Sulfated Galactofucans

Subjects: Others

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Fucoidans encompass versatile and heterogeneous sulfated biopolysaccharides of marine origin, specifically brown algae and marine invertebrates. The reported studies revealed diverse chemical skeletons in which l-fucose is the main sugar monomer. However, other sugars, i.e., galactose, mannose, etc., have been identified to be interspersed, forming several heteropolymers, including galactofucans/fucogalactans (G-fucoidans). Particularly, sulfated galactofucans are associated with rich chemistry contributing to more promising bioactivities than fucans and other marine polysaccharides. The previous reports showed that G-fucoidans derived from *Undaria pinnatifida* were the most studied; 21 bioactivities were investigated, especially antitumor and antiviral activities, and unique biomedical applications compared to other marine polysaccharides were demonstrated.

Keywords: bioactives ; brown seaweeds ; fucoidans ; heteropolysaccharides ; structural features ; sulfated galactofucans

1. Introduction

Fucoidans are unique products of marine organisms, specifically sulfated polysaccharides derived from brown algae and marine invertebrates [1]. They have gained great interest in the last few decades from different fields of sciences, including chemistry, biology, medicine, nutrition, and formulations [2][3][4][5]. All this interest is attributed to the diverse physicochemical, chemical, and biological characteristics [6][7]. These characteristics are relatively related to each other and have been studied previously in a wide variety of literature [8][9][10][11][12][13]. Hence, biological investigations are always performed after full chemical and physicochemical characterizations of purified fucoidans [14][15][16][17]. Monosaccharide composition, molecular weight, sulfation pattern, and sulfation content were found to be the most predominant factors that contribute to fucoidans' molecular mechanisms [11][12][18][19].

The aforementioned characteristics of fucoidans were demonstrated to be highly dependent on many factors, including downstream processes such as extraction either by classical solvent or non-conventional extraction methods [20][21][22], fractionation and purification methods [23][24][25], biogenic sources [24][26][27], and season of harvesting [28]. For instance, fucoidans isolated from sea cucumber showed a homogeneous chemical structure in comparison with brown seaweeds [27]. All of these factors have contributed to the chemical diversity and complexity of fucoidans, the lack of reproducibility of investigational results, and the difficulty of their approval by drug authorities and clear understanding of structure–activity relationships [29].

The chemical diversity of fucoidans has resulted in various backbones that can be classified according to monomeric composition into sulfated fucans (F-fucoidans), galactofucans/fucogalactans (G-fucoidans or G-fucans), fucomannoglucuronans (GA or U-fucoidans), and others [10][30][31][32]. Representative examples are demonstrated in **Figure 1**.

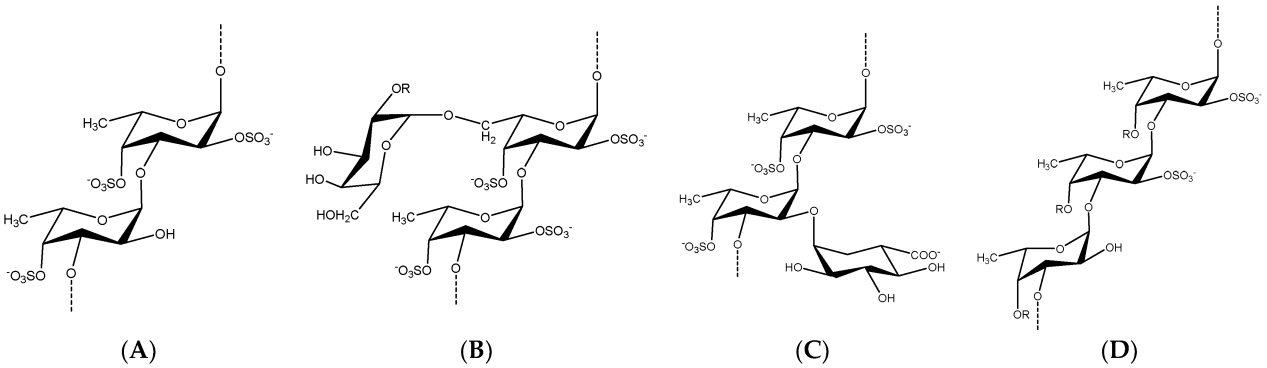

Figure 1. Different chemical backbones of fucoidans isolated from marine seaweeds in which *α*-l-fucopyranosyl residue (Fuc*p*) is the major sugar monomer. (**A**) A sulfated fucan (F-fucoidans) isolated from *Lessonia* sp., where the Fuc*p*

monomers are linked by *α*(1→3) and sulfated at *O*-4 and partially at *O*-2 [30]. (**B**) A sulfated galactofucan (G-fucoidans) isolated from *Hormophysa cuneiformis*. *β*-d-Galactopyranosyl residues (Gal*p*) are found mostly at the periphery of molecules as (1→6)-linked (R=H or SO_3^-) [32]. (**C**) Fucoidan containing uronic acid at *O*-2 isolated from *Cladosiphon okamuranus* [33]. (**D**) A sulfated xylofucan from *Punctaria plantaginea*. *β*-d-Xylopyranosyl residues (R=H or Xyl*p*) randomly substitute Fuc*p* monomers at *O*-4 [34].

2. Occurrence, Distribution, and Chemistry

Brown seaweeds, in contrast to marine invertebrates, can synthesize more complicated, diverse, and heterogeneous fucoidan backbones, including glycosidic linkages, monomeric composition, and branching sites [35][36][37]. Therefore, various G-fucoidans with different fucose:galactose ratios have been reported in the different brown algae orders, including Fucales, Laminariales, and Dictyoales [38][39].

Traces of other sugars may be found, as in the case of *Dictyota menstrualis* [40] and *Sargassum* sp. [41]. Nevertheless, the presence of high percentages of glucose, i.e., fucose:galactose:glucose ratio of 1:0.3:0.25, may indicate contamination of the G-fucoidan with laminarin [42]. In such cases, fucoidans are partially purified by ethanol or cetyltrimethylammonium bromide (CTAB) precipitation and not purified by a specific chromatographic method, including anion exchange resin using diethylaminoethyl cellulose (DEAE-C) [43] or affinity chromatography [44].

In addition, previous studies, with the aid of advanced spectral analyses, i.e., 2D NMR (e.g., HMQC, TOCSY, and NOESY) and mass spectrometry, have attempted to reveal many structural features of G-fucoidans of various biogenic sources, including glycosidic linkages, sugar configuration, branching sites, sulfation pattern, and galactose position [6][45][46]. In addition, they could deduce tentative structure bioactivity relationships, as in the case of the anti-inflammatory mechanism of galactofucan isolated from *Saccharina japonica* [47].

The results of spectral analyses showed that *α*-l-fucopyranose (Fuc*p*) and *β*-d-galactopyranose (Gal*p*) are identified mainly, in which Fuc*p* forms the major backbone and is linked via (1→4) and/or (1→3), while the *β*-d-galactopyranose molecules are found at branching sites, usually at (1→6), as in case of the G-fucoidan isolated from *Hormophysa cuneiformis*. In addition, the sulfation pattern is variable based on the glycosidic linkages. For instance, sulfate groups may occupy 2-*O* and 4-*O* in →3Fuc*p*1→ or 2-*O* and 3-*O* in →4Fuc*p*1→, in addition to 2-*O* in →3,4Fuc*p*1→ [32]. Other models of sulfated galactofucans derived from *Sargassum thunbergii* were found to possess →3Fuc*p*1→ as a main backbone with a 2-*O*-sulfated and 2,4-*O*-disulfated pattern, while the Gal*p* residues interspersed Fuc*p* in the main chain were linked mainly with →6Gal*p*1→ and 4-*O* sulfation [48]. Moreover, G-fucoidan isolated from *S. polycystum* was built up mainly of a 4-*O* sulfated →3Fuc*p*1→ backbone containing single →2Gal*p*1→ residues sulfated similarly at the 4-*O* position [49]. Several other models are demonstrated in **Figure 2** and **Table 1** and in relation to their biomedical applications.

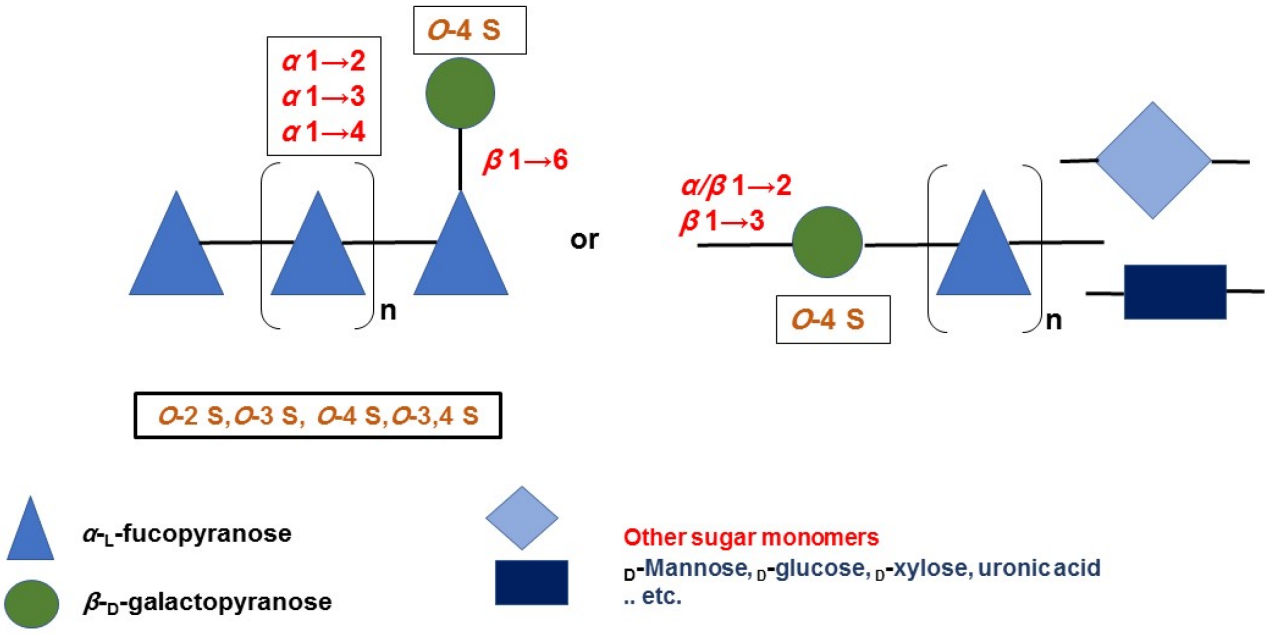

Figure 2. Structure models of sulfated galactofucans isolated from brown algae showing several possibilities of glycosidic linkages and sulfation patterns.

Table 1. Marine species of brown macroalgae (Phaeophyceae) producing G-fucoidans highlighting various structural features.

Brown Algae (Seaweed) Species	Source of Seaweed Biomass	Structural Characteristics						References
		Monosaccharide Composition	Glycosidic Bonds of Backbone	Molecular Weight (kDa)	Fucose/Galactose Ratio	Sulfate Content (%)	Sulfation Pattern	
Dictyotales								
Canistrocarpus cervicornis	Wild	Gal, fuc, glcAc, xyl,	ND		2	16.5	ND	[50]
Dictyota dichotoma	Wild	Gal, fuc, man, xyl, ara, rha, glc		23.6	1.5	33	ND	[51]
D. implexa	Wild	Gal, fuc	ND		1	18.3	ND	[52]
Lobophora variegata	Wild	Gal, fuc, Glc, man, xyl, glcAc; Gal, fuc; Gal, fuc, Glc	(1,3)- and (1,4)-α-l-fuc, and (1,3)-β-d-gal	35; ND; 1400	0.79; 0.5; 0.5	32.6; 0.2 *;15	At C4 (fuc)	[53][54]
L. variegata	ND	Gal, fuc	ND	360–1600	0.3	23.3–35.5	ND	[55]
Padina boryana	Wild	Gal, fuc	(1,4)-α-l-fuc, and (1,3)-β-d-gal	317.5/8.5	1.1	18.6	At C2 and C4 (fuc and gal)	[56]
Spatoglossum schroederi	Wild	Gal, fuc, xyl, glcAc; Gal, fuc, xyl;	(1,4)-*β*-d-gal, (1,4)-*α*-l-fuc, and (1,4)-*β*-d-xyl	21.5; 21.5–24	0.5; 0.5	19; 2.1–2.9 *	At C3 (gal) and C4 (fuc)	[57][58][59][60]
Ectocarpales								
Adenocystis utricularis	Wild	Gal, fuc, rha, man; Gal, fuc, rha; Gal, fuc, man	(1,3)-*α*-l-fuc	>100	5.53; 4.82; 5.53	23; 24; 23	At C4 (fuc and gal)	[61][62]
Scytosiphon lomentaria	Wild	Gal, fuc, rha, xyl, man, uronic acid	(1,3)-*α*-l-fuc, and (1,6)-*β*-d-gal	8.5	7.33	29.5	At C3 and C4 (fuc), and C3 (gal)	[63]

Brown Algae (Seaweed) Species	Source of Seaweed Biomass	Structural Characteristics						References
		Monosaccharide Composition	Glycosidic Bonds of Backbone	Molecular Weight (kDa)	Fucose/Galactose Ratio	Sulfate Content (%)	Sulfation Pattern	
Fucales								
Cystoseira compressa	Wild	Gal, fuc	(1,3)- and (1,4)-*α*-l-fuc	100	2.32	14.7	At C2 and C4 (fuc)	[46]
Sargassum duplicatum	Wild	Gal, fuc	(1,4)-α-l-fuc and *β*-d-gal (alternating)	34–191	1	31.7	ND	[14]
S. feldmannii	Wild	Gal, fuc	(1,3)-*α*-l-fuc	183–184	2–2.6	25.3–32	At C2, C3 and C4 (fuc), and C2, C3, C4 and C6 (gal)	[14][64]
S. fusiforme	Wild	Gal, fuc, xyl, Glc, glcAc, man, uronic acid; Gal, fuc, xyl, man, rha, glcAc, Glc	(1,3)- and (1,4)-*α*-l-fuc	90; 118.3/3.9	2; 3.7	17.5; 28.5	At C3 (fuc)	[65][66]
S. hemiphyllum	Wild	Gal, fuc	(1,6)-*β*-d-gal, (1,3)- and (1,4)-*α*-l-fuc, and (1,3)-β-d-gal	148	4.5	32	At C2 and C4 (fuc)	[67]
S. mcclurei	Wild	Gal, fuc; Gal, fuc, man, xyl, glc	(1,3)-*α*-l-fuc	ND	1.4; 2	35; 30.5	At C2 and C4 (fuc)	[68][69]
S. patens	Wild	Gal, fuc, man, xyl, Glc, galactosamine	ND	424	1.9	14.4	ND	[70][71][72]
S. polycystum	Wild	Gal, fuc, glc; Gal, fuc, man, xyl, glc	(1,3)-*α*-l-fuc, and (1,6)-*β*-d-gal	39.5; ND	5.84; 1.48	33.6; 23.4	At C2 and C4 (fuc)	[69][73]

Brown Algae (Seaweed) Species	Source of Seaweed Biomass	Structural Characteristics						References
		Monosaccharide Composition	Glycosidic Bonds of Backbone	Molecular Weight (kDa)	Fucose/Galactose Ratio	Sulfate Content (%)	Sulfation Pattern	
S. siliquosum	Wild	Gal, fuc, glc, xyl, man, rha; Gal, fuc, Glc, xyl, man, rha, uronic acid	(1,3)- and (1,4)-*α*-l-fuc	107.3; ND	1.9; 1.9	19.5; 20	At C4 and C6 (gal)	[10][74]
S. thunbergii	Wild	Gal, fuc	(1,3)-*α*-l-fuc	7.2–333.5	5.26–5.88	27.2–30.1	At C2 and C4 (fuc), and C4 (gal)	[45][48]
S. thunbergii	Purchased from local store	Gal, fuc	(1,4)-*α*-d-gal, and (1,3)-*β*-l-fuc	373	1.2	ND	NA	[75]
S. wightii	Wild	Gal, fuc, Glc, man; Gal, fuc	(1,3)-*α*-l-fuc	>3.5; ND	0.6; 3–3.5	379.1 †; 8.1–19.5	At C2 and/or C4 (fuc), or C2 and C3 (gal)	[76][77][78]
Turbinaria ornata	Wild	Gal, fuc; Gal, fuc, man, xyl, glc	(1,3)-*α*-l-fuc	ND	5; 1.2	32; 25.6	At C2 and/or C4 (fuc), and/or C2, C3, C4/C6 (gal)	[69][79]
Laminariales								
Alaria angusta	Wild	Gal, fuc	(1,3)-*α*-l-fuc	ND	1.1	24	At C2 (fuc), and C2 and C4 (gal)	[80]
Costaria costata	Wild	Gal, fuc, man, rha, xyl	ND	ND	1.2	18.9	ND	[81]
Ecklonia cava	Wild	Gal, fuc, man, rha; Gal, fuc, rha, glc	ND	ND	4.8; 3.6	19.1; 22.2	At C2 (fuc)	[81]

Brown Algae (Seaweed) Species	Source of Seaweed Biomass	Structural Characteristics						References
		Monosaccharide Composition	Glycosidic Bonds of Backbone	Molecular Weight (kDa)	Fucose/Galactose Ratio	Sulfate Content (%)	Sulfation Pattern	
Laminaria hyperborea	ND	Gal, fuc	(1,3)-*α*-l-fuc	469	44.5	53.8	At C2 and C4 (fuc)	[12]
Saccharina angustata	Wild	Gal, fuc, xyl, uronic acid	(1,3)-, (1,4) and (1,2)-*α*-l-fuc	56	9.1	4.2	At C4 (fuc and gal)	[82]
S. gurjanovae	Wild	Gal, fuc	(1,3)-*α*-l-fuc	123	3.2	25.1	At C2 and C4 (fuc), and C2 and/or C3 (gal)	[83]
S. japonica	Wild	Gal, fuc; Gal, fuc, man, xyl; Gal, fuc, man, rham, xyl; Gal, fuc, uronic acid, man, glcAc; Gal, fuc, Glc, man, rha, xyl; Gal, fuc, xyl, Glc, glcAc, rha, uronic acid	(1,3)-*α*-l-fuc	195/13.7; 1800; ND; 106.3; 23.5; 11	3.6; 1.1; 1.8; 9.1; 0.5; 10	21; 23.3; 23; 36.9; 18; 41.3	At C2 and C2/C4 (fuc)	[66][84][85][86][87]
S. japonica	Cultivated	Gal, fuc; Gal, fuc, man, rham, xyl, Glc; Gal, fuc, man, Glc, rha, xyl, uronic acid	(1,3)- and (1,4)-*α*-l-fuc	261.7; 131.5; 8.1	3.8; 2.1; 5.8	11.4; 9.1; 41.8	At C4 (fuc)	[47][88][89]
S. japonica	Provided by Fujian Yida Food Co.	Gal, fuc, man	ND	527.3	0.9	26.7	ND	[90]
S. japonica	ND	Gal, fuc	(1,3)-*α*-l-fuc, and (1,6)-*β*-d-gal	>10	3.5	48.3	At C4 and/or C2/C4 (fuc), and C4 and/or C3/C4 (gal)	[91]

Brown Algae (Seaweed) Species	Source of Seaweed Biomass	Structural Characteristics: Monosaccharide Composition	Glycosidic Bonds of Backbone	Molecular Weight (kDa)	Fucose/Galactose Ratio	Sulfate Content (%)	Sulfation Pattern	References
S. latissima	Wild	Gal, fuc; Gal, fuc, xyl, man, Glc	(1,3)-*α*-l-fuc	416–449; 453	7.8; 4.1	0.8 ‡; 0.6 ‡	ND	[92][93]
S. longicruris	Wild	Gal, fuc, xyl, man, Glc, glcAc; Gal, fuc, xyl, man, Glc, gal, glcAc	ND	1529; 638	0.8; 0.4	17.6; 19.1	At C4 (fuc) and C3 (gal)	[94]
Undaria pinnatifida	Wild	Gal, fuc, man; Gal, fuc, rha; Gal, fuc, Glc, man, rha, xyl, ara	(1,3)- or (1,4)-*α*-l-fuc	ND; 290; ND	1.1; 1.2; 1.3	29; 0.94 ‡; ND	At C2, C3, C4 (fuc), or C2 and C4 (fuc and/or gal)	[84][95][96]
Saccharina latissima	Wild	Gal, fuc, xyl, man	(1,3)-*α*-l-fuc	>150	1.5	15	ND	[97][98]
S. thunbergii	Cultivated	Gal, fuc; Gal, fuc, man; Gal, fuc, xyl, man; Gal, fuc, man, xyl, uronic acid	(1,3)-*α*-l-fuc and (1,4)-, (1,6)-*β*-d-gal	ND; 1.4–3.7; 1246; 2100	1.4; 1.1; 1.1; 1	31; 8.4; 9.2; 7.4	At C2/C4 (fuc), and C3/C6 (gal)	[99][100][101]
U. pinnatifida (sporophylls)	From mussel farms	Gal, fuc, xyl, Glc, man; Gal, fuc, xyl, Glc, man, uronic acid	ND	171; >150	1.5; 1.5	15; 15	ND	[102][103]
U. pinnatifida (sporophylls)	From Marine Resources Pty Ltd.	ND	ND	ND	ND	ND	ND	[104]
U. pinnatifida	From Marine Pty Ltd.	Gal, fuc, xyl, man	(1,3)-*α*-l-fuc	51.7	1.3	21.5	At C2 and C4 (fuc)	[105]
Adenocystis utricularis	ND	0.6–0.9 µg/mL (HIV-1)		ND	ND	ND	ND	[61][62][106]
		0.3 µg/mL (HSV-1) and 0.5 µg/mL (HSV-2)			No			[61]
Dictyota dichotoma		7.5 µg/mL (HSV-1), and 15.6 µg/mL (CVB3)			Yes. Superior to ribavirin			[51]

ND, not detailed; NA, not applicable; * reported as molar ratio to fucose; † reported as mg/g fucoidan; ‡ reported as degree of sulfation.

3. Potential Pharmacological Activities

3.1. Anticancer/Antitumor Activity

Several studies have reported the anticancer/antitumor activities of galactofucans in different cancer cell lines, as well as antiproliferative, antimetastasis, and antiangiogenic effects (**Table 2**).

Table 2. G-fucoidans showing anticancer/antitumor activity with their respective sources and half-maximal inhibitory concentrations (IC_{50}). Comparisons with standard or commercial compounds are also shown.

Source	IC_{50}	Compared with Standard/Commercial Compounds?	References
Saccharina latissima	0.35 µg/mL (elastase inhibition)	Yes. Superior to commercial heparins (UFH and tinzaparin)	[92]
Sargassum polycystum	84.63 µg/mL (leukemia cells) and 93.62 µg/mL (breast cancer cells)	No	[69][73]
S. thunbergii	29.7–93.5 µg/mL (inhibition of FGF1 binding) and 4.0–6.8 µg/mL (inhibition of FGFR binding)	No	[99][100][101]
Undaria pinnatifida (sporophylls)	0.10 mg/mL (breast adenocarcinoma) and 0.15 mg/mL (lung carcinoma)	Yes. Superior to commercial fucoidan from *Fucus* for both cancer cell lines	[102][103][111]

3.2. Antiviral Activity

Galactofucans show antiviral properties against a number of highly pathogenic viruses, including the human immunodeficiency virus (HIV-1) (**Table 3**).

Table 3. Summarized antiviral activity of G-fucoidans with their respective sources and half-maximal effective or inhibitory concentrations (EC_{50}/IC_{50}). Comparisons with antiviral drugs are also shown.

Source	EC_{50}/IC_{50}	Compared with Antiviral Drugs?	References
Adenocystis utricularis	0.6–0.9 µg/mL (HIV-1)	Yes. Superior to azidothymidine	[61][62][106]
	0.3 µg/mL (HSV-1) and 0.5 µg/mL (HSV-2)	No	[61]
Dictyota dichotoma	7.5 µg/mL (HSV-1), and 15.6 µg/mL (CVB3)	Yes. Superior to ribavirin	[51]

Source Brown Algae (Seaweed) Species	EC_{50}/IC_{50} Source of Seaweed Biomass	Structural Characteristics Monosaccharide Composition	Glycosidic Bonds of Backbone	Molecular Weight (kDa)	Compared with Antiviral Drugs? Fucose/Galactose Ratio	Sulfate Content (%)	Sulfation Pattern	References
Saccharina japonica	0.001–0.005 μg/mL (HIV-1)				No			[85]
	0.2–25 μg/mL (HSV-1)				Yes. Inferior to acyclovir and similar to heparin			[82]
U. pinnatifida (sporophylls)	ND	Gal, fuc; Gal, fuc, uronic acid; Gal, fuc, xyl, man	(1,3)-*α*-l-fuc, and (1,3)-, (1,4)-, (1,6)-*β*-d-gal	9; 9; 104.4	0.9; 0.9; ND	10.4; 10.4;	At C2 (fuc), and C3 and C6 (gal)	[107][108][109]
Sargassum mcclurei	0.96 μg/mL (HIV-1)				Yes. Inferior to AMD3100 (plerixafor)			[69]
Sphacelariales								
Sphacelaria indica	1.3 μg/mL (HSV-2), 5.5 μg/mL (HSV-1), and 4.1 μg/mL (HSV-1 acyclovir-resistant strain)	Gal, fuc, xyl, man, Glc	(1,3)-*α*-l-fuc	26	No 3.3	4	At C4 (fuc)	[110]
S. patens	>50 μg/mL (virucidal activity against HSV-2), 1.3–1.65 μg/mL (plaque formation), 1.85–3.5 μg/mL (inhibition of virus adsorption)				No			[70][71][72]
	1.5–5.5 mg/mL (HSV-1 replication) and 3–4 mg/mL (HSV-1 adsorption)				Yes. Similar to acyclovir			
S. polycystum	0.34 μg/mL (HIV-1)				Yes. Inferior to AMD3100 (plerixafor)			[69]
Scytosiphon lomentaria	0.76 μg/mL (HSV-1) and 1.34 μg/mL (HSV-2)				No			[63]
Sphacelaria indica	1.3 μg/mL (HSV-1)				Yes. Superior to acyclovir when added to the overlay medium after penetration of the viruses into the host cell			[110]
Turbinaria ornata	0.39 μg/mL (HIV-1)				Yes. Inferior to AMD3100 (plerixafor)			[69]
Undaria pinnatifida	0.77 μg/mL (HSV-1)				Yes. Superior to acyclovir			[96]
	32 μg/mL (HSV-1) and 0.5 μg/mL (HSV-2)				Yes. Superior to acyclovir			[106]
U. pinnatifida (sporophylls)	2.5 μg/mL (HSV-1), 2.6 μg/mL (HSV-2), and 1.5 μg/mL (HCMV)				No			[107][108][109]
U. pinnatifida	1.1 μg/mL (HSV-1), 0.1 μg/mL (HSV-2), and 0.5 μg/mL (HCMV)				No			[84][95][96]
	3.1 μg/mL (HSV-1) and 1.6 μg/mL (HSV-2)				No			[104]

3.3. Anti-Inflammatory, Immunomodulatory, and Anticomplement Activities

Jin et al. have studied different factors that may affect the anticomplement activity of G-fucoidans. Among them were extraction methods, molecular weight, fucose:galactose molar ratio, sulfate content, uronic acid, type of glycosidic linkage,

branching, and monomeric composition. The study concluded that larger molecular weights were more related to better activities [66]. G-fucoidans might also represent a novel and safer treatment strategy for chronic inflammation or related ailments. Six brown algal species have shown promising anti-inflammatory effects. Galactofucans from *Sargassum wightii* showed superior activity to aspirin, with EC_{90} values ranging from 0.2 to 1.22 mg/mL for inhibition of inflammatory-related enzymes [77][78]. Only the galactofucans from *Saccharina japonica* and *Lobophora variegata* have been tested in vivo with positive results [47][53][54][89]. Chen et al. showed that the investigated galactofucans from *S. japonica* were non-cytotoxic in the range of 3.125 to 25 µg/mL [47]. The anti-inflammatory was investigated in the form of fucoidan-based cream using fucoidan derived from *F. vesiculosus* of fucose:galactose ratio 1.0:0.05.

3.4. Anticoagulant and Antithrombotic Activities

Fucoidans are well-known for their anticoagulant and antithrombotic activities. These polysaccharides have attracted extensive interest in discovering safer anticoagulants, with less hemorrhagic risk and good antithrombotic activity [112]. As part of this complex class of molecules, G-fucoidans also represent a source of potential antithrombotic drugs. For example, a sulfated galactofucan from *Spatoglossum schroederi* was 2-fold more potent than heparin in stimulating the synthesis of antithrombotic heparan sulfate by endothelial cells of rabbit aorta. In vivo experiments were key to clarifying the antithrombotic activity of this galactofucan, which initially did not show an anticoagulant effect during in vitro experiments. Such an effect was demonstrated for the fraction C at 100 µg/mL with an MW of 24 kDa [57]. Fucoidans can also enhance the plasma level of recombinant tissue plasminogen activator (rtPA), a protein commonly used as a non-interventional treatment to recanalize vessels occluded by acute thrombosis.

3.5. Antioxidant Activity

The scavenging effect of fucoidans on harmful oxidants, such as superoxide anion, hydrogen peroxide, hydroxyl radicals, and singlet oxygen, has attracted considerable interest from the food and pharmaceutical industries [113]. In this regard, galactofucan from the Tunisian brown seaweed *Cystoseira compressa* exhibited valuable antioxidant properties when subjected to various antioxidant tests, i.e., ferrous ion chelation, ferric ion reduction, and DPPH radical scavenging assays (**Table 4**). For instance, the DPPH assay resulted in an IC_{50} value of 430 µg/mL compared to 560 µg/mL for sodium alginate isolated from the same organism [46].

Table 4. G-fucoidans showing antioxidant activity with their respective sources and half-maximal effective or inhibitory concentrations (EC_{50}/IC_{50}). Comparisons with standard or commercial compounds are also shown.

Source	EC_{50}/IC_{50}	Compared with Standard/Commercial Compounds?	References
Cystoseira compressa	0.43 mg/mL (DPPH)	Yes. Inferior to ascorbic acid and butylated hydroxyanisole	[46]
Sargassum siliquosum	2.58 mg/mL (DPPH)	No	[10]
S. thunbergii	0.22 mg/mL (superoxide radical), and 0.88 mg/mL (hydroxyl radical)	Yes. Similar (hydroxy radical) or superior (superoxide radical) to vitamin C	[75]

3.6. Other Biological Activities

Two recent studies have reported that galactofucans from *Sargassum siliquosum* exhibited antilipogenesis properties. According to the authors, the purified G-fucoidans (80 µg/mL) from this species induced a 28.9% reduction in lipid synthesis in human hepatoma cell line HepG2 after being induced by lipid accumulation with 1.0 mM oleate. The study used pioglitazone as a positive control at a concentration of 40 µg/mL [10][74]. In addition, the hypolipidemic effect was reported for a sulfated galactofucan from *Saccharina japonica* via inhibition of pancreatic lipase activity in a dose-dependent manner. Interestingly, this polysaccharide was not degraded by the human digestive system, likely due to its high molecular weight. Hence, this research might correlate such bioactivity not to the systemic effect, but through modulation of the microbiota composition. These results suggested that galactofucans could serve as fat-reducing health supplements without affecting the total sugar level [90].

Other properties reported for G-fucoidans, such as elastase inhibition and neuron protection activities, might be correlated to other well-studied activities (e.g., antitumor, antioxidant, or anti-inflammatory) [88][93]. Moreover, Pozharitskaya et al. used a G-fucoidan ioslated from *F. vesiculosus*, revealing its anti-hyperglycemic activity based on its inhibition of dipeptidyl peptidase-IV (DPP-IV) at IC_{50} 1.11 µg/mL [114].

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