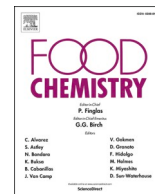




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Beneficial effects of seaweed-derived dietary fiber: Highlights of the sulfated polysaccharides

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ABSTRACT

Seaweeds and their derivatives are important bioresources of natural bioactive compounds. Nutritional studies indicate that dietary fibers derived from seaweeds have great beneficial potentials in human health and can be developed as functional food. Moreover, sulfated polysaccharides are more likely to be the main bioactive components which are widely distributed in various species of seaweeds including *Phaeophyceae*, *Rhodophyceae* and *Chlorophyceae*. The catabolism by gut microbiota of the seaweeds-derived dietary fibers (DFs) may be one of the pivotal pathways of their physiological functions. Therefore, in this review, we summarized the latest results of the physiological characteristics of seaweed-derived dietary fiber and highlighted the roles of sulfated polysaccharides in the potential regulatory mechanisms against disorders. Meanwhile, the effects of different types of seaweed-derived dietary fiber on gut microbiota were discussed. The analysis of the structure–function correlations and gut microbiota related mechanisms and will contribute to further better applications in food and biotherapeutics.

1. Introduction

Dietary fiber (DF) is a group of edible carbohydrate polymers that is resistant to the digestive enzymes and is non-absorbable in the small intestine, thus can directly interact with gut microbes and lead to the productions of beneficial metabolites such as short-chain fatty acids (SCFAs) (Makki, Deehan, Walter, & Backhed, 2018). Numerous studies have suggested that DFs confer favorable benefits on host health such as maintaining metabolic homeostasis, ameliorating inflammation and preventing gut microbiota from dysbiosis (Holscher, 2017). Seaweeds enriched with DFs have long been consumed as traditional foods in Asian countries. And seaweed-derived DFs displayed multiple beneficial properties including anticoagulant, anti-inflammatory, antioxidant, anticarcinogenic, and antiviral activities (Tanna & Mishra, 2019) which may vary greatly due to different types and sources. Thus, seaweeds-derived DFs have been widely applied in food, pharmaceuticals, and cosmetics.

Sulfated polysaccharides (SPs) are considered as characteristic group in seaweed-derived DF which are rarely to be found in the terrestrial plant. SPs are composed of a cluster of complex carbohydrate macromolecules with different proportions of sulfate groups. Besides

seaweeds, marine animals such as sea cucumbers and marine microorganisms also possess SPs, but with less abundance and diversities in comparison to seaweed-derived DFs, which are predicted to be directly related to a great of biological activities (Kang et al., 2021).

Furthermore, the analysis of the structure–function correlations and the catabolism by gut microbiota of the seaweed-derived DFs will facilitate the decipher of the underlying mechanisms and contribute to further and better applications.

2. The main structure features of major seaweed-derived dietary fiber

Marine macroalgae can be classified into three classes based on the color of the thallus: brown seaweeds (*Phaeophyceae*), red seaweeds (*Rhodophyceae*) and green seaweeds (*Chlorophyceae*) (Holdt & Kraan, 2011). In general, seaweed-derived DFs are consisted of soluble DFs and insoluble DFs. Alginate, laminarin, and fucoidan in brown seaweeds, carrageenan, agar and agarose in red seaweeds, as well as ulvan of green seaweeds are typical soluble seaweed-derived DFs. And insoluble DFs are referring to cellulose, lignin, hemicellulose and starch, and the majority of which possess few bioactive activities. But the specific

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monosaccharide compositions, linkage patterns, sulfate contents and yields 33of DFs would alter due to the differentiated sources and extraction methods (Table 1), which further influence the industrial application.

2.1. DF from brown seaweed

Fucoidan is a group of complex polysaccharides constituting a backbone of L-fucopyranose residues with sulfation at O-2 and/or O-3, and branched chains of α -(1 \rightarrow 2) bond linked L-fucose 4 sulfate with C3 ester group and a trace quantity of xylose, galactose, mannose and uronans (Praveen, Parvathy, Balasubramanian, & Jayabalan, 2019). Generally, there are two types of backbones from seaweed-derived fucoidan (Fig. 1), the first is composed of (1, 3)-linked α -L-fucopyranosyl residues with sulfate groups at O-2 and O-4 positions of fucose. The other backbone structure is composed of alternating linked (1,3)- and (1,4)- α -L-fucopyranosyl residues with sulfate groups at O-2, O-3 and O-4 positions of fucose (Tanna & Mishra, 2019). The molecule weight of fucoidans varies greatly ranging from <43 kDa to 1600 kDa (Rioux, Turgeon, & Beaulieu, 2007). Conventional extraction methods such as hot water extraction (HWE) (Daub, Mabate, Malgas, & Pletschke, 2020) and acid extraction (AE) (Zhao, Xu, & Xu, 2018) are time- and energy-consuming and can motive the partial cleavage of sulfate esters, leading to bioactivity loss. Thus, innovative extraction technologies including subcritical water extraction (SCWE, also known as pressurized hot water) (Alboofetileh, Rezaei, Tabarsa, You, Mariatti, & Cravotto, 2019), ultrasound-assisted extraction (UAE), enzyme-assisted extraction (EAE) and microwave-assisted extraction (MAE) have been established to gently and efficiently obtain fucoidan of intact structures from brown seaweeds (Otero et al., 2021). For example, fucoidan extracted from *Fucus distichus* under the assistance of alginate lyase from *Sphingomonas* sp. possessed molecular weight (MW) of 200–400 kDa which was significantly higher than those from AE method (MW = 150–500 kDa) (Thuan Thi et al., 2020). Nonetheless, although UAE method performed higher yield (14.61 g/100 g) of fucoidan from *Sargassum wightii* than HWE method (10.59/100 g), fucoidan obtained by HWE had higher content of fucose (Hanjabam, Kumar, Tejpal, Elavarasan, & Kumar, 2019). These results indicate that UAE method may damage the cell wall structure of seaweed. Moreover, low molecular weight fucoidan (5–30 kDa) fractions possess the enhanced anticancer activity and are more widely used in food supplements and pharmaceutical products, while those crude fucoidan of higher molecule mass (>30 kDa) with high viscosity display limitations in applications as therapeutic agents (Florez-Fernandez, Dolores Torres, Jesus Gonzalez-Munoz, & Dominguez, 2018).

Alginate and laminarin (Fig. 1) are the two typical seaweed-derived non-sulfated polysaccharides. Alginate is considered as a group of linear and non-repeating polyuronides containing blocks of α -1,4-guluronate (G) residues and (1,4)-linked β -D-mannuronate (M) (Lorbeer et al., 2017). G blocks provide a tough cross-linking among internal molecule with divalent cations to form gelation while M blocks offer linearity and flexible to maintain linear structure of alginates. Different types of polymer blocks such as homogeneous poly-M or poly-G and heterogeneous poly-MG lead to differentiated structures, molecule weight, and rheological properties including gelling and thickening (Hentati et al., 2018). Alginate has been applied for wound healing, drug delivery, and tissue engineering (Lee & Mooney, 2012), but is greatly limited due to its low bioavailability. Thus, modification of alginate by degradation into oligosaccharides with low molecular weight is of great interests for better applications. Laminarin is neutral polysaccharides with low molecular weight of approximately 4–5 kDa. It is composed of D-glucopyranose residues linked by β -(1,3) and β -(1,6) glycoside bonds (García-Vaquero, Rajauria, O'Doherty, & Sweeney, 2017), and interchain hydrogen bonds are existed for the molecular stabilization. The reducing end of polymer chains contribute to the classification of the polysaccharides into M-type with D-mannitol residues and G-type carrying

glucose (Faiez et al., 2020), and the ratio of which varies according to the algae species and growing conditions and determines the biological activities of laminarin (García-Vaquero, Rajauria, O'Doherty, & Sweeney, 2017). In addition, laminarins don't have gelling or thickening properties compared with other seaweed-derived polysaccharides (Kadam, Tiwari, & O'Donnell, 2015). Therefore, various approaches for modifying the backbone of laminarin such as irradiation, sulfation, reduction or oxidation, have been developed to broaden the application area and enhance the biological activities (Zargarzadeh, Amaral, Custódio, & Mano, 2019).

2.2. DF from red seaweed

Carrageenan is a class of linear sulfated galactans with the basic structural features of repeating disaccharides units, which are alternatively consisted of β -1,3- and α -1,4-linked galactose residues or 4-linked 3,6-anhydro- α -D-galactopyranose (Campo, Kawano, da Silva, & Carvalho, 2009). Carrageenan can be classified into six forms: Iota (i-), Kappa (κ -), Lambda (λ -), Mu (μ -), Nu (ν -) and Theta (θ -) carrageenan, according to the degree and position of sulfation (Dong, Wei, & Xue, 2021). The molecular weight of commercial carrageenan is between 200 and 800 kDa (Weiner, Mckim, & Blakemore, 2017). Extraction methods may contribute to the final structural characteristics of carrageenan including sulfate content, molecule weight, and negative charge, which directly influence the physiological properties (Jiang, Zhang, Ni, & Shao, 2021). In general, carrageenan can be extracted from hot alkali solution (HAE) (Manuhara, Praseptianga, & Riyanto, 2016) and is insoluble in alcohol and certain salt solutions (D. Yang & Yang, 2020). UAE and EAE are developed for enhancing the yields and preventing excessive effects on the chemical structure and molecule weight distribution of carrageenans (Otero et al., 2021). Similar chromatograms were observed in the extracted carrageenan by size exclusion chromatography with or without ultrasound (Yousouf et al., 2017). Carrageenan is generally used as thickeners, gelatinizers and stabilizers in the foods, pharmaceuticals, and cosmetics industry. Kappa (κ -) and Iota (i-) carrageenan are two major gelatinizers among all carrageenans and are differentiated in gel properties due to the distinct chemical structures. However, both of them can not completely satisfy the steadily increasing demand in food industry. Thus, κ /i-hybrid carrageenan has recently been developed as alternative algae-derived additives and can be used in dairy products, the gel elasticity of which is negatively correlated with molecular weight and the content of i-carrageenan disaccharide units (Souza, Hilliou, Bastos, & Goncalves, 2011).

Agars and agaroids are the other two typical sulfated galactans from red seaweeds. Agars are identified as mixtures of agarose and agaropectin at variable rates depending on the algal species. Agarose, also acknowledged as agarobiose, is composed of neutral disaccharides of D-galactose and 3,6-anhydro-L-galactose, which contributes up to 70% of the agar polysaccharides (Lee, Lim, Leow, Namasivayam, Abdullah, & Ho, 2017). Agaropectin has a similar structure as agarose but the hydroxyl group of L-galactose unit is heavily substituted with charged groups such as sulfate, methoxyl, and pyruvate ketal (Lee, Lim, Leow, Namasivayam, Abdullah, & Ho, 2017), which acts as a precursor for agarose in the course of enzymatic polymerization and desulfation processes (Lim, Lee, Leow, Namasivayam, Abdullah, & Ho, 2018). The solubilities and the gelation properties of agar is determined by the relative hydrophobicity of the galactose disaccharide. Moreover, agars have similar applications like carrageenans as gelatinizers and thickeners in food, but possess advantages in withholding sugar without forming crystals or losing its gelling properties (Lim, Lee, Leow, Namasivayam, Abdullah, & Ho, 2018). Agaroids have similar structural features to agars and can be divided into funorans and porphyran. Funorans are constituted of a succession of 6-O-SO₃- and 2-O-SO₃- units and are widely used in the field of adhesives. Porphyrans, mainly extracted from Porphyra, are composed of alternating 1,4-linked α -L-galactopyranose-6-sulfate and 1,3-linked β -D-galactopyranose (Qiu,

Table 1
Physicochemical properties of DFs from various seaweeds by distinct extraction methods.

Species	Type of DFs	Principal monosaccharide composition	MW (kDa)	Sulfate contents	Yields of DFs	Extraction methods	References
Brown seaweeds							
<i>Ecklonia maxima</i>	Fucoidan	L-fucose	10	6.01 ± 0.53%	6.89%	HWE	(Daub, Mabate, Malgas, & Pletschke, 2020)
<i>Laminaria japonica</i>	Fucoidan	Fucose, glucose, glucuronic acid, rhamnose and arabinose	64.04	27.95%	~6%	AE	(Zhao, Xu, & Xu, 2018)
<i>Fucus distichus</i>	Fucoidan	Fucose, glucose, galactose, xylose, rhamnose, mannose, mannitol and uronic acids (mannuronic acid, guluronic acid, and glucuronic acid)	200–400 150–500	21.4 ± 0.5% 38 ± 0.4%	40% 43%	EAE AE	(Thuan Thi et al., 2020)
<i>Sargassum wightii</i>	Fucoidan	Fucose	ND	17.62 ± 0.88% 17.55 ± 0.06%	14.61% 10.59%	UAE EAE	(Hanjabam, Kumar, Tejpal, Elavarasan, & Kumar, 2019)
<i>Nizamuddinina zanardinii</i>	Fucoidan	Fucose, galactose, mannose, glucose and xylose	694 ± 3.8	ND	25.98%	SCWE	(Alboofetileh, Rezaei, Tabarsa, You, Mariatti, & Cravotto, 2019)
<i>Sargassum angustifolium</i>	Alginate	Mannuronic acid and guluronic acid	480.3 ± 5.93 × 10 ³ 557.1 ± 1.48 × 10 ³ g/mol 357 ± 3.67 × 10 ³	—	3.30% 3.40% 3.50%	HWE AE EAE	(Borazjani, Tabarsa, You, & Rezaei, 2017)
<i>Laminaria hyperborea</i>	Laminarin	ND	5.7–6.2	—	368.0 ± 2.1 mg/g	HAE	(Rajauria, Ravindran, Garcia-Vaquero, Rai, Sweeney, & O'Doherty, 2021)
Red seaweeds							
<i>Eucheuma spinosum</i>	ι-carrageenan	ND	50	ND	24.49–30.33%	HWE	(Yang & Yang, 2020)
<i>Kappaphycus alvarezii</i>	κ-carrageenan	Sulfated galactose	ND	7.75%	34.3%	HAEE	(Manuhara et al., 2016)
<i>Euchema denticulatum</i>	κ-/ι-hybrid carrageenans	ND	180, 4400, 21400, 277,000	ND	50–55%	UAE	(Youssef et al., 2017)
<i>Hypnea musciformis</i>	κ-/ι-hybrid carrageenans	ND	ND	15.8% 19.8%	37.8% 18.9–22.7%	HAE MAE	(Vazquez-Delfin, Robledo, & Freile-Pelegrin, 2014)
<i>Gracilaria lemaneiformis</i>	Agar	ND	791 1936 852	1.8 ± 0.03% 4.51 ± 0.09% 3.56 ± 0.06%	13.11 ± 0.26% 17.29 ± 0.46% 16.08 ± 0.14%	HAE EAE HEE	(Chen, Xiao, Weng, Zhang, Yang, & Xiao, 2020)
<i>Gracilaria vermiculophylla</i>	Agar	ND	ND	1.73 ± 0.13%	14.4 ± 0.4%	MAE	(Sousa, Alves, Morais, Delerue-Matos, & Gonçalves, 2010)
Green seaweeds							
<i>Ulva intestinalis</i>	Ulvan	Rhamnose, glucose, xylose, uronic acid	ND	13.75 ± 0.41%	29.15 ± 0.19%	HWE	(Klongklaew, Praiboon, Tamtin, & Srisapoom, 2021)
<i>Ulva lactuca</i>	Ulvan	Rhamnose, xylose, glucuronic acid and iduronic acid	673700 g/mol 562590 g/mol	< 0.5% 14.3 ± 0.6%	18 ± 2 % 11 ± 3 %	AE HWE	(Wahlstrom et al., 2020)
<i>Ulva pertusa</i>	Ulvan	Rhamnose, glucose, xylose, galactose	283.3 351.91 404.07	13.2 ± 0.2% 9.2 ± 0.6% 6.8 ± 0.0%	17.8 ± 0.6% 20.6 ± 1.2% 25.3 ± 1.3%	HWE UAE EAE	(Chen et al., 2021)
<i>Monostroma latissimum</i>	Rhamnan sulfate	Rhamnan sulfates, uronic acids residues	800	ND	53.1 ± 7.2%	MAE	(Tsubaki, Oono, Hiraoka, Onda, & Mitani, 2016)

Abbreviations: AE, acid extraction; EAE, enzyme-assisted extraction; HEE, H₂O₂-assisted enzymatic extraction; HWE, hot water extraction; HAE, hydrothermal-assisted extraction; HAEE, hot alkaline-assisted extraction; MAE, microwave-assisted extraction; ND, not determined; UAE, ultrasound-assisted extraction; SCWE, subcritical water extraction.

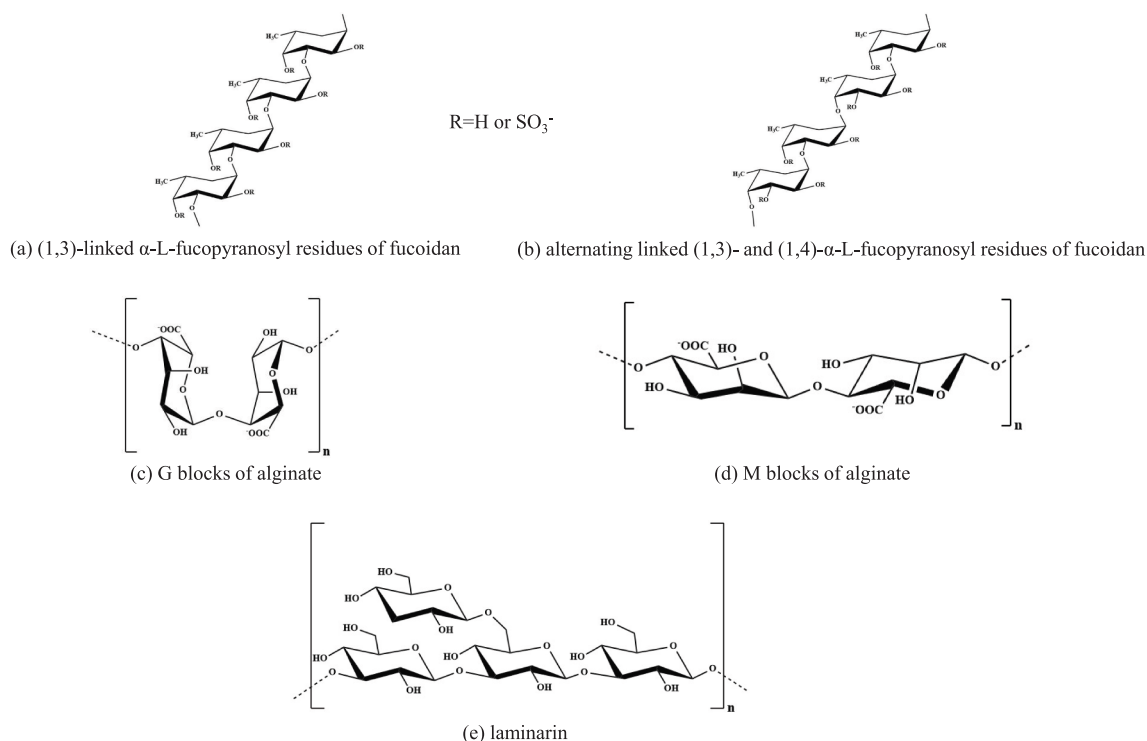


Fig. 1. Chemical structures of seaweed-derived DFs from brown seaweed (Tanna & Mishra, 2019), redrawn by ChemBioDraw.

Jiang, Fu, Ci, & Mao, 2021). Unlike the carrageenans and agars, agaroids do not have gelling properties unless they were converted into partially methoxylated agarose after alkaline treatment (Cosenza, Navarro, Ponce, & Stortz, 2017).

2.3. DF from green seaweed

Ulvan is one of typical SPs in green seaweed, primarily consisted of rhamnose, sulfate group, glucuronic acid, xylose and a low amount of mannose, galactose, and arabinose (Sari-Chmayssem, Taha, Mawlawi, Guegan, Jeftic, & Benvegnu, 2019). Chemical research on ulvan isolated from different species indicated that the backbone is generally composed of α -1,4- and α -1,2,4- linked L-rhamnose, β -1,4- and terminally linked D-glucuronic acid and β -1,4-linked D-xylose (Tziveleka, Ioannou, & Roussis, 2019), with sulfation at C-3 and/or C-2 of rhamnose. The conformation of ulvan in solution is pH dependent and is also influenced by the presence of counter-ions. In aqueous solutions with low pH, ulvan could fold into a condensed bead-like conformation leading to the low viscosity, as well as influencing gel strength and activity, while ulvan had a more open conformation so as to increase the intermolecular interactions that resulted in higher viscosities and greater gel strengths in high pH solutions (pH \sim 13) (Kidgell, Magnusson, de Nys, & Glasson, 2019). The impacts of extraction procedures on ulvan were observed in chemical structure, MW, and consequentially biological activities (Guidara et al., 2021). EAE is supposed to be the promising method for enhancing extraction yield and purity over the traditional chemical extraction methods. However, the lack of stable enzymes has limited EAE from large-scale industrial production. MAE and UAE were found effective for the production of ulvan from green seaweeds lately, but the expensive cost restricted commercial application. Thus, extraction methods of ulvan still need to be further modified.

Conventional extraction methods of seaweed-derived DFs such as water- and chemical reagents-based extraction are commonly used for efficient production and food development. But in terms of yield and quality, including specific molecular composition, structure integrity and functional groups, it is not comparable to the physical technology-

based (like microwave and ultrasonication) and enzyme assisted methods. However, expensive cost and high energy consumption are major limitations of these modern methods in present.

3. The physiological characteristics of seaweed-derived dietary fiber

Seaweed-derived DFs possess various biological activities (Fig. 2) and structural characteristics, especially the unique sulfated groups, plays a significant role in the potential mechanisms of biological activities. The SPs from the seaweed-derived DFs can be divided into three categories according to the main form of the sulfated groups, i) fucose-containing SPs, like fucoidans, ii) sulfated galactans-containing SPs, like carrageenans, and iii) sulfated rhamnan-containing SPs, like ulvans (Liu et al., 2019). Therefore, we focused on the biological activities of the three typical sulfates-enriched DFs from three different kinds of seaweeds and discussed the associated potential signaling pathways in details (Table 2).

3.1. Regulating metabolic disorders

Unhealthy lifestyle habits including sedentariness and excessive calorie intake can lead to metabolic syndrome (MetS), which have been regarded as one of the major public health concerns that is rapidly spreading in the world. MetS gathers complicated symptoms including obesity, insulin resistance, type 2 diabetes, and cardiovascular complications. The pathogenesis of metabolic syndrome involves a multitude of factors and has not been fully understood. DFs from different seaweed species exhibited ameliorating effects on MetS-associated systematic symptoms via multiple pathways.

Fucoidans from brown seaweeds such as *Laminaria japonica* and *Ascophyllum nodosum*, were capable of reducing the body weight, fasting blood glucose, hepatic steatosis and systematic inflammation in high fat diet (HFD)-induced MetS mice (Shang et al., 2017). The anti-dyslipidemic effects of fucoidans are likely to be associated with bile acid transformation and cholesterol transportation (Fig. 3). For example,

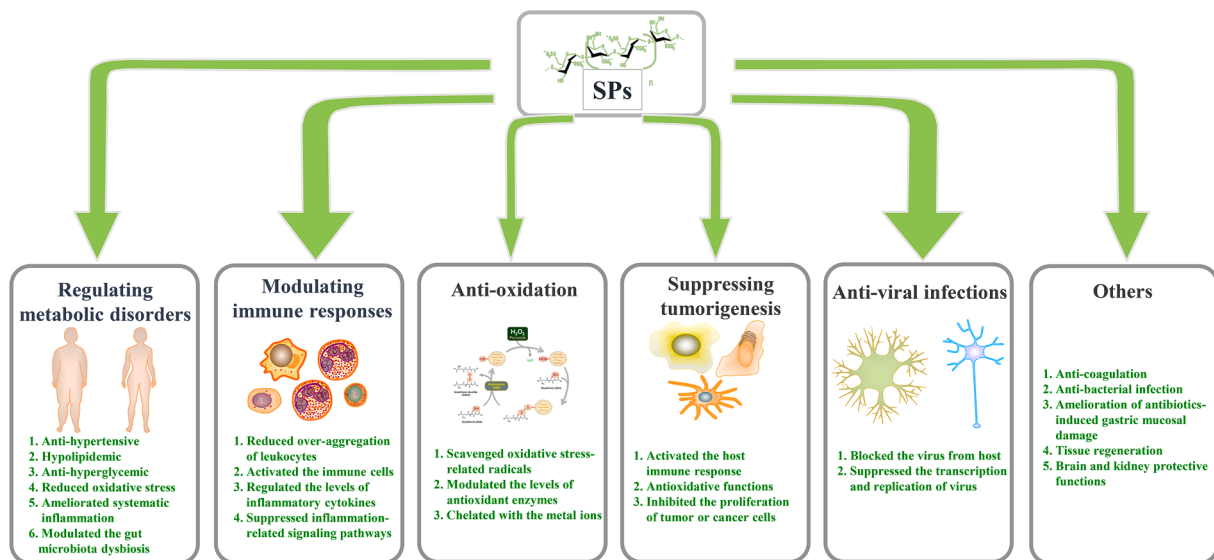


Fig. 2. Multiple biological activities of seaweeds-derived SPs.

fucoidan from *Undaria pinnatifida* were found to decrease serum lipid levels in HFD-induced dyslipidemia rats by increasing the expression of cholesterol 7- α hydroxylase (CYP7A1) in liver, and bile salt hydrolyase (BSH) activity of small intestinal contents (Q. Chen et al., 2019). Fucoidan from *Ascophyllum nodosum* substantially increased the mRNA expression of low-density lipoprotein receptor (LDLR), scavenger receptor B type 1 (SR-B1), CYP7A1, liver X receptor (LXR) β , ATP-binding cassette transporter (ABC) A1 and sterol regulatory element-binding protein (SREBP) 1c, and reduced the expression of peroxisome proliferator-activated receptor (PPAR), thereby enhancing lipid transfer from plasma to the liver in C57BL/6J mice (Yang et al., 2019). Moreover, the underlying mechanisms of the anti-MetS effects of fucoidan were predicted to be related with the amelioration of excessive oxidative stress and inflammation. Fucoidan from *Fucus vesiculosus* (FvF) remarkably improved the sodium palmitate (PA)-induced insulin resistance in HepG2 cells by lowering the levels of reactive oxygen species (ROS) through the ROS-mediated JNK and Akt signaling pathways (Wang et al., 2019). Fucoidan from *Acaudina molpadioides* improved insulin resistance by reducing serum and fecal lipopolysaccharide (LPS) and increasing the concentrations of SCFAs through modulation of the gut microbiota, which was associated with activating AMPK signaling and inhibiting the LPS/TLR4 signaling in muscle tissues of HFD-fed mice (Hu, Wang, Wang, Yang, Yan, & Su, 2019). In addition, fucoidan from *Cladosiphon okamuranus* markedly reduced the thickness of the lipid-rich plaque in the aorta in HFD-fed apolipoprotein E-deficient mice (Yokota, Nomura, Nagashima, & Kamimura, 2016). Further research indicated that fucoidan fraction (8.177 kDa) from *Saccharina japonica* prevented macrophages from developing into foam cells and prevented smooth muscle cells from migrating into the intimal layer of the aorta, and thereby inhibiting the formation of atherosclerotic plaques in apoE-knockout mice (Xu, Xu, Ge, Tian, Zhao, & Guo, 2018).

Carrageenans from red seaweeds displayed controversial effects in the treatment of MetS. On the one hand, the supplement of carrageenans could attenuate symptoms including weight gain, hypertension and dyslipidaemia in HFD-induced MetS rats (Du Preez et al., 2020), and could lead to normalization of lipid profiles in cardiovascular disease patients (Sokolova, Bogdanovich, Ivanova, Byankina, Kryzhanovskiy, & Yermak, 2014). Yao et al. compared the anti-obesity effects of κ -carrageenan (CGN) with the leftover fraction of sans-carrageenan (SCGN) from *Kappaphycus alvarezii* in HFD-treated rats and found that CGN mainly increased lipid metabolism and ameliorated leptin resistance by significantly upregulating the mRNA expression of adipor2 in hepatic tissues, while SCGN reduced fatty acid synthesis, which could possibly

be to the reason of smaller adipocytes (Chin, Mi, Cao, Lim, Xue, & Tang, 2019). In addition, the lipid lowering properties of carrageenans could be caused by the impressive potentials to influence enterohepatic cyclings via preventing bile salt permeation through the gastrointestinal barrier (Sokolova, Kravchenko, Sergeeva, Davydova, Bogdanovich, & Yermak, 2020). Moreover, the low-molecular-weight carrageenan (MW < 2 kDa) extracted from *Eucheuma spinosum* exhibited better anti-hyperglycemic and anti-hypolipidemic effects in HFD-treated rats diet compared to commercial carrageenan (Qiu & Zhong, 2018), which may be related to its increased absorption owing to its lower molecular weight. On the other hand, λ - and λ - κ carrageenan could impair glucose tolerance and give rise to insulin resistance in human HepG2 cells and in C57BL/6J mice (Bhattacharyya, Feferman, & Tobacman, 2015), which were probably mediated by the upregulation of inflammation-associated Ser(P)307-IRS1 and the downregulation of GRB10-associated Tyr(P)-IRS1 (Bhattacharyya, Feferman, & Tobacman, 2015). Long-term consumption (13 weeks) of κ -carrageenan from *Eucheuma cottonii* also impaired the glucose metabolism in C57BL/6 mice by inhibiting the insulin PI3K/AKT signaling pathway followed by interfering with insulin binding to receptor (Zhou et al., 2021). These inconsistent evidences indicated that further investigations were required for carrageenans in aspects of regulating lipid and glucose metabolism.

Ulvans from green seaweeds are also promising anti-hyperlipidemic agents depending on the molecule weight and sulfate contents. For example, ulvan fractions from *Ulva pertusa* with low molecule weight (38.93 kDa) and high sulfate content (28.1%) were more effective in regulating body weight gain and serum TC, TG, HDL-C and LDL-C levels compared to those of high molecule weight (143.47 and 87.49 kDa) and low sulfate content (14.5% and 20.1%) in male Kunming mice fed with a cholesterol-rich diet (Li et al., 2020). In the meantime, the ulvan fraction with the lowest molecule weight (83.094 kDa) and the highest sulfate content (23.99%) extracted from *Ulva pertusa* exhibited the strongest antioxidant activities in regulating hepatic MDA, SOD, and CAT in the model of hyperlipidemic Kunming mice (Li et al., 2018). Furthermore, the mechanism of antihyperlipidemic effects of the highly sulfated ulvan may be associated with improved lipid profiles either through upregulating FXR and PPAR γ and downregulating LXR in liver of high-cholesterol fed rats (Qi and Sheng, 2015), or by exerting bile acids after combination with the indigestible ionic colloids molecules (Sardari & Karlsson, 2018) (Fig. 3).

Table 2
Differentiated biological activities of SPs from various seaweeds.

Biological activities	Type of SPs	Models	Dosage and duration	MW (kDa)	Sulfate content	Indexes for pathological improvement	References
Regulating metabolic disorders	Fucoidan from <i>Acaudina molpadioides</i>	<i>In vivo</i> HFD-fed male C57BL/6J mice	80 mg/kg for 10 weeks	1614.1	3.19%	↓Body weight, insulin resistance, blood glucose, fecal LPS	(Hu, Wang, Wang, Yang, Yan, & Su, 2019)
	Fucoidan from <i>Saccharina japonica</i>	<i>In vivo</i> atherogenic diet-fed apoE (-/-) mice	200 mg/kg for 11 weeks	8.177	36.85%	↓Serum TC, TG, LDL-C, atherosclerotic plaque, liver and aorta ox-LDL levels	(Yokota, Nomura, Nagashima, & Kamimura, 2016)
	Fucoidan from <i>Sargassum fusiforme</i>	<i>In vivo</i> HFD-fed male Kunming mice	100 and 400 mg/kg for 7 weeks	703	ND	↓Body weight, serum LPS, NEFA ↑Serum HDL-C	(Liu et al., 2021)
	Carrageenan from <i>Eucheuma spinosum</i>	<i>In vivo</i> HFD-treated rats	Supplement with 1% and 3% LC diets	1.398	ND	↓Body weight, serum TC, TG, LDL-C ↑Serum HDL-C	(Qiu & Zhong, 2018)
	Ulvan from <i>Ulva pertusa</i>	<i>In vivo</i> cholesterol-rich diet-fed male Kunming mice	125, 250 and 500 mg/kg for 30 days	143.47 87.49 38.93	14.5% 20.1% 28.1%	↓Body weight, Serum TC, TG, LDL-C ↑Serum HDL-C	(Li et al., 2020)
Modulating immune responses	Fucoidan from <i>Sargassum crassifolium</i> and <i>Padina australis</i>	<i>In vivo</i> Peyer's patch cells of C3H/HeJ mice	200 µg/ml	230 179	27.5 21.9	↑Proliferation	(Yuguchi et al., 2016)
	Fucoidan-like SPs from <i>Sargassum horneri</i>	<i>In vitro</i> LPS-induced RAW 264.7 cells	25, 50, and 100 µg/mL for 24 h	< 5 5–10	ND	↓NO, PGE ₂ , TNF-α, IL-6 production <i>in vitro</i>	(Sanjeeva et al., 2018)
		<i>In vivo</i> zebrafish embryo model	25, 50, and 100 µg/mL for 1 h	10–30 > 30		↓Toxicity, cell death, NO production <i>in vivo</i>	
	λ-carrageenan from <i>Chondrus ocellatus</i>	<i>In vivo</i> spleen cells from ICR mice	200 mg/kg for 7 days	9.3, 15, 140, 240, 650	21.8%, 27.8%, 28.4%, 30.5%, 29.1%	↑NK cells and lymphocyte	(Zhou, Sun, Xin, Zhang, Li, & Xu, 2004)
	κ-carrageenans hexamer from <i>Thalassospira</i> sp. Fjfst-332	<i>In vitro</i> LPS-induced RAW 264.7 cells	10, 25 and 50 µg/mL for 24 h	ND	ND	↓TNF-α, IL-β, IL-8, NO production, mTNF-α, mIL-β, mIL-8 genes expression, iNOS, COX-2 proteins	(Guo et al., 2018)
	Ulvan from <i>Ulva ohnoi</i>	<i>In vitro</i> LPS-stimulated RAW264.7 murine macrophage cells	100 µg/mL for over 48 h	7–209	ND	↑IL-1β and IL-6 production	(Kidgell et al., 2020)
Anti-oxidation	Fucoidan from <i>Cystoseira compressa</i>	<i>In vitro</i> assays	—	1 × 10 ⁵ g/mol	14.65%	↑Ferrous ion chelation, DPPH radicals ↓Ferric ion	(Hentati et al., 2018)
	Fucoidan from <i>Undaria pinnatifida</i>	<i>In vitro</i> assays	—	> 300 300	22.83 ± 1.00% 20.01 ± 0.82%	↓DPPH, hydroxyl radicals	(Koh, Lu, & Zhou, 2019)
	Sulfated galactan from <i>Gracilaria abirdiae</i>	<i>In vitro</i> assays	0.1–2.0 mg/mL	3.7 × 10 ⁶ g/mol	8.4%	↓DPPH, hydroxyl radicals	(Souza et al., 2012)
	Agar-type galactan from <i>Gracilaria caudata</i>	<i>In vivo</i> oxidative stress rats	3 and 10 mg/kg for 18 h	116.51	0.14%	↑Liver CAT, SOD	(Cavalcante Alencar et al., 2019)
	Ulvan from <i>Ulva pertusa</i>	<i>In vitro</i> assays	—	143.47 87.49 38.93	14.5% 20.1% 28.1%	↓Superoxide, hydroxyl radicals	(Li et al., 2020)
Suppressing tumorigenesis	Fucoidan from <i>Undaria pinnatifida</i>	<i>In vitro</i> PC-3, HeLa, A549, and HepG2 cell lines	0.1–0.8 mg/ml for 24 h	1246	0.97 sulfate/total sugar	↓Cell viability	(Synytsya et al., 2010)
	ι-carrageenan from <i>Solieria chordalis</i>	<i>In vitro</i> human peripheric blood mononuclear cells	—	913	33.54 ± 0.3	↑NK cells, lymphocyte	(Stephanie, Eric, Sophie, Christian, & Yu, 2010)
	Carrageenans from <i>Laurenciapapillosa</i>	<i>In vitro</i> MCF-7 human breast cancer cells	25 and 50 µM of LPW2 for 24 h 12.5 and 25 µM of LPW3 for 24 h	560000 g/mol 258000 g/mol	ND	↑PARP, P53 and Bax/Bcl-2 genes expression	(Ghannam, Murad, Jazzara, Odeh, & Allaf, 2018)
	Ulvan from <i>Ulva lactuca</i>	<i>In vitro</i> HepG2, MCF7 and HeLa cancer cells	0.8, 4, 20, 100 µg/mL for 48 h	347	18.9%	↓Cell viability	(Thanh, Quach, Nguyen, Luong, Bui, & Van Tran, 2016)
Anti-viral infections	Fucoidan from <i>Sargassum henslowianum</i>	<i>In vitro</i> HSV-1 and HSV-2 cells	1, 10, 100, and 1000 µg/mL for 1 h	655 589	31.92% 31.89%	↓Virus plaques	(Sun et al., 2020)
	κ-carrageenan oligosaccharides	<i>In vitro</i> MDCA cells	0, 6.25, 12.5, 25, 50, 100 for 48 h	1–3	0.8–1.0 mol/mole of disaccharide	↓Virus replication	(Wang et al., 2012)
	Ulvan from <i>Ulva pertusa</i>	<i>In vitro</i> vesicular stomatitis virus	10 and 100 µg/mL for 16 h	1068.2 38.5 17.8 5.2	17.70% 17.92% 18.13% 17.88%	↓Virus replication	(Chi, Zhang, Wang, Fu, Guan, & Wang, 2020)
	λ-carrageenan	—	—	11	1.1%	↓Heparanase expression	(Poupard et al., 2017)

(continued on next page)

Table 2 (continued)

Biological activities	Type of SPs	Models	Dosage and duration	MW (kDa)	Sulfate content	Indexes for pathological improvement	References
Others	Fucoidan from <i>Laminaria japonica</i>	<i>In vitro</i> HSkMEC, MCF-7, and MDA-MB-231 cell lines <i>In vitro</i> antibacterial assay	3.125, 6.25, 12.5, 25, and 50 mg/mL for 24 h	< 6 6–20 20–50 50–80 > 80	ND	↓ <i>Escherichia coli</i> and <i>Staphylococcus aureus</i> abundance	(Liu et al., 2017)
	Ulvan from <i>Ulva reticulata</i>	<i>In vitro</i> agar plate surface	10 mg/ml for 24 h	331	17.6%	↓ <i>E. coli</i> , <i>P. aeruginosa</i> and <i>E. cloacae</i> abundance	(Tran et al., 2018)

Abbreviations: CAT, catalase; DPPH, diphenyl-1-picrylhydrazyl; FRAP, ferric reducing antioxidant power; HDL-C, high-density lipoprotein cholesterol; IL-6, interleukin-6; IL- β , interleukin- β ; IL-8, interleukin-8; IL-1 β , interleukin-1 β ; LDL-C, low-density lipoprotein cholesterol; LC, low-molecule-weight carrageen; ND, not determined; NK cells, natural killer cells; NEFA, non-esterified fatty acid; NO, nitric oxide; ox-LDL, oxidative lipoproteins; PGE₂, prostaglandin E₂; SOD, superoxide dismutase; TC, total cholesterol; TG, total triglyceride; TNF- α , tumor necrosis factor- α .

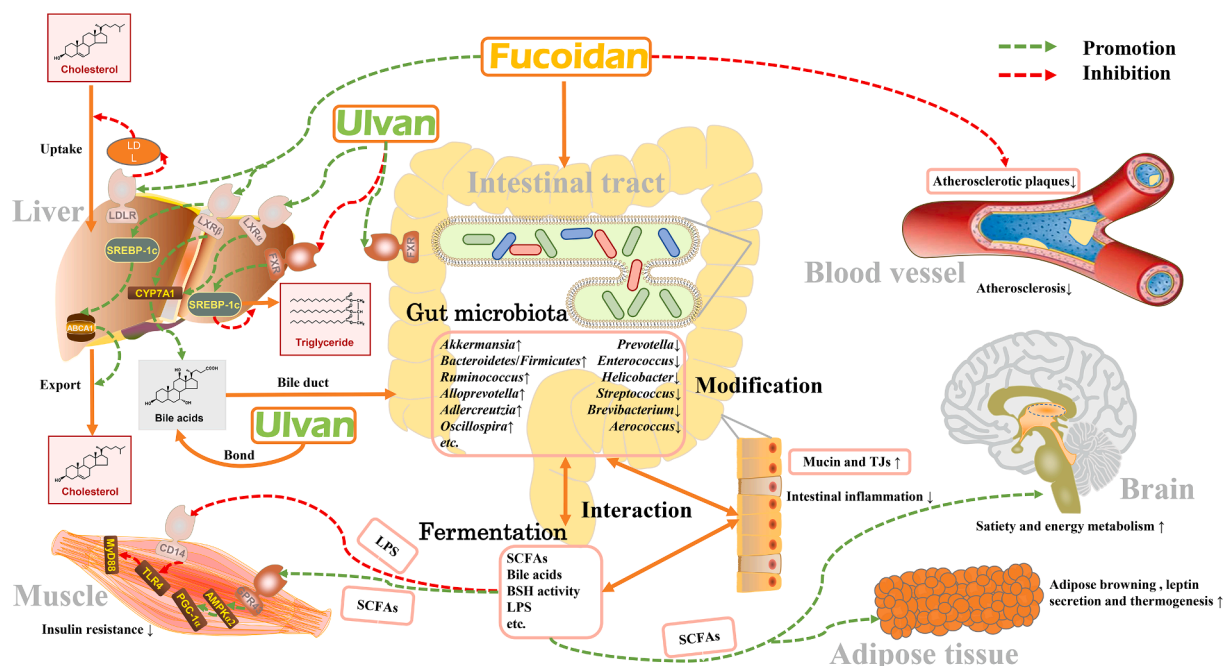


Fig. 3. Potential molecular pathways of seaweeds-derived fucoidan and ulvan on alleviating metabolic disorders. Abbreviations: ABCA1, ATP-binding cassette transporter A1; AMPK α 2, Adenosine 5'-monophosphate (AMP)-activated protein kinase α 2; BSH, bile salt hydrolase; CYP7A1, cholesterol 7- α hydroxylase; CD14, cluster of differentiation 14; FXR, farnesoid X receptor; GPR43, G protein-coupled receptor 43; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LXR α , liver X receptor α ; LXR β , liver X receptor β ; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; PGC-1 α , peroxisome proliferator-activated receptor- γ coactivator-1 α ; SREBP-1c, sterol regulatory element-binding protein 1c; SCFAs, short-chain fatty acids; TLR4, toll like receptor 4; TJs, tight junction proteins.

3.2. Modulating immune responses

Immuno-stimulation refers to the self-protection behavior against external substances including pathogens, viruses, and anaphylactogen. The mechanisms of immune regulation are associated with the interactions among immune cells including lymphocytes, monocytes, and natural killer cells (NK cells) (Kim et al., 2012). SPs from seaweeds exhibit marvelous immunomodulatory abilities that may be of potential application in stimulating the immune response or controlling immune cell activity to mitigate associated negative effects, such as inflammation.

Over-aggregation of leukocytes may lead to intense inflammatory responses, which can be interfered by seaweed DFs. For instance, administration of fucoidans from *Fucus vesiculosus*, *Laminaria* spp., *Fucus* spp., *A. nodosum*, and *C. okamuranus* reduced leukocytes recruitment to the peritoneum in rats model of acute peritonitis due to the combination of fucoidan with the critical cell adhesion molecules in the recruitment

process like L- and P-selectins (Jiao, Yu, Zhang, & Ewart, 2011). In addition, fucoidans possess the abilities of directly stimulating immune cells, activating macrophages and NK cells, and thereby reducing pro-inflammatory indicators (iNOS, COX-2, PGE₂, TNF- α , IL-1 β , INF- γ , and IL-6) and NO production both *in vitro* and *in vivo* (Manikandan et al., 2020). And the stimulatory activities of fucoidans on macrophage cells are likely to be positively associated with molecule weight and the content of sulfate groups (Ferreira, Passos, Madureira, Vilanova, & Coimbra, 2015). It was observed that fucoidan-like SPs from brown seaweed *Sargassum horneri* of high molecule weight (>30 kDa) rather than those with lower MW possessed anti-inflammatory activities in LPS-induced *in vivo* zebrafish embryo model (Sanjeeva et al., 2018). The hyposulfated fucoidan from *Fucus evanescens* exhibited diminished immune-stimulatory activities in bone marrow-derived dendritic cells and macrophages than the native fucoidan (Khil'chenko et al., 2011). Furthermore, numerous studies reported that blocking NF- κ B related signaling pathways was the crucial mechanisms of fucoidans against

inflammation, but the downstream pathway varied greatly including MAPK and TLR pathways (Sanjeewa et al., 2019).

The effects of carrageenans on immuno-stimulation are still doubtful, which may be due to the various dosages used in the intervention and the structural features. For example, high dose (>10 ng/mL) of five different types of carrageenan extracted from red seaweeds of *Gigartinales* and *Tichocarpaceae* increased the levels of pro-inflammatory IL-6 and TNF- α in human blood cells, while enhanced the secretion of anti-inflammatory IL-10 in a positive dose-dependent manner when they were given at low doses (1–10 ng/mL) (Yermak et al., 2012). κ - or ι -carrageenan derived oligosaccharides showed promisingly anti-inflammatory effects by significantly and dose-dependently decreasing the levels of TNF- α secreted from LPS-treated BV-2 cells, while polymeric carrageenans such as λ - and ι -carrageenan displayed co-effects of pro-inflammation with LPS (Ai et al., 2018). Low MW λ -carrageenan of 9.3 and 15 kDa increased NK cells activity and promoted lymphocyte proliferation compared to 140, 240 and 650 kDa derivatives in spleen cells of ICR mice (Zhou, Sun, Xin, Zhang, Li, & Xu, 2004). In addition, an investigation of four κ -carrageenan oligosaccharides from *Thalassospira* sp. Fjfst-332 with different degrees of polymerization and numbers of sulfated groups found that κ / ι -neocarrahexaose with the highest degrees of polymerization and the largest number of sulfated groups displayed the best inhibitory effect of ROS production in LPS-induced RAW 264.7 macrophages (Guo et al., 2018).

Ulvan from green seaweed also have mild immunomodulatory effects. Ulvan from *Ulva armoricana* activated the PI3K/Akt signaling pathway via TLR4 to induce intestinal cytokine production in both porcine intestinal epithelial (IPEC-1) cells and human embryonic kidney (HEK) 293 reporter cells (Berri et al., 2017). The immune regulatory activities of ulvans are closely related to their structural characteristics such as molecule weight and sulfate contents. For instance, purified ulvan fractions from *Ulvan ohnoi* with high molecular weight (209 kDa) enhanced the secretion of anti-inflammatory IL-10 and prostaglandin E2 (PGE2) in LPS-induced RAW264.7 murine macrophages in comparison to those with MW of 7, 9, 13, and 21 kDa (Kidgell et al., 2020). Similar to fucoidans, the immunostimulatory activities of ulvan from *Ulvan rigida* greatly diminished during desulfurization (Leiro, Castro, Arranz, & Lamas, 2007). The synthetic ulvan-like sulfated tetrasaccharide constructed by α -(1 \rightarrow 4)-glycosidic bonds was found to significantly improve the phagocytic activity of macrophage RAW264.7 cells (Zhang, Wang, Hua, Wang, Liu, & Yang, 2020), which emphasized the crucial roles of the glycosidic bonds of ulvans were closely associated in the immunomodulatory activities of ulvan. Moreover, a recent study revealed a transcript-metabolite correlation network including biosynthesis of amino acids, glycerophospholipid metabolism, and carbon metabolism that contributed to the enhanced proliferation and reduced pro-inflammatory TNF- α and IL-6 in RAW264.7 cells by ulvan fractions from *Ulva pertusa* (Han et al., 2021).

3.3. Anti-oxidation

The oxidative stress is generally caused by the disturbed balance between production and neutralization of free radicals, which gives rise to various degenerative diseases (Sinha, Das, Pal, & Sil, 2013). DFs from seaweed are regarded as important sources of antioxidants for eliminating total oxidants, diphenyl-1-picrylhydrazyl (DPPH), hydrogen peroxide radical scavenging (H₂O₂) and lipids (Otero et al., 2021) and thereby are widely applied in the food and cosmetics industry. Scavenging of intracellular ROS by fucoidan from *Hizikia fusiforme*, for example, was associated with the increased expression of the endogenous antioxidant enzymes induced by elevating total nuclear factor (erythroid-derived 2)-like 2 (Nrf2) levels in H₂O₂-treated Vero cells (Wang et al., 2020). Moreover, fucoidan from *Undaria pinnatifida* seaweeds can chelate with iron so as to relieve the associated oxidative stress (Phull, Majid, Haq, Khan, & Kim, 2017). The agar-type galactans (3 and 10 mg/kg) from red seaweed *Gracilaria caudata* increased the

hepatic catalase (CAT) and superoxide dismutase (SOD) levels in rats with by 2,2'-azobis (2-methylpropionamide) dihydrochloride (ABAP)-induced oxidative stress (Cavalcante Alencar et al., 2019). In addition, carrageenan (500, 750 and 1000 mg/kg) from *Kappaphycus alvarezii* exhibited antioxidant activity, in a positive dose-dependent manner, by increasing the levels of antioxidant enzymes (CAT, GPx, SOD, GST, and GSH) in kidneys of the alloxan-induced diabetic rats (Sanjivkumar, Chandran, Suganya, & Immanuel, 2020). It is noteworthy that the antioxidant capacity of sulfated galactan derived from red seaweed *Porphyra haitanensis* also displayed antioxidative capacities in the aged Kunming mice (Zhang, Li, Liu, Zhao, Li, & Xu, 2004). Moreover, ulvan derivatives exhibited improved antioxidant abilities in the hyperlipidemic Kunming mice by downregulating the expression of glutathione peroxidase, superoxide dismutase, malondialdehyde, and catalase in the liver.

The increasing evidences suggested that the sulfate groups in the DFs from seaweed may be responsible for their antioxidative abilities (Li et al., 2018). The sulfated fucans obtained from *Sargassum fulvellum* are more powerful NO scavengers than commercial antioxidants such as α -tocopherol and butylated hydroxyanisole (BHA) (Suresh, Kumar, Murugan, Palani, Rengasamy, & Anbazhagan, 2012). Fucoidan from *Cystoseira compressa* showed stronger antioxidant activities according to the DPPH and ferric reducing antioxidant power (FRAP) assays compared to the sodium alginate, whose functional groups were probably the carboxylic groups (-COOH) of the D-ManpA and L-GulpA units rather than the sulfate groups (Hentati et al., 2018). In addition, low MW (300 kDa) fucoidan from *Undaria pinnatifida* displayed higher antioxidant capacity than fucoidan with MW >300 kDa (Koh, Lu, & Zhou, 2019).

However, ulvan fractions with low sulfate content (11.67% and 12.15%) from *Ulva fasciata* showed higher antioxidant activities such as scavenging superoxide, hydroxyl and ABTS radicals, than those of ulvan fractions with high sulfate content (17.24% and 23.69%), which highlighted the important roles of protein, uronic acid and molecular weight in the antioxidative activities (Shao, Chen, Pei, & Sun, 2013). For instance, the fucan fractions with low molecule weight extracted from *Sargassum tenerrimum* exhibited promising metal chelating and DPPH and ABTS radical scavenging activities (Raguraman et al., 2019). The damaged subcellular structure of the HK-2 cells could be recovered by four degraded seaweed polysaccharides with sulfate groups, mediated by the scavenging functions of radicals (Ma, Sun, Yu, Gui, Gui, & Ouyang, 2017). Nevertheless, the locations and distributions of sulfated groups in the polymer chain of carrageenans may further impact the catalytic activities of SOD and FRAP (Sokolova, Barabanova, Homenko, Solov'eva, Bogdanovich, & Yermak, 2011).

3.4. Suppressing tumorigenesis

The suppressing tumorigenesis activities of DFs from seaweeds are mostly presented as inhibitory effect on various tumors or cancer cells including cervical cancer cells (HeLa), human hepatocellular carcinomas cells (HepG₂), MKN45 gastric cancer cells, DLD intestinal cancer cells, human breast cancer T-47D and melanoma SK-MEL-28 cell lines. The antitumor mechanisms of DFs from seaweeds mainly refer to directly antagonizing tumor cells and indirectly activating the host immune response. Furthermore, the anti-oxidative functions of the seaweeds-derived DFs play significant roles in inhibiting the proliferation of tumor cells.

The direct interactions between tumor cells with DFs from seaweeds may induce apoptosis of tumor or cells and affect the cell cycles. The experimental results showed that the apoptosis could be initiated by the inhibition of tumor-associated genes such as p53 and p21 (Delma et al., 2019), which could stimulate the expressions of cell apoptosis-related factors including Bax and Bad (Wang, Chen, Wang, Liu, & Zhao, 2014). These phenomenons have been witnessed during the treatments of oligo-fucoidan in HepG₂ cells (Yan, Lin, & Hwang, 2019) and sulfated

heterorhammans from the green seaweed *Gayralia oxysperma* in human glioblastoma cells (Ropellato et al., 2015). Different phases in cell cycles may be disturbed during the interventions of DFs from seaweeds. For example, sulfated polysaccharides extracted from red seaweed *Laurencia papillosa* could cause DNA damages and prevent MDA-MB-231 human breast cancer cells from entering S phase (Murad et al., 2016). Porphyrin from red seaweed *Pyropia yezoensis* could also block the HeLa cell cycle at the G2/M phase by regulating cyclin-dependent kinase 1 (CDK1) and cyclin B1 (He et al., 2019).

The immune status of the body has great influences on the occurrence and development of tumors. DFs from seaweeds as the immune enhancer can regulate the biological activities of a series of immune cells so as to improve their abilities of recognizing and reducing tumors cells, the investigations of which were mostly focused on the carrageenans from red seaweeds (Li et al., 2017). κ -Carrageenan oligosaccharides could significantly inhibit the growth of the transplanted sarcoma S180 and improve the phagocytosis of macrophages, the secretion of antibodies from spleen cells, the proliferation of spleen lymphocytes, the activities of NK cells, and serum levels of IL-2 and TNF- α level in the S180-bearing mice (Yuan, Song, Li, Li, & Dai, 2006).

It has been hypothesized that the sulfate content and molecule weight of DFs from seaweeds are critical factors influencing the anti-tumor or anticancer activity. Both the 2-linked disulfate rhamnose residues and the molecular weight are critically correlated with the cytotoxic effects of the sulfated heterorhammans from green seaweed *Gayralia oxysperma* U87MG cells (Ropellato et al., 2015). Shao and his colleagues compared the anticancer activities of three sulfated polysaccharides isolated from three algae including green seaweed *Ulva fasciata* (UFP), red seaweed *Gloiopeltis furcata* (GFP) and brown seaweed *Sargassum henslowianum* (SHP), turned out that SHP with the lowest sulfate content showed the highest inhibitory effects on the growth of MKN45 gastric cancer cells and DLD intestinal cancer cells, which may be due to synergistic effects of the sulfate groups and uronic acid groups (Shao, Chen, & Sun, 2013). Moreover, the anti-proliferative activities of carrageenans increased along with the reduction of their molecular weight, as carrabiose displayed the most effective inhibition against cell proliferation and metastasis of the LM2 tumor cells (Calvo et al., 2019).

3.5. Anti-viral infections

DFs from seaweeds such as fucoidans, carrageenans, and ulvans possess robust abilities to inhibit the invasions of enveloped viruses including herpes simplex virus (HSV), human immunodeficiency virus (HIV), human cytomegalovirus, dengue virus and respiratory syncytial virus. Researches have hypothesized the anti-virus mechanisms of seaweed-derived DFs such as blocking the electrostatic interactions during the viral attachment to the host cell surfaces by the affinity for viral glycoprotein (Chi, Zhang, Wang, Fu, Guan, & Wang, 2020). Therefore, the charge density of DFs from seaweeds is one of the critical structural features in this pathway. In addition, the activation of intracellular signals should also be taken into consideration when studying the antiviral mechanisms of the seaweed-derived DFs. For instance, the sulfated glucuronorhamnan from the green seaweed *Monostroma nitidum* could bind the virus EV71 to downregulate intracellular phosphoinositide 3-kinase /protein kinase B signaling pathway and block its early life cycles (Wang et al., 2019).

The dominating factors impacting the antiviral activities of seaweeds-derived DFs refer to: (i) degrees of sulfation, (ii) molecule weight and (iii) structural features such as monosaccharide composition and specific position of sulfate groups (Mukherjee et al., 2019). The sulfate content of sulfated xylogalactofucan and alginic acid derived from brown seaweed *Laminaria angustata* appeared to be an important hallmark of anti-HSV-1 activities (Saha, Navid, Bandyopadhyay, Schnitzler, & Ray, 2012). Usually the antiviral activity of sulfated polysaccharides are positively correlated with the molecular weight of the chain (Ghosh, Chattopadhyay, Marschall, Karmakar, Mandal, & Ray,

2009). From another perspective, the inhibition of viral spread may require the penetration capability of DFs, and hence low molecule size is one of the decisive factors. For instance, κ -carrageenan oligosaccharides with low molecule weight (1–3 kDa) could effectively inhibit influenza A virus infection in MDCK cells in a positive dose-dependent manner (Wang et al., 2012). In addition, specific position of the sulfate groups is of great importance for antiviral activities, the high antiviral selectivity (the antiviral evaluation index SI > 5000 for HSV-1 and SI > 10000 for HSV-2) of purified fucoidans SHAP-1 and SHAP-2 isolated from *Sargassum henslowianum* indicated that the importance of the sulfated groups occupies on the C-2 and C-4 positions of the α -(1 \rightarrow 3)-linked 1-Fucp backbone in the effectively anti-HSV activities (Sun et al., 2020). Nowadays, COVID-19, as the emerging pandemic, is greatly threatening human health and is urgently required effective therapeutics in worldwide. Carrageenan is one of the most frequently reported seaweed-derived DFs for anti-COVID-19 (Hans, Malik, & Naik, 2021), which could effectively disrupt the interactions between COVID-19 and host cell receptors, thereby blocking the internalization of virus particles (Nagle, Gaikwad, Pawar, & Dasgupta, 2020).

3.6. Others

There are other physiological characteristics for DFs from seaweeds including anti-coagulation, anti-bacterial infection, amelioration of antibiotics-induced gastric mucosal damage (Raghavendran, Srinivasan, & Rekha, 2011), tissue regeneration (Tytgat et al., 2019), and brain and kidney protective functions. DFs exhibited structure dependence on the anticoagulant and antibacterial properties. For instance, fucoidan with lower molecular weight (<6 kDa) displayed higher antibacterial rates than other fractions (\geq 6 kDa) for both *Escherichia coli* and *Staphylococcus aureus* (Liu et al., 2017). λ -Carrageenan with the MW of 11 kDa by depolymerization through glycol splitting exhibited effective anticoagulant activity (inhibiting heparanase) in comparison with the 16 kDa unfractionated heparin (Poupard et al., 2017). The anticoagulant activities of fucoidan are closely related with the molecule weight, degree of sulfation, sulfation mode, sulfate/total sugar ratio, and glycoside branching (Zhang et al., 2014). The sulfated galactans from *Eucluea serra* showed antibacterial activities by destructing the permeability and integrity of the enterotoxigenic *Escherichia coli* K88 cells (Liu et al., 2020). Alzheimer's disease (AD) is a progressive neurodegenerative disorder, with rapidly increasing prevalence in the aging population, and has limited effective treatments (Wan et al., 2020). Sulfate groups of fucoidan from brown seaweeds had inhibitory effects on the activities of acetyltransferase, acetylcholine esterase, amyloid- β production, and tau hyperphosphorylation, so as to ameliorate the fibrils of A β protein, which was regarded as promising nutraceuticals to treat AD (Gao et al., 2012). Urolithiasis affects approximately 10% of the world population which is strongly associated with calcium oxalate (CaOx) crystals, and could be reduced by fucoidan from brown seaweed *Fucus* through the combination of negatively charged groups such as sulfate and calcium ions so as to influence the crystallization dynamics (Gomes et al., 2019). Due to the impact of the various and complex structural characteristics of the DFs from seaweeds, it is noteworthy that deciphering the structure–activity relationships is the key for the further mechanism studies and industrial applications.

Collectively, sulfate content and molecule weight are so far regarded as the most important factors to influencing the multiple physiological characteristics of seaweed-derived DFs. For instance, seaweed-derived DFs with high sulfate content are likely to possess more robust physiological functions potentially owing to the interactions between sulfate clusters and cationic proteins. However, the exceptions (Shao, Chen, Pei, & Sun, 2013) or different functional targets (Wijesekara, Pangestuti, & Kim, 2011) correlated with various structural features emphasized that the combination of multiple complex factors is the essential constraint for us to further decipher the structure–activity relationships (Tan & Nie, 2021). Therefore, to establishing methodologies of obtaining highly

purified fractions of seaweed-derived DFs are crucial.

4. Interactions of seaweed-derived dietary fiber with gut microbiota

Indigestible dietary fibers can reach the large bowel intactly without being hydrolyzed by enzymes in the digestive track, and interact with

Table 3
Impact of SPs from various seaweeds on gut microbiotaA.

A. <i>In vitro</i> fermentation					
SPs	Dosage and duration	Microbiota diversity and composition	Metabolites	References	
Fucoidan from <i>Undaria pinnatifida</i>	20 g/L for 24 h	<i>Lactobacillus casei</i> DM8121†	ND	(Chen et al., 2019)	
Fucoidan from <i>Undaria pinnatifida</i>	0, 0.8, 8, and 80 mg/mL overnight	<i>Lactobacillus rhamnosus</i> †; <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , and <i>Enterococcus faecalis</i> ↓	ND	(Zhu et al., 2021)	
Fucoidan from <i>Sargassum fusiforme</i>	5 mg/mL for 24 h	<i>Faecalibacterium</i> , <i>Phascolarctobacterium</i> , <i>Bifidobacterium</i> , <i>Ruminococcaceae</i> _UCG-014, and <i>Lactobacillus</i> †; <i>Prevotella</i> _9 and <i>Blautia</i> ↓	Acetic acid, propionic acid and butyric acid†	(Kong, Zhang, You, Ma, Liao, & Pedisic, 2021)	
Fucoidan from <i>Laminaria japonica</i>	0.8 g for 48 h	<i>Lactobacillus</i> and <i>Bifidobacterium</i> †; <i>Salmonella</i> sp., <i>Escherichia coli</i> , and <i>Clostridium perfringens</i> ↓	Acetate and butyrate†	(Kong, Dong, Gao, & Jiang, 2016)	
κ-carrageenan oligosaccharides	10 mg/mL for 72 h	<i>Prevotellaceae</i> , <i>veillonellaceae</i> and <i>Bifidobacteriaceae</i> †; <i>Enterobacteriaceae</i> , <i>Desulfovibrionaceae</i> , <i>Ruminococcaceae</i> , <i>Lachnospiraceae</i> , <i>Bacteroidaceae</i> and <i>Porphyromonadaceae</i> ↓	Acetic acid, propionic acid and butyric acid†	(Sun, Cui, Duan, Ai, Song, & Chen, 2019)	
Agaro-oligosaccharide from <i>Gracilaria lemaneiformis</i>	10 mg/mL for 48 h	<i>Firmicutes/Bacteroidetes</i> and <i>Actinobacteria</i> †	Acetic acid, propionic acid and butyric acid†	(Zhang et al., 2020)	
Ulvan	10 mg/mL for 12 and 24 h	<i>Bifidobacteria</i> and <i>Lactobacilli</i> †	Lactate and acetate†	(Seong, Bae, Seo, Kim, Kim, & Han, 2019)	
B. <i>In vivo</i> models					
SPs	Model	Dosage and duration	Microbiota diversity and composition	Metabolites	References
Fucoidan from <i>Ascophyllum nodosum</i> and <i>Laminaria japonica</i>	Standard diet-fed C57BL/6 mice	100 mg/kg for 6 weeks	<i>Lactobacillus</i> and <i>Ruminococcaceae</i> †; <i>Peptococcus</i> ↓	LPS↓	(Shang, Shan, Cai, Hao, Li, & Yu, 2016)
Fucoidan from <i>Laminaria</i> spp.	Basal diet-fed weaned pigs	720 g/kg for 8 days	<i>Escherichia coli</i> ↓	Acetic acid†	(Walsh, Sweeney, O'Shea, Doyle, & O'Doherty, 2013)
Carrageenan	Standard diet-fed C57BL/6J mice	20 mg/mL for 6 weeks	<i>Bacteroidales</i> S24-7 group norank, <i>Bacteroides</i> spp., <i>Lachnospiraceae</i> NK4A136 group and <i>Alistipes</i> spp.,† <i>Akkermansia muciniphila</i> ↓	ND	(Shang et al., 2017)
Fucoidan from <i>Fucus vesiculosus</i>	Standard chow-fed autoimmune diabetes in male mice	300 mg/kg and 600 mg/kg for 5 weeks	<i>Lactobacillus</i> , <i>Akkermansia</i> , <i>Clostridium</i> XLVa, <i>Alloprevotella</i> †; <i>Bacteroides</i> , <i>Enterorhabdus</i> , and <i>Mucispirillum</i> ↓	ND	(Xue et al., 2019)
Fucoidan from <i>Ascophyllum nodosum</i> and <i>Laminaria japonica</i>	HFD-induced MetS in male C57BL/6J mice	200 mg/kg for 16 weeks	<i>Akkermansia</i> , <i>Alloprevotella</i> , <i>Blautia</i> , <i>Bacteroides</i> and <i>Clostridiales</i> vadinBB60†; <i>Rikenellaceae</i> and <i>Alistipes</i> ↓	ND	(Shang et al., 2017)
Fucoidan from <i>Sargassum fusiforme</i>	HFD-fed male Kunming mice	100 and 400 mg/kg for 7 weeks	<i>Firmicutes/Bacteroidetes</i> ↓	ND	(Liu et al., 2021)
Fucoidan from <i>Undaria pinnatifida</i>	HFD-fed induced dyslipidemia in male SD rats	100 mg/kg for 8 weeks	<i>Bacillus</i> , <i>Ruminococcus</i> , <i>Adlercreutzia</i> , <i>Prevotella</i> , <i>Oscillospira</i> and <i>Desulfovibrio</i> †; <i>Clostridium</i> , <i>Corynebacterium</i> , <i>Staphylococcus</i> and <i>Lactobacillus</i> ↓	BSH activity†	(Chen et al., 2019)
Fucoidan from <i>Acaudina molpadioides</i>	HFD-fed male C57BL/6J mice	80 mg/kg for 10 weeks	<i>Bacteroides</i> , <i>Lachnospiraceae</i> _NK4A136 group, <i>Lachnospiraceae</i> _UCG_014, <i>Bidobacterium</i> , <i>Clostridium sensu stricto</i> _1, and <i>Alistipes</i> †; <i>Rikenellaceae</i> _RC9_gut_group, <i>Ruminococcus</i> _1, <i>Oscillibacter</i> , <i>Anaeroplasma</i> , and <i>Coriobacteriaceae</i> _UCG-002↓	LPS†; acetate, propionate and butyrate†	(Hu, Wang, Wang, Yang, Yan, & Su, 2019)
Fucoidan from <i>Sargassum fusiforme</i>	STZ-induced diabetic in mice	100 mg/kg for 6 weeks	<i>Bacteroidetes/Firmicutes</i> †; <i>Alloprevotella</i> , <i>Alistipes</i> , <i>Odoribacter</i> , <i>Millionella</i> , <i>Roseburia</i> , <i>Erysipelatoclostridium</i> , <i>Aerococcus</i> , <i>Rikenella</i> , <i>Lachnoclostridium</i> , <i>Acetatifactor</i> ↓ → <i>Firmicutes/Bacteroidetes</i>	ND	(Cheng et al., 2019)
ι-carrageenan from <i>Sarconema filiforme</i>	HFD-induced MetS in male rats	Supplement with 5% <i>Sarconema filiforme</i> for 8 weeks	<i>Firmicutes/Bacteroidetes</i> , <i>Clostridia</i> , <i>Erysipelotrichaceae</i> , <i>Blautia</i> and <i>Butyrivimonas</i> †; <i>Prevotellaceae</i> and <i>Alistipes</i> †	Butyrate and isobutyrate†	(Chin, Mi, Cao, Lim, Xue, & Tang, 2019)
κ-carrageenan from <i>Kappaphycus alvarezii</i>	HFD-fed induced obesity in C57BL/6J mice	Supplement with 5% carrageenan for 6 weeks	<i>Paraprevotella</i> , <i>Akkermansia</i> , and <i>Parasutterella</i> †; <i>Proteus</i> and <i>Enterococcus</i> ↓	Acetate and butyrate†	(Wang et al., 2020)
Fucoidan from <i>Ascophyllum nodosum</i>	CiMe-induced colonic inflammation in antibiotic-treated C57BL/6J mice	400 mg/kg for 4 weeks	<i>Paraprevotella</i> , <i>Akkermansia</i> , and <i>Parasutterella</i> †; <i>Proteus</i> and <i>Enterococcus</i> ↓	Acetate and butyrate†	(Wang et al., 2020)
κ-carrageenan from <i>Kappaphycus alvarezii</i>	Carrageenan-induced colitis in HFD C57BL/6J mice	ND for 6 weeks	<i>Alistipes finegoldii</i> , <i>Burkholderiales</i> bacterium YL45 and <i>Bacteroides acidifaciens</i> †; <i>Akkermansia muciniphila</i> ↓	ND	(Ye, Yao, Wan, Yao, & Tang, 2020)
Sulfated galactan from <i>Gelidium pacificum</i> <i>Okamura</i>	Antibiotic-associated diarrhea in male C57BL/6 mice	75, 150, and 300 mg/kg for 9 days	<i>Bacteroides</i> , <i>Oscillospira</i> , <i>Bifidobacterium</i> †; <i>Parabacteroides</i> , <i>Sutterella</i> , <i>AF12</i> , and <i>Coprococcus</i> ↓	Acetate, propionate and butyrate†	(Cui, Zhou, Wang, Zhang, Liu, & Ma, 2020)

Abbreviations: BSH, bile salt hydrolase; CiMe, ciprofloxacin-metronidazole; HFD, high fat diet; LPS, lipopolysaccharide; ND, not determined; STZ, streptozocin.

100 trillion microbial communities inhabiting in gut. The gut microbes possess a huge numbers of genes which are 150 times larger than those in the human body (Qin et al., 2010). The most remarkable genes are those encoding the unique carbohydrate-active enzymes (CAZymes) including glycoside hydrolases (GHs) for cleaving the glycosidic linkages between two or more carbohydrate units, polysaccharide lyases (PLs) for hydrolyzing the acidic sugar unit linkages, and carbohydrate esterases (CEs) for catalyzing the breakage of ester linkages (Zheng, Chen, & Cheong, 2020), which ultimately contribute to the degradation of DF in gut and the generations of metabolite profiles such as short-chain fatty acids (SCFAs). Thus, different physicochemical characteristics such as monosaccharide composition, glycosidic linkage, MW and sulfate content, and sources of DFs from seaweeds impact utilization rates of intestinal bacteria, resulting in different gut microbiota composition and consequential metabolites which may further determine the metabolic and immune status of the host (Boulangue, Neves, Chilloux, Nicholson, & Dumas, 2016). Collectively, the interactions between seaweed-derived dietary fiber and gut microbiota may be one of the most important mechanism pathways explaining the bioactivities of seaweed-derived DFs (Table 3), which will be summarized in this section.

4.1. *In vitro*

Artificial gastro-intestinal models have been widely used in analyzing the DF-gut microbiota interactions due to the advantages of reproducibility. From the phylum level, SPs from seaweed could increase the ratio of Bacteroidetes to Firmicutes, which were reported to be related to obesity risk (Zhang et al., 2020). Moreover, agar-oligosaccharides derived from *Gracilaria lemaneiformis* were found to increase the abundance of Firmicutes and Actinobacteria while its polymers with sulfated groups increased the abundance of Bacteroidetes and decreased the abundance of Firmicutes (Zhang et al., 2020). The abundance of Proteobacteria were also observed to be changed with lowering pH values under the presence of sulfated polysaccharides from *Gracilaria lemaneiformis* (Han, Pang, Wen, You, Huang, & Kulikouskaya, 2020). From the genus level, seaweeds-derived DFs such as sulfated polysaccharides from seaweeds *Enteromorpha prolifera* and *Laminaria japonica* and ulvan from green seaweed could stimulate the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, leading to the production of metabolites such as lactate and acetate (Kong, Dong, Gao, & Jiang, 2016; Seong, Bae, Seo, Kim, Kim, & Han, 2019). Fucoidan from brown seaweed *Sargassum fusiforme* significantly increased the abundance of *Faecalibacterium*, *Phascolarctobacterium*, *Bifidobacterium*, *Ruminococcaceae_UCG-014*, and *Lactobacillus*, decreased the abundance of *Prevotella_9* and *Blautia*, and accumulated total SCFAs after 24-hour anaerobic fermentation with fecal microbiota from a healthy donor (Kong et al., 2021). In addition, fucoidan from *Undaria pinnatifida* promoted the growth of *Lactobacillus casei* DM8121 and enhanced the secretion and function of BSH compared to glucose *in vitro* (Chen et al., 2021).

The fermentabilities and accompanying physiological functions of SPs from seaweeds are closely related to its concentration and molecule weight. For example, the morphology, metabolism and antibacterial abilities of *Lactobacillus rhamnosus* were enhanced along with the increased concentration of fucoidan from brown seaweed *Undaria pinnatifida* (Zhu et al., 2021). Oligosaccharides with higher degree of polymerization (DP) derived by short-term enzyme-digestion from commercial κ -carrageenan significantly promoted the populations of *Lactobacillus* and *Bifidobacterium* and the production of SCFAs after 24-hour *in vitro* fermentation, while those with smaller DP after long-term digestion downregulated SCFA and activated the pro-inflammatory IL-1 β and TNF- α in HT29 cells (Sun, Cui, Duan, Ai, Song, & Chen, 2019). In addition, low molecule weight SPs from *L. japonica* had better prebiotic activity than high molecular weight ones in the regulation of pH and production of SCFAs including acetate, butyrate, and lactic acid (Kong,

Dong, Gao, & Jiang, 2016).

4.2. *In vivo*

The progress of many diseases are generally accompanies by the dysbiosis of gut microbiota (Ding et al., 2020), and thus the intervention outcomes of gut microbiota by seaweed-derived DFs may be differentiated according to the health status of the host.

Oral administration of dietary fucoidans from *Ascophyllum nodosum* and *Laminaria japonica* significantly increased the abundance of beneficial bacteria including *Lactobacillus* and *Ruminococcaceae*, while decreased the abundance of opportunistic pathogenic bacteria such as *Peptococcus* in standard laboratory diet-fed C57BL/6 mice (Shang, Shan, Cai, Hao, Li, & Yu, 2016). Fucoidan from *Laminaria* spp. significantly decreased the abundance of attaching and effacing *Escherichia coli* in weaned pigs (Walsh, Sweeney, O'Shea, Doyle, & O'Doherty, 2013), which prevented the associated infection. Six-week treatments of carrageenans could stimulate Firmicutes and suppress Bacteroidetes and Verrucomicrobia in healthy C57BL/6J mice (Shang et al., 2017). More specifically, κ -carrageenan promoted the *Bacteroidales* S24-7 and *Bacteroides*, while ι - and λ -carrageenan upregulated the *Lachnospiraceae* NK4A136 and *Alistipes*. But *Akkermansia muciniphila* was found inhibited by all isotopes of carrageenan, which was predicted to be the mechanism of the potential pro-inflammatory feature of carrageenan.

In addition, the ratio of Firmicutes to Bacteroidetes (F/B) has been regarded to be one of the markers of obesity and diabetes (Yang & Kweon, 2016). Treatment with fucoidan from *Sargassum fusiforme* decreased the abundance of F/B in streptozotocin (STZ)-induced diabetic mice (Cheng et al., 2019). However, intake of ι -carrageenan from *Sarconema filiforme* attenuated modulated the gut microbiota of MetS mice without changing the ratio of F/B (Du Preez et al., 2020), which suggested other microbial factors participating in the alteration. *Akkermansia* has been reported to be poorly enriched in overweight adults (Dao et al., 2016). Fucoidan from *Laminaria japonica*, *Ascophyllum nodosum*, and *Fucus vesiculosus* could promote the population of *Akkermansia* in high-fat diet-fed mice and non-obese diabetic (NOD) mice (Shang et al., 2017; Xue et al., 2019; Zhang et al., 2021), which was predicted as an effective pathway to improve metabolic status. κ -Carrageenan from *kappaphycus alvarezii* decreased the abundance of *Akkermansia muciniphila* in HFD-fed C57BL/6J mice which may be the underlying reason of the development of metabolic inflammation and gave rise to the inconsistent results of the biological functions of carrageenan (Ye, Yao, Wan, Yao, & Tang, 2020). Fucoidan from *Undaria pinnatifida* upregulated the abundance of *Bacillus*, *Ruminococcus*, *Adlercreutzia*, *Prevotella*, *Oscillospira* and *Desulfovibrio* in HFD-induced dyslipidemia rats (Chen et al., 2019), and thereby stimulated the enzyme activities of BSH in the small intestine which consequently improved the serum profiles of bile acids. Moreover, fucoidan from *Ascophyllum nodosum* could enrich the SCFA-producing group including Verrucomicrobia, *Bacteroides*, *Akkermansia*, *Clostridiales vadin* BB60, *Alloprevotella* and *Blautia* in HFD-fed C57BL/6J mice (Shang et al., 2017; Zhang et al., 2021). Although both κ -carrageenan and sans-carrageenan from *Kappaphycus alvarezii* upregulated *Prevotellaceae* and *Alistipes* in HFD-induced obesity mice, κ -carrageenan upregulated the fecal concentration of isobutyrate, while sans-carrageenan increased that of butyrate (Chin, Mi, Cao, Lim, Xue, & Tang, 2019).

Previous investigations indicated that SCFAs were generally in positive correlations with metabolic homeostasis of host (Fig. 3). For instance, SCFAs could stimulate the secretion of gut hormones such as PYY and GLP-1 and improve the intestinal gluconeogenesis (IGN), leading to satiety, enhanced thermogenesis, and decreased hepatic glucose production by G protein-coupled receptor, and thereby improving glucose and energy homeostasis (Kassem, Deehan, Jens, & Fredrik, 2018). In addition, the production of SCFAs fermented from SPs is associated with the improvement of gut barrier so as to ameliorate the associated metabolic inflammation through multiple pathways, such as

limiting the penetration of oxygen by providing energy to colonocytes for β -oxidation (Byndloss, Pernitzsch, & Bäumlner, 2018); stimulating the secretion of tight junction protein from intestinal epithelial cells through hypoxia-inducible factor-1 (HIF-1) pathway (Fachi et al., 2019); and activating antimicrobial peptides including RegIII γ and defensins produced by epithelial cells which may consequently decrease the production and translocation of bacterial LPS (Zhao et al., 2018). However, it is noteworthy that administration of acetate could induce the generation of hepatic monounsaturated fatty acid and increase the secretion of ghrelin and glucose-stimulated insulin in chow-fed mice, which may be important factors to promote MetS (Kindt et al., 2018). Thus, the specific concentration and compositions of SCFAs should be taken into consideration when investigating the pros and cons of impacts on the development of MetS.

Chronic and relapsing inflammatory disorders of the intestine is closely related to the dysbiosis of gut microbiota and the accumulated harmful metabolites (Caruso, Lo, & Núñez, 2020). Fucoidan from *Ascophyllum nodosum* could alleviate the antibiotic-induced disorders of gut microbiota by increasing the abundance of *Ruminococcaceae* UCG_014 and *Akkermansia*, and decreasing the abundance of *Proteus* and *Enterococcus* in C57BL/6J mice (Wang et al., 2020). Sulfated galactan from *Gelidium pacificum* Okamura was capable of upregulating *Bacteroides*, *Oscillospira* and *Bifidobacterium* and SCFA concentrations in mice with antibiotic-associated diarrhea (Cui, Zhou, Wang, Zhang, Liu, & Ma, 2020).

SPs, especially fucoidans, were recognized as recalcitrant as no bacteria strains have yet been found to achieve entire digestion. Microorganisms corresponding to Bacteroidetes, Gammaproteobacteria and Verrucomicrobia have been reported to degrade maximum 60% of fucoidan (van Vliet, Ayudthaya, Diop, Villanueva, Stams, & Sanchez-Andrea, 2019), during which numerous genes including GH107 and GH29 would be synergistically activated for encoding highly specific enzymes (Sichert et al., 2020; Vickers et al., 2018). However, the degradation patterns of gut commensals require further investigation for revealing the precise mechanisms of the seaweeds-derived SPs.

5. Conclusions

Seaweed-derived DFs, especially those with sulfated groups, possess a variety of biological activities including metabolic modulation, immune regulation, antioxidation, anticoagulation, and anti-tumorigenesis, which are promising for depth development of products in health industry based on the research achievements of the structure–function correlations and molecular mechanisms. Thus, further investigations including the accurate catabolism mechanism of seaweeds-derived SPs by gut microbiota and the systematic pathways activated by the consequential microbial metabolites are necessary, especially for the SPs like carrageenan with inconsistent biological activities. Nevertheless, methodologies of manufacturing SPs from seaweeds also require update for better quality and higher cost performance in industry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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