degradation
LPS	lipopolysaccharide
NO	nitric oxide
HFD	high-fat diet
VAOS	vanadyl AOS
NSCLC	non-small cell lung cancer
CSA	chondroitin sulfate A
S-PM	sulfonated Poly M
BaCl2	barium chloride
PGE2	prostaglandin E2
iNOS	inducible NO synthase-20
COX-2	cyclooxygenase-2
S-MOS	sulfated mannuronate oligosaccharides
NMR	nuclear magnetic resonance
MOS	mannuronate oligosaccharides
CF	cystic fibrosis
AD	Alzheimer's disease
FMT	fecal microbiota transplantation
TNFR1	TNF receptor 1
p38	p38 kinases
ERK	extracellular signal-regulated kinases
JNK	c-Jun N-terminal kinases
SOD	superoxide dismutase
CAT	catalase
GSH	glutathione
HUVECs	human umbilical vein endothelial cells
MDA	malondialdehyde

Abbreviation	Definition
ET-1	endothelin-1
SAOS	saturated AOS
ACC	acetyl-CoA carboxylase
TG	triglyceride
LDL-C	low-density lipoprotein cholesterol
SCFAs	short-chain fatty acids
Aβ	amyloid-β
NFTs	neurofibrillary tangles
APP	amyloid precursor protein
BACE	β-secretase
POS	posaconazole
MS	mass spectrometry
UMOS	Unsaturated mannuronate oligosaccharides
UAOS	unsaturated alginate oligosaccharides
APP	amyloid precursor protein
HPLC	High-performance liquid chromatography
EVAR	endovascular aortic repair
TLR	toll-like receptor
MAPK	mitogen-activated protein kinase
NF-κB	nuclear factor kappa B
IL-1	interleukin 1
IL-6	interleukin 6
Sdc-1	sulfate proteoglycan syndecan-1
HGF	Human growth factor
AKT	activating protein kinase B
ROS	reactive oxygen species
PTEN	phosphatase and tensin homolog on chromosome 10
PTPases	protein tyrosine phosphatases

Conflict of Interest: The authors declare no conflict of interest.
Financing: The study was performed without external funding.
Ethical consideration: The study was approved by University of Iran.

REFERENCES

[1] Lavaud J, Goss R. The peculiar features of non-photochemical fluorescence quenching in diatoms and brown algae. In: Demmig-Adams B, Garab G, Adams III WW, Govindjee, editors. Non-photochemical quenching and energy dissipation in plants, algae and cyanobacteria. Springer; 2014. p. 421-43. doi:10.1007/978-94-017-9032-1_22.

[2] Bartsch I, Wiencke C, Bischof K, Buchholz CM, Buck BH, Eggert A, et al. The genus Laminaria sensu lato: recent insights and developments. European journal of phycology. 2008;43(1):1-86. doi:10.1080/09670260701711376.

[3] de Mesquita M, Crapez M, Teixeira V, Cavalcanti D. Potential interactions bacteria-brown algae. Journal of Applied Phycology. 2019;31:867-83. doi:10.1007/s10811-018-1616-0.

[4] Afonso NC, Catarino MD, Silva AM, Cardoso SM. Brown macroalgae as valuable food ingredients. Antioxidants. 2019;8(9):365. doi:10.3390/antiox8090365.

[5] Øverland M, Mydland LT, Skrede A. Marine macroalgae as sources of protein and bioactive compounds in feed for monogastric animals. Journal of the Science of Food and Agriculture. 2019;99(1):13-24. doi:10.1002/jsfa.9143.

[6] Ford L, Stratakos AC, Theodoridou K, Dick JT, Sheldrake GN, Linton M, et al. Polyphenols from brown seaweeds as a potential antimicrobial agent in animal feeds. ACS Omega. 2020;5(16):9093-103. doi:10.1021/acsomega.9b03687.

[7] Zou P, Lu X, Zhao H, Yuan Y, Meng L, Zhang C, et al. Polysaccharides derived from the brown algae Lessonia nigrescens enhance salt stress tolerance to wheat seedlings by enhancing the antioxidant system and modulating intracellular ion concentration. Frontiers in Plant Science. 2019;10:48. doi:10.3389/fpls.2019.00048.

[8] Sari-Chmayssem N, Taha S, Mawlawi H, Guégan JP, Jeftić J, Benvegnu T. Extracted and depolymerized alginates from brown algae Sargassum vulgare of Lebanese origin: Chemical, rheological, and antioxidant properties. Journal of Applied Phycology. 2016;28:1915-29. doi:10.1007/s10811-015-0676-4.

[9] Lee K, Mooney DJ. Alginate: properties and biomedical applications. Progress in Polymer Science. 2012;37(1):106-26. doi:10.1016/j.progpolymsci.2011.06.003.

[10] Fan Y, Li Y, Zhang J, Ding X, Cui J, Wang G, et al. Alginate enhances memory properties of antitumor CD8+ T cells by promoting cellular antioxidation. ACS Biomaterials Science & Engineering. 2019;5(9):4717-25. doi:10.1021/acsbiomaterials.9b00373.

[11] Zhu B, Ni F, Xiong Q, Yao Z. Marine oligosaccharides originated from seaweeds: Source, preparation, structure, physiological activity and applications. Critical Reviews in Food Science and Nutrition. 2021;61(1):60-74. doi:10.1080/10408398.2020.1716207.

[12] Trincone A. Short bioactive marine oligosaccharides: Diving into recent literature. Current Biotechnology. 2015;4(3):212-22.

[13] Rioux LE, Turgeon SL. In: Tiwari BK, Troy DJ, editors. Seaweed carbohydrates. Elsevier; 2015. p. 141-92.

[14] Grasdalen H. High-field, 1H-nmr spectroscopy of alginate: sequential structure and linkage conformations. Carbohydrate Research. 1983;118:255-60.

[15] Plazinski W. Molecular basis of calcium binding by polyguluronate chains. Revising the egg-box model. Journal of Computational Chemistry. 2011;32(14):2988-95. doi:10.1002/jcc.21880.

[16] Zhou R, Shi X, Gao Y, Cai N, Jiang Z, Xu X. Anti-inflammatory activity of guluronate oligosaccharides obtained by oxidative degradation from alginate in lipopolysaccharide-activated murine macrophage RAW 264.7 cells. Journal of Agricultural and Food Chemistry. 2015;63(1):160-8. doi:10.1021/jf503548a.

[17] Tusi SK, Khalaj L, Ashabi G, Kiaei M, Khodagholi F. Alginate oligosaccharide protects against endoplasmic reticulum-and mitochondrial-mediated apoptotic cell death and oxidative stress. Biomaterials. 2011;32(23):5438-58. doi:10.1016/j.biomaterials.2011.04.024.

[18] Salimi S, Sotudeh-Gharebagh R, Zarghami R, Chan SY, Yuen KH. Production of nanocellulose and its applications in drug delivery: A critical review. ACS Sustainable Chemistry & Engineering. 2019;7(19):15800-27. doi:10.1021/acssuschemeng.9b02744.

[19] Liu S, Liu G, Yi Y. Novel vanadyl complexes of alginate saccharides: Synthesis, characterization, and biological activities. Carbohydrate Polymers. 2015;121:86-91. doi:10.1016/j.carbpol.2014.11.069.

[20] Zhou L, Yi Y, Yuan Q, Zhang J, Li Y, Wang P, et al. VAOS, a novel vanadyl complexes of alginate saccharides, inducing apoptosis via activation of AKT-dependent ROS production in NSCLC. Free Radical Biology and Medicine. 2018;129:177-85. doi:10.1016/j.freeradbiomed.2018.09.016.

[21] Etcheverry SB, Williams PA, Baran EJ. Synthesis and characterization of oxovanadium (IV) complexes with saccharides. Carbohydrate Research. 1997;302(3-4):131-8. doi:10.1016/S0008-6215(97)00132-8.

[22] Bi D, Li X, Li T, Li X, Lin Z, Yao L, et al. Characterization and neuroprotection potential of seleno-polymannuronate. Frontiers in Pharmacology. 2020;11:21. doi:10.3389/fphar.2020.00021.

[23] Bi D, Lai Q, Li X, Cai N, Li T, Fang W, et al. Neuroimmunoregulatory potential of seleno-polymannuronate derived from alginate in lipopolysaccharide-stimulated BV2 microglia. Food Hydrocolloids. 2019;87:925-32. doi:10.1016/j.foodhyd.2018.09.013.

[24] Guo JJ, Ma LL, Shi HT, Zhu JB, Wu J, Ding ZW, et al. Alginate oligosaccharide prevents acute doxorubicin cardiotoxicity by suppressing oxidative stress and endoplasmic reticulum-mediated apoptosis. Marine Drugs. 2016;14(12):231. doi:10.3390/md14120231.

[25] Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Research. 2019;29(10):787-803. doi:10.3791/52739.

[26] Chen J, Hu Y, Zhang L, Wang Y, Wang S, Zhang Y, et al. Alginate oligosaccharide DP5 exhibits antitumor effects in osteosarcoma patients following surgery. Frontiers in Pharmacology. 2017;8:623. doi:10.3389/fphar.2017.00623.

[27] Xu X, Bi D, Wu X, Wang Q, Wei G, Chi L, et al. Unsaturated guluronate oligosaccharide enhances the antibacterial activities of macrophages. The FASEB Journal. 2014;28(6):2645-54. doi:10.1096/fj.13-247791.

[28] Wang Y, Li L, Ye C, Yuan J, Qin S. Alginate oligosaccharide improves lipid metabolism and inflammation by modulating gut microbiota in high-fat diet fed mice. Applied Microbiology and Biotechnology. 2020;104:3541-54. doi:10.1007/s00253-020-10449-7.

[29] Xu X, Wu X, Wang Q, Cai N, Zhang H, Jiang Z. Immunomodulatory effects of alginate oligosaccharides on murine macrophage RAW264.7 cells and their structure–activity relationships. Journal of Agricultural and Food Chemistry. 2014;62(14):3168-76. doi:10.1021/jf405633n.

[30] Pritchard MF, Oakley JL, Brilliant CD, Rye PD, Forton J, Doull IJ, et al. Mucin structural interactions with an alginate oligomer mucolytic in cystic fibrosis sputum. Vibrational Spectroscopy. 2019;103:102932. doi:10.1016/j.vibspec.2019.102932.

[31] Ermund A, Recktenwald CV, Skjåk-Bræk G, Meiss LN, Onsøyen E, Rye PD, et al. OligoG CF-5/20 normalizes cystic fibrosis mucus by chelating calcium. Clinical and Experimental Pharmacology and Physiology. 2017;44(6):639-47. doi:10.1111/1440-1681.12744.

[32] Belik A, Silchenko A, Malyarenko O, Rasin A, Kiseleva M, Kusaykin M, et al. Two new alginate lyases of PL7 and PL6 families from polysaccharide-degrading bacterium Formosa algae KMM 3553T: Structure, properties, and products analysis. Marine Drugs. 2020;18(2):130. doi:10.3390/md18020130.

[33] Bi D, Yao L, Lin Z, Chi L, Li H, Xu H, et al. Unsaturated mannuronate oligosaccharide ameliorates β-amyloid pathology through autophagy in Alzheimer's disease cell models. Carbohydrate Polymers. 2021;251:117124. doi:10.1016/j.carbpol.2020.117124.

[34] Costa MJ, Marques AM, Pastrana LM, Teixeira JA, Sillankorva SM, Cerqueira MA. Physicochemical properties of alginate-based films: Effect of ionic crosslinking and mannuronic and guluronic acid ratio. Food Hydrocolloids. 2018;81:442-8. doi:10.1016/j.foodhyd.2018.03.014.

[35] Grant GT, Morris ER, Rees DA, Smith PJ, Thom D. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Letters. 1973;32(1):195-8. doi:10.1016/0014-5793(73)80770-7.

[36] Stokke BT, Smidsrød O, Zanetti F, Strand W, Skjåk-Bræk G. Distribution of uronate residues in alginate chains in relation to alginate gelling properties—2: Enrichment of β-d-mannuronic acid and depletion of α-l-guluronic acid in sol fraction. Carbohydrate Polymers. 1993;21(1):39-46. doi:10.1016/0144-8617(93)90115-K.

[37] Ashikin WHNS, Wong TW, Law CL. Plasticity of hot air-dried mannuronate-and guluronate-rich alginate films. Carbohydrate Polymers. 2010;81(1):104-13. doi:10.1016/j.carbpol.2010.02.002.

[38] Szekalska M, Wróblewska M, Trofimiuk M, Basa A, Winnicka K. Alginate oligosaccharides affect mechanical properties and antifungal activity of alginate buccal films with posaconazole. Marine Drugs. 2019;17(12):692. doi:10.3390/md17120692.

[39] Hu X, Jiang X, Gong J, Hwang H, Liu Y, Guan H. Antibacterial activity of lyase-depolymerized products of alginate. Journal of Applied Phycology. 2005;17:57-60.

[40] ; Non-reducing end unsaturated mannuronic acid oligosaccharides and compositions containing same as active ingredient. ; 2018.

[41] Leung AC, Hrapovic S, Lam E, Liu Y, Male KB, Mahmoud KA, et al. Characteristics and properties of carboxylated cellulose nanocrystals prepared from a novel one-step procedure. Small. 2011;7(3):302-5. doi:10.1002/smll.201002263.

[42] Huang L, Zhou J, Li X, Peng Q, Lu H, Du Y. Characterization of a new alginate lyase from newly isolated Flavobacterium sp. S20. Journal of Industrial Microbiology and Biotechnology. 2013;40(1):113-22. doi:10.1007/s10295-012-1210-1.

[43] Fu Q, Liang T, Li Z, Xu X, Ke Y, Jin Y, et al. Separation of carbohydrates using hydrophilic interaction liquid chromatography. Carbohydrate Research. 2013;379:13-7. doi:10.1016/j.carres.2013.06.006.

[44] Han Y, Zhang L, Yu X, Wang S, Xu C, Yin H, et al. RETRACTED ARTICLE: Alginate oligosaccharide attenuates α2, 6-sialylation modification to inhibit prostate cancer cell growth via the Hippo/YAP pathway. Cell Death & Disease. 2019;10(5):374.

[45] Yang Y, Ma Z, Yang G, Wan J, Li G, Du L, et al. Alginate oligosaccharide indirectly affects toll-like receptor signaling via the inhibition of microRNA-29b in aneurysm patients after endovascular aortic repair. Drug Design, Development and Therapy. 2017:2565-79.

[46] Gambella M, Palumbo A, Rocci A. MET/HGF pathway in multiple myeloma: from diagnosis to targeted therapy? Expert Review of Molecular Diagnostics. 2015;15(7):881-93. doi:10.1586/14737159.2015.1046436.

[47] Aref S, Goda T, El-Sherbiny M. Syndecan-1 in multiple myeloma: relationship to conventional prognostic factors. Hematology. 2003;8(4):221-8. doi:10.1080/1024533031000153630.

[48] Arlov O, Aachmann FL, Feyzi E, Sundan A, Skjåk-Bræk G. The impact of chain length and flexibility in the interaction between sulfated alginates and HGF and FGF-2. Biomacromolecules. 2015;16(11):3417-24. doi:10.1021/acs.biomac.5b01125.

[49] Moskowitz SM, Foster JM, Emerson J, Burns JL. Clinically feasible biofilm susceptibility assay for isolates of Pseudomonas aeruginosa from patients with cystic fibrosis. Journal of Clinical Microbiology. 2004;42(5):1915-22. doi:10.1128/jcm.42.5.1915-1922.2004.

[50] Stokniene J, Powell LC, Aarstad OA, Aachmann FL, Rye PD, Hill KE, et al. Bi-functional alginate oligosaccharide–polymyxin conjugates for improved treatment of multidrug-resistant gram-negative bacterial infections. Pharmaceutics. 2020;12(11):1080. doi:10.3390/pharmaceutics12111080.

[51] Powell LC, Pritchard MF, Ferguson EL, Powell KA, Patel SU, Rye PD, et al. Targeted disruption of the extracellular polymeric network of Pseudomonas aeruginosa biofilms by alginate oligosaccharides. npj Biofilms and Microbiomes. 2018;4(1):13.

[52] Bales PM, Renke EM, May SL, Shen Y, Nelson DC. Purification and characterization of biofilm-associated EPS exopolysaccharides from ESKAPE organisms and other pathogens. PloS one. 2013;8(6):e67950. doi:10.1371/journal.pone.0067950.

[53] Pritchard MF, Jack A, Powell LC, Sadh H, Rye PD, Hill KE, et al. Alginate oligosaccharides modify hyphal infiltration of Candida albicans in an in vitro model of invasive human candidosis. Journal of Applied Microbiology. 2017;123(3):625-36. doi:10.1111/jam.13516.

[54] Jiang Z, Zhang X, Wu L, Li H, Chen Y, Li L, et al. Exolytic products of alginate by the immobilized alginate lyase confer antioxidant and antiapoptotic bioactivities in human umbilical vein endothelial cells. Carbohydrate polymers. 2021;251:116976. doi:10.1016/j.carbpol.2020.116976.

[55] Jana A, Pahan K. Fibrillar amyloid-β-activated human astroglia kill primary human neurons via neutral sphingomyelinase: implications for Alzheimer's disease. Journal of Neuroscience. 2010;30(38):12676-89. doi:10.1523/JNEUROSCI.1243-10.2010.

[56] Feng W, Yang X, Feng M, Pan H, Liu J, Hu Y, et al. Alginate oligosaccharide prevents against D-galactose-mediated cataract in C57BL/6J mice via regulating oxidative stress and antioxidant system. Current Eye Research. 2021;46(6):802-10. doi:10.1080/02713683.2020.1842456.

[57] Guo JJ, Xu FQ, Li YH, Li J, Liu X, Wang XF, et al. Alginate oligosaccharide alleviates myocardial reperfusion injury by inhibiting nitrative and oxidative stress and endoplasmic reticulum stress-mediated apoptosis. Drug Design, Development and Therapy. 2017:2387-97. doi:10.2147/DDDT.S139353.

[58] Lazarov O, Demars MP. All in the family: how the APPs regulate neurogenesis. Frontiers in neuroscience. 2012;6:81. doi:10.3389/fnins.2012.00081.

[59] Zhao J, Han Y, Wang Z, Zhang R, Wang G, Mao Y. Alginate oligosaccharide protects endothelial cells against oxidative stress injury via integrin-α/FAK/PI3K signaling. Biotechnology Letters. 2020;42:2749-58. doi:10.1155/2017/8073798.

[60] Ogawa H, Kajimoto N, Hiura N, Chaki T. Effects of sodium alginate oligosaccharide on serum lipids, serum minerals and urinary minerals in rats. 2001.

How to cite this article

Mohammed M.; Jabber H.N.; Abdul Jabbar F.M.; Biomedical Applications of Alginate Oligosaccharides: Exploring Their Therapeutic Potential and Modification Techniques. Trends in Pharmaceutical Biotechnology (TPB). 2024;2(1):22-34. doi: 10.57238/tpb.2024.152722.1011