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## Seaweed polysaccharides: Emerging extraction technologies, chemical modifications and bioactive properties

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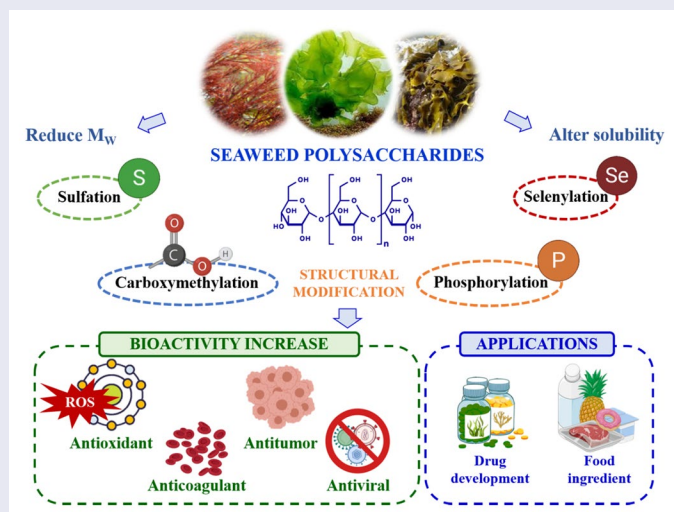
### ABSTRACT

Nowadays, consumers are increasingly aware of the relationship between diet and health, showing a greater preference of products from natural origin. In the last decade, seaweeds have outlined as one of the natural sources with more potential to obtain bioactive carbohydrates. Numerous seaweed polysaccharides have aroused the interest of the scientific community, due to their biological activities and their high potential on biomedical, functional food and technological applications. To obtain polysaccharides from seaweeds, it is necessary to find methodologies that improve both yield and quality and that they are profitable. Nowadays, environmentally friendly extraction technologies are a viable alternative to conventional methods for obtaining these products, providing several advantages like reduced number of solvents, energy and time. On the other hand, chemical modification of their structure is a useful approach to improve their solubility and biological properties, and thus enhance the extent of their potential applications since some uses of polysaccharides are still limited. The present review aimed to compile current information about the most relevant seaweed polysaccharides, available extraction and modification methods, as well as a summary of their biological activities, to evaluate knowledge gaps and future trends for the industrial applications of these compounds.

### KEY TEACHING POINTS

- Structure and biological functions of main seaweed polysaccharides.
- Emerging extraction methods for sulfate polysaccharides.
- Chemical modification of seaweeds polysaccharides.
- Potential industrial applications of seaweed polysaccharides.
- Biological activities, knowledge gaps and future trends of seaweed polysaccharides.

### GRAPHICAL ABSTRACT



Several seaweeds' polysaccharides have gained the attention of industry due to their properties and bioactivities.

### KEYWORDS

Algae polysaccharides;  
novel extraction methods;  
chemical modification;  
biological activities

## 1. Introduction

Macroalgae or seaweeds are plant-like organisms that generally occupy the benthic littoral zone. They are usually classified in green algae (Chlorophyta), brown algae (Phaeophyta) and red algae (Rhodophyta) (Otero et al. 2018). Nowadays, about thirty two million tons of macroalgae (wet weight) is processed worldwide, being the largest harvesting in the South East of Asia (Jönsson et al. 2020). The nutritional potential of the algae is widely recognized (Otero, López-Martínez, and García-Risco 2019). Seaweeds have been consumed for many years in countries like China, Indonesia and Philippines and have recently gained a considerable interest in Europe due to their multiple bioactive compounds with applications in the culinary and functional food industries. These organisms contain high value molecules like proteins, omega-3 polyunsaturated fatty acids, minerals, polyphenols, alkaloids, terpenes, pigments (chlorophylls, carotenoids and phycobilins) and polysaccharides (SP) (Pereira et al. 2021). This diversity of compounds are involved in biological activities like antioxidant, antimicrobial, anticancer, anti-allergic, antiviral and anticoagulant (Barkia, Saari, and Manning 2019; Kosanić, Ranković, and Stanojković 2015), showing also multiple applications in cosmetic and pharmaceutical industries (Alves et al. 2016).

Specifically, SP are the major components in seaweeds. They usually occur in the range of 5 to 75% of their dry weight (w/w, DW) depending on the species, age or season of harvesting, among other factors (Hentati et al. 2020). For example, the laminarin SP is usually found in the genus *Laminaria* up to 50% (DW) (Patil et al. 2018). The importance of SP lies with the fact that many of them are sulfated polysaccharides (SFP), not present in terrestrial plants and linked to several health benefits like prebiotic effects and cholesterol excretion (Ciancia, Fernández, and Leliaert 2020). Their occurrence is specific for each macroalgae species (Hentati et al. 2020). For instance, green algae contain ulvan, brown seaweeds are rich in alginate, laminarin, fucans and fucoidans, while red macroalgae are composed by carrageenan, agar, floridean starch, but also other galactans. These differences in their chemical structure result in the different properties of SP (De Jesus Raposo, De Morais, and De Morais 2015). Generally, they possess several biological activities such as antioxidant, antimicrobial, antitumor, anticoagulant, anti-hyperlipidemic and anti-inflammatory. However, some SP do not entail a sufficient biological activity for cosmetic, food or nutraceutical applications. Degradation (generally, hydrolysis) and chemical modification (phosphorylation, sulfation or selenylation, among others) of SP has demonstrated to enhance their biological activities (Shi et al. 2017). For instance, different studies have proven that hydrolysis could improve the antioxidant capacity of SP from *Enteromorpha* species (Li et al. 2013; Shi et al. 2017). Other studies have shown that the introduction of carboxymethyl and hydroxamate groups improved the antioxidant and antimicrobial activity when compared to native SP from *E. prolifera* (Shao et al. 2017). In addition, structure and chemical composition of SFP is different according to the algae species. (Karnjanapratum and You

(2011) concluded that SFP differences in chemical composition are possible and may be due to differences in the growing conditions of seaweed and the employment of analytical methods and extraction procedures. However, the relation between the structure of algae SFP and their biological structure is not entirely clear (Bilan and Usov 2008). The chemical structure of SFP such as the degree of sulfation, sulfation position, molecular weight ( $M_w$ ) or glycosidic branching are factors that can affect their biological activities.

In seaweeds, SFP are mostly found as part of cellular walls, so extraction techniques are essential to obtain rich extracts of these bioactive molecules. Traditionally, solid to liquid extraction with hot water has been the most used method for extracting SP. However, in recent years, innovative extraction techniques have arisen to recover SP in a more efficient and clean way, usually followed by further purification and fractionation procedures (Xu, Huang, and Cheong 2017; Tang et al. 2020). SFP possess many applications, due to their hydrocolloid properties. Traditionally, they have been employed in the biomedicine field as gelling materials, as is the case of the agarose in bacterial cultures and electrophoresis gels (Beaumont et al. 2021). In addition, they are part of new diagnostic and therapeutic nanotechnology tools in development intended for human use. For instance, fucoidans have been used in biocompatible scaffolds for small drug, gene and protein deliveries, and for tissue engineering in regenerative medicine as well as for stabilizers of nanoparticles (Chollet et al. 2016). A recent study has been shown that marine carbohydrates, especially SFP, possess potent inhibitory effect on the low-pathogenic human coronaviruses HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 (Mohammed, Naveed, and Jost 2021). In this context, the growing applications of seaweed SP and deeper knowledge about their structure and functions will entail a simultaneous development and optimization of the employed extraction techniques. The aim of this article is to review the main SP obtained from seaweeds and most used extraction techniques, as well as to revise their structural characterization and modification methods that could allow improving their potential biological properties.

## 2. Seaweeds-derived polysaccharides occurrence and types: structure and composition

Algae SP can be classified according their source, as they are unique to green, brown or red algae but also depending on their sulfation degree (Tanna and Mishra 2019). In general terms, a greater polymerization and sulfation degree of these SP is related to a higher extent of their bioactivities, although it may also impact their hydrocolloidal properties (Kopplin et al. 2018). More sulfated SP include fucoidan and carrageenan, whereas the lower sulfated SP are ulvan and agar. Alginate and laminarin do not contain sulfate substitutions in nature (Jiao et al. 2011). Another relevant molecule is floridean starch, an storage starch-like molecule with markedly different characteristics to terrestrial plants starch and does not contain sulfate groups (Grünwald and

Alban 2009). As SP are part of cell wall and matrix components, different taxonomic families of seaweeds show diverse SP types. Nevertheless, structure, composition and levels of these SP not only vary depending on the taxonomic origin but are also influenced but ecophysiological characteristics of the growth environment and time of harvest (Yaich et al. 2014). As such, a single species may display highly different content of P. Moreover, albeit each SP group share a common skeletal structure, their monosaccharide residues may greatly vary among species, which especially occurs in ulvan, carrageenan and fucoidan (Qi and Kim 2017). A broad perspective on the major addressed SP sources and composition is presented in Table 1.

### 2.1. Polysaccharide's occurrence

SP are generally found in high content (around 50% DW), thus seaweeds have consistently been employed as a natural source of SP (Kraan 2012). In addition, macroalgae biomass is easily recovered from shored or cultured seaweeds. On top of that, due to globalization, some species (ex. *Ulva* sp., *Codium* sp., *Gracilaria* sp.) display invasive ecological behaviors and may also proliferate in abundance in eutrophicated waters, which has made SP extraction from them an alternative (Yaich et al. 2014). These facts make macroalgae the most feasible source of these SP over microalgae, although some other marine organism such as *Spirulina* sp., *Chlorella* sp., *Dunaliella* sp., *Phaeodactylum* sp. or *Porphyridium* sp. also contain significant levels of SP integrated in their cell wall and vacuoles (De Jesus Raposo, De Morais, and De Morais 2013). Here below a comparison about SP from the main three macroalgae groups (green, brown and red seaweeds) is carried out.

Green algae (Chlorophyta) are the macroalgae groups with less diverse SP content, yet the only one accounted to contain ulvan. This is the foremost extracted SP from *Ulva* species including *U. lactuca*, *U. rotundata*, *U. rigida*, or *U. fasciata* (Pangestuti and Kurnianto 2017). Although red algae are the main source of sulfated galactans, green algae have also been identified to have this SP in low quantities (e.g. around 5% DW in the pacific algae of the genus *Codium*) (Farias et al. 2008). This is especially relevant, as no other sulfated galactans have been reported out of red algae and green algae. On the other hand, *U. ohnoi* has been described as a feasible source of starch, similar to that of terrestrial plants albeit present in low quantities (>10% DW) (M. Prabhu et al. 2019).

Brown algae (Phaeophyta) pose a significant source of SP, like alginate, fucoidan and laminarin. Current alginate sources are *L. hyperborea*, *L. digitata*, *L. japonica*, *A. nodosum*, and *M. pyrifera*, as the amount of alginate is consistently higher than other brown algae species (Kraan 2012). For example, the alginate content in *M. pyrifera*, the largest consumed kelps in East Asia, can reach 30% DW (Lorbeer et al. 2017) and the alginate content in *L. digitata* and in *S. muticum* is reported around 20% and 15% DW, respectively (Flórez-Fernández, Domínguez, and Torres 2019). On the contrary, fucoidan is a less extensively exploited SP, mainly obtained from *Fucus vesiculosus* (fucoidan content of 20%

DW), from *U. pinnatifida* and from *L. japonica* (Bittkau, Neupane, and Alban 2020). *Sargassum* sp. is also a source of fucoidan, although it has generally much lower content, about 5% DW (Jacobsen et al. 2019). While the levels of fucoidan and alginate generally remain constant throughout the year, the concentration of laminarin greatly shifted due to its energy storage role. Broadly, laminarin reaches its maximum content in autumn and the lowest in winter time in harvested seaweeds (Schiener et al. 2015). As its name hints, algae from the genus *Laminaria* are the richest source of laminarin, whose content is around 30–35% DW in *L. digitata*, *L. hyperborea* and *S. latissima* (Kadam, Tiwari, and O'Donnell 2015).

Red algae (Rhodophyta) are the unique source of the sulfated galactans agar and carrageenans, but also the only natural source of floridean starch. These three SP may be concurrent, but generally agarophytes belong to the *Gelidium*, *Gracilaria*, *Pterocladia*, and *Gelidiella* genera, being *Gracilaria* species the first source (Sousa, Rocha, and Gonçalves 2020). In *Gelidium* and *Gracilaria* species, agar content is around 30–40% DW (Lee et al. 2017). *Gelidium*, *Euclima*, *Gigartina* and *Euclima* species are also the major global raw material to obtain carrageenans, especially  $\lambda$ ,  $\kappa$  and  $\iota$ -carrageenans, which are the most valued by several industries due to their gelling properties (Li et al. 2014). Other minor sources of carrageenans include *Porphyra* and *Furcellaria* species, which contain characteristically branched carrageenans labeled as porphyrans and furcellarans (Saluri et al. 2021). These algae are also harvested depending on their primary type of carrageenans. For example, *Gigartina* and *Chondrus* species are richer in  $\lambda$ -carrageenans (Jiao et al. 2011). Floridean starch is mainly obtained from species of the Florideophyceae family, including *Gracilaria* and *Gracilariopsis* genera (Yu et al. 2007).

### 2.2. Main seaweed-derived polysaccharides

#### 2.2.1. Ulvan

Ulvan has a distinct heterogeneous composition, with repeated sequences of disaccharides as sulfated rhamnose, uronic acids (glucuronic or iduronic acids) and xylose (Lahaye and Ray 1996). Hence, the two most frequently repeated disaccharides are aldobiouronic acids, which are designated as type A ( $\beta$ -D-glucuronic acid  $\alpha$ -1 $\rightarrow$ 4L-rhamnose 3-sulfate) and type B ( $\alpha$ -L-iduronic acid  $\alpha$ -1 $\rightarrow$ 4L-rhamnose 3-sulfate) ulvanobiouronic acids (Robic, Bertrand, et al. 2009). In minor proportion, ulvan is also composed of disaccharide aldobioses, called ulvanobioses. These consist of  $\beta$ -D-xylose  $\alpha$ -(1 $\rightarrow$ 4) linked to L-rhamnose 3-sulfate, that may also display an additional sulfate group attached to the xylose C<sub>2</sub> (Figure 1, Table 1). In general terms, ulvan is composed of around 65% ulvanobiouronic acid and 30% uronic acids, with minor fractions of galactose, mannose and arabinose (Pangestuti and Kurnianto 2017). Sulfate content of this SP may range between 3 and 8% of DW and its rise is related to a higher anticoagulant activity (Robic, Gaillard, et al. 2009). However, its sulfation pattern is heterogeneous, with some regions exhibiting a sulfate group every 2 monosaccharides while other regions remain almost unsulfated

**Table 1.** Differential composition and structure of major seaweed hydrocolloid polysaccharides obtained from most relevant seaweed species. Data presented as average molecular composition (%) of dry and/or purified SP extracts.

P	Source	S	Glc	Xyl	Gal	Man	Rha	Fuc	UA	Ref.
Ulvan	<i>U. rotundata</i>	4.6	30.8	3.6	0.9	–	5.4	–	5.5	(Robic, Sassi, and Lahaye 2008)
	<i>U. fasciata</i>	5.7	11.7	1	–	9.6	9	–	3.2	(Madany et al. 2021; Shao, et al. 2014)
	<i>U. lactuca</i>	15.6	6.9	2.4	0.6	0.1	15.2	–	23.6	(Yaich et al. 2014)
	<i>U. rigida</i>	15	12.2	8	–	–	49	–	31	(Kidgell et al. 2021; Adrien et al. 2019)
	<i>E. compressa</i>	8	33	17	7	4	37	–	31	(Ray 2006; Kidgell et al. 2021)
Fucoidan	<i>E. intestinalis</i>	16.3	43.5	10.8	11.3	–	37	–	5	(Tabarsa et al. 2018)
	<i>F. vesiculosus</i>	18.2	13.6	12.6	10.4	2.7	1.4	59.2	7.2	(Bittkau, Neupane, and Alban 2020)
	<i>F. serratus</i>	12.3	43.2	10.4	4.2	1.7	–	40.6	5.5	(Bilan et al. 2006; Bittkau, Neupane, and Alban 2020)
	<i>S. latissima</i>	28.8	–	6.7	7.5	–	2.1	83.8	6	(Bittkau, Neupane, and Alban 2020)
	<i>L. digitata</i>	19.5	–	13.7	14	5.2	–	67.1	10.4	(Bittkau, Neupane, and Alban 2020)
	<i>L. japonica</i>	33	1.93	–	24.3	6	n.a.	29.1	1.93	(J. Wang et al. 2008)
	<i>E. cava</i>	25.2	1.3	6.1	31.8	–	3.6	63.5	14.8	(Lee et al. 2012)
	<i>U. pinnatifida</i>	28	1.9	1.8	28.6	9	n.a.	16.4	4.9	(Skriptsova et al. 2010)
	<i>M. pyrifera</i>	18.6	0.4	3.7	2.4	0.4	–	16.2	13.9	(Lorbeer et al. 2017)
	Alginate <sup>a</sup>	<i>A. nodosum</i>		F <sub>M</sub>	F <sub>G</sub>	F <sub>GC</sub>	F <sub>MM</sub>	F <sub>GC</sub>		M/G
<i>F. vesiculosus</i>			0.46	0.54	0.28	0.28	0.36		1.07	(Rioux, Turgeon, and Beaulieu 2007)
<i>F. spiralis</i>			0.59	0.41	0.22	0.39	0.22		1.17	(Rioux, Turgeon, and Beaulieu 2007)
<i>M. pyrifera</i>			0.48	0.52	0.33	0.33	0.37		0.92	(Bouissil et al. 2020)
<i>S. muticum</i>			0.61	0.39	0.38	0.38	0.16		0.64	(C. G. Gomez et al. 2009)
<i>S. angustifolium</i>			0.39	0.61	0.23	0.23	0.45		0.64	(Florez-Fernández, Domínguez, and Torres 2019)
<i>L. hyperborea</i>			0.47	0.87	n.a.	n.a.	n.a.		0.54	(Borazjani et al. 2017)
<i>B. bifurcata</i>			0.33	0.67	0.23	0.23	0.56		0.49	(Aarstad et al. 2012)
			0.32	0.68	0.09	0.09	0.45		0.47	(Bouissil et al. 2020)
			S	Gal	Gal	Gal	3,6-AnGal			
Agar	<i>G. gracilis</i>	6	6	38			50			(Martin et al. 2013)
	<i>G. birdiae</i>	8.4	8.4	65			34			(Souza et al. 2012)
	<i>G. lemaneiformis</i>	8.5	66				33			(X. Wang, Duan, and Fu 2016)
	<i>G. persica</i>	n.a.	52				31			(Salehi et al. 2011)
	<i>G. robustum</i>	4	60				40			(Hurtado et al. 2011)
	<i>G. amansii</i>	7.4	58				38			(X. Wang, Duan, and Fu 2016)
Carrageenan		S	Gal	Gal	Gal	3,6-AnGal	MC			
	<i>G. skottsbergii</i>	30	59			41	κ / ι, λ			(Hughes et al. 2018)
	<i>E. cottonii</i>	35.6	20			35.6	κ			(Gereniu, Saravana, and Chun 2018)
	<i>H. musciformis</i>	19.8	n.a.			29.5	κ / ι			(Vázquez-Delfín, Robledo, and Freile-Peigrín 2014)
	<i>F. lumbicalis</i>	14.1	50.1			31.6	κ / β			(Correc et al. 2012; Yu et al. 2007)
	<i>C. armatus</i>	22	37			33	κ / λ			(Yermak et al. 2012)
	<i>S. chordalis</i>	33	52			37	ι			(Stephanie et al. 2010)
	<i>M. stellatus</i>	14.3	86			–	κ / ι			(Gómez-Ordóñez, Jiménez-Escrig, and Rupérez 2014)
	<i>M. pacificus</i>	26.3	36.1			22.8	κ			(Krauchenko et al. 2020)

Abbreviations: S: Sulfate; Glc: Glucose; Xyl: Xylose; Gal: Galactose; Man: Mannose; Rha: Rhamnose; Fuc: Fucose; UA: Uronic acid; 3,6-AnGal: 3,6 anhydrogalactose; MC: Main carrageenan type; n.a.: not analyzed.

<sup>a</sup>Storage polysaccharides (laminarin, floridean starch) not displayed.

<sup>b</sup>Conformation composition as reported by <sup>1</sup>H NMR.

(Adrien et al. 2019). Studies on its structure revealed that depending on medium, salinity and pH, ulvan subunits assemble and polymerize autonomously in different manners. At low pH, the carboxyl groups of aldobiouronic acid groups ionize, while the sulfate groups remain stable, which alters its aggregation dynamics and leads to the dispersion of bead-like shaped aggregates with reduced solubility. Conversely, at high pH, ulvan may form a very dense film, aggregating in a net-like shape (Robic, Gaillard, et al. 2009). Although all SP are hydrocolloids, ulvan has generally lesser affinity with water in comparison with others, making it a less viscous gelling agent in comparison with alginate or laminarin (Morelli and Chiellini 2010).

### 2.2.2. Alginate

Alginate is the main cell wall and cell matrix SP in almost all brown seaweeds, which are the primary source of this SP. It is an acidic molecule in nature. Alginate is essentially composed of two linearly linked monomers:  $\alpha$ -L-guluronate (G-blocks)  $\alpha$ -(1 $\rightarrow$ 4) linked to  $\beta$ -D-mannuronate (M-blocks) (Cardoso, Costa, and Mano 2016), and these can appear as consecutive block sequences (G-G-G, M-M-M) or intercalated (M-G-M) (Figure 1). Depending on the order and proportion of these sequences and M/G ratio, the resulting conformational structure will be different in  $M_w$  and properties. Only G-blocks of alginate are believed to participate in intermolecular cross-linking with divalent cations (e.g.  $Ca^{2+}$ ) to form hydrogels (George and Abraham 2006). Thus, this is a feature that contributes to ease precipitation in alginate extraction. The composition (M/G ratio, mineralization), the sequence type and G-block length are critical factors affecting the physical properties of alginate and its resultant hydrogels. Therefore, higher guluronate proportions will yield more rigid alginate hydrogels (Rioux, Turgeon, and Beaulieu 2007). A species and tissue dependence is also established, as alginates from *A. nodosum*, *M. pyrifera* and species of the genus *Laminaria* have higher M-block indexes (yielding weaker gels), while alginates from cortex or older blades from *L. hyperborea* are accounted for significantly higher G-block composition (Draget 2009).

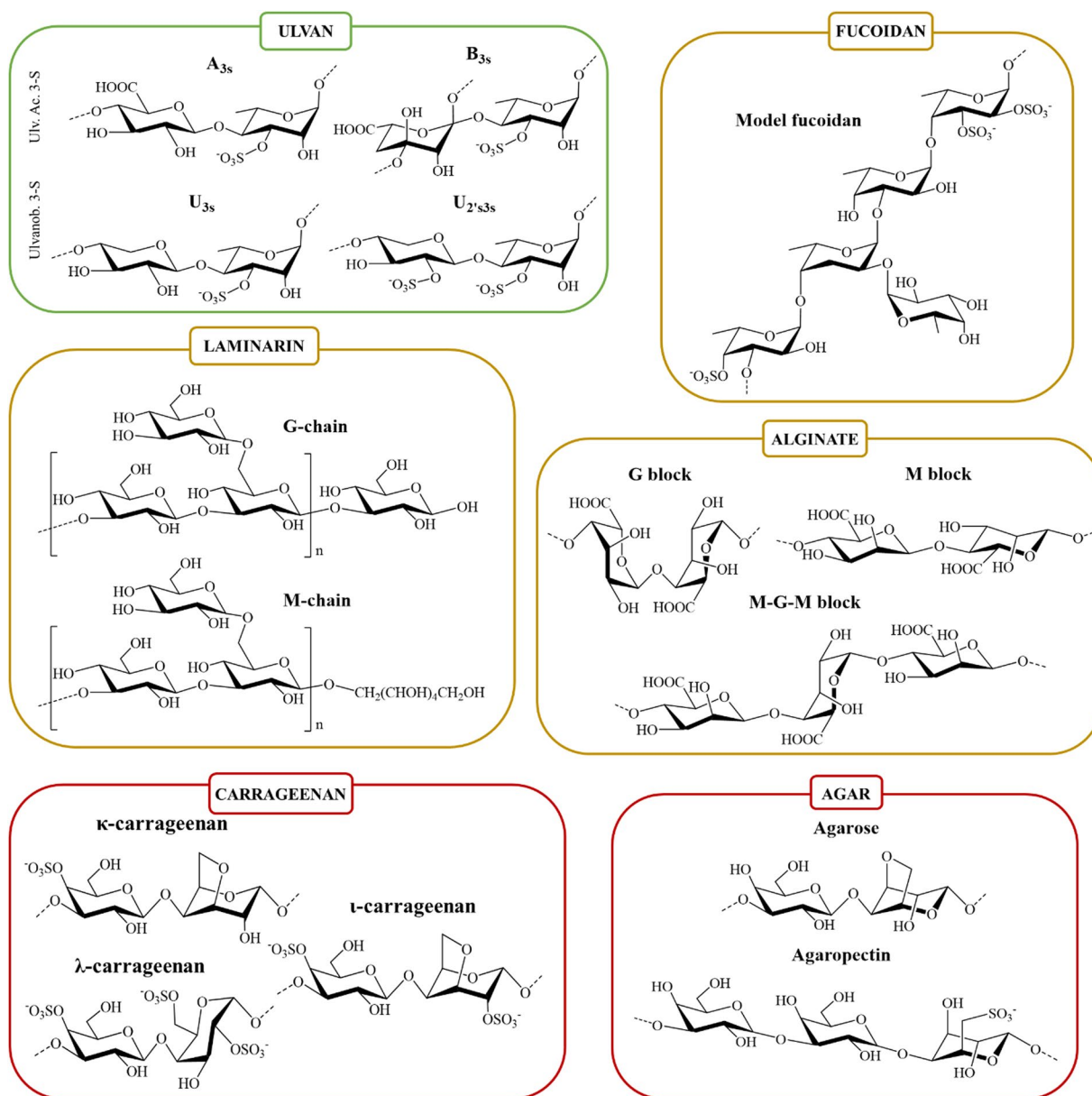
### 2.2.3. Fucoidan

Fucoidan belongs to the group of fucans and present in brown macroalgae and is characterized by containing L-fucose (fucopyranose) as its main backbone monosaccharide. Generally, fucose content is around 40% of the total monosaccharides of fucoidan, but in some species it may rise up to 80% (Table 1) (Bittkau, Neupane, and Alban 2020). The other monosaccharides commonly found in fucoidan include mannose, galactose, glucose, xylose, and glucuronic acid (X. Liu et al. 2020). The structure of fucoidan is usually highly heterogeneous (with numerous branches) and varies according to the algae species. However, it can be broadly differentiated based on their structure between the order Fucales and other brown macroalgae. Analyses carried on representative Fucales like

*Sargassum* and *Fucus* species showed that their central chains are composed of consecutive linked  $\alpha$ -(1 $\rightarrow$ 3) and  $\alpha$ -(1 $\rightarrow$ 4) L-fucose residues. On the other hand, fucoidan from other seaweeds, of which Laminariales are the main representative, have their central chains composed of  $\alpha$ -(1 $\rightarrow$ 3) linked L-fucose residues without any  $\alpha$ -(1 $\rightarrow$ 4) linkages (Ale, Mikkelsen, and Meyer 2011). The heterogeneity in fucoidan structure, attained by variations in sulfate content, constituent monosaccharides, and  $M_w$ , is highly influenced by both the biological source of fucoidan and the applied extraction methods as the latter may also hydrolyze in diverse patterns certain residues (Garcia-Vaquero et al. 2017). A large number of studies found in the bibliography about fucoidan sources and structure has allowed to elucidate that sulfation commonly takes place at  $C_2$  of  $\alpha$ -(1 $\rightarrow$ 3)-linked and  $C_2$  or  $C_4$  of  $\alpha$ -(1 $\rightarrow$ 4)-linked L-fucose residues (S. H. Wang et al. 2020). Sulfation degree is also heavily altered among species, with sulfate groups substituting L-fucose residues on  $C_2$  or  $C_4$  and in rare cases on  $C_3$  (Shen et al. 2018). For example, fucoidan produced from *Fucus* species tends to have higher levels of  $\alpha$ -(1 $\rightarrow$ 3) and  $\alpha$ -(1 $\rightarrow$ 4)-linked L-fucose residues, whereas from *A. nodosum* also shows  $\alpha$ -(1 $\rightarrow$ 3)-linked L-fucose residues with a sulfate group at the position of  $C_2$ . In addition, fucoidan produced from *S. stenophyllum* consisted of a backbone composed of  $\beta$ -(1 $\rightarrow$ 6)-D-galactose and  $\beta$ -(1 $\rightarrow$ 2)-D-mannose residues, which revealed that sulfated galactose could be the other major sugar of fucoidan in some species (Duarte et al. 2001). A model of fucoidan structure with possible alterations is showed in Figure 1.

### 2.2.4. Laminarin

Laminarins are low  $M_w$  storage SP of chain-linked  $\beta$ -(1 $\rightarrow$ 3)-D-glucan, with occurring 6-O- branching of D-glucan in the main chain. Furthermore, some repeated  $\beta$ -(1 $\rightarrow$ 6) intra-chain links are also present (Cui et al. 2021). Laminarin is also characterized by being smaller (in average) when compared to other SP, showing a polymerization degree in the range of 20–25 glucose moieties. While it is mostly an homopolymer, two types of laminarin chains can be distinguished, based on the monosaccharide found in their reducing end: M chains and G chains. M chains end with a  $\beta$ -(1 $\rightarrow$ 3)-D mannitol, whereas G chains end with glucose as the reducing end (Figure 1). In the case of *Laminaria* and *Fucus* species, 40–75% of these reducing end groups are linked to one of the primary hydroxyl groups of D-mannitol (Kadam, Tiwari, and O'Donnell 2015). The structural features of laminarin vary with algal species, for example, its structure can vary according to the M:G chain ratio (in some cases M chains are absent), the polymerization and branching degree and the proportion of  $\beta$ -(1 $\rightarrow$ 3) and  $\beta$ -(1 $\rightarrow$ 6)-glycosidic bonds (Jin et al. 2014). For example, laminarin isolated from *E. bicyclis* is composed of a linear chain of these  $\beta$ -(1 $\rightarrow$ 3) but also  $\beta$ -(1 $\rightarrow$ 6) linkage in a ratio of 2:1 of  $\beta$ -(1 $\rightarrow$ 3)-D-glucans (Shin et al. 2009). Laminarin is one of the SP with the



**Figure 1.** Oligosaccharide subunits conforming ulvans, fucoidan and alginate. Ulv. Ac. 3-S: Ulvanobiuronic acid 3-sulfate; Ulv. nob. 3-S: Ulvanobiose 3-sulfate; G-block:  $\alpha$ -L-gulonate; M:  $\beta$ -D-mannuronate.

strongest affinity for water due to its abundance in alcohol groups in the glucan monomer, while it does not contain sulfate in its structure. One of its characteristics is its ability to form web-like structures that consequently contribute to its wound-healing properties (Tanna and Mishra 2019). This structure may change as a result of modifications *e.g.* sulfation, as the introduced anions alter the overall chain charge and result in the appearance of hydrogen bonds that lead laminarin to form helix conformations (Zargazadeh et al. 2020).

### 2.2.5. Agar

Agar is one of the most valued and exploited SP, as it is accounted for excellent hydrocolloidal properties due to its composition. Agars are linear SP built up of alternating

$\beta$ -(1 $\rightarrow$ 3)-D-galactopyranose and  $\alpha$ -(1 $\rightarrow$ 4)-linked L-galactopyranose residues with intermittent sulfate groups at C<sub>6</sub> (Rodríguez et al. 2009). Moreover,  $\alpha$ -(1 $\rightarrow$ 4)-linked 3,6-D-anhydrogalactopyranose may also appear, which the higher levels of this residue confer enhanced hydrocolloid properties. For this backbone structure composition agar, together with carrageenan, are classified as sulfated galactans. The  $\beta$ -(1 $\rightarrow$ 3)-linked residue is the D-enantiomer while the  $\alpha$ -(1 $\rightarrow$ 4)-residue is the L-enantiomer, which can also appear linked next in the chain and constitutes one marked difference with carrageenans (Yu et al. 2007). Depending on sulfation degree and pattern, anionic charge of the polymer will be altered, which has led to refer to the more neutral agar SP as agarose and the higher sulfated agaropectin (Armisen and Galatas 2009). Agarose is defined

by the presence of 3,6-D-anhydrogalactopyranose, which strengthens agarose gel viscosity making it more desirable for gelling applications (Sousa, Rocha, and Gonçalves 2020). Moreover, agarpectin is also characterized for higher presence of acetate and pyruvate substitutions. These differences impact its structure and properties, as agarpectin-rich agar display lower water solubility (Y. Zhang et al. 2019).

### 2.2.6. Carrageenan

With a similar structure to agar, carrageenan is composed of linear  $\beta$ -(1 $\rightarrow$ 3)- and  $\alpha$ -(1 $\rightarrow$ 4)-linked D-galactopyranose disaccharides. However, it presents substitutions in C<sub>4</sub> with ester sulfate groups and  $\alpha$ -(1 $\rightarrow$ 4)-linked 3,6-D-anhydrogalactopyranose (Cheong et al. 2018). Sulfation and 3,6-anhydrogalactopyranose proportions and patterns thus define the diverse groups of carrageenan (J. Liu et al. 2015). Six types of structures of carrageenan are known, which are  $\mu$ ,  $\nu$ ,  $\lambda$ ,  $\kappa$ ,  $\iota$  and  $\theta$ -carrageenan. In general terms,  $\mu$  &  $\kappa$ -carrageenan share the same  $\beta$ -(1 $\rightarrow$ 3)-galactopyranoside, but the  $\alpha$ -(1 $\rightarrow$ 4) galactoside is a sulfated galactopyranoside in  $\mu$ , while in  $\kappa$  this is substituted for a 3,6-D-anhydrogalactopyranose. This same relation, with different alcohol and ester sulfate substitutions, is observed between  $\nu/\iota$ -carrageenan and  $\lambda/\theta$ -carrageenan (Jiao et al. 2011). Ester sulfate abundancy ranges between 25% and 35% among carrageenan types, with  $\kappa$ -carrageenan showing the lowest sulfation while  $\lambda$ -carrageenan exhibits the highest, as it has three ester sulfate groups for each disaccharide monomer (Li et al. 2014). This is relevant as the anionic sulfate groups bind to positively charged groups on proteins in food, for example, resulting in the thickening and stabilizing properties of carrageenan (McKim et al. 2019). Nonetheless, technological properties of carrageenan are directly reliant on their structure and proportion of disaccharides. For example, higher abundance of  $\kappa$  and  $\iota$ -carrageenans results in better gelling carrageenan due to their conformational changes and lesser sulfation degree (Gomez-Zavaglia et al. 2019). Natural carrageenan appear as hybrid polymers like  $\mu/\kappa$ -hybrids,  $\nu/\iota$ -hybrids,  $\kappa/\iota$ -hybrids and so on, being these proportions related to the source species (Jiao et al. 2011).  $\kappa$ ,  $\iota$  and  $\lambda$ -carrageenan are considered as the most relevant carrageenan due to their industrial applications (Cheong et al. 2018) and their structure is presented in Figure 1.

### 2.2.7. Floridean starch

Floridean starch is not a sulfated nor a cell-wall SP, but one of the few amylopectin containing SP with an energy storage role. It is composed entirely of amylopectin and in contrast with vegetal starches, it is a short-chain, highly branched SP more akin to animal glycogen than land plants starch (Martinez-Garcia, Stuart, and van der Maarel 2016). Its polymeric structure consists of  $\alpha$ -(1 $\rightarrow$ 4)-D-glucoses with  $\alpha$ -(1 $\rightarrow$ 6)-branching chains, which appear as clusters and abundancy of  $\alpha$ -(1 $\rightarrow$ 6) branches is directly correlated with

shorter chain length (Shimonaga et al. 2008). Because of this linkage pattern, structure and absence of amylose, floridean starch is regarded as an starch-like molecule with low caloric value while sharing many physico-chemical properties with vegetal starches (Olatunji 2020).

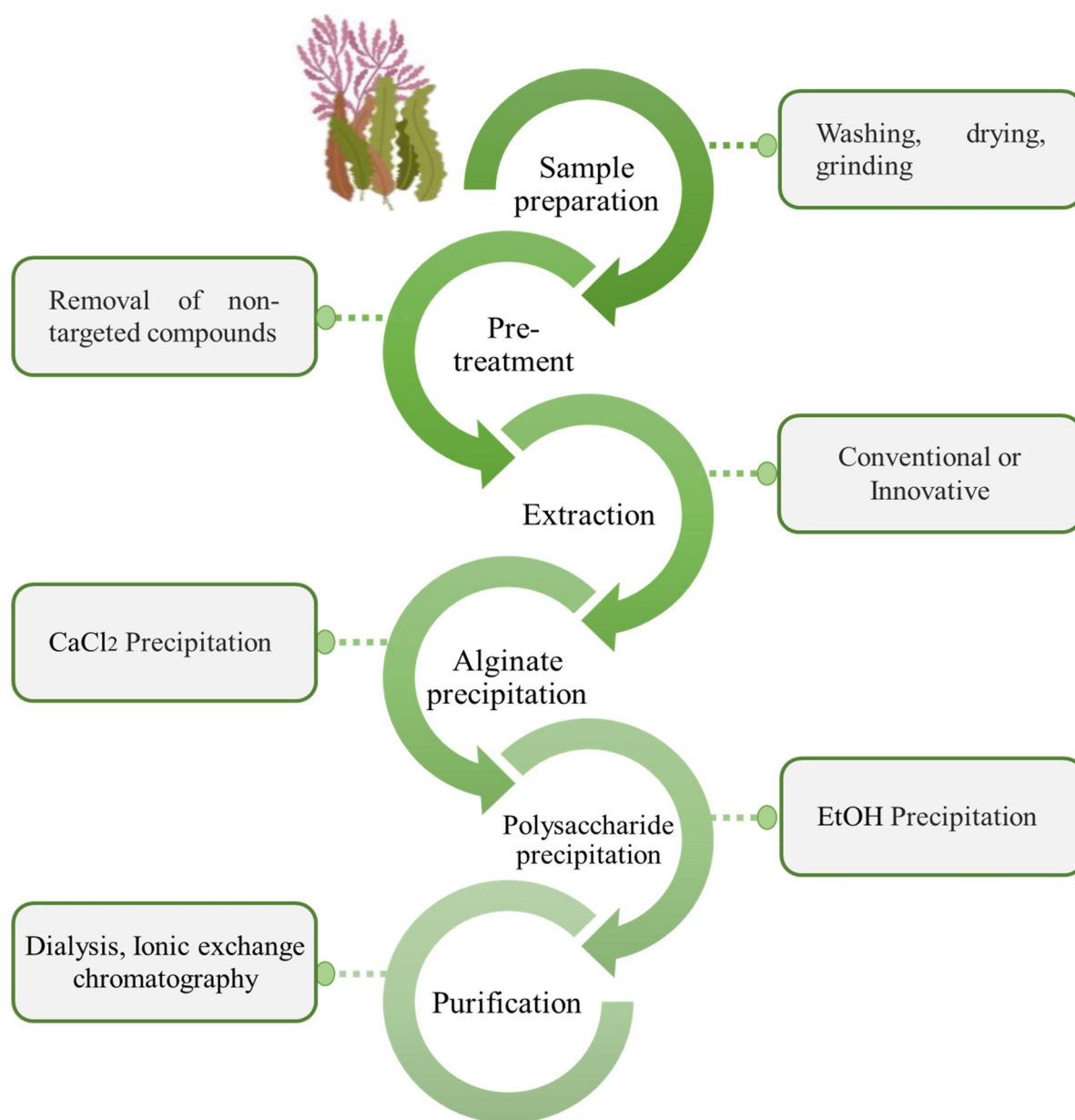
## 3. From traditional to emerging extraction technologies of seaweeds' polysaccharides

Several properties of SP such as film-formation and also biological activities have favored the development of diverse extraction systems to obtain these compounds for their further use in industrial applications (L. P. Gomez et al. 2020). To obtain these compounds in large quantities and high purity may involve different stages, represented in Figure 2. Briefly, the first stage involves the preparation of the macroalgae, which includes process like washing to eliminate salt and impurities, freeze-drying, or grinding to obtain a homogenous powder. Next, the samples could be submitted to a pretreatment to eliminate compounds that may interfere with the SP extraction, such as pigments or lipids (Dobrinčić et al. 2020). Following this stage, the macroalgae are extracted using different techniques (explained below) and afterwards, algae biomass is submitted to further treatments to separate the compounds of interest. In the case of alginates and carrageenans, it is usually employed alkali treatments (Abdul Khalil et al. 2018; Imbs et al. 2016; L. P. Gomez et al. 2020). The next step is to add ethanol to precipitate the SP present in the supernatant and to purify them by dialysis, filtration and chromatographic techniques (Dobrinčić et al. 2020). The composition and amount of SP not only are influenced by raw material (species, season, or place of harvest), but also by factors concerning extraction conditions and techniques (traditional or innovative techniques). Thus, it is necessary to optimize the parameters of the extraction techniques (traditional and innovative techniques) to improve their yields.

### 3.1. Traditional techniques

Traditional techniques like heat-assisted extraction (HAE) and Soxhlet extraction are commonly used in both research and industry. HAE is a solid to liquid extraction technique that typically involves heat and/or agitation to improve the solubility of the compounds of interest in the solvent utilized (Garcia-Vaquero, Rajauria, and Tiwari 2020). Among the consulted bibliography, the extraction of SP from macroalgae is generally performed using hot water as solvent (Bhardwaj et al. 2020), but some studies have employed other solvents (Deghrigue Abid et al. 2019) and also acidic solutions (Menshova et al. 2015; Yaich et al. 2017; Imbs et al. 2016) (Table 2). Extraction temperature varies from room temperature to  $\geq 100^\circ\text{C}$  and extraction time usually ranges from several hours up to 48 h (Table 2). On the other hand, Soxhlet extraction is characterized by the continuous flow of solvent through the sample, which enhances the extraction yield in comparison to HAE (Garcia-Vaquero, Rajauria, and





**Figure 2.** Schematic mechanism of polysaccharide extraction from macroalgae.

Tiwari 2020). However, few studies have shown to employ this system. In fact, it is usually used as a preliminary treatment before the extraction of macroalgae to remove non-targeted compounds present in the samples (Ammar et al. 2015; Bittkau, Neupane, and Alban 2020; Deghrigue Abid et al. 2019). As in the HAE, hot water is the most used solvent. However, in some cases and in order to precipitate alginates, calcium chloride was also added (Ammar et al. 2015; Bittkau, Neupane, and Alban 2020). The continuous flow also significantly reduces the extraction time, which ranged between 2 and 3 h (Table 2). Nowadays, several drawbacks of traditional techniques have been widely highlighted, such as large amount of solvents (sometimes toxic), long procedure times, high temperatures, degradation of compounds, etc. (L. P. Gomez et al. 2020; Garcia-Vaquero, Rajauria, and Tiwari 2020). To solve these problems and improve the efficiency of the extraction, innovative

technologies for the extraction of SP are currently being evaluated.

### 3.2. Innovative techniques

The most currently employed innovative techniques for SP extraction are microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), pressurized liquid extraction (PLE) and enzymatic assisted extraction (EAE) and pulse-electric field extraction (PEF). In general terms, these techniques present less drawbacks than conventional ones, but still, may have limitations.

#### 3.2.1. Microwave-assisted extraction (MAE)

Currently, this technique is considered one of the most efficient innovative systems. MAE employs microwaves to

heat the samples, evaporating the intracellular fluids. This causes an increase in pressure and the consequent cell breakage liberation of intracellular compounds into the solvent. Compared to conventional techniques, MAE reduces the amount of solvent needed and improves the efficiency. In addition, it is easy to combine it with other extraction technologies. Nevertheless, the main drawback of this technique is that thermo-labile compounds may be altered or degraded (Dobrinčić et al. 2020; Garcia-Vaquero et al. 2017).

As in the case of HAE, water (Alboofetileh, Rezaei, Tabarsa, Rittà, et al. 2019; Ren et al. 2017) and acidic solutions (Yuan et al. 2018; Okolie et al. 2019; Garcia-Vaquero et al. 2020) are the most employed solvents, but other solvents have been reported (Shang et al. 2021; Cao et al. 2018) (Table 2). Generally, the extraction temperature is around 90 °C, although it may oscillate in the range between 38 and 168 °C, while microwave's potency varies between 500 and 1000 W. Finally, MAE is usually performed during a few minutes, but longer times have been also reported (Table 2).

### 3.2.2. Ultrasound-assisted extraction (UAE)

Another example of innovative techniques for extraction of SP is the UAE, which is based on the application of ultrasound waves above 20 kHz to create bubbles and zones of high and low pressure. The growth and collapse of those bubbles leads to the breakdown of cell walls and particles, favoring the contact between the sample and the solvent. UAE is considered a suitable technique for an industrial scale, due to its simplicity, low-cost equipment and its rapidity. In addition, it operates at low temperatures, which allows the preservation of thermo-labile compounds and is feasible to be combined with other extraction methods, especially with MAE (Ciko et al. 2018; Y. Wang et al. 2021).

Usually, water or acidic solutions are the most employed solvents for UAE (Kadam et al. 2015; S. H. Wang et al. 2021; Youssouf et al. 2017), but other solvents have been investigated. UAE is often carried out at room temperature (RT) (Hmelkov et al. 2018; Kadam et al. 2015; Okolie et al. 2019), although temperatures between 50–90 °C have been also used (Rahimi, Tabarsa, and Rezaei 2016; Youssouf et al. 2017). Among bibliography, extraction frequency employed is generally 20 kHz, (Okolie et al. 2019; Alboofetileh, Rezaei, Tabarsa, Rittà, et al. 2019) but higher frequencies have been selected (Rahimi, Tabarsa, and Rezaei 2016; Hmelkov et al. 2018) Regarding extraction time, this technique also employs short times, generally less than 1 h (Table 2).

### 3.2.3. Pressurized liquid extraction (PLE)

Pressurized liquid extraction (PLE) is also known as accelerated solvent extraction or subcritical water extraction, when water is used as solvent (Jacobsen et al. 2019). This technique is based on the use of water or other solvents at high temperatures and pressures, maintaining the solvent in the liquid state. The operation conditions usually vary between 50–200 °C for temperature and 35–200 bar for pressure (Otero et al. 2020; Navarro del Hierro et al. 2020; Ciko

et al. 2018; Abdul Khalil et al. 2018). Some advantages of PLE include the use of less amount of solvent, short times or high efficiency (Saravana et al. 2016). However, the use of high temperatures may lead to undesired reactions or degradation of compounds and its application at industrial scale is still limited, since it requires expensive equipment and high amount of energy (Jacobsen et al. 2019).

Considering the compiled studies, water is the most used solvent in PLE for the recovery of SP, both alone or in combination with co-solvents, such as acids, deep eutectic solvents or ionic liquids, in variable concentration (Gereniu, Saravana, and Chun 2018; Saravana et al. 2016; Alboofetileh, Rezaei, Tabarsa, Rittà, et al. 2019) (Table 2). For temperature and pressure, operating conditions ranged between 60–180 °C and 20–103 bar, respectively. Regarding time, the extraction was performed between 5–25 min (Table 2).

### 3.2.4. Enzymatic assisted-extraction (EAE)

This technique consists in the use of digestive enzymes to degrade the complex cell wall of seaweeds and release the cytoplasmic content, improving the extraction rate. Some of the enzymes employed for SP extraction include proteases, such as Alcalase or Flavourzyme, or carbohydrases like Viscozyme or Celluclast (Dobrinčić et al. 2020) (Table 2). In EAE, temperature, pH and solvent (water or buffer) and ratio enzymes/sample are important factors that affect its efficiency and should be carefully considered for an optimized extraction (Abdul Khalil et al. 2018). Due to the nature of enzymes, this technique is considered highly specific, eco-friendly, and nontoxic. However, its industrial application is limited due to the high price of some type of enzymes (Dobrinčić et al. 2020; Garcia-Vaquero et al. 2017).

### 3.2.5. Pulse-electric field (PEF)

This extraction method is based on the application of intense electric pulses to disrupt the linkages between cell wall SP molecules and thus creating pores in its structure. Main parameters are the distance between electrodes and intensity. It is considered a green extraction method since no polluting solvents are generally required (Polikovskiy et al. 2016). There are very few reports on the use of PEF for SP extraction. Foremost, PEF extraction on seaweeds has been focused on minerals, polyphenols and protein recovery (Robin et al. 2018). Nonetheless, a very recent study assesses the extraction of starch from *U. ohnoi* by PEF and revealed that it could be a feasible extraction procedure for this type of SP, among other components (M. S. Prabhu et al. 2019).

## 3.3. Comparison of extraction techniques

Due to the great variety of matrices in the literature with different experimental conditions (solvents, time, instrumental parameters, etc.), and the variety of target SP, as reflected in (Table 2), the comparison among extraction techniques has resulted in a difficult task. The comparison was focused in evaluating the most efficient techniques in terms of

Table 2. Conventional and innovative technologies to extract polysaccharides from macroalgae.

Species	Pretreatment	Extraction	Purification	Recovery	Ref.
Heat-assisted extraction (HAE)					
<i>T. ornata</i>	95% EtOH	H <sub>2</sub> O, 95°C, 3 h	EtOH pr.	TSP	(Bhardwaj et al. 2020)
<i>S. fusiforme</i>	–	H <sub>2</sub> O, 100°C	EtOH pr. CaCl <sub>2</sub> pr. // IEC	Fuc.	(Cong et al. 2016)
<i>G. persica</i> , <i>E. intestinalis</i>	85% EtOH, RT, overnight	H <sub>2</sub> O, 65°C, 2 h	EtOH pr. // Filtration	TSP	(Safavi et al. 2019)
<i>N. zanzardinii</i>	85% EtOH, RT, overnight	H <sub>2</sub> O, 65°C, 3 h (x2)	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (5.2%)	(Alboofetleeh, Rezaei, Tabarsa, Rittà, et al. 2019)
<i>S. siliquosum</i>	95% EtOH, 4 h	H <sub>2</sub> O, 100°C, 1 h	Dialysis (14 kDa) // EtOH pr. // IEC	Fuc. (5.08%)	(S. H. Wang et al. 2021)
<i>D. membranacea</i> , <i>P. pavonica</i>	–	MeOH:DCH, RT, 48 h	CaCl <sub>2</sub> pr. // EtOH pr.	Na-Alg. (18.93%, 66.72%)	(Deghrigue Abid et al. 2019)
<i>U. lactuca</i>	–	H <sub>2</sub> O-HCl (pH 1.5, 2), 80 and 90°C, 1 h	EtOH pr.	Ulv. (3.04–13.06%)	(Yaich et al. 2017)
<i>A. angusta</i>	Deffated	0.1M HCl, 60°C, 2 h (x2)	Dialysis	Lam. & Fuc. (5.5%)	(Menshova et al. 2015)
<i>C. langsdorffi</i>	96% EtOH, 40°C, 24 h	0.1M HCl, RT, 3 h	Dialysis // EtOH pr. // IEC	Alg. (13.3% d-DW) // Lam. (0.4% d-DW) // Fuc.: (3.0–46.0% d-DW)	(Imbs et al. 2016)
<i>A. nodosum</i>	80% EtOH, RT, 20 h // 70°C, 5 h	0.01 M HCl, 70°C, 3 h	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (11.9%)	(Okolie et al. 2019)
<i>A. nodosum</i> , <i>L. hyperborea</i>	–	0.1 M HCl, 70°C, 150 min // H <sub>2</sub> O, 70°C, 150 min	EtOH pr. // Dialysis (10 kDa)	Lam. (4.3%); 4.6%	(Kadam, O'Donnell, et al. 2015)
Soxhlet extraction					
<i>F. vesiculosus</i> , <i>F. serratus</i> , <i>F. evanescens</i> , <i>D. foeniculaceus</i> , <i>L. digitata</i> , <i>S. latissima</i>	99% EtOH	2% CaCl <sub>2</sub> , 85°C, 2 h	EtOH pr. // Dialysis	Fuc. (10.9–31.7% DW)	(Bittkau, Neupane, and Alban 2020)
<i>R. pseudopalimata</i> , <i>S. filiformis</i> , <i>H. cornea</i> , <i>S. fluitans</i>	MeOH, AcO	H <sub>2</sub> O, 90°C, 2 h	EtOH pr.	TSP	(Bedoux et al. 2017)
<i>T. ornata</i>	–	Hot H <sub>2</sub> O	–	TSP (12% DW)	(Subash et al. 2016)
Microwave-assisted extraction (MAE)					
<i>U. prolifera</i>	–	0.01–0.1M HCl, 90–120°C, 500W, 15 min	Neutralization NaOH // EtOH pr.	TSP	(Yuan et al. 2018)
<i>S. pallidum</i>	–	EtOH (19–27%) and (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> (20–24%); 70–110°C; 600–100W, 5–25 min	Dialysis (3 kDa) // EtOH pr.	TSP (7.56%)	(Cao et al. 2018)
<i>A. nodosum</i>	80% EtOH, RT, 20 h // 70°C, 5 h	0.01 M HCl, 90°C, 15 min	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (5.71%)	(Okolie et al. 2019)
<i>N. zanzardinii</i>	85% EtOH, RT, overnight	H <sub>2</sub> O, 90°C, 700 W, 20 min (x2)	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (6.17%)	(Alboofetleeh, Rezaei, Tabarsa, Rittà, et al. 2019)
<i>S. thunbergii</i>	–	H <sub>2</sub> O, 60–80°C; 500–700W, 15–25 min	EtOH pr.	TSP (2.48%)	(Ren et al. 2017)
<i>S. siliquosum</i>	95% EtOH, 4 h	H <sub>2</sub> O, 750W, 10 min	Dialysis (14 kDa) // EtOH pr. // IEC	Fuc. (6.94%)	(S. H. Wang et al. 2021)
<i>F. vesiculosus</i>	–	DES, 168°C, 35 min	Column separation	TSP (11.63% DW)	(Shang et al. 2021)
<i>U. lactuca</i> , <i>G. lemaneiformis</i> S. <i>ceylonensis</i> , <i>D. antarctica</i>	–	H <sub>2</sub> O, 70°C, 500W, 50 min	EtOH pr. // IEC	TSP (11.09; 13.32; 12.49; 14.21% DW)	(He et al. 2016)
Ultrasound-assisted extraction (UAE)					
<i>A. nodosum</i>	80% EtOH, RT, 20 h // 70°C, 5 h	0.01M HCl, RT, 20kHz, 35 min	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (4.56%)	(Okolie et al. 2019)
<i>A. nodosum</i> , <i>L. hyperborea</i>	–	0.1 M HCl // H <sub>2</sub> O, RT, 750W, 15 min	EtOH pr. // Dialysis (10 kDa)	Lam. (6.24% // 5.97%)	(Kadam, O'Donnell, et al. 2015)
<i>L. digitata</i>	0.1 M HCl, 10 min	0.1 M HCl, 52.5°C, 20 kHz, 500W, 10 min	Filtration	TSP (1.07%)	(García-Vaquero et al. 2018)
<i>N. zanzardinii</i>	85% EtOH, RT, overnight	H <sub>2</sub> O, 55°C, 20 kHz, 200W (x2)	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (3.51%)	(Alboofetleeh, Rezaei, Tabarsa, Rittà, et al. 2019)
<i>F. evanescens</i>	70% EtOH, RT, 10 days	H <sub>2</sub> O, RT, 35kHz, 150W, 5–30 min	CaCl <sub>2</sub> pr. // EtOH pr. IEC	Fuc. (3.99–4.75%)	(Himelkov et al. 2018)

<i>S. siliquosum</i>	95% EtOH, 4 h	H <sub>2</sub> O, RT, 21–25 kHz, 950 W, 10 min	Dialysis (14 kDa) // EtOH pr. // // IEC	Fuc. (4.78%)	(S. H. Wang et al. 2021)
<i>Silvetia compressa</i>	–	25% EtOH, 57.5 °C, 30 min	MeOH pr.	TSP (25.13%)	(Vázquez-Rodríguez et al. 2020)
<i>K. alvarezii</i> , <i>E. denticulatum</i>	80% EtOH, RT, overnight	H <sub>2</sub> O, 90 °C, 25 kHz, 150 W, 15–30 min	Hot filtration	Carr. (50%; 55% DW)	(Youssof et al. 2017)
<i>U. intestinalis</i>	80% EtOH, RT, overnight (x2)	H <sub>2</sub> O, 66 °C, 53 kHz, 180 W, 40 min	EtOH pr.	Ulv. (8.30%)	(Rahimi, Tabarsa, and Rezaei 2016)
Pressurized liquid extraction (PLE)	–	0.1% NaOH, 140 °C, 50 bar	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (8.23%)	(Saravana et al. 2016)
<i>S. japonica</i>	–	H <sub>2</sub> O-DES (50–70%), 100–150 °C, 5–50 bar, 10–25 min	CaCl <sub>2</sub> pr. // EtOH pr.	Alg. (5–27.2%) Fuc. (5–14.9%)	(Saravana, Cho, Woo, et al. 2018)
<i>S. japonica</i>	SC-CO <sub>2</sub> , 50 °C, 300 bar, 4 h	0.1% NaOH, 100–180 °C, 20–80 bar, 5–15 min	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (0.10–12.8%)	(Saravana, Tilahun, et al. 2018)
<i>N. zanardinii</i>	85% EtOH, RT, overnight	H <sub>2</sub> O, 150 °C, 10 min, x2	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (13.1% DW)	(Alboofetleeh, Rezaei, Tabarsa, Rittà, et al. 2019)
<i>N. zanardinii</i>	85% EtOH, RT, overnight	H <sub>2</sub> O; 90–150 °C, 7.5 bar, 10–30 min	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (4.9–23.7% DW)	(Alboofetleeh, Rezaei, Tabarsa, You, et al. 2019)
<i>K. alvarezii</i>	–	H <sub>2</sub> O, (60–180 °C), 50 bar, 5 min 1% ILS, (60–180 °C), 50 bar, 5 min	2-Propanol pr.	κ-carr. (55–70%)	(Gereniu, Saravana, and Chun 2018)
Enzyme-assisted extraction (EAE)	–	Cellulase, Protease, pH 7, 50 °C, 2 h	Dialysis // EtOH pr.	Ulv. (17.14%)	(Yaich et al. 2017)
<i>U. lactuca</i>	–	Cellulase, pH 4.5, 50 °C, 24 h	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (3.89%)	(Okolie et al. 2019)
<i>A. nodosum</i>	80% EtOH, RT, 20 h // 70 °C, 5 h	Alcalase, pH 8, 50 °C, 24 h Flavourzyme, pH 7, 50 °C, 24 h	CaCl <sub>2</sub> pr. // EtOH pr.	Fuc. (5.58%) (4.36%)	(Alboofetleeh, Rezaei, Tabarsa, Rittà, et al. 2019)
<i>F. distichus</i> subsp. <i>evanescens</i> , <i>S. latissima</i>	–	Cellulase, pH 4.5, 50 °C, 24 h Viscozyme, pH 4.5, 50 °C, 24 h Cellulase // alginate lyase, pH 6, 40 °C, 24 h	CaCl <sub>2</sub> pr. // EtOH pr. // IEC	Fuc. (40% // 29%)	(Nguyen et al. 2020)
<i>S. fulvellum</i>	–	Cellulast, pH 4.5, 50 °C, 24 h	EtOH pr.	TSP (23.62%)	(L. Wang et al. 2019)
<i>P. boryana</i>	–	Cellulast, pH 4.5, 100 °C, 10 min	EtOH pr.	TSP (42.14%)	(Jayawardena, Wang, et al. 2020)
<i>C. fragile</i>	–	Cellulast, pH 4.5, 50 °C, 24 h	EtOH pr.	TSP (55.78%)	(L. Wang et al. 2020)

Abbreviations: pr: precipitation; TSP: total polysaccharides; Alg: alginate; Fuc: fucoidan; Ulv: laminarin; Ulv: carrageenan; DW: dry weight; d-DW: defatted dry weight; RT: room temperature; EtOH: ethanol; AcO: acetone; CHCl<sub>3</sub>: chloroform; DCT: dichloromethane; DMF: anhydrous N,N-dimethylformamide; IEC: ion-exchange chromatography; DES: deep eutectic solvents; Hx: hexane; MeOH: methanol; ILS: ionic liquids; SC-CO<sub>2</sub>: Supercritical carbon dioxide extraction.

recovery rates. Thus, studies using the same species and targets, but different extraction methods were selected. For example, Alboofetileh et al. employed conventional and different innovative extractions, using water as solvent, to obtain fucoidans from *N. zanardinii*. Conventional extraction showed an extraction yield of 5.2% DW. MAE and PLE achieved higher rates, 6.17 and 13.15%, respectively, while UAE was the less efficient technique, with a 3.51% of recovery. The results of EAE ranged between 5.5 to 4.2%, depending on the employed enzyme (Alboofetileh, Rezaei, Tabarsa, Rittà, et al. 2019). A study assessed ulvan extraction from *U. lactuca* using HAE in an acidic solution (pH 1.5–2) and EAE. Results showed that EAE significantly increased the extraction efficiency, compared to HAE. Specifically, traditional extraction yields ranged between 3.04 and 13.06% (80 and 90 °C, respectively), while EAE achieved a 17.15% of ulvan recovery (Yaich et al. 2017). In another study, the authors evaluated two different solvents (water and 0.1% HCl solution) and two different extraction techniques (HAE and UAE) for the extraction of laminarin from *A. nodosum* and *L. hyperborea*. In this case, UAE enhanced the efficiency of the extraction with both solvents in two seaweeds (5.28–6.24%), compared to traditional HAE (3.25–4.6%). Regarding solvents, water achieved better results when using HAE, while 0.1% HCl was more efficient when using UAE (Kadam et al. 2015). Recently, a study compared HAE, MAE, UAE and EAE fucoidan extraction recovery from *A. nodosum*. Unlike other works, none of the innovative techniques was able to match the extraction yield of HAE, showing the following results: 11.9, 5.71, 4.56 and 3.89%, respectively (Okolie et al. 2019).

Considering reported results, innovative techniques are usually efficient alternatives to traditional extraction, achieving suitable recovery rates. However, it can also be observed that it is necessary to optimize these methods and operating conditions (solvent, temperature, time, etc.) for the selected matrix to obtain the maximum extraction efficiency.

#### 4. Structural characterization of polysaccharides from seaweeds

As mentioned, SP are structurally complex, with predominant monomers like galactose, rhamnose, xylose, fucose, uronic acid, etc. Thus, the structure elucidation of SP requires specialized methods to clearly analyze their composition. In fact, it seems that it is recommendable a mixture of several techniques. For example, to elucidate a water-soluble heteropolysaccharide from the algae *E. prolifera*, it was necessary to use up to four techniques, Fourier transform infrared spectroscopy (FTIR), high performance liquid chromatography (HPLC), multi-angle laser light scattering (MALLS), and nuclear magnetic resonance (NMR) spectroscopy (Lin et al. 2020). In general, to obtain the complete sequence of the molecule, the SP is usually degraded into oligosaccharide repeating units in a controlled manner, involving depolymerization into smaller oligosaccharides by either partial acid or enzymatic hydrolysis. Thus, the resulting oligosaccharides mixture is fractionated, and

each oligosaccharide fully characterized (Amicucci et al. 2019). Table 3 collects the most used techniques for the elucidation and identification of oligosaccharides from algae. In this sense, NMR spectroscopy is one of the most used techniques to clarify the composition and structure of non-complex SP. It helps to elucidate the monosaccharide composition and their sequence, the presence of  $\alpha$ - or  $\beta$ -type carbohydrates and linkage features (Cheong et al. 2018). For one dimensional NMR ( $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$ ) spectrum, a signal in the region of 5.1–5.7 ppm is associated to the  $\alpha$ -configuration, whereas the  $\beta$ -configuration occurs in the range of 4.5–4.8 ppm in  $^1\text{H-NMR}$  spectrum. However, SP of high  $M_w$  are not properly characterized using this technique. For example, to clearly distinguish the signal of fucoidans from  $M_w$  upper 20,000 Da, they have to be cleaved to be fully identified (Holtkamp et al. 2009). In this sense, gas chromatography coupled to mass spectrometry (GC-MS) is also a powerful method for structurally analyzing SP after a complete acid hydrolysis and derivatization process, due to the presence of multiple nonpolar groups with low volatility. In this process, the active hydrogen from hydroxyl groups is replaced by more nonpolar groups. The hydrolysis to release the neutral sugars is generally with trifluoroacetic acid at high temperature (for example 100 °C for 3 h or 120 °C for 90 min) and after that, a reduction with  $\text{NaBH}_4$  is performed (Hentati et al. 2018). GC-MS columns are usually composed of a polysiloxane phase with lengths ranging from 30–60 m, 0.2–0.4 mm diameter and 0.1–0.5  $\mu\text{m}$  pore size (Table 3) (P. Li et al. 2018; Cheng et al. 2011; Rioux, Turgeon, and Beaulieu 2010; X. T. Xie et al. 2020; Hentati et al. 2018). For identification of different monomers, temperature gradient ranges from 60 °C to 280 °C. It is convenient to highlight that one drawback of GC-MS is the difficulty to analyze a variety of monosaccharides due to the low sensitivity. In addition, it requires a derivatization process, extending the analysis times (Amicucci et al. 2019).

Other attempts to analyze the structure of SP comprise HPLC. There are several modes of HPLC operation for the characterization of oligosaccharides, such as ionic exchange chromatography (IEC). Given the anionic nature of SP, IEC is one of the most useful and efficient methods for separation and characterization of these P (Mak et al. 2013; Khajouei et al. 2018; Glasson et al. 2017; Spicer et al. 2017). Regarding detection, the refractive index is one of the most common detectors and it does not require prior derivatization of carbohydrates. Ultraviolet and fluorometric detectors are also widely used, but in these cases a prior derivatization is necessary due to the absence of chromophore or fluorophore groups in these molecules (Saravana, Cho, Patil, et al. 2018). In addition, mass spectrometry (MS) is the most powerful detection method to identify the oligosaccharide structure. The MS chromatograms provide valuable information concerning the molecular mass, fragmentation mode, chain length distribution and the composition of the monosaccharide units (Cheong et al. 2018). The recent development of matrix assisted laser desorption/ionization (MALDI) combined with the time of flight (TOF) separation system has resulted in the method of choice for structural characterization of oligosaccharides by many researcher groups,

**Table 3.** Analytical methodology employed for the identification of algae polysaccharides.

Species	SP	Composition	Column (*)	T or E gradient	Ref.
Gas chromatography-mass detection (GC-MS)					
<i>U. flacca</i>	Ulvan	$\alpha$ -(4 $\rightarrow$ 1)-L-Rha and 4-linked- $\beta$ -D-glucuronic acid residues	DB 225 (CPP) (30 10 <sup>2</sup> $\times$ 0.25)	100–220°C (5°C/min) // 220°C 15 min.	(P. Li et al. 2018)
<i>C. compressa</i>	n.s.	Trimethyl silylated monosaccharides: CF, sodium alginate composed of $\alpha$ -(1 $\rightarrow$ 3), $\alpha$ -(1 $\rightarrow$ 4)-linked L-FucSPas main backbone	OPTIMA-1 MS (PDMS) (30 $\cdot$ 10 <sup>3</sup> $\times$ 0.32, 0.25)	100°C (8°C/min), 3 min // 200°C (8°C/min), 1 min // 215°C (5°C/min), 19 min.	(Hentati et al. 2018)
<i>S. longicuris</i>	GI-F, laminarin	D-xylose, D-mannose, D-glucose, D-galacturonic acid // D-glucuronic acid, D-galactose, D-glucose and D-uronic acid	CP-Sil-5CB (PDMS) (60 $\cdot$ 10 <sup>3</sup> $\times$ 0.25).	50°C, 1 min // 120°C (20°C/min) // 240°C (2°C/min).	(Rioux, Turgeon, and Beaulieu 2010)
<i>P. haitanensis</i> , <i>E. galetinae</i> , <i>G. amansii</i> , <i>G. chouae</i> , <i>G. blodgettii</i> , <i>G. lemaneiformis</i>	n.s.	Monosaccharide, AnGal	Rtx-5MS (dPDMS) (30 10 <sup>2</sup> $\times$ 0.25, 0.1)	60°C, 2 min // 120°C (30°C/min), 1 min // 250°C (25°C/min), 30 min	(X. T. Xie et al. 2020)
High performance anion exchange chromatography (HPAEC)					
<i>N. zanardini</i>	Alginate	L-guluronic and D-mannuronic acids in sodium alginate	CarboPac PA-1 (4 $\times$ 50) and CarboPac PA-1 (4 $\times$ 250)	A: 100 mM NaOH // B: 1 M NaOAc, 100 mM NaOH. Linear gradient 0–100% of B in A (60 min)	(Khajouei et al. 2018)
<i>C. racemosa</i> var <i>peltata</i>	Novel water-soluble SP	Mannose, galactose, glucose, galacturonic acid and glucuronic acid	CarboPac™ PA20 (150 $\times$ 3, 6.5)	n.s.	(Hao et al. 2019)
<i>U. ohnoi</i>	Ulvan	Rhamnose, glucuronic acid, iduronic acid and xylose	CarboPac PA-1 (4 $\times$ 250) equilibrated in 30 mM NaOH.	A: NaOH (30–10 mM, 0–25 min) // B: (10–100 mM, 25–30 min), 50 min // C: NaCH <sub>3</sub> COO, 0–500 mM, 30–50 min.	(Glasson et al. 2017)
<i>F. serratus</i> , <i>F. vesiculosus</i> , <i>F. spiralis</i> , <i>P. canaliculata</i> , <i>L. hyperborea</i> , <i>A. nodosum</i>	Laminarin	Linear $\beta$ -(1 $\rightarrow$ 3) glucans with intrachain $\beta$ -(1 $\rightarrow$ 6) branching in laminarin oligomers	CarboPac PA-100 (250 $\times$ 4) and PA-100 guard (50 $\times$ 4)	A: W // B: 100 mM NaOH // C: 1.0 M NaCH <sub>3</sub> COO, 100 mM NaOH	(Spicer et al. 2017)
HPLC-MALDI-TOFMS <i>F. evanescens</i>	Fucoidan	$\beta$ -(1 $\rightarrow$ 3)-linked 2-O-sulfonated fucose residues (1 to 4 monomers), 2-O- and 4-O- $\alpha$ -(1 $\rightarrow$ 4) sulfonated xylose and galactose residues.	Silasorb C18 (24 $\times$ 250)	W: Isocratic gradient	(Anastyuk et al. 2009)

**Abbreviations:** SP: Polysaccharide; T: temperature; E: elution; n.s. not specified; CPP: cyanopropylmethyl phenylmethyl polysiloxane; GI-F: Galactofucan; PDMS: dimethyl polysiloxane; dPDMS: diphenyl dimethyl polysiloxane.

\*Column order: Name - C atoms (phase) (L in mm $\times$ ID in mm, particle size in  $\mu$ m).

including sequencing, branching and linkage and profiling of oligosaccharides (Anastyuk et al. 2009). Advantages of MALDI over other ionization methods include its wide mass range, high sensitivity (fmol-pmol) and mass measurement accuracy. In addition, sample preparation and experiment are relatively easy to operate, and the technique is also tolerant of buffers, salts, and detergents.

## 5. Modification methods of polysaccharides from seaweeds: main challenges

Molecular modification of SP is a method commonly used to change the structure,  $M_w$ , and types, number, and positions of the substituent's groups of SP, with impacts on bioactivities. It can be carried out by enzymes or chemical reagents. In the enzymatic modification, the degradation of

SP occurs by catalysis with enzymes which is a highly efficient and environmentally friendly process. However, the use of this kind of modification is nowadays limited to the degradation of only certain type of SP. Perhaps the study of specific enzymes like transferase and synthase will boost the application of the enzyme technology (Li et al. 2016). So far, chemical modification is the most widely used method or algae SP to bring new biological activities by changing functional groups. Despite modifying the biological activities, it can also result in SP degradation, change  $M_w$  and improve solubility (L. Xie et al. 2020; Qiu et al. 2014; Duan et al. 2019; Safavi et al. 2019; Li et al. 2016). The main chemical modifications of SP include sulfation, carboxymethylation, phosphorylation and selenylation. The major activities and applications of these modifications are collected in Table 3.

### 5.1. Sulfation

In regard of SP, sulfation is a reaction in which a pure SP is mixed with a sulfated reactant that allows that these sulfate groups link side hydroxyl groups of the SP chain together. The degree of sulfate groups bonding to hydroxyl groups on SP is monitored by adjusting the molar ratio of reactants (L. Xie et al. 2020). The sulfation modification of algae SP is mainly based on chlorosulfonic acid pyridine methods in which sulfation is carried out by dissolving the pure SP in N,N-dimethylacetamide prior adding the sulfation reagent (a mixture of chlorosulfonic acid: pyridine), in different proportions, 1:4, 1:5, 1:6, 1:7 and 1:8 (v/v) (Zhao et al. 2019; Xiao et al. 2019). Afterwards, the mixture is heated at 60–70 °C for 2–3 h. After sulfation, the mixture is neutralized to pH 7 with a solution of sodium hydroxide, for example NaOH 20% and then, precipitated by adding ethanol before dialyzed against distilled water for 2–3 days. Using this protocol, Jim and coworkers performed the sulfation of SP from *S. thunbergii*, *S. japonica* and *E. prolifera* (Jin et al. 2020). Parallel, Xiao and coworkers sulfated eight SP from *S. pallidum* and observed that all SFP exhibited higher hypoglycemic activity than native SP and also four of them displayed the best antioxidant effect (Xiao et al. 2019). In this case, the substitution degree of algae SFP was in a range of 0.85–1.19. Some algae SFP have shown dramatically more significant antioxidant and antitumor activities following several methods like the superoxide radical, hydroxyl radical and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assays (Shao, Chen, and Sun 2014).

### 5.2. Carboxymethylation

The carboxymethylation modification consists in the incorporation of carboxymethyl groups into the SP chain. It is performed in two steps. First, the hydroxyl groups of SP react with sodium hydroxide to form the alkoxide groups and then, these groups react with monochloroacetic acid to generate the carboxymethyl groups by a  $SN_2$  reaction (Chakka and Zhou 2020). For example, Barros and colleagues performed carboxymethylation of ulvan from *U. lactuca* by dissolving the amount of 10 g of pure ulvan in 0.1 L of isopropanol before adding 0.05 L of sodium hydroxide (40%, w/w) at a constant flow. After that, the mixture was heating to 60 °C for 3 h (under nitrogen atmosphere) after the addition of 12 g of monochloroacetic acid (Barros et al. 2013). Afterwards, the pH was neutralized to 7 with glacial acetic acid after the addition of 8.5 mL of cold distilled water. Finally, the resultant SP was filtered, washed with methanol: water (70:30) and anhydrous methanol before dried. Using the same scheme, Duan and coworkers were carried out the carboxymethylation of fucoidan from *L. japonica* (Duan et al. 2019). Authors observed that carboxymethylation enhanced the antioxidant activity of fucoidan, so that it could be used as a natural preservative.

### 5.3. Phosphorylation

The phosphorylation modification is an esterification process in which the hydroxyl groups of the branched chain are

substituted by a phosphate group yielding a phosphorylated derivative (Chen et al. 2016). Common reagents for this modification are phosphoric acid, phosphoric anhydride, phosphorus trichloride and phosphates (disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium triphosphate, sodium trimetaphosphate, phosphorus oxychloride, sodium trimetaphosphate and polyphosphate) (Huang and Huang 2020). One of the most used phosphorylation methods in algae is the polyphosphoric acid-tributylamine-dimethyl formamide method. For example, Wang and colleagues were carried out the phosphorylation of low-molecular-weight SP from *E. linza* by dissolving 2 g of ulvan in 100 mL formamide and 15 mL tributylamine and then, it was added 6 g polyphosphoric acid (Z. Zhang et al. 2014). The mixture is usually stirred and then poured into ethanol. Precipitate is dissolved in water, dialyzed against distilled water and lyophilized to give phosphorylated SP. After this process, the physicochemical and biological properties of SP are altered, enhancing hydrocolloid properties.

### 5.4. Selenylation

Selenylation modification consists of the introduction of selenium into the polymeric chain of the SP. Since the insufficiency of natural seleno-polysaccharides, it is an effective measure to develop new selenium source and also, make the physiological and pharmacological function of selenium (Q. Wang et al. 2019). Selenylation highly improved the properties (antioxidant, anti-cancer, anti-diabetic, and immunomodulatory activities) respect to the native SP. Among SP-selenylation modification methods, nitric acid–sodium selenite ( $HNO_3$ - $Na_2SeO_3$ ) method is frequently used due to the simple reaction conditions, fast production and high selenium content of modifier (Qiu et al. 2014). As an example of this reaction, Ji and colleagues carried out the optimization of the synthesis of Seleno-SP in *S. fusiforme* by dissolving 1 g of  $Na_2SeO_3$  and 1 g of SP in 100 mL  $HNO_3$  (0.05%) (Ji et al. 2013). They fixed the optimum reaction time and temperature in 8 h and 71 °C, respectively. After the selenylation reaction, it was added  $Na_2CO_3$  to adjust pH to 5–6. In addition, it was shown that to include in the algae growth medium selenium in the form of sodium selenite ( $Na_2SeO_3$ ) at levels of 500 mg/L is a proper approach to incorporate the selenium molecule into their the structure and increase the antioxidant activities of algae SP (Sun et al. 2017).

## 6. Biological properties of polysaccharides from seaweeds

### 6.1. Anticoagulant

According to the World Health Organization (WHO), cardiovascular diseases are the first cause of human death worldwide. The formation of thrombosis is a major problem that, if not detected on time, it can result in serious hazards and ultimately, death (Owens and Mackman 2010). Currently, heparin is the main commercial antithrombotic agent. Nonetheless, it can cause several side effects, such as the development of thrombocytopenia, hemorrhagic effect,

ineffectiveness in congenital or acquired antithrombin deficiencies and incapacity to inhibit thrombin bound to fibrin. In addition, the use of heparin may increase the risk of pollution by animal pathogens, since it is obtained from pig intestine and bovine lungs (Paluck, Nguyen, and Maynard 2016). For this reason, many researchers are interested in finding new alternative sources to obtain substitute agents with anticoagulant features. In this sense, SFP from marine algae with anticoagulant and antithrombotic activities are being investigated (Table 4).

The anticoagulant activity can be determined by partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PT). PT is associated with extrinsic via, whereas the prolongation of APTT suggests inhibition of the intrinsic pathways of coagulant, and an increase in TT indicates the thrombin inhibition (Qin et al. 2020). For instance, arabinogalactan (AB) obtained from *C. linum* presented high anticoagulant activity in vivo (APTT = 200 s and TT = 60 s), comparable to the effects of heparin. In a similar manner, ulvan from *U. lactuca* has been demonstrated to inhibit intrinsic and extrinsic coagulation pathways (Reis et al. 2020).

Anticoagulant responses depend on: i) chemical structure of SP, ii)  $M_w$  and iii) specific sulfation patterns (Sudharsan et al. 2015). In addition, carboxyl groups may increase the anticoagulant activity by appropriate interactions with proteins involved in the coagulation cascade. A recent study suggested that the anticoagulant activity of *U. fasciata* ulvan depends on the amount of sulfate groups present in the original polymer and the content of carboxyl groups (de Carvalho et al. 2018). For example, showing longer times in the case of polycarboxylic ulvan (p-ulvan) compared to native ulvan (n-ulvan) when APTT, TT or PT were tested (Table 4).

Regarding  $M_w$ , generally, the higher  $M_w$ , the least anticoagulant activity. According to some authors, SFP with  $M_w > 850$  kDa, generally present low anticoagulant activity (Shanmugam and Mody 2000). However, other authors have found several polymers improved the anticoagulant activity the higher  $M_w$ . For example, *S. fusiforme* SFP with  $M_w$  227 kDa presented higher anticoagulant effects than other low  $M_w$  SFP (36 kDa) (Table 4). They suggest SFP present a suitable molecular structure for interacting with proteins involved in the coagulation cascade (Sun et al. 2018; Chandía and Matsuhira 2008).

The amount of sulfate may be an important factor which could affect in APTT and TT. For instance, it has been determined that the minimum sulfation degree from low  $M_w$  fucoidan extracts to exhibit anticoagulant activity must be over 20% (Ale, Mikkelsen, and Meyer 2011). Also, two different extracts of agar from *G. acerosa* with different sulfate content (I: 14.5%; II: 27.71%) were tested and it was found that fraction II showed higher anticoagulant activity (II: APTT = 71.1 s, heparin = 40.05 s) than I (APTT = 70.3 s, heparin = 141.3 s) (Table 4) (de Queiroz et al. 2014; Chagas et al. 2020). Results were similar in another study in which ulvan extracted from *U. conglobata* with high content of sulfate (35%) prolonged the value of APTT until 250 s using a concentration of 5  $\mu$ g/mL (Mao et al. 2006).

Regarding the antithrombotic activity, it can be assessed by different methods: thrombus formation (TF), thrombus weight (TW) and clot lytic rate (CLR). According to some authors, some SFP present high antithrombotic activity although they have low anticoagulant activity. For instance, agar may inhibit thromboplastin-induced thrombus formation in rats as agar from *G. acerosa* (1 mg/kg) was demonstrated to reduce TF in 80% whereas heparin (0.05 mg/kg) achieved 65%. However, results from anticoagulant activity were not so high (Table 4) (Chagas et al. 2020), in accordance with other works (Quinderé et al. 2014). Nonetheless, some SFP display significant antithrombotic and anticoagulant responses, for example, sulfated arabino-galactans from the green alga *C. linum* presented an important antithrombotic activity in vitro and high anticoagulant responses in vitro and in vivo (Qin et al. 2020). Moreover, carrageenan possesses important effects on platelet aggregation. In the same study, galactan-SFP (100  $\mu$ g/ $\mu$ L) reduced 32%, while heparin (100  $\mu$ g/ $\mu$ L) only reduced 15%. In another study, carrageenan from *T. crinitus* (100  $\mu$ g/ $\mu$ L) reduced 55% of platelet aggregation (Byankina Barabanova et al. 2013).

## 6.2. Antioxidant

In cellular respiration, oxidizing agents called free radicals or reactive oxygen species (ROS) get accumulated (Chatterjee 2016). So, the use of antioxidants could counteract the imbalance of the oxidant/antioxidant ratio (Circu and Aw 2010). These antioxidant agents can exert their function directly by donating an electron or by breaking the oxidation chain (Filomeni, De Zio, and Cecconi 2015). In this regard, SP are accounted for significant antioxidant properties. For instance, ulvans have been reported as one of the most potent antioxidant SP. A study used a SFP extract of *U. intestinals* (5 mg/mL) with antioxidant activity that was able to remove 74% of 2,2-diphenyl-picryl-hydrazyl radical (DPPH) radicals and showed a reducing power of around 88% (Rahimi, Tabarsa, and Rezaei 2016) (Table 4). However, not all SFP have high antioxidant activities, since several factors such as  $M_w$ , monomer residue composition, degree of sulfation and sulfate substitution position can significantly alter their antioxidant activity (Zhong et al. 2019). The higher  $M_w$  of SP can lead to a reduced solubility, which complicates their penetration into cells to perform functions. Therefore, low  $M_w$  SP present higher antioxidant activity (Choi and Kim 2013). In this sense, the degradation of SP by enzymatic methods can be a good choice to improve their antioxidant responses, since the decrease of  $M_w$  of the SP could lead to the exposure of more functional groups. A study concluded the use of pectinase enzyme was able to degrade the SFP from *P. haitanensis* (Li et al. 2020). Other authors confirmed glucoamylase enzyme was able to degrade SP from *E. proliferata* (Xu et al. 2016). In addition, a new study used together pectinase and glucoamylase to degrade the fucoidan from *S. fusiforme*. In this study, enzymatically degraded *S. fusiforme* SP showed higher antioxidant activity than the natural *S. fusiforme* fucoidan (Wen et al. 2021) (Table 4).



Table 4. Examples of sulfated polysaccharides (SP) obtained from marine algae with relevant biological activities.

Species	SP	Assay	Activity // Control	Ref.
Anticoagulant				
<i>G. acerosa</i>	Agar	APTT PAI TF* BT APTT	Agar: 1 mg/mL, 70.3 s // (+) HSMW: 0.001 mg/mL, 141.3 s Agar: 0.1 mg/mL, 32% compared to ADP Agar*: 1 mg/kg, 80% // (+) HSMW*: 0.05 mg/kg, 65% Agar: 1 mg/kg, 2627s // (+) HSMW: 0.05 mg/kg, 7300s AB: 200 µg/mL, >200 s // (+) Heparin: 10 µg/mL, >200 s AB*: 30 mg/kg, 200 s // (+) Heparin*: 0.5 mg/kg, 80 s AB: 200 µg/mL, 85.1 s // (+) Heparin: 10 µg/mL, >120 s AB*: 30 mg/kg, 60 s // (+) Heparin*: 0.5 mg/kg, 60 s AB: 200 µg/mL, 20.5 s // (+) Heparin: 50 µg/mL, >120 s AB: 200 µg/mL, 143.7 mg/dL // (+) Heparin: 25 µg/mL, <80 g/dL AB: 30 mg/mL, 47.6% // (+) Urokinase: 100 U/mL, 34.1% F50UL: 1 µg/mL // (+) Heparin: 0.025 µg/mL, 3x F50UL: 1 µg/mL // (+) Heparin: 0.025 µg/mL, -1.5x F50UL*: 20 µg/g, 56% reduction // (+) Heparin: 1.5 µg/g, 92% reduction n-Ulvan: 150 µg/mL, 45.6 s; p-Ulvan: 150 µg/mL, 222.0 s // (+) Heparin: 10 µg/mL, >300 s n-Ulvan: 150 µg/mL, 21.8 s; p-Ulvan: 150 µg/mL, 28.5 s // (+) Heparin: 20 µg/mL, >100 s n-Ulvan: 150 µg/mL, 37.1 s; p-Ulvan: 150 µg/mL, 42.2 s // (+) Heparin: 10 µg/mL, >100 s SFP: 32 µg/mL, 203.5 s; LSFP-4: 32 µg/mL, 60 s SFP: 32 µg/mL, 66 s; LSFP-4: 32 µg/mL, 45 s SFP: 32 µg/mL, 53 s; LSFP-4: 32 µg/mL, 44 s	(Chagas et al. 2020)  (Qin et al. 2020)  (Reis et al. 2020)  (de Carvalho et al. 2018)  (Sun et al. 2018)
<i>U. lactuca</i>	F50UL (n.s.)	PT APTT PT TW*		(Rahimi, Tabarsa, and Rezaei 2016)
<i>U. fasciata</i>	n-Ulvan, p-Ulvan	DPPH RP	5 mg/mL, 74% 5 mg/mL, 88 % // (+) Ascorbic acid 0.01 mg/mL	(Saravana et al. 2016)
<i>S. fusiforme</i>	n.s.	DPPH ABTS HO <sup>-</sup> O <sub>2</sub> <sup>-</sup> DPPH RP	CF: 0.1% NaOH, 41.88% // (+) Trolox: 71.26% CF: 0.1% formic acid, 60 % // (+) Trolox: 95% ESFP: IC <sub>50</sub> = 4.780, SFP: IC <sub>50</sub> = 6.82 ESFP: IC <sub>50</sub> = 0.412, SFP: IC <sub>50</sub> = 0.723 ESFP: IC <sub>50</sub> = 0.530, SFP: IC <sub>50</sub> = 0.768 ESFP: 5 mg/mL, 40%, SFP: 5 mg/mL, 30%	(Wen et al. 2021)
<i>P. pavonica</i>	Alg (<14kDa)	DPPH RP	Alg: 1 mg/mL, 77.6% // (+) Ascorbic acid: 1 mg/mL, 96% Alg: IC <sub>50</sub> = 0.4 // (+) Ascorbic acid: 1 mg/mL, 96%	(Arunkumar et al. 2021)
<i>A. rigida</i>	n.s.	DPPH ABTS DPPH	1 mg/mL, 58.24% 1 mg/mL, 52.03%	(Gopu and Selvam 2020)
<i>P. hornemannii</i>	Carr (<14 kDa)	DPPH	Carr: 1 mg/mL, 28% // (+) Ascorbic acid: 1 mg/mL, 96%	(Arunkumar et al. 2021)
<i>S. hypnoides</i>	Agar (<14kDa)		Agar: 1 mg/mL, 38% // (+) Ascorbic acid: 1 mg/mL, 96%	
<i>A. taxiformis</i>			Agar: 1 mg/mL, 31% // (+) Ascorbic acid: 1 mg/mL, 96%	
<i>C. clavulatum</i>			Agar: 1 mg/mL, 28% // (+) Ascorbic acid: 1 mg/mL, 96%	
Antitumor				
<i>C. prolifera</i>	n.s.	MTT	HeLa, ICSP (0.1 mg/L) = 57.1% HeLa, ICSP (0.1 mg/L) = 61.1% HeLa, ICSP (2.0 mg/L) = 61.0% HeLa, ICSP (2.0 mg/L) = 58.4%	(Costa et al. 2010)
<i>S. filipendula</i>			PANC-1, IC <sub>50</sub> (80–100 µg/mL) = 20 µg/mL	
<i>D. deliculata</i>			SPC-A-1, WR (40 mg/kg SFP) = 50%	(Etman, Abdallah, and Ehnaggar 2020)
<i>D. menstruallis</i>	FDC/Lf	MTT	HUVEC, AR (300 mg/mL SFP) = 40%	(Chen et al. 2017)
<i>U. pinnatifida</i>	SFP	CCK-8 CCK-8 WST-1	AGS (500 µg/mL) = 75.4 % HeLa (500 µg/mL) = < 40%	(Karnjanapratum and You 2011)
<i>S. fusiforme</i>	n.s.	WST-1	U937, ICSP (100 µg/mL) = 90%	(Teruya, Konishi, and Uechi 2007)
<i>M. nitidum</i>		MTT	HeLa, IC <sub>50</sub> (<0.1 mg/mL) = 1.059 µg/mL	(Arunkumar et al. 2021)
<i>C. okamuraanus</i>	S-fucoidan	MTT	BCCL, IC <sub>50</sub> = 40 µg/mL	(Gopu and Selvam 2020)
<i>P.pavonica</i>	Alginat	MTT		
<i>A. rigida</i>	n.s.	MTT		
Anti-inflammatory				

<i>S. swartzii</i>	Fucoidan	NO-PIP LPS induced RAW 264.7	RAW 264.7, <40% compared to LPS PGE <sub>2</sub> = < 50% compared to control TNF-α = < 70% compared to control IL-1β = < 50% compared to control IL-6 = < 55% compared to control PEV (50 mg dose) = 52% reduction 0.21 mm // (+) Zymosan: 0.62 mm 23.8 U/mL // (+) Zymosan: 59.5 U/mL 1857 pg/mL // (+) Zymosan: 4776 pg/mL IL-1β = 129.27 pg/mL TNF-α = < 25% compared to control SIGA = < 39.25% compared to control Mucin2 = < 15.83% compared to control	(Jayawardena, Asanka Sanjeeewa, et al. 2020)  (Manikandan et al. 2020) (Oliveira et al. 2020)  (Sun et al. 2020)
<i>T. decurrens</i> <i>G. caudata</i>	Fucoidan n.s.	PEV Edema* MPO* IL-1β* LPS induced HT29		(Manikandan et al. 2020) (Oliveira et al. 2020)
<i>C. lentillifera</i>	GLGP4			(Sun et al. 2020)
Antimicrobial <i>F. vesiculosus</i>	Fucoidan	DM	MIC ( <i>Escherichia coli</i> , <i>Staphylococcus epidermidis</i> , <i>S. aureus</i> and <i>Bacillus licheniformis</i> ) = 4 mg/mL	(Ayrapetyan et al. 2021)
<i>L. japonica</i>	Fucoidan	DM	<i>S. aureus</i> (MIC) = 8 mg/mL, <i>S. aureus</i> (MBC) = 12.5 mg/mL <i>E. coli</i> (MIC) = 6.25 mg/mL, <i>E. coli</i> (MBC) = 10 mg/mL <i>Pasteurella multocida</i> (MIC) = 0.156–0.391 mg/mL	(M. Liu et al. 2017)
<i>U. armoricana</i>	Ulvan	DM	<i>Mannheimia haemolytica</i> (MIC) = 0.391 mg/mL <i>Erysipelothrix rhusiopathiae</i> (MIC) = 3.125 mg/mL <i>S. aureus</i> (MIC) = 3.125 mg/mL <i>Streptococcus suis</i> (MIC) = 6.25 mg/mL	(Berri et al. 2016)
Antiviral <i>U. pertusa</i> <i>S. lomentaria</i>	Ulvan Fucoidan (GI-F)	MTT, GFP-FI MTT, Vero cells	MTT: < 40.75% (U-F <sub>0</sub> ), GFP-FI: < 40.13% (U-F <sub>1</sub> ) HSV-1, IC <sub>50</sub> = 0.76 μg/mL HSV-2, IC <sub>50</sub> = 1.34 μg/mL	(Chi et al. 2020) (Ponce et al. 2019)

Abbreviations: HSMW: Heparin sodium of high molecular weight; APTT: Activated partial thromboplastin time; PAI: Platelet aggregation inhibition; ADP: adenosine diphosphate; TF: Thrombus formation; BT: bleeding time; TT: thrombin time; FIB: Fibrinogen content assay; PT: prothrombin time; CLR: Clot lytic rate; F50UL: sulfated polysaccharide with 50 mL acetone; TW: thrombus weight; DPPH: 2,2-diphenyl-picryl-hydrazyl radical; RP: reducing power; Trolox: 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; CF: crude fucoidan; ESFP: enzymatically degraded *S. fusiforme* polysaccharide; Alg: alginate; Carr: carrageenan; p-Ulvan: poly-carboxyl ulvans, n-Ulvan: native ulvans; HO: hydroxyl radical; O<sub>2</sub>: superoxide anion radical, AB: Arabinogalactan; WR: weight reduction; ICP: Inhibition of cell proliferation; NO-PIP: Nitric Oxide Production Inhibition Potential; S-fucoidan: oversulfated fucoidan; FDC/Lf: Polysaccharide/protein hybrid nanoparticles; SPC-A-1: human lung adenocarcinoma cells; AR: apoptosis rate; WST-1: (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)]-2H-5-tetrazolol-1,3-benzene disulfonate); AGS: human gastric carcinoma cell; Hela: human cervical cancer cell; BCCL: breast cancer cell lines; LPS: lipopolysaccharide; MPO: Myeloperoxidase colorimetric activity; PEV: paw edema volume; HT29: human colon cancer cell line; MPO = myeloperoxidase activity; DM: Diffusion method; GLGP4: xylogalactomanan; MIC: Minimum inhibitory concentration; MBC: Minimum bactericidal concentration; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; VSV: vesicular stomatitis virus; GFP-FI: green fluorescence protein - fluorescence intensity; RBV: Ribavirin; GI-F: Galactofucan. n.s. not specified; \* in vivo experiments.

On the other hand, many studies described that degraded or chemically modified SP improved their antioxidant activities compared to the native SP. For example, a study assessing several red algae species and found that the brown algae *P. pavonica* showed higher antioxidant activity than several red algae (Table 4). This study suggest that the content of sulfate is not the main parameter that affects antioxidant response, but the type of monomers also play an important role (Arunkumar et al. 2021). Besides, different investigations have concluded high levels of uronic acid, protein and low  $M_w$  can lead to stronger DPPH and ABTS scavenging activity (Chen et al. 2020). For example, the SFP extracted from red algae *A. rigida*, which contained major amounts of uronic acid and protein, showed high capacity of removing DPPH and ABTS radicals (Gopu and Selvam 2020) (Table 4).

### 6.3. Antitumor

Polysaccharides anticancer efficacy was first described in a 1946 study, in which it was discovered that some bacterial polysaccharides could weaken tumor development in cancer patients (Nauts, Swift, and Coley 1946). These compounds can inhibit tumor growth through four mechanisms: i) prevention strategy by direct consumption of active preparations; ii) the inhibition of tumor metastasis; iii) induction of tumor cell apoptosis and iv) stimulation of the immune system (Zong, Cao, and Wang 2012; Costa et al. 2010).

As previously stated, sulfate groups and  $M_w$  of SFP also influence the anticancer activities. Authors suggested the anticancer activities of fucoidan and ulvan depend on the sulfate content (Karnjanapratum and You 2011). The green seaweed *M. nitidum* was used to extract SFP and evaluate anticancer effect against HeLa and AGS cell lines. The results concluded that native SFP (500 µg/mL) of *M. nitidum* showed inhibition of cell proliferation of 75.4% on AGS cells, while less than 40% on HeLa cells (Table 4). The results may be due to the content of sulfate (13.5%) and  $M_w$  ( $158 \times 10^3$  g/mol) (Karnjanapratum and You 2011). Another study performed with four species of algae (*C. prolifera*, *S. filipendula*, *D. delicatula* and *D. menziesii*) showed there was a positive correlation between the sulfate content and the inhibition of HeLa cell proliferation. *S. filipendula* showed the greater inhibition with 61.1% at 0.1 mg/L concentration (Costa et al. 2010) (Table 4). The structure feature of SP is fundamental for their antiproliferative activity. Similar results were shown in a study where oversulfated fucoidan (sulfate content of 32.8%) inhibited the proliferation of U937 cells (up to 90% at 100 µg/mL), whereas native fucoidan (sulfate content of 13.5%) did not show significant inhibition (Teruya, Konishi, and Uechi 2007) (Table 4). Another study showed that fucoidan of *S. fusiforme* was able to inhibit the proliferation of tumor cells SPC-A-1, promote the apoptosis and cell cycle arrest of HUVECs umbilical cord cell line and to inhibit endothelial growth factor VEGF-A/VEGFR2 expression (Chen et al. 2017). Also, fucoidan from *P. pavonica* reduced SPC-A-1 tumor weight up to 50% at 40 mg/kg and increased

apoptosis rates up to 40% with 300 mg/mL. In addition, this fucoidan extract showed inhibition against the proliferation of HeLa cells ( $IC_{50} = 1.059$  µg/mL) (Arunkumar et al. 2021), whereas SP obtained from *A. rigida* had significant anticancer activity against breast cancer BCCL cells ( $IC_{50} = 40$  µg/mL) (Gopu and Selvam 2020). In a recent study exploring the use of fucoidan nanoparticles, it was reported that found their  $IC_{50}$  (20 µg/mL) against PANC-1 cells was 2.3 folds lower than fucoidan extracts ( $IC_{50} = 53$  µg/mL) (Table 4). As such, the use of novel technologies incorporating SP may prove a suitable technology to enhance these molecules properties (Etman, Abdallah, and Elnaggar 2020).

### 6.4. Immunomodulating and anti-inflammatory

Inflammation is a defense mechanism involved in physiological and pathologic immune system responses. It consists on the liberation of many inflammatory mediators (cytokines, chemokines and reactive oxygen/nitrogen intermediates) triggering this process. The normal process of inflammation promotes the elimination of harmful stimuli and induces wound healing. However, the inflammation process can be altered by many factors and result in dysregulated inflammation, causing unusual increased liberation of inflammatory mediators. This can lead to develop other chronic diseases such as allergies, rheumatoid arthritis, Crohn's disease, type II diabetes and Alzheimer's disease, among many others (Gupta et al. 2018). Hence, both industry and academy have focused on finding suitable molecules to modulate or suppress inflammation effects. Therefore, SP have gained attention for their described anti-inflammatory properties (Fernando, Nah, and Jeon 2016). For example, agar extracted from *G. caudata* was administered (3–30 mg/kg) to mice with induced arthritis, showing a significant reduction of edema and hypernociception (Table 4) (Oliveira et al. 2020). Fucoidan is also reported to be an effective anti-inflammatory molecule. However, being highly heterogeneous in its structure and composition, the extent and effectiveness of its anti-inflammatory properties may be variable. A study showed a purified fucoidan fraction from *S. swartzii* inhibited inflammatory mediators such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), nitric oxide (NO), and pro-inflammatory cytokines (Jayawardena, Asanka Sanjeewa, et al. 2020). Another study concluded that an isolated fucoidan from *T. decurrens* could reduce the expression of interleukin 1β (IL-1β), COX-2 and matrix metalloproteinase 9 (MMP-9) as well as anti-inflammatory activity against lipopolysaccharide (LPS) induced IC-21 macrophages (Table 4) (Manikandan et al. 2020).

Furthermore, sulfation degree of the SP molecule can affect anti-inflammatory activity. Several studies demonstrated the higher sulfate content, the better anti-inflammatory responses. For example, a purified fucoidan fraction with the highest sulfate content could inhibit to a higher extent the production of inflammatory mediators and reduce the inflammatory effect under LPS stimulated conditions

(Jayawardena et al. 2019; Sun et al. 2020). The composition of monosaccharides is also another important parameter that influences anti-inflammatory responses. Several studies found high anti-inflammatory activities in those SFP rich in fucose-rich fucoidan (Sanjeewa et al. 2018; Cui et al. 2019; Li and Shah 2016). For example, SFP from *C. lentilifera*, which contained galactose (43.23%), mannose (38.73%) and xylose (18.04%), presented important anti-inflammatory responses (Table 4) (Sun et al. 2020).

### 6.5. Antimicrobial, antiviral and antiparasitic

Recently, different problems regarding the resistance of bacteria to drugs have increased. Therefore, many industries have been interested in the antimicrobial activities that SFP from seaweed can exert. For this purpose, some determinations such as the minimum inhibition concentration (MIC) or the minimum bactericidal concentration (MBC) are employed (Table 4).

Also, some factors such as sulfation degree, uronic acid level or  $M_w$  can affect SFP antimicrobial properties. For example, fucoidan was extracted from five different brown algae (*S. fusiforme*, *K. crassifolia*, *L. japonica*, *S. honeri* and *U. pinnatifida*) but only *U. pinnatifida* (7.8%) and *K. crassifolia* (8.6%) exhibited antimicrobial activity. In addition, in this study, two samples of commercial fucoidan from *F. vesiculosus* had different sulfate content (14% and 7.5%) and only the one with a high sulfate degree showed prominent antimicrobial activity (Jun et al. 2018). In the case of uronic acid level, its role is still unclear. Fucoidan from *L. japonica* was used to analyze its antimicrobial activity and the fraction which had the highest uronic acid and sulfate content, exhibited the highest antimicrobial activity (M. Liu et al. 2017). Similar results were reported in a study where the fucoidan with higher sulfate and uronic acid content showed a major antimicrobial activity degree than purified fucoidan (Ayrapetyan et al. 2021). Nevertheless, (Ashayerizadeh, Dastar, and Pourashouri 2020) concluded that a fraction of *S. tenerrimum* with less uronic acid content showed the least antimicrobial activity. At last,  $M_w$  role in antimicrobial activity of SFP is not very clear. For example, a study concluded that SFP with  $M_w < 6$  kDa showed the highest antimicrobial activity. However, another study showed the fucoidan extract with  $M_w$  of 735 kDa showed higher antibacterial activity than extract with 343.8 kDa (M. Liu et al. 2017).

In addition, SFP antiviral activities have been also explored. For example,  $\iota$ -carrageenan has antiviral activity against respiratory viruses (Eccles et al. 2015). In this case, Ghosh et al. (2009) established the following patrons that affect the antiviral activity of SP: i) degree of sulfation: generally, the higher it is, the better antiviral activity; ii) specific positioning of sulfates; iii)  $M_w$ : generally, the higher  $M_w$ , the better antiviral effect. However, low  $M_w$  SP can display a significant antiviral activity when its degree of sulfation is great, and a minimum chain length and they can inhibit the propagation of virus more efficiently.

An example of SFP with antiviral activity against human and avian influenza viruses by suppressing the viral

multiplication process are ulvans (Ivanova et al. 1994). In a study, ulvan lyase was used for assisted structural analysis of ulvan from *U. pertusa*. Results of this study showed ulvan fractions with high  $M_w$  (U-FO and U-F1) possessed higher antiviral activity than those with low  $M_w$ . Concretely, U-FO and U-F1 could reduce the infection and replication of vesicular stomatitis virus (VSV) (Chi et al. 2020) (Table 4). These results are in accordance to  $M_w$  pattern. Similar results were found in another study (H. Liu et al. 2005). It is thought that long chains have more opportunities to interact with the viral attachment proteins and could cross-link with the virus (Ghosh et al. 2009). In another study, a galactofucan showed antiviral activity against Herpes simplex virus (HSV). Also, a positive correlation between antiviral activity and sulfate content, and a negative correlation with uronic acid content was predicted (Ponce et al. 2019).

### 6.6. Anti-hyperlipidemic

Hyperlipidemia can be considered as a lipid metabolic imbalance issue, which consist of high levels of free fatty acids, apolipoprotein B (apo B), total cholesterol (TC), triglycerides (TG) and low-density lipoprotein (LDL), together with low levels of high-density lipoprotein (HDL). Many cardiovascular and cerebrovascular diseases are originated by lipid mechanism disorder. Therefore, researches are focused in finding and obtaining polysaccharides with anti-hyperlipidemic activities from seaweed (Knouff et al. 2004; Taghizadeh et al. 2019).

Recently, several studies showed many polysaccharides from marine algae presented excellent anti-hyperlipidemic properties. Concretely, the green alga *U. pertusa*, was employed in several studies to assess hypolipidemic activity of ulvan (W. Li et al. 2018; Jiang et al. 2020). In addition, there is scientific evidence that conclude structure modifications of polysaccharides can improve the anti-hyperlipidemic activity. In particular, SP with high sulfate content showed higher anti-hyperlipidemic responses than native ulvan (H. Qi et al. 2012). Another study used modified phosphorylated ulvans in mice with hyperlipidemia and it was demonstrated to decrease TC, TG and LDL levels and increase HDL levels with even better anti-hyperlipidemic responses than nicotinic acid used as positive control (Jiang et al. 2020).

## 7. Final remarks and future perspectives

This review explores the use of main SP, ulvan, alginates, fucoidan, laminarin, agar, carrageenans and floridean starch in terms of nutritional properties, evidence-based health benefits, and their obtaining from algae by emerging extraction techniques. SP, especially SFP, are molecules of high potential value, not present in terrestrial plants. Besides shown antioxidant, anticancer, antimicrobial, and antiviral activities, they are also associated to various health benefits including prebiotic effects and cholesterol excretion. The revised literature shows macroalgae constitute a cost-effective and useful source for recovering SP with high potential on

innovative biomedical, functional food and technological applications.

In the biomedical field, several applications of SP have been proposed, like the improvement of drugs' formulation, particles for delivery systems and even in tissue engineering (Cosenza et al. 2017). In this field, it seems that one of the most promising molecules is fucoidan. This molecule present applications in nanomedicine as imaging agents and drug carriers due to their intrinsic properties (Chollet et al. 2016). However, to ensure a progress in this field, still there is a need for reproducible and well characterized chemical composition. Fucoidan fractions can vary considerably according to the natural source. These molecules can represent an enormous opportunity for biomedical market if alternative methods to produce SP with consistent properties can be developed, since these properties critically influence the biological activities of the compound (Liang et al. 2014). In addition, it is important to research on the mechanism of action of SFP since it is usual to observed contradicting activities. As stated, this difference in the biological effects can be due to difference in  $M_w$  and degree of branching among molecules. An understanding of the mechanism of action is key to the successful use of a SP in nanomedicine field.

In food industry, carrageenan, alginates, and agar are the most widely used SP, due to their due to their rheological properties. Agar is the most utilized in confectionary products like donuts and cakes to maintain the hydration of the products as well as in fruit jelly confections and in the meat industry as a fat reducing agent. Alginates are becoming popular for encapsulation and delivery systems of probiotics to the large intestine and colon as well as in vegetable industries for their ability to prevent the growth of microorganisms. Moreover, carrageenan is used to improve the stability and texture of different products and is also gaining interest in the improvement of formulation of gluten-free, vegetarian and vegan foods (Alba and Kontogiorgos 2018; Cosenza et al. 2017). Apart from food industry, some SP are also used in cosmetic formulations, like shampoos, moisturizers or dental-care products (Lourenço-Lopes et al. 2020).

Although the wide use of SP in industrial applications and functional foods, several issues must still be overcome. Some uses of SP are limited due to their low solubility in neutral pH. In this sense, chemical modification of their structure is a useful process to improve their properties, and thus to enlarge the field of their potential applications. In recent years, enzymatic modification of SP seems to be a solid alternative to toxic chemical approaches. The enzymatic process include polymer  $M_w$  reduction, transesterification, oxidation, glycosylation and ester formation (Cheng and Gu 2012). Enzyme modification is a promising tool for obtaining more defined targeted biomolecules, although some enzymes can be expensive. Another approach that could be employed to enhance the biological properties and the potential applications of SP is the complexation with other molecules, like polyphenols (Li et al. 2021).

To sum up, this review focused on structural differences between the most relevant algae SFP, available modification methods, as well as a summary of their biological activities.

In addition, novel methods which are being developed to facilitate and improve the extraction processes of SP are also described since one issue to deal with is the need to reduce the use of chemical reagents and optimize operations to improve yields (Karaki et al. 2016). In this context, more research is needed on the extraction and purification processes of the SP.

#### Macroalgae species

Chlorophyta: *Caulerpa* (C.): *C. lentillifera*, *C. proliferata*, *C. racemosa*. *Chaetomorpha* (C.): *C. linum*. *Codium* (C.): *C. fragile*. *Enteromorpha* (E.): *E. compressa*, *E. intestinalis*, *E. linza*, *E. proliferata*. *Monostroma* (M.): *M. nitidum*. *Ulothrix* (U.): *U. flacca*. *Ulva* (U.): *U. armoricana*, *U. congoblata*, *U. fasciata*, *U. intestinalis*, *U. lactuca*, *U. ohnoi*, *U. pertusa*, *U. proliferata*, *U. rigida*, *U. rotundata*.

Rhodophyta: *Amphiroa* (A.): *A. rigida*. *Asparagopsis* (A.): *A. taxiformis*. *Centroceras* (C.): *C. clavulatum*. *Chondrus* (C.): *C. armatus*. *Euclima* (E.): *E. cottoni*, *E. denticulatum*, *E. galetinae*. *Furcellaria* (F.): *F. lumbricalis*. *Gelidiella* (G.): *G. acerosa*. *Gelidium* (G.): *G. amansii*, *G. corneum*. *Gigartina* (G.): *G. skottsbergii*. *Gracilaria* (G.): *G. birdiae*, *G. blodgettii*, *G. caudata*, *G. chouae*, *G. gracilis*, *G. lemaneiformis*. *Gracilariopsis* (G.): *G. lemaneiformis*, *G. persica*. *Gelidium* (G.): *G. robustum*, *G. amansii*. *Hydropuntia* (H.): *H. cornea*. *Hypnea* (H.): *H. musciformis*. *Kappaphycus* (K.): *K. alvarezii*. *Mastocarpus* (M.): *M. pacificus*. *Porphyra* (P.): *P. boryana*, *P. haitanensis*. *Portieria* (P.): *P. hornemannii*. *Rhodymenia* (R.): *R. pseudopalmata*. *Sarcodia* (S.): *S. ceylonensis*. *Spyridia* (S.): *S. hypnoides*. *Tichocarpus* (T.): *T. crinitus*

Phaeophyta: *Alaria* (A.): *A. angusta*. *Ascophyllum* (A.): *A. nodosum*. *Bifurcaria* (B.): *B. bifurcata*. *Cladosiphon* (C.): *C. okamuranus*. *Coccolophora* (C.): *C. langsdorffii*. *Cystoseira* (C.): *C. compressa*. *Dictyopteris* (D.): *D. membranacea*. *Dictyosiphon* (D.): *D. foeniculaceus*. *Dictyota* (D.): *D. deliculata*, *D. menstrualis*. *Durvillaea* (D.): *D. antarctica*. *Eisenia* (E.): *E. bicyclis*. *Fucus* (F.): *F. distichus*, *F. evanescens*, *F. serratus*, *F. spiralis*, *F. vesiculosus*. *Kjellmaniella* (K.): *K. crassifolia*. *Laminaria* (L.): *L. digitata*, *L. hyperborea*, *L. japonica*. *Macrocystis* (M.): *M. pyrifera*. *Nizamuddinina* (N.): *N. zanzardinii*. *Padina* (P.): *P. pavonica*. *Pelvetia* (P.): *P. canaliculata*. *Saccharina* (S.): *S. japonica*, *S. latissima*, *S. longicuris*. *Sargassum* (S.): *S. angustifolium*, *S. fluitans*, *S. filipendula*, *S. fusiforme*, *S. fulvellum*, *S. honeri*, *S. muticum*, *S. pallidum*, *S. stenophyllum*, *S. siliquosum*, *S. swartzii*, *S. tenerrimum*, *S. thunbergii*. *Scytosiphon* (S.): *S. lomentaria*. *Silvetia* (S.): *S. compressa*. *Solieria* (S.): *S. chordalis*, *S. filiformis*. *Spyridia* (S.): *S. filamentosa*. *Turbinaria* (T.): *T. conoides*, *T. decurrens*, *T. ornata*. *Undaria* (U.): *U. pinnafitida*.

**Abbreviations General Terms:** AB: Arabinogalactan; ABTS: 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ; apo B: Apolipoprotein B; APTT: Activated Partial Thromboplastin Time; CF: Crude Fucoidan; CLR: Clot Lytic Rate; COX-2: Cyclooxygenase-2; DPPH: 2,2-diphenyl-picryl-hydrazyl radical; DW: Dry weight; ESFP: Enzymatically degraded *Sargassum fusciforme* polysaccharides; HDL: High-Density Lipoprotein; HSV: Herpes simplex virus; IL-1 $\beta$ : Interleukin 1 $\beta$ ; iNOS: inducible nitric oxide synthase; LDL: Low-Density Lipoprotein; LPS: Lipopolysaccharide;  $M_w$ : Molecular Weight; MBC: Minimum Bactericidal Concentration; MIC: Minimum Inhibition Concentration; MMP-9: Matrix metalloproteinase 9; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NO: Nitric Oxide; n-ulvan: Native ulvan; p-ulvan: Polycarboxylic ulvan;

PT: Prothrombin time; ROS: Reactive oxygen species; SFP: Sulfated Polysaccharides; SP: Seaweed Polysaccharides; TC: Total Cholesterol; TF: Thrombus Formation; TG: Triglycerides; TT: Thrombin Time; TW: Thrombus Weight; VSV: Vesicular Stomatitis Virus; WHO: World Health Organization; Extraction Techniques: EAE: Enzyme-assisted extraction; MAE: Microwave-assisted extraction; PLE: Pressurized liquid extraction; UAE: Ultrasound-assisted extraction; SC-CO<sub>2</sub>: Supercritical carbon dioxide extraction; Identification Techniques: FTIR: Fourier transform infrared spectroscopy; GC-MS: Gas chromatography coupled to mass spectrometry; HPLC: High performance liquid chromatography; MS: Mass spectrometry; MALDI: Matrix Assisted Laser Desorption/Ionization; MALLS: Multi-angle laser light scattering; NMR: Nuclear magnetic resonance; TOF: Time of flight












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The authors declare no conflict of interest.

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