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Chapter 1

Introductory Chapter: Seaweed-Derived Biomaterials

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Additional information is available at the end of the chapter

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1. Introduction

Natural polymers and their application in the pharmaceutical industry are covered by the presence of synthetic polymers. Natural polysaccharides have gained popularity in the pharmaceutical, biomedical and food industry owing to their lucrative properties, namely biodegradability and biocompatibility and nontoxicity [1].

Polysaccharides can be obtained from a number of sources including seaweeds, bacteria, fungi and plants. When the polysaccharide is composed of only one kind of repeating monosaccharide, it is known as homo-polysaccharides, e.g., starch and cellulose. However, if the polysaccharide is composed of two or more different monomeric units, it is termed as heteropolysaccharides, e.g., agar, alginate and carrageenan [2].

Further, the polysaccharides can be anionic, cationic and nonionic. Because they are extracted from natural resources, their composition and physicochemical properties vary considerably. Seaweed may belong to one of the several groups of multicellular algae: the red algae, green algae and brown algae. They are the rich sources of polysaccharides. Among the seaweed polysaccharides, alginates and carrageenan have been widely characterised and studied for the possible drug delivery application as well as their therapeutic potentials. In subsequent section of this introductory chapter, the therapeutic potential of these two polysaccharides is described.

2. Therapeutic potential of alginate

Alginate is derived from marine brown algae cell walls. Alginate is an anionic polysaccharide consisting of linear copolymer chain of (1-4)-linked β-D-mannuronic acid and α-L-guluronic acid in different arrangements of residues. Alginate is a natural, biodegradable and

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mucoadhesive polymer that does not produce toxicity in administration [3, 4]. This seaweed polysaccharide is most widely studied for the development of various kinds of drug delivery carriers. Its gel-forming ability in presence of divalent calcium ions has been extensively utilised for the fabrication of microparticles, nanoparticles and hydrogels in an attempt to achieve control drug release profiles. However, its bioactive potential has also been investigated and is described as follows.

Ueno and Oda [5] studied the effect of molecular weight and ratio of mannuronic acid/guluronic acid residues on TNF-α (tissue necrosis factor alpha) reducing activity in murine macrophage cell line. The alginates with molecular weight of 38,000 and the said ratio of 2.24 demonstrated potent TNF-α-inducing activity. They further noted that lyase depolymerised alginates were keen on inducing nitric oxide production from RAW264.7 cells compared to native alginate. However, both the polymers were equally effective with regards to their hydroxyl radical scavenging activities.

Its biocompatibility and similar gel texture and stiffness to that of the extracellular matrix have promoted alginate for its application in the field of tissue engineering and regeneration. Injectable alginate implants have been found to possess great potential in inhibiting the damaging events after myocardial infarction, leading to myocardial repair and tissue reconstruction [6]. Park et al. [7] depolymerised alginate following extraction from *Laminaria japonica*, and they found that the alginate lyase enzyme-treated 307 kDa alginate reduced the accumulation of lipid droplet and triglyceride in 3 T3-L1 preadipocytes in a dose-dependent manner and can be developed further for antiobesity treatment. The TNF-α secretion-inducing activity of alginate oligomers following enzymatic (lyase) hydrolysis of polyguluronate and polymannuronate differed in RAW264.7 cells and was dependent on the oligomer structures [8]. The encouraging preclinical results of cell-free alginate hydrogel implants in dogs with heart failure towards ventricle restoration have led to the initiation of clinical investigation for intramyocardial delivery of alginate implants in patients with acute myocardial infarction [9]. Houghton et al. [10] demonstrated that alginate in a bread vehicle can maintain its lipase inhibition properties despite cooking and digestion and therefore offers potential for the treatment of obesity. Wilcox et al. [11] reported that high-guluronic acid alginates isolated from *Laminaria hyperborea* seaweed could inhibit pancreatic lipase to a significantly higher degree than that obtained from *Lessonia nigrescens*. Therefore, lipase inhibition could be attributed to the variable structure of alginate. Their food use at high concentration could reduce the uptake of dietary triacylglycerol aiding in weight management. In another work by Chater et al. [12], the inhibitory effect of alginate on the gastro-oesophagus reflux aggressors trypsin and pepsin was investigated. The pepsin activity was reduced by up to 53.9% *in vitro*, although trypsin inhibition was trivial. The pepsin-reducing activity was correlated with the frequency of mannuronate residues in alginate. A significant proteolytic inhibition of dietary protein substrates was noted in the gastric phase of digestion, but not in the small intestinal phase.

3. Therapeutic potential of carrageenan

Carrageenan is a naturally occurring anionic sulphated linear polysaccharide extracted from certain red seaweed of the Rhodophyceae family [13]. Carrageenan consists of alternate units

of D-galactose and 3,6-anhydro-galactose joined by α-1,3- and β-1,4-glycosidic linkage. Based on the amount and position of sulphate groups, carrageenan can be classified into lambda (λ), kappa (κ), iota (ι), nu (υ), mu (μ), theta (θ) and Ksi (ξ), all containing about 22–35% of sulphate groups [14]. Carrageenans have been extensively investigated for their anticoagulant, antiviral, cholesterol-lowering effects and immunomodulatory and antioxidant activity both *in vitro* and *in vivo* [15].

Sokolova et al. [16] reported that the antioxidant activity of carrageenans, i.e., their inhibitory effects on hydroxyl radicals and superoxide anion radicals, depends on the polysaccharide structure. Yuan et al. [17, 18] hydrolysed kappa-carrageenan to obtain oligosaccharides which were further sulphated, acetylated and phosphorylated. All the derivatives exhibited significant antioxidant activities; however, their antioxidant activity differs in different systems. The sulphated and acetylated derivatives scavenged superoxide radicals; the acetylated derivatives scavenged hydroxyl radicals, whereas the phosphorylated ones scavenged both hydroxyl radicals and DPPH radicals. The chemical modification of carrageenan oligosaccharides could enhance their antioxidant activity *in vitro*.

Carrageenan demonstrated encouraging antiviral activity against several animal viruses [19]. At a dose of 5 μg/ml, the destruction of the cell monolayer by herpes simplex virus type 1 (HSV-1) could be prevented. No evidence of cytotoxic effects was apparent up to a carrageenan concentration of 200 μg/ml. Girond et al. [20] reported a potent inhibitory effect of sulphated iota-, lambda- and kappa-carrageenans on the replication of hepatitis A virus (HAV) in the human hepatoma cell line, without any cytotoxic effects up to a strength of 200 μg/ml. Based on their selectivity indices, lota- and lambda-carrageenan was identified as promising candidates for chemotherapy of acute hepatitis A.

Carrageenans from *Gigartina acicularis* and *Eucheuma denticulatum* are more sulphated than those from *Kappaphycus cottonii*. At 0.75 mg/ml, no virucidal activity against HHV-1 or poliovirus was noticed. Their antiviral effect could be due to lower inhibition of the virus attachment and by the interference in the virus replication cycle [21].

Algal polysaccharides such as carrageenan are good sources of dietary fibre. Previous studies have shown that native carrageenan (κ) extracted from *Kappaphycus alvarezii* and commercial carrageenan have hypoglycaemic effects [22]. Panlasigui et al. [23] demonstrated that regular inclusion of carrageenan in the diet may result in reduced blood cholesterol and lipid levels in human subjects. Anderson et al. [24] reported that λ-carrageenans and κ-carrageenans from *Chondrus crispus* and *Polyides rotundus* possessed anticoagulant activity on intravenous injection in the rabbit. The differences in sulphate content between the carrageenans did not directly correlate with variable anticoagulant action and toxicity.

4. Conclusion

The literature reports suggested that seaweed polysaccharides possess potential pharmacological activities including antidiabetic, antiviral, antioxidant, anticoagulant, pepsin- and lipase-reducing and lipid-lowering activity. These polysaccharides either in their native form or modified form can be developed as therapeutic agents for the treatment of various diseases.

Further, they have been widely investigated as polymers for designing drug delivery carriers and tissue scaffolds. Overall, the exploration of these seaweed polysaccharides must be more focused to make them clinically useful as therapeutic agents.

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