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(REVIEW ARTICLE)

Comprehensive review on the impact of alginate oligosaccharides (AOs) on human health

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Abstract

Alginate Oligosaccharides (AOs) are bioactive compounds prepared through the enzymatic degradation of alginate polysaccharides by alginate lyase. These Oligosaccharides have become a focus of growing interest in scientific community, largely because of their array of bioactive attributes, which include immunomodulatory, antioxidant, anti-inflammatory and prebiotic effects. This review critically examines the current scientific literature on Alginate Oligosaccharides (AOs), encompassing in vitro studies, animal models and preliminary human clinical trials. It also addresses the safety profiles of AOs, focusing on toxicological assessments, to provide a comprehensive view of their risk-to-benefit ratio. Additionally, the review assesses the existing information regarding the impact of Alginate Oligosaccharides (AOs) on human health. It aims to identify the current research gaps and outline potential future directions for their therapeutic application.

Keywords: Alginate; Alginate lyase; Alginate Oligosaccharides (AOs); Bioactive Properties

1. Introduction

The exploration of bioactive compounds for their multifaceted roles in human health has become a cornerstone in both medical research and the growing field of nutraceuticals. Among the myriad of compounds scrutinized for their health-promoting effects, Alginate Oligosaccharides (AOs) have emerged as particularly compelling candidates, obtained chiefly through the enzymatic degradation of alginate polysaccharides.

Alginate Oligosaccharides (AOs) have garnered significant attention due to their multifaceted biological activities, encompassing a diverse array of health-related implications. These encompass a broad spectrum of effects, including antitumor potential [1], promising antidiabetic properties [2], notable antihypertensive attributes [3], potent anti-inflammatory capabilities [4,5], compelling antimicrobial qualities [6], robust antioxidant potential [7], considerable anticancer prospects [8], remarkable immunomodulatory impacts [9,10] and noteworthy anti-radiation defenses [11,12]. This extensive repertoire of bioactivities underscores the impressive versatility of AOs, rendering them applicable in both proactive health management and therapeutic interventions. The antitumor and anticancer activities of AOs have been the subject of research investigations that have demonstrated promising results in preclinical models [1,8]. In the realm of metabolic disorders, AOs have been shown to exert antidiabetic effects through mechanisms that are still under investigation but are believed to involve the modulation of insulin signaling pathways [2]. Likewise, antihypertensive properties suggest a potential role in cardiovascular health, possibly through endothelial function enhancement or the inhibition of angiotensin-converting enzymes [3]. Furthermore, the anti-inflammatory and immunomodulatory capabilities of AOs offer exciting avenues for research in autoimmune diseases and inflammatory disorders [4,13,14]. The compound's antioxidant effects could make it valuable in combating oxidative stress, a factor implicated in aging and numerous diseases [7]. Moreover, antimicrobial and anti-radiation activities extend the possible applications of AOs into fields like infection control and radiation therapy [11,15].

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This review embarks on a comprehensive exploration of Alginate Oligosaccharides (AOs), delving into their multifaceted bioactivities. Reflecting on their diverse applications and benefits AOs stand at the forefront of health science, offering remarkable insights and considerable potential in enhancing our understanding of human well-being.

2. Alginate oligosaccharides (AOs)

AOs are shorter carbohydrate chains derived from the degradation of alginate, a natural polysaccharide found in brown seaweeds, primarily by the action of the enzyme alginate lyase. Alginate is comprised of repeating monomeric units of α-L-guluronate and β-D-mannuronate, and its enzymatic degradation leads to the formation of AOs. [16]. Specifically, alginate lyases play a critical role in this degradation by selectively cleaving glycosidic bonds in alginate molecules, resulting in smaller, biologically active fragments known as unsaturated alginate oligosaccharides (UAOs). Notably, these lyase-induced processes provide a more environmentally sustainable approach to alginate depolymerization compared to traditional physicochemical methods, which often require harsh conditions and may result in loss of bioactivity [16]. Research has shown that the unsaturated delta units in UAOs are not merely structural but also contribute to the molecule's various biological activities. Therefore, AOs serve as a focal point in a growing field that spans marine biology, enzymology, biomedical sciences and materials science, making them an intriguing subject for in-depth research and exploration.

3. Therapeutic potential and biological activities of alginate oligosaccharides (AOs)

AOs possess a wide array of biological functions, including roles as prebiotics, antioxidants, antimicrobials, and antitumor agents, among others [17]. Their efficacy is influenced by several factors like molecular conformation, size, M/G ratio, and MG sequence [18]. Notably, AOs with low molecular weight (500-3000 Da) and higher M/G ratios (>1) promote plant growth [18,19]. Unsaturated AOs variants have demonstrated enhanced biological activity, stimulating growth in *Bifidobacterium* sp. and elevating cytotoxic cytokines in human cells, unlike their saturated counterparts [8]. This pattern was same in *C. reinhardtii*, where unsaturated AOs enhanced growth and fatty acid production, underscoring the significance of unsaturation in AOs functionality [20]. Furthermore, oligomers rich in guluronate, especially with a degree of polymerization (DP) of 5, have been effective in promoting root growth in specific plants [21]. In medicine, the therapeutic promise of AOS for various ailments, especially metabolic and chronic disorders, has been a subject of in-depth exploration.

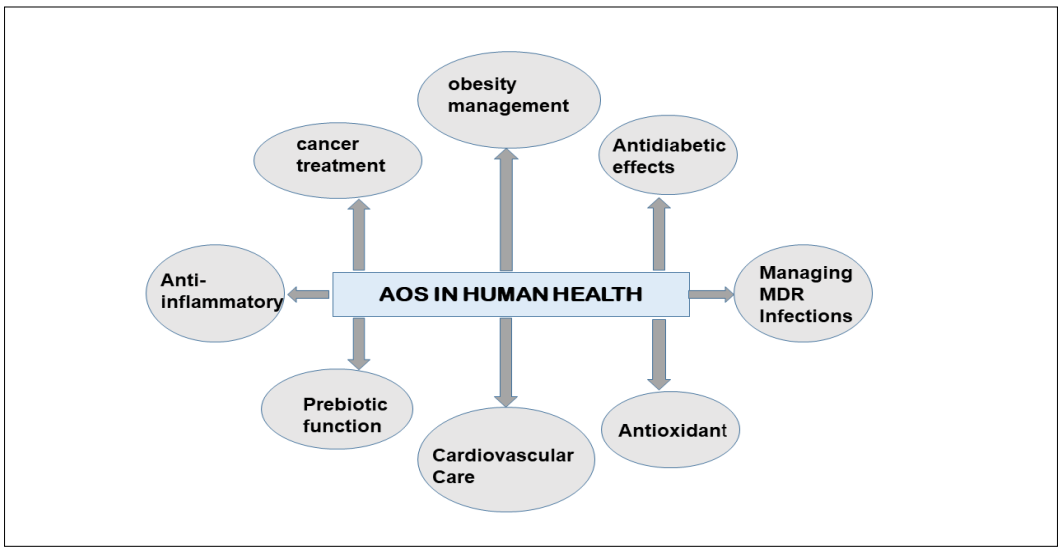

Figure 1 Overview of health-related applications of alginate oligosaccharides (AOs)

In alignment with the focus of this review, Fig. 1 provides a graphical outline of the specific health-related applications of Alginate Oligosaccharides (AOs). The subsequent sections concentrate on a comprehensive analysis of AOs roles in obesity management, antidiabetic effects, cardiovascular health, inflammation-related conditions, cancer treatment, management of multi-drug resistant infections, prebiotic functions and antioxidant effects.

3.1. AOs: targeting obesity through metabolic regulation and gut microbiota modulation

Obesity remains a global health crisis with limited effective treatments [22]. Alginate oligosaccharides (AOs) offer a promising avenue for obesity management through multiple mechanisms. In a mouse model, AOS counteracted obesity by activating AMP-activated protein kinase (AMPK), an essential regulator of lipid and glucose metabolism [23,24]. This activation led to inhibited fat cell differentiation and lipid synthesis [23]. Moreover, unsaturated AOs demonstrated higher anti-obesity effects compared to saturated forms, implying enzymatic methods as preferable for producing effective AOs [23]. Further studies in zebrafish have shown AOs role in lipid metabolism modulation, inflammation reduction, and immune function improvement, mediated partly by inhibiting the mitochondrial protein STOML2 [25]. Additionally, AOS supplementation in a high-fat diet mouse model modified the gut microbiota, including the growth promotion of *A. muciniphila*, a microbe linked to obesity reduction and lower inflammation [26].

3.2. AOs: potential in diabetes management

AOs present a promising alternative to conventional type 2 diabetes treatments like insulin therapy and synthetic hypoglycemic drugs, which can carry side effects [27,28]. Research indicates that AOs can modulate key cellular pathways involved in glucose and lipid metabolism. Specifically, studies have shown that AOS derivatives such as oligomannuronate and its chromium (III) complexes (OM, OM2, and OM4) can upregulate the AMPK-PGC1α signaling pathway in adipocytes, thereby enhancing mitochondrial function and reducing lipid accumulation [24,29]. Notably, these compounds also improved insulin sensitivity by modulating insulin receptor and glucose transporter 4 (GLUT4) expression in skeletal muscle cells [30]. Moreover, AOs may exert antidiabetic effects by microbiome modulation. AOS has been found to increase the abundance of gut bacteria like *L. reuteri* and *L. gasseri*, which are implicated in enhancing insulin secretion and glucose tolerance [26]. Additionally, AOs fosters the growth of short-chain fatty acids (SCFAs) producing bacteria, such as *Akkermansia* and *Alloprevotella*. These SCFAs can activate free fatty acid receptors FFAR2/GPR43 and FFAR3/GPR41, affecting appetite, energy metabolism and potentially alleviating insulin resistance [31,32].

3.3. AOs: addressing cardiovascular complications

Cardiovascular diseases (CVD) remain a significant global health challenge, often exacerbated by poor diet and gut microbiota imbalances [33,34]. AOs have shown promise in mitigating key risk factors, such as elevated levels of low-density lipoprotein (LDL) [35]. Research indicates that AOs improves lipid metabolism and modulates gut microbiota, displaying hypolipidemic effects [36,37]. The underlying mechanisms involve upregulation of the LDL receptor (LDLR) via the PI3K/Akt/GSK3β pathway and activation of SREBP-2, thereby facilitating LDL uptake and reducing its degradation in liver cells [37]. AOs also alters gut bacterial populations, like *Bacteroides* and *Clostridiales*, linked to CVD risks [38]. Beyond general CVD, AOs has been investigated for its efficacy in treating pulmonary arterial hypertension (PAH), a specific cardiovascular condition [39]. Animal studies show that AOS alleviates PAH symptoms, likely due to its antioxidant properties and modulation of TGF-β1 and p-Smad2 levels [40,41]. AOs has also shown to reduce lipid peroxidation and inflammation markers while enhancing anti-inflammatory cytokines [40]. A human trial further supports these findings, revealing a dose-dependent cardiovascular benefit of AOs [42]. Therefore, AOs holds promise as a multi-faceted approach for addressing both CVD and its specific subtypes like PAH.

3.4. AOs: targeting inflammation by LPS and TLR4 inhibition

Alginate oligosaccharides (AOs) have been studied for their anti-inflammatory effects, particularly in the context of mitigating the inflammatory response triggered by lipopolysaccharides (LPS). LPS are primary components of the outer membranes of gram-negative bacteria and play a crucial role in inducing inflammation. The activation of toll-like receptors (TLR), specifically TLR4, and cluster of differentiation (CD) 14 by LPS can lead to a cascade of intracellular signaling. This cascade subsequently stimulates the production of various inflammatory markers and molecules, including nuclear factor (NF)-κB, mitogen-activated protein (MAP) kinases, protein kinase B (Akt), phosphoinositide 3-kinase (PI3K), nitric oxide (NO), prostaglandin E2 (PGE2), reactive oxygen species (ROS), nitric oxide synthase (iNOS), and cyclooxygenase (COX)-2, along with a variety of pro-inflammatory cytokines [43,44]. In a study involving murine macrophage RAW 264.7 cells, pre-treatment with guluronate oligosaccharides (GOs), a form of AOS, demonstrated promising results. Specifically, GOd inhibited the binding of LPS to TLR4 and CD14, which in turn led to the deactivation of the NF-κB and MAP kinases signaling pathways [45]. This deactivation resulted in a significant reduction in the levels of inflammatory molecules such as NO, PGE2, ROS, iNOS, COX-2 and other pro-inflammatory cytokines. Therefore, AOS, particularly its GOS form, shows strong potential as a therapeutic agent for managing inflammation-associated health issues.

3.5. AOs: a multifaceted candidate for cancer treatment and reproductive health

Alginate oligosaccharides (AOs), derived from marine algae, show promise in cancer treatment, acting through various pathways that are not yet fully understood [46,47]. Among its potential mechanisms of action, AOs may inhibit the proliferation and metastasis of cancer cells, modulate immune response, exhibit antioxidant activities and possess anti-inflammatory effects [48]. In particular, AOs has been demonstrated to inhibit epithelial-mesenchymal transition (EMT), a key process involved in the spread of cancer cells [49]. Oxidative stress, characterized by an imbalance between free radicals and antioxidants, has been implicated in the progression of osteosarcoma, a type of cancer [50]. Enzymatically-prepared AOs with a molecular weight of 1009 Da (DP5) has shown beneficial effects on patients with highly malignant osteosarcoma, enhancing antioxidant capacity and mitigating inflammation, although the exact molecular mechanisms remain unclear [1]. In addition to its anti-tumor activities, AOs also shows promise in preventing the progression and spread of prostate cancer through downregulating the expression of the enzyme sialyltransferase (ST6 Gal-1) and affecting the Hippo/YAP/c-Jun signaling pathway [51]. Beyond cancer treatment, AOs may have a role in preserving male fertility during chemotherapy; specifically, a mouse study indicated that AOs, when combined with the chemotherapy drug busulfan, significantly increased sperm concentration and motility, possibly by regulating lipid metabolism and gut microbiota [52].

3.6. AOS: a promising strategy for managing multidrug-resistant infections

The rise of antibiotic resistance poses a significant threat to global health, calling for alternative approaches to tackle multidrug-resistant bacteria. Alginate oligosaccharides (AOS) have emerged as a potent solution, notably Guluronate oligomer (OligoG CF-5/20), which has demonstrated dose-dependent inhibition of bacterial growth and biofilm formation [53]. Although it was initially postulated that OligoG exerted its bacteriostatic effects by chelating iron [54], current theories suggest the antibiofilm activity might be due to the absence of G block in bacterial alginate [53]. OligoG does not compromise bacterial membrane permeability but seems to alter bacterial cell structure in an as-yet-unexplained way [53]. Additionally, the composition of AOS, particularly the M/G ratio, appears crucial for its antibacterial effects. While OligoM (100% M) and OligoMG (46% G) did not exhibit comparable biofilm-modulating activity to OligoG (90-95% G), OligoG has been shown to influence the surface charge and flagellar action of *P. aeruginosa*, causing cellular aggregation [55]. Moreover, AOs can interact with bacterial lipopolysaccharides (LPS) in the presence of calcium ions, it does not cause substantial structural alterations in LPS. This mechanism is recognized as a factor contributing to the emergence of resistant pathogens [56]. OligoG CF-5/20, in its nebulized form, has been demonstrated to be safe for human use, specifically in treating cystic fibrosis patients (NCT02157922; NCT02453789). The compound has also been effective against the gram-positive bacterium, *S. mutans*, especially when combined with triclosan [57]. Calcium scavenging by AOs is thought to play a role in its antibacterial efficacy [58]. In cystic fibrosis, the secreted high molecular weight alginate from mucoid *P. aeruginosa* contributes to the increased mucus viscosity [59]. OligoG CF-5/20 has the capability to alter the rheological characteristics of cystic fibrosis sputum, interacting with mucin to interfere with its high molecular weight alginate associations [60]. AOs has been found to suppress the production of quorum sensing (QS) components in *P. aeruginosa*, influencing cellular communication and the synthesis of virulence factors [61]. This suppression, in turn, makes *P. aeruginosa* more susceptible to hydrogen peroxide [62].

3.7. AOs: potential prebiotics for gut health

Alginate oligosaccharides (AOs) have been reported to serve as effective prebiotics, a category of substances known for their gut health benefits. These water-soluble oligosaccharides resist degradation by digestive enzymes, ensuring that they reach the gut intact. The primary mechanism by which AOs function as prebiotics is through the enhancement of beneficial lactic acid bacteria populations, such as *Bifidobacterium* and *Lactobacillus*, in the gastrointestinal tract. Concurrently, they work to reduce the numbers of harmful pathogenic bacteria. This microbial balance leads to an increased production of health-promoting compounds, thereby contributing to overall well-being [63]

3.8. AOs: as an antioxidant

Alginate oligosaccharides (AOs) have garnered attention for their potent antioxidant properties, which make them potential candidates for the prevention and treatment of various oxidative stress-related diseases. Antioxidants work by neutralizing free radicals—unstable molecules that can cause cellular damage and contribute to aging and diseases, including cancer. AOs ability to scavenge free radicals is particularly useful in conditions where oxidative stress plays a significant role. For instance, in cardiovascular diseases like pulmonary arterial hypertension (PAH), oxidative stress is believed to contribute to vascular alterations. AOs has been found to attenuate these oxidative effects, possibly through the suppression of pro-oxidant markers like lipid peroxidation and the upregulation of anti-oxidant enzymes [4]. Moreover, AOs also plays a role in the regulation of pro-inflammatory and anti-inflammatory cytokines, which can further mitigate the oxidative stress response [4]. In the context of cancer, oxidative stress can induce DNA damage and

mutations, facilitating cancer development and progression. AOs has been shown to enhance antioxidant capacity and reduce inflammation, thus potentially inhibiting the initiation and spread of cancerous cells [1].

4. Safety and toxicology assessment of alginate oligosaccharides (AOs)

The safety profile and toxicological assessment of Alginate Oligosaccharides (AOs) are critical factors for consideration, especially if AOs is to be developed into a therapeutic agent for various medical conditions. While existing data predominantly from in vitro studies and animal models indicate a relatively benign safety profile, it is essential to corroborate these findings through rigorous testing, including human clinical trials. [64]

4.1. Acute toxicity

Initial tests for acute toxicity generally involve administering a high dose of AOs to animal models and observing for any signs of distress, organ failure, or death. So far, acute toxicity studies on rodents have shown no significant adverse effects, even at high dosages. This establishes a promising foundation for the compound's overall safety.

4.2. Chronic toxicity

Chronic toxicity assessments, spanning several months to a year in duration, are formulated to ascertain the enduring safety of administering AOs. However, there is currently no available data regarding chronic toxicity of AOs.

4.3. Metabolism and excretion

Gaining insight into the metabolism and excretion pathways of AOs holds paramount importance in evaluating its safety. Initial investigations indicate that AOs undergoes predominant hepatic metabolism and is subsequently eliminated via renal excretion. The absence of identified toxic metabolites further reinforces its safety profile, despite the current absence of reported data.

4.4. Interaction with other drugs

It's essential to understand how AOs interacts with other drugs, especially if it is to be used in conjunction with existing treatments for diseases like cancer or diabetes. No significant drug interactions have been reported in the current literature, but more exhaustive studies are necessary to confirm this.

4.5. Human clinical trials

Human clinical trials are the gold standard for evaluating the safety and efficacy of any new compound. To date, human studies on AOs are limited but are crucial for establishing a robust safety profile.

4.6. Special populations

It is also vital to conduct studies on how AOs affects special populations such as pregnant women, children, and individuals with compromised immune systems. These studies can provide a comprehensive understanding of any potential risks involved.

4.7. Regulatory approval

For Alginate Oligosaccharides (AOs) to be widely adopted in medical applications, they must meet the stringent safety and efficacy criteria established by global health regulatory agencies, such as the FDA in the United States, the EMA in Europe, the Central Drugs Standard Control Organization (CDSCO) in India and other equivalent bodies worldwide. These agencies require a comprehensive collection of data regarding the safety and toxicological profiles of AOs, ensuring their compliance with both international and regional regulatory standards.

5. Conclusion

In conclusion, this review underscores the versatility of Alginate Oligosaccharides (AOs) and their broad spectrum of bioactivities impacting human health. Their potential in treating cancer, metabolic disorders, and cardiovascular diseases, along with their anti-inflammatory, antioxidant and antimicrobial properties, highlight their significant therapeutic promise. Continued research into AOs could lead to major advancements in healthcare and disease management.

Future perspectives

The accumulating evidence on Alginate Oligosaccharides (AOS) suggests an impressive range of biological activities, including their potential roles in obesity management, type 2 diabetes treatment, cardiovascular disease alleviation, anti-inflammatory mechanisms, cancer therapy, and even as an approach to manage antibiotic-resistant infections. Notably, AOs interactions with the gut microbiota and its antioxidant capabilities have emerged as particularly compelling mechanisms of action that warrant further investigation. While the early data are promising, there are still numerous questions that need to be addressed to translate these findings into clinical practice. Primarily, clinical trials in humans are necessary to corroborate findings from animal models and in vitro studies. Such trials should aim to determine optimal dosages, evaluate long-term safety, and assess the efficacy of AOs against a control or standard treatment. Additionally, it would be valuable to understand the pharmacokinetics and pharmacodynamics of AOs fully. How are these compounds metabolized, and what are their sites of action?

Furthermore, the potential of AOs as a multi-target therapeutic agent suggests the need for studies examining their synergistic effects with existing treatments. For instance, could AOs improve the efficacy of current cancer therapies or offer added benefits to traditional diabetes management approaches?

Developing cost-effective methods for AOs production and formulation will be critical for its widespread application and accessibility. An additional critical area of focus should be the development of personalized medicine strategies based on AOs. Given their ability to modulate the gut microbiota, could they be tailored to individuals based on their unique microbiome composition for maximum efficacy?

Could AOs derivatives be developed that are more potent or offer more targeted delivery?

AOs holds great promise as a multifunctional bioactive compound. By continuing to elucidate its mechanisms of action and optimizing its clinical applications, we may find that AOs represents a significant leap forward in our ability to manage a wide range of health conditions.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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