Trends in Food Science & Technology 92 (2019) 46–64

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

An overview of extraction and purification techniques of seaweed dietary fibers for immunomodulation on gut microbiota

M. Ajanth Praveen[a,1], K.R. Karthika Parvathy[b,1], P. Balasubramanian[a,*], R. Jayabalan[b,**]

[a] Department of Biotechnology & Medical Engineering, National Institute of Technology Rourkela, 769008, India
[b] Department of Life Science, National Institute of Technology Rourkela, 769008, India

ARTICLE INFO

Keywords:
Seaweeds
Dietary fiber
Polysaccharide extraction techniques
Immunomodulation
Gut microbiota
Prebiotics

ABSTRACT

Background: Nutritional well-being is the prerequisite condition for a sustainable improvement in human welfare. Human gut microbiota plays a magnificent role in balancing the condition of metabolic syndrome management. Currently, the gut microbiome mediated immune system is gaining attention for the treatment of several health ailments such as diabetes, gastrointestinal disorders, and malnourishment. Bioactive compounds from marine polysaccharides from seaweeds are found beneficial for enhancing the activity of gut microbes.

Scope and approach: There were limited reviews in recent times to discuss the updates on extraction, purification and biological activities of dietary fibers using non-conventional methods. The present review inspects on the proximal and structural composition of seaweed polysaccharides and their methods of extraction and purification aspects. It also focuses on the immune modulating mechanisms of prebiotic-probiotic synergetic interaction by stimulating beneficial gut microbial activity and by the production of short-chain fatty acids. The mutual relationship between prebiotics and probiotics that leads to a healthy gut was targeted in the present review.

Key findings and conclusions: Marine seaweeds polysaccharides are the untapped bioresources to be explored for its biotherapeutic properties of dietary fibers. The practical complications on extracting polysaccharides by a single technique could be overcome by adopting the strategy of utilizing combinatorial extraction and purification techniques. Its prebiotic effect aids in the enhancement of gut microbial activity by exhibiting the properties of non-digestibility, fermentability, and pathogen inhibition potential. The impending benefits of dietary fiber from seaweed polysaccharides as prebiotics for formulating functional food ingredients along with probiotic microbes to exhibit immunomodulation applications. Therefore, intended human clinical trials should be carried out to evaluate and discover the probiotic-prebiotic relationship in the human gut, which could step out the research to the next level in the medicinal world.

1. Introduction

Human gut microbiota occupies a magnificent role in balancing the condition of health benefits and deadly disease management. Scientist nowadays stepped targeting towards gut microbiota mediated immune system development for the treatment of several diseases like diabetes, cancer, obesity etc. (Clemente, Ursell, Parfrey, & Knight, 2012; Rooks et al., 2016). Bioactive compounds are found beneficial for enhancing the activity of gut microbes. Marine macroalgae or seaweeds, an unexploited resource of nature are rich in bioactive compounds like polysaccharides that are called to be as dietary fibers.

Dietary fibers provide a potential prebiotic effect on human health. Seaweeds contain total dietary fiber of range 25–70%, in which soluble dietary fiber ranges from 50 to 80% (Raposo, de Morais, A. M. M. B, & de Morais, 2016). Dietary fibers of macroalgae possess several biological properties like antioxidant property (Chandini, Ganesan, & Bhaskar, 2008; Charoensiddhi, Franco, Su, & Zhang, 2015), anti-inflammatory activity (Kang et al., 2008; Sanjeewa et al., 2017; Suleria, Gobe, Masci, & Osborne, 2016), anticoagulant potency (Jin, Zhang, Wang, & Zhang, 2013; Pushpamali et al., 2008) and antiviral activity (Lozano, Wacyk, Carrasco, & Cortez-San Martín, 2016; Sinha, Astani, Ghosh, Schnitzler, & Ray, 2010). Prebiotics and probiotics are worldwide expanding the concept with currently emerging novel ideas. Molecules that can trespass to the colon without being digested and gets

* Corresponding author.
** Corresponding author.
E-mail addresses: biobala@nitrkl.ac.in (P. Balasubramanian), jayabalanr@nitrkl.ac.in (R. Jayabalan).
[1] First and second authors contributed equally.

https://doi.org/10.1016/j.tifs.2019.08.011
Received 26 September 2018; Received in revised form 27 June 2019; Accepted 12 August 2019
Available online 14 August 2019
0924-2244/

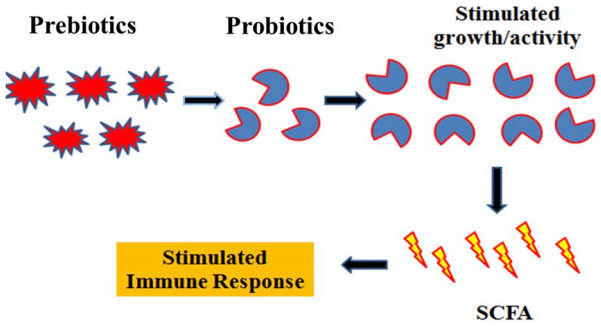

Fig. 1. Stimulation of immune response in the host system by prebiotics and probiotics.

digested after reaching colon are said to be prebiotic compound. Prebiotics induce an immune response (Fig. 1) by modulating the gastrointestinal microbial activity and leads to the fermentation and production of SCFA (Short Chain of Fatty Acids), which in turn, confers to several physiological effects on the host.

Several emerging extraction and purification technologies are reported so on such as conventional solvent extraction (CSE), microwave aided extraction (MAE), ultrasound aided extraction (UAE) and enzyme-aided extraction (EAE). The appropriate extraction methods are chosen based on its composition and biological activity to minimize the damage to the polysaccharide (Cui et al., 2018). The extracted polysaccharides are crude mixtures with monosaccharide composition, sulfate groups and variable molecular weight followed by purification procedures like chromatography, filtration techniques (Xu, Huang, & Cheong, 2017). This review gives a detail knowledge about the structure of various seaweed polysaccharides, novel extraction and purification methodologies of seaweed polysaccharides and its immunomodulatory effects on gut microbiota.

2. Marine macroalgal seaweeds

Seaweeds are an unexploited resource that holds boundless taxonomic diversity with high contents of polysaccharides, proteins, dietary fibers, etc. Seaweeds are multicellular and macroscopic simple plants that had been widely used all over the centuries for several therapeutic and industrial applications such as edible healthy supplementary food, pesticides, fertilizers, gelling substance and for many other purposes (Imbs, Ermakova, Malyarenko, Isakov, & Zvyagintseva, 2016). Seaweeds or marine macroalgae usually continue to exist by attaching themselves to rough surfaces like rock and other hard substrates that are found along the coastal regions. Seaweeds are rich in dietary fiber and it contributes a larger nutritional value compared to the terrestrial plants. They possess amino acids that are most essential, omega 3 fatty acids and vitamins like A, B, C and E. Marine macroalgae are primarily classified into three types based on the colour of the thallus. They are Chlorophyceae (green seaweeds), Rhodophyceae (red seaweeds) and Phaeophyceae (brown seaweeds). Brown seaweeds are rich in polysaccharides when compared to the green and red seaweeds which is illustrated in Fig. 2.

Chlorophyceae or green seaweeds obtain their green colour because of the presence of pigments chlorophyll *a* and *b* in equal amount. They also possess yellow pigments called beta-carotene and brown pigments named xanthophylls. It was found that more than 4500 species of green seaweeds exist in this world. Out of the 4500 species, 3100 species are found favourable to freshwater and 1500 species are marine. Green seaweeds contain polysaccharides such as starch, cellulose, and ulvan which comprised of building blocks such as glucose, mannose, rhamnose, xylose, uronic acid and glucuronic acid (Fernández, Raffo, Alberghina, & Ciancia, 2015; Jung, Lim, Kim, & Park, 2013; Wei, Quarterman, & Jin, 2013).

The most diversified class of seaweed is the red algae that obtain their colour from the pigments named phycoerythrin and phycocyanin that covers other pigments such as chlorophyll *a*, particular and certain xanthophylls pigment and beta-carotene (Kravchenko, Barabanova, Glazunov, Yakovleva, & Yermak, 2018). It was found that more than 6500 species of red seaweeds are available all over the world. Most commonly they are marine favourable and are established along the interior tidal and subtidal region of the ocean. Red seaweeds are mostly found at a depth that ranges from 40 to 250 m. Red seaweeds are rich in polysaccharides such as carrageenan, agar, cellulose, and lignin which comprised of building blocks such as glucose, galactose and agarose (Jung et al., 2013; Wei et al., 2013).

The supremacy pigment found in the brown seaweeds is fucoxanthin from which they obtain the brown colour that covers the other pigments such as chlorophyll *a*, chlorophyll *c*, beta-carotene and erstwhile xanthophylls. More than 1800 species of brown seaweeds are available all over the world and most of them are marine species. Universally most brown algae are established and found their growth in cold water. Majorly Fucales and Laminariales are the species that constitute maximum biomass of brown seaweeds worldwide (Lim et al., 2017, pp. 27–46). Brown seaweeds are rich in polysaccharides such as laminarin, mannitol, alginate, fucoidan, cellulose which comprised of building blocks such as glucose, rhamnose, galactose, fucose, xylose, mannose, uronic acid, glucuronic acid and mannuronic acid (Jung et al., 2013; Wei et al., 2013). The phlorotannin and phlorotannin-rich seaweed extracts has large spectrum of activity (anti-inflammatory and anti-allergic potential) with minimum toxicity (Barbosa, Lopes, Andrade, & Valentão, 2019). The high content of phlorotannin seaweed extract obtained from both *A. nodosum* and *F. vesiculosus* equally prevents lipid oxidation in canola oil under accelerated conditions in foods (Jacobsen, Sørensen, Holdt, Akoh, & Hermund, 2019). Vasconcelos et al. (2018) observed that the suitable marine glycans/glycoconjugates are interrelated with their structural properties such as (i) monosaccharide composition, (ii) the degree of substituents (sulfation and/or acetylation), (iii) length of the sugar chains, (iv) the presence and type.

2.1. Proximal composition of seaweeds

2.1.1. Protein

. The protein content of the majorly available seaweed ranges from 5 to 20% by dry weight. Factors such as the temperature of the saline water, salinity, availability of nutrients and exposure to light determine the chemical composition of the macroalgae. Many studies on proximal composition reported that protein content of brown seaweed lies between 3 and 15% and green or red seaweeds between 10 and 47% (Chan et al., 2017). The protein content among various types of seaweed is listed below in Table 1.

2.1.2. Carbohydrate

In general, seaweeds are rich in polysaccharide than the terrestrial plants. The complex cell wall of seaweed contains polysaccharides intertwined with proteins and other contents. Mostly seaweeds constitute carbohydrate content that ranges of about 50–60% by their dry weight (McDermid and Stuercke., 2003). Red seaweeds constitute 40–70% carbohydrate by dry weight that is higher than that of the carbohydrate content in brown and green seaweeds (30–60%) by dry weight (Chan and Matanjun, 2017). The carbohydrate content among various types of seaweeds is listed below in Table 2.

2.1.3. Lipids

Seaweeds are not a good resource for biodiesel because of their less lipid content (Zubia et al., 2003; Chan and Matanjun, 2017). Seaweeds contain a higher level of PUFA (Poly Unsaturated Fatty Acids) namely omega three and six fatty acids. Seaweeds because of the content of polyunsaturated fatty acids play a vital role in the treatment, prevention and control of osteoarthritis, diabetes and cardiac diseases (Mendis

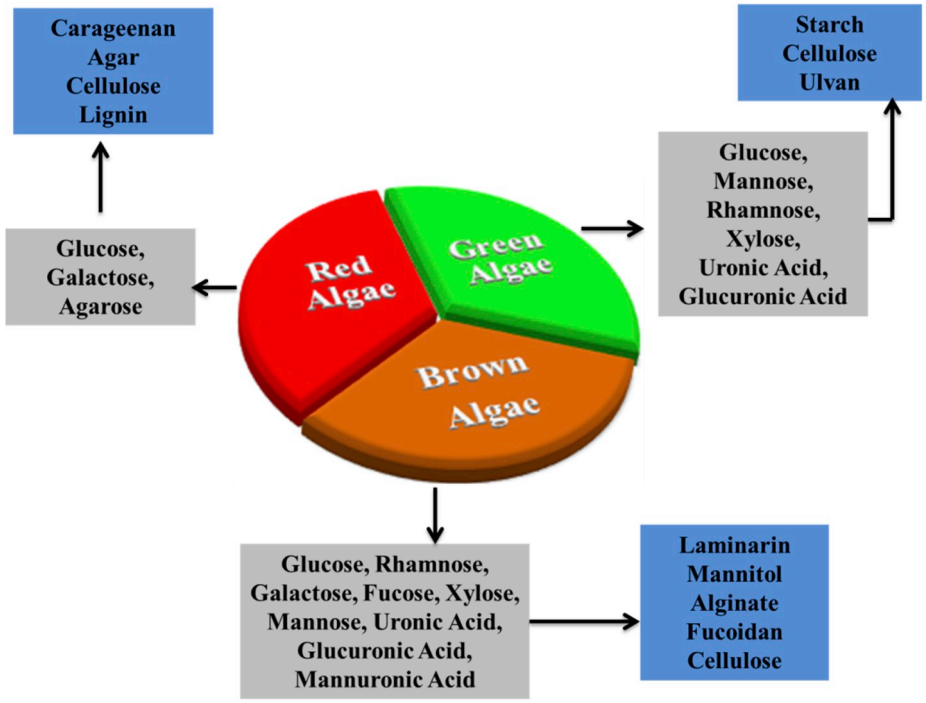

Fig. 2. List of predominant polysaccharides and its building blocks that are found in various classes of seaweeds.

and Kim, 2011). The lipid content of seaweeds mostly lies between the ranges of 1–5% that are shown in Table 3.

2.1.4. Dietary fiber from edible seaweeds

The non-digestible polymers of carbohydrate that are edible in nature can be termed as dietary fiber. Dietary fiber can be found naturally in terrestrial plants and marine seaweeds. Seaweeds naturally contribute and comprised more amount of dietary fiber by their physique (Raposo et al., 2016). As described earlier carbohydrate polymers that are resistant to gastrointestinal enzymes and that possess specific characters of selectivity and fermentability are been stated as dietary fibers. The dietary fiber content among various types of seaweeds is listed in Table 4.

2.2. Structural composition of macroalgal polysaccharides

The structural composition and the concentration of the dietary fibers in seaweeds vary from region to region based on pigmentation. Phaeophyta or brown seaweed contains polysaccharides such as laminarins, alginate, and fucans (Haugan, 1994; Lim and Aida, 2017). Chlorophyta or green seaweed contains ulvan, cellulose, and starch (Robic, Gaillard, Sassi, Lerat, & Lahaye, 2009; Fernández et al., 2015). Rhodophyta or red seaweed contains agar and carrageenans (Mchugh, 2003; Kravchenko et al., 2018).

The green seaweed polysaccharides composed of majorly, cellulose, glucans, mannans, xylans, rhamnose, galactose, arabinose, xylose, and starch. Polysaccharides of the green algae mostly contain sulphate and uronic groups (Lahaye, 1991). The cell wall comprised of a huge amount of sulfated polysaccharide with sulfate content up to 16% and uronic acids of range 15–20% (Fernández et al., 2015). Ulvan from *U. lactuca* composed of a linear arrangement of subunits of β-(1 → 4)-xyloglucan, cellulose, and glucuronan. Ulvan was found to be soluble in water and resistive to human digesting enzymes stimulates beneficial colonic bacterial growth (Ray & Lahaye, 1996).

Brown seaweed polysaccharides comprised of three different groups such as laminarians, fucans, and alginates. Alginates are polyuronide, a gelling substance comprised of 20–30 units of alternative binding sequences of β-(1 → 4) bonded D-mannuronic acid. Most reserved group of polysaccharide associated with the brown algae is laminarians, structurally composed of β-(1 → 3) D glucose with (1,6) linkages. Linkages sometimes replaced by mannitol group. Fucans are of three types namely fucoidans, glycurono galactofucans, xylofucoglycuronans. Fucoidans constitute branched chains of α-(1 → 2) bond linked L-fucose 4 sulphate with C3 ester group and a trace quantity of xylose, galactose, mannose and uronans. Glycouronogalactofucans primarily comprised of (1 → 4)-D-galactose with C5 L-fucose 3, sulphate (replaced by uronic acids). Xylofucoglycouronans constitute primary groups of β-(1 → 4) bond linked D-mannuronic acid along with the presence of 3-O-D linked xylosyl, L-fucose,4 -sulphate (replaced by uronic acids) (Fleury & Lahaye, 1991; Ale, Mikkelsen, & Meyer, 2011).

Red seaweed contains sulfated galactans, carrageenans, and agar that constitute xylans, mannans and cellulose. The cell walls of red seaweed comprised of three sections namely fibrillar wall, glycoprotein domain, and amorphous matrix structure. Dry matter accounts for about 65% (w/w) in the cell wall. The reticulated cell wall is formed by a fibrillar wall containing polysaccharides and the glycoprotein domain held together by the amorphous matrix structure (Kravchenko et al., 2018). Cellulose the most common element along with other polysaccharides in the fibrillar wall is mostly inert. D-glucose units that are linked by β-(1 → 4) glycosidic bond act as the backbone of the cellulose. D-mannose or D-xylose units that are linked by β-(1 → 4), β-(1 → 3) glycosidic bonds act as a substitute for D-glucose for some cases (Miller et al., 1997). The amorphous matrix structure is formed by sulfated galactans with repeated A and B subunits. The D-conformation of β-galactose corresponds for A subunits and D, L-conform monomers of α-galactose correspond for the B subunits. B units in certain cases are replaced by 3,6-anhydrogalactopyranose. Carrageenans that are chemically modified by substituting same or different molecule at various ratio leads to form a different structure called as hybrid carrageenan.

Red seaweeds of order *Gigartinales* mostly synthesize the polysaccharide carrageenan. The red seaweed species that come under order *Gigartinales* are *Gigartina, Chondrus crispus, Eucheuma, and Hypnea*. Carrageenan is composed of repetitive A and B subunits. β-D-galactopyranose corresponds to A subunit and α-D-galactopyranose corresponds to B subunit (Kravchenko et al., 2018). The sulfation degree in carrageenans is higher than that of the agarans (Vázquez-Delfín,

Table 1
Variation of protein content among different seaweeds.

Edible seaweeds	Protein (%)	References
Brown seaweeds		
Adenocystis utricularis	7–15	Ponce, Pujol, Damonte, Flores, and Stortz (2003)
Ascophyllum nodosum	7–15	Fleurence (1999)
Dictyota dichotoma	9.4	Anantharaman et al. (2013)
Fucus spp.	7–15	Fleurence (1999)
Hizikia fusiformis	13.9	Jang, Cho, Jeong, and Kim (2012);
	7–15	Dawczynski, Schubert, and Jahreis (2007)
Laminaria japonica	14.8	Jang et al. (2012)
Laminaria digitata	7–15	Fleurence, (1999)
Laminaria ochroleuca	7.4	Dawcznski et al. (2007)
Laminaria spp.	7–15	Dawczynski et al. (2007)
S. boveanum	13.9	Qasim (1981)
S. coreanum	14.4	Heo, Lee, Song, and Jeon (2003)
S. echinocarpum,	10.3	Heo et al. (2003)
S. filipendula	<10	Dawes. (1987)
S. fulvellum	13.0	Kim, Li, Jung, Chang, and Lee (2011);
	14.2	Heo et al. (2003);
	19.9	Jang et al. (2012)
S. hemiphyllum	<10	Chan, Cheung, and Ang (1997)
S. henslowianum,	11.3	McDermid and Stuercke (2003)
S. horneri	17.2	Heo et al. (2003)
S. japonica	10.6	Jang et al. (2012)
S. lomentaria	16.8	Marinho-Soriano, Fonseca, Carneiro, and Moreira (2006)
S. mangarevense	13.2	Zubia, Payri, Deslandes, and Guezennec (2003)
S. myriocystum	<10	Matanjun, Mohamed, Mustapha, and Muhammad (2009)
S. obtusifolium	13.0	Zubia et al. (2003)
S. patens	<10	Badrinathan, Suneeva, Shiju, and Pragasam (2011)
S. polycystum	<10	Murakami et al. (2011)
S. pteropleuron	11.0	Prince and Daly., (1981)
S. thunbergii	13.8	Zubia et al. (2003)
S. vulgare	15.7	Marinho-Soriano et al. (2006)
S. wightii	8–13	Robledo and Pelegrin (1997)
Sargassum filipendula,	8.7–10	Wong and Cheung., (2001)
Turbinaria ornate	14.6	Anantharaman et al. (2013)
U. pinnatifida	18.3	Jang et al. (2012)
Undaria pinnatifida	18–19	Sánchez-Machado, López-Cervantes, Lopez-Hernandez, and Paseiro-Losada (2004)
Green seaweeds		
Codium fragile	11	Kulshreshtha et al. (2015)
E. intestinalis	14.5	Anantharaman et al. (2013);
	12.2	Chirapart, Praiboon, Puangsombat, Pattanapon, and Nunraksa (2014)
E. linza	31.6	Jang et al. (2012)
Enteromorpha compressa	13.8	Anantharaman et al. (2013)
Rhizoclonium riparium	13.9	Chirapart et al. (2014)
U. fasciata	22.2	Mairh, Ohno, and Matsuoka (1991)
U. lactuca	20.6	Kim et al. (2011)
Ulva rigida	6.6	Satpati and Pal., (2011)
Red seaweeds		
Chondrus crispus	27	Kulshreshtha et al. (2015)
Gracilaria amansii	15–21	Cirik, Çetin, Ak, Cirik, and Göksan (2010)
	13.1	Kim et al. (2011);
	18.3	Jang et al. (2012)
G. cervicornis	19.7–22.9	Marinho-Soriano and Bourret (2003)
G. changii	6.9	Norziah and Ching (2000)
	12.5	Cui et al. (2018)
G. cornea,	5.4	Robledo and Pelegrin (1997)
G. coronopifolia	10.5	Ortiz et al. (2009)
G. cylindrical	14.0	Esteves, Taouil, and Suzuki (2005)
G. parvispora	7.6	Norziah and Ching (2000)
G. salicornia	18.7	Chirapart et al. (2014)
G. salicornia	5.6	McDermid and Stuercke (2003)
G. tenuistipitata	6.8	Chirapart et al. (2014)
G. verrucosa	24.0	Marrion et al. (2005)
Gracilaria chilensis	13.7	Roesijadi, Jones, Snowden-Swan, and Zhu (2010)
Gracilaria corticata	12.4 – summer 7.6 – monsoon	Kalesh and Muraleedharan, 2003
Gracilaria crassa	11.4	McDermid and Stuercke (2003)
Gracilaria verrucosa	10–15	Msuya and Neori (2002);
	9.8	Anantharaman et al. (2013)
Hypnea musciformis	13.5	Anantharaman et al. (2013)
Gracilaria spp.	<5	Prasad, (1986)
Pyropia tenera	36.88	Hwang, Ki, and Chung (2013)
P. haitanensis	32.16	Hwang et al. (2013)

Robledo, & Freile-Pelegrín, 2014). The structure of carrageenan is determined by the number and location of sulphate groups, pyranosidic ring conformation of 3,6-anhydrogalactopyranose (Vázquez-Delfín et al., 2014). More than 15 different structures of carrageenans are traditionally named using Greek letters. The most commercial interested structure are kappa, iota, and lambda that find their application as gelling, stabilizing and thickening agents in food, cosmetics and pharmaceutical industries based on their rheological properties (Al-Alawi, Al-Marhubi, Al-Belushi, & Soussi, 2011).

Agar constitutes the chemical entity of D-galactose and 3,6, anhydrous L-galactose. *Pyropia*, *Gracillaria,* and *Gelidium* are certain species that contains polysaccharide agar. Due to the presence of agar content, these seaweeds undergo gelation while cold water extraction. The variety in the structure is due to substituent groups like sulfate, pyruvate, and methoxy (Melo, Feitosa, Freitas, & De Paula, 2002). Agar synthesized by *Porphyra* species are named as porphyrans. These porphyrans have a high substitution of β-D-galactose and 6-O-methyl-β-D-galactose than the subunits of α-L-galactose, α-L-galactose-6-sulfate (Jiang, Hama, Yamaguchi, & Oda, 2011).

3. Seaweed polysaccharide extraction methods

The preferred and desired compounds of seaweeds that own therapeutic potential which can be ingested are removed with the help of technologically developed, compatible and economically feasible methods. Seaweeds and their typical cell wall act as an obstacle to all these techniques. The chemical composition and biological activity of the seaweed polysaccharides play a significant role in determining the suitable extraction method (Ale et al., 2011; Fitton, Stringer, & Karpiniec, 2015). Water-based (aqueous) extraction, diluted acidic extraction, and other chemical-based extraction has been used and are considered as the conventional methodology of extracting marine algal polysaccharides (Ale et al., 2011; Rioux, Turgeon, & Beaulieu, 2007). Technology-based (microwave, ultrasonication) and enzyme assisted methods have been introduced because of the increased yield, bioactivity, the industrial and therapeutic relevance of the seaweed polysaccharides. In the same time, these methods also aid in upholding the chemical composition, their interior structure, and several imperative properties. Aqueous based extractions are cheap and eco-friendly but the efficiency of the yield is too low compared to technology-based techniques (Garcia-Vaquero, Rajauria, O'Doherty, & Sweeney, 2017). Aqueous based extractions are found to be compatible and can be used for functional food development. Conventional solvent extraction methods are based on solvents like chloroform, butanol, and hexane and are not favourable for functional food development. To date, techniques involved in extracting seaweed polysaccharides are conventional solvent extraction (CSE), microwave aided extraction (MAE),

Table 2
Variation of carbohydrate content among different seaweeds.

Edible seaweeds	Total Carbohydrate (%)	References
Brown seaweeds		
Dictyota dichotoma	10.0	Anantharaman et al. (2013)
Hizikia fusiformis	59.0	Jang et al. (2012)
L. japonica	51.9	Jang et al. (2012)
S. coreanum	67.2	Heo et al. (2003)
S. filipendula	55–65	Dawes, (1987)
S. filipendula	55–65	Dawes, (1987)
S. fulvellum	39.6	Kim et al. (2011);
	44.5	Jang et al. (2012);
	62.4	Heo et al. (2003)
S. hemiphyllum	17.9	Wong and Cheung. (2001)
S. horneri	55.4	Heo et al. (2003)
S. japonica	66.0	Jang et al. (2012)
S. myriocystum	18.0	Badrinathan et al. (2011)
S. polycystum	33.4	Matanjun et al. (2009)
S. pteropleuron	55–68	Dawes, (1987)
S. thunbergii	63.6	Heo et al. (2003)
S. vulgare	67.8	Marinho-Soriano et al. (2006)
S. wightii	50–57	Manivannan, Thirumaran, Devi, Hemalatha, and Anantharaman (2008)
		Kumar, (2013)
Turbinaria ornate	15.4	Anantharaman et al. (2013)
U. pinnatifida	52.0	Jang et al. (2012)
Green seaweeds		
E. intestinalis	63.3	Chirapart et al. (2014);
	28.5	Anantharaman et al. (2013);
	30.5	Chakraborty and Santra. (2008)
E. linza	37.4	Jang et al. (2012)
Enteromorpha compressa	24.0	Anantharaman et al. (2013)
Rhizoclonium riparium	45.0	Chirapart et al. (2014)
U. lactuca	54.3	Kim et al. (2011);
	35.2	Chakraborty and Santra. (2008)
Ulva rigida	22.0	Satpati and Pal. (2011)
Red seaweeds		
G. corticata	17.0	Anantharaman et al. (2013)
G. salicornia	63.8	Chirapart et al. (2014)
G. tenuistipitata	67.1	Chirapart et al. (2014)
G. changii	41.5	Cui et al. (2018)
Gelidium amansii	55–60	Wi, Kim, Mahadevan, Yang, and Bae (2009);
	77.2	Kim et al. (2011);
	74.4	Jang et al. (2012)
Gracilaria cervicornis	68.8	Marinho-Soriano et al. (2006);
	>60	Ortiz et al. (2009)
Gracilaria verrucosa	56–60	Marinho-Soriano et al. (2006)
Hypnea musciformis	27.0	Anantharaman et al. (2013)

Edible seaweeds	Insoluble Carbohydrate (%)	References
G. verrucosa	23.0	Kumar, (2013)
S. wightii	18.0	Kumar, (2013)
S. echinocarpum	<5	McDermid and Stuercke. (2003)
S. obtusifolium	<5	McDermid and Stuercke. (2003)
S. fillipendula	35–55	Dawes (1987, 1989)
S. pteropleuron	35–55	Dawes (1987, 1989)
Gracilaria spp.	10–30	Prasad (1986)
Edible seaweeds	Soluble carbohydrates (%)	References
G. cornea	36.2	Kumar, (2013)
G. coronopifolia	15.0	Kumar, (2013)
G. parvispora	23.0	Kumar, (2013)
G. salicornia	20.0	Kumar, (2013)
G. verrucosa	~34	Kumar, (2013)
S. wightii	35.0	Kumar, (2013)
S. echinocarpum	11–12	McDermid and Stuercke. (2003)
S. obtusifolium	11–12	McDermid and Stuercke. (2003)
S. fillipendula	10–23	Dawes (1987, 1989)

Table 3
Variation of lipid content among different seaweeds.

Edible seaweed	Total Lipid content (%)	References
Brown seaweeds		
Sargassum sp.	1.5-3.5	Chan et al. (1997); Heo et al. (2003); Wong and Cheung (2001); Zubia et al. (2003); Manivannan et al. (2008)
C. abrotanifolia;	~1	Abdel-Fattah and Hussein et al. (1970)
Cystoseira barbata	~1	Abdel-Fattah and Hussein et al. (1970)
Dictyota dichotoma	3.7	Anantharaman et al. (2013)
Hizikia fusiformis	0.4	Jang et al. (2012)
L. japonica	1.8	Jang et al. (2012)
Laminaria ochroleuca	<2	Sánchez-Machado et al. (2004)
S. echinocarpum	3.8	Wong and Cheung. (2001)
S. fulvellum	0.3	Heo et al. (2003);
	1.4	Kim et al. (2011);
	0.5	Jang et al. (2012)
S. henslowianum	4.5	McDermid and Stuercke. (2003)
S. horneri	0.5-1.0	Marinho-Soriano et al. (2006);
	5–11	Wong and Cheung. (2001)
S. japonica	1.6	Jang et al. (2012)
S. lomentaria	0.6	Matanjun et al. (2009)
S. mangarevense	3.4	McDermid and Stuercke. (2003)
S. patens	6.1	Wong and Cheung. (2001)
S. polycystum	0.3	Murakami et al. (2011)
S. pteropleuron	0.6-2.7	Heo et al. (2003);
S. thunbergii	0.3	Marinho-Soriano et al. (2006)
S. vulgare	0.45	Matanjun et al. (2009)
S. wightii	2–3	Kumar, (2013)
Sargassum linifolium.	~0.5	Abdel-Fattah and Hussein et al. (1970)
Turbinaria ornate	3.4	Anantharaman et al. (2013)
U. pinnatifida	1.8	Jang et al. (2012)
Undaria pinnatifida	<1	Sánchez-Machado et al. (2004)
Green seaweeds		
E. intestinalis	5.3	Anantharaman et al. (2013)
Enteromorpha compressa	4.3	Anantharaman et al. (2013)
Ulva rigida	12	Satpati and Pal et al. (2011)
Red seaweeds		
Gracilaria sp.	<3	Norziah and Ching (2000); Kalesh (2003); Marinho-Soriano et al. (2006); McDermid and Stuercke (2003); Manivannan et al. (2008, 2009); Ortiz et al. (2009)
G. changii	0.3	Cui et al. (2018)
G. corticata	3.1	Anantharaman et al. (2013)
G. cylindrical	6.0	Esteves et al. (2005)
G. salicornia	1.9	Chirapart et al. (2014)
G. tenuistipitata	0.3	Chirapart et al. (2014)
G. verrucosa	5–6.5	Kumar et al. (2013)
Gelidium amansii	1.1	Kim et al. (2011);
	0.0	Jang et al. (2012)
Gracilaria cervicornis	0.4	Marinho-Soriano et al. (2006)
Hypnea musciformis	3.9	Anantharaman et al. (2013)

ultrasound aided extraction (UAE) and enzyme-aided extraction (EAE).

3.1. Conventional solvent extraction

Brown seaweed polysaccharides are generally extracted by the conventional solvent extraction method since it is the ancient and extensively applied method. Diluted acidic extraction of the brown seaweed polysaccharides contained mostly fucose with laminarin, alginate, alginic acid and mannitol (Kylin, 1913). In addition to HCL acid dilution step, Hoagland and Lieb. (1915) attempted a soaking step of sodium carbonate for brown seaweed polysaccharides precisely for alginate extraction. Rioux et al. (2007) introduced stepwise extraction of the seaweed polysaccharides that involves crude extraction with solvents such as ethanol, petroleum ether, t-butanol, chloroform in order

Table 4
Variation of total dietary fiber content among different seaweeds.

Edible seaweed	Total dietary fiber (%)	References
Brown seaweeds		
A. esculenta	42.8	Kraan, (2013)
C. abies-marina	56.3	Kraan, (2013)
E. bicyclis	10–75	Patara, Visbeck, Masina, Krahmann, and Vichi (2011)
Laminaria sp.	36.0	Dawczynski et al. (2007)
S. fusiforme	35–45.9	Burtin (2003)
S. hemiphyllum	61.3	Chan et al. (1997)
S. henslowianum	61.1	Wong and Cheung. (2001)
S. horneri	42–55	Murakami et al. (2011)
S. mangarevense	42.8	Zubia et al. (2003)
S. patens	54.8	Wong and Cheung. (2001)
S. polycytum	39.6	Zubia et al. (2003)
S. wightii	44–53	Zubia et al. (2003)
S. wightii	48.0	Prosky, Asp, Schweizer, DeVries, and Furda (1988)
U. pinnatifida	16–51	Dawczynski et al. (2007)
Green seaweeds		
C. racemosa	33–40	Patara et al. (2011)
Enteromorpha sp.	33.4	Patara et al. (2011)
U. compressa	41.1–55.4	Patara et al. (2011); Anantharaman et al. (2013)
U. lactuca	38.1–43	Burtin (2003)
U. pertusa	52.1	Yoshie, Suzuki, Shirai, and Hirano (1997)
U. reticulate	65.7	Yoshie et al. (1997)
U. rigida	38–40	Yoshie et al. (1997)
Ulva sp.	38.0	Patara et al. (2011)
Red seaweeds		
E. cottonii	25.5	Msuya and Neori. (2002)
G. changii	22.7	Marinho-Soriano et al. (2006)
	64.7	Cui et al. (2018)
G. crassa	22.7	MacArtain, Gill, Brooks, Campbell, and Rowland (2007)
G. verrucosa	52.0	Wong and Cheung. (2000)
G. verrucosa	50–56	Zubia et al. (2003)
H. charoides	50.3	Wong and Cheung. (2000)
H. japonica	53.2	Norziah and Ching. (2000)
P. capillacea	52.0	MisurCoVa et al., (2010)
P. umbilicalis	33.7	MisurCoVa et al., (2010)
Palmaria palmate	33.7	Matanjun et al. (2009)
Porphyra sp.	48.6	Matanjun et al. (2009)

to eliminate the proteins, pigments, and other contaminants (Rioux et al., 2007). Once pretreated with the solvents, the residue is treated with the diluted acid or water and placed in an external heat source such as a water bath in order to undergo hydrolysis. Calcium chloride helps in precipitation and immobilization of the alginic acids and other polysaccharides. Alginate is commonly extracted with the help of sodium carbonate. Precipitation and extraction of polysaccharides are generally processed with polar solvents like ethanol and acetone because polysaccharides are insoluble in the polar solvents. Once they are precipitated, polysaccharides are obtained with the help of downstream techniques such as membrane filtration or centrifugation.

3.2. Emerging techniques

3.2.1. Microwave-aided extraction

Electromagnetic waves that possess wavelength of range from 1 m to 1 mm and frequency of 0.3 GHz–300 GHz are termed as microwaves. The frequency of microwave as by federal communication commission is associated with scientific, medical and industrial purpose is 2.45 GHz and 915 MHz. Microwave frequency associated with lab work and domestic work is 2.45 GHz (Garcia-Vaquero et al., 2017). Conventional heating makes use of the heat from peripheral sources such as the heating mantle, water bath, and oil bath. The heat from the peripheral or external source protrudes from the outer surface of the material to the internal surface by means of conduction. This mechanism makes the heating process a bit slow. Some portion of heat energy is wasted in heating the container rather than the material inside (Okolie, CK Rajendran, Udenigwe, Aryee, & Mason, 2017). In the case of microwave heating, heat energy is directly applied to the material by the molecular interaction of the electromagnetic waves so that overall volumetric heating occurs.

Microwave aided extraction is important because of the benefits compared with conventional chemical extraction. Factors that provoke one to utilize microwave aided extraction are controllability, time efficiency and energy efficiency. Minimum extraction time, minimum use of solvent and maximum recovery and yield increased the attention of scientist towards microwave aided extraction (Routray & Orsat, 2012). The volumetric distribution of heat energy by ionic conduction of dispersed ions and the dipolarisation of the solvent hold the principle of microwave extraction. As reported earlier, microwave heating is considered to be more fast, effective, efficient and controllable in comparison with the conventional heating (Yuan & Macquarrie, 2015).

Microwave aided extraction is found to be the optimal method for extraction of biomass and pyrolysis. Molecular vibration enhances the temperature of the material and increases the loss of water thus leads to the cell death and discharge of the interior molecule (Hahn, Lang, Ulber, & Muffler, 2012). Fucoidan extracted from the *F. vesiculosis* by microwave heating with the pressure of 120 psi for 1-min time duration resulted in a yield of about 18%. The short time yield provides more attention to microwave heating than the multiple step extraction (Rodriguez-Jasso, Mussatto, Pastrana, Aguilar, & Teixeira, 2011). Extraction of polysaccharide fucoidan from brown seaweed *Ascophyllum nodosum* showed greater antioxidant activity (Yuan & Macquarrie, 2015). The MAE has been considered to be the most effective compared to all other methods, because it extracts structurally desirable fucoidan from *Ascophyllum nodosum* (Okolie, Mason, Mohan, Pitts, & Udenigwe, 2019). Though microwave aided technique can be fast, time saving and controllable, it can be executed in the lab scale process only (Fitton et al., 2015). In the case of industrial-scale use of microwave heating is finding an obstacle that can be overcome soon.

3.2.2. Ultrasound-aided extraction

Ultra-sonication works on the principle of compression and rarefaction induced by the ultrasonic waves that range from 20 to 20000 Hz. The ultrasonic waves induce small vacuum bubble formation and breakage of the bubble that ends up in cavity formation leading to cell wall breakdown and lysis of cells. Ultrasonic waves aided extraction are the substitutive energy input based extraction that assists in releasing favourable and desired compounds. The cavitation induced by localized pressure and heat energy solubilize the polysaccharides (Kadam, Tiwari, Smyth, & O'Donnell, 2015). Further, they identified that extraction with ultrasound aided technique provides more yield of about 11% than microwave aided extraction with a yield of 9.56% and conventional chemical extraction in a shorter time with 4.67% yield (Okolie et al., 2017). The high input waves with pressure can be unfavourable because it could damage the integral structure and complex chemical composition of the desired polysaccharides.

3.2.3. Enzyme-aided extraction

Enzyme-aided extractions are substantial because of its action and hydrolysis process over heterogeneous algal cell wall in order to release internal compounds like polysaccharides and proteins. The cell wall of macroalgae is complex consisting of polysaccharides embedded with proteoglycans to form an extracellular matrix. Polysaccharides intertwined with the protein and bounded ions like calcium and potassium make the extraction process hard and time-consuming. Enzyme-aided extraction helps to overcome the complication with other extraction

techniques. Many scientists provided high recovery results with the enzymatic methods with solvent-free nature (Charoensiddhi et al., 2015, 2016). The improvement in yield and recovery of bioactive components with enriched biological properties leads to emerging of novel food products (Charoensiddhi, Conlon, Franco, & Zhang, 2017). Carbohydrase enzymes like viscozyme, celluclast and ultraflo were used and reported with convincible results. Protease enzymes like alkalase, neutrase and flavoenzymes were used. The optimum temperature for these enzymes ranges from 50 to 60 °C. Mostly used buffers were phosphate and acetate buffer. The carbohydrases enzymes are endo-β-glucanase and cellulase enzymes that cleave at 1,3 or 1,4 linkages in the β glucans and cellulose. Protease enzymes reported were endoprotease and exoprotease assists in cleaving the internal and external peptide bonds. Polysaccharides intertwined with the protein and sulfated groups are released easily with less time consumption (Sanjeewa et al., 2017). The utilization of the commercial enzymes enhanced the extraction efficiency to 5–20% than the conventional chemical extraction. Higher recovery of bioactive compounds up to 70% using protease from *E. radiata* was reported. Enzymatic extractions also assist in improving the antioxidant properties of seaweed polysaccharides (ORAC assay) from 30% to 90% (Charoensiddhi et al., 2015). The overall benefits and bottlenecks of various extraction methods in view of energy requirement and yield were presented in Table 5.

4. Polysaccharide purifying techniques

After successful extraction of seaweed polysaccharides by different methods, the polysaccharides are subjected to purification. The extracted polysaccharides are mostly composed of monosaccharides and sulfate (Geng et al., 2018). Other than this little quantity of phenolic, flavonoid and other compounds that exhibit several immunological activities in both in-vitro and in-vivo condition are present (Ale et al., 2011). Purification techniques were adopted to enhance and enrich the mixture of compounds with selective and desired polysaccharide compound of interest (Jin et al., 2013). Techniques that are most frequently used for polysaccharide purification are chromatographic and filtration techniques.

4.1. Chromatography

4.1.1. Ion-exchange chromatography

Ion exchange chromatography works on the principle based on the affinity of ions or polar molecules towards the ion exchanger. Ion exchange chromatography is commonly used in several pharmaceutical industries because of its application in separating the desired charged drug molecule. The separating principle behind this chromatographic technique is binding or adsorption of charged molecules over the immobilized oppositely charged ion exchange groups. Elution of the sample is done by altering the pH or concentration of the running buffer (Rieman & Walton et al., 2013). Other than polysaccharides, purification of proteins, amino acids and nucleotides can be done. Anion exchange and cation exchange are the two types of Ion chromatography. When the desired molecule is positively charged, cation exchange chromatography is utilized. The negatively charged stationary phase attracts the positively charged molecule (pH < pI). When the desired molecule is negatively charged anion exchange chromatography is utilized. The stationary phase is positively charged that attracts the desired negatively charged molecule (pH > pI). Ion exchange chromatography is the most frequently used chromatographic-liquid technique for purification because of its wide application on high efficiency, high resolution, huge sample handling capacity and automated and cost-effective (Acikara, 2013). For polysaccharide purification anion exchange

Table 5
Comparison of different seaweed polysaccharide extraction methods.

Principle	Energy requirement	Yield (%)	Advantage	Disadvantage	References
Conventional solvent extraction (CSE)					
Polarity based extraction and thermal hydrolysis using a water bath	_	4.67	✓ Traditionally used method ✓ No energy input is required ✓ Easy handling ✓ Easy availability ✓ of solvents	✓ Time-consuming ✓ Low yield ✓ High solvent Requirement ✓ Presence of Residues ✓ Not suited for functional food development	Garcia-Vaquero et al. (2017); Okolie et al. (2017); Moumita et al. (2017,2018)
Microwave-aided extraction (MAE)					
Dielectric and overall volumetric heating by microwaves	2.45 GHz	9.56	✓ Less solvent Consumption ✓ Improved yield ✓ Automated process ✓ Less time consumption	✓ Energy input required ✓ Cause damage to heat sensitive compounds ✓ Loss of property can occur	Yuan and Macquarrie. (2015); Fitton et al. (2015); okoli et al., (2019)
Ultrasound-aided extraction (UAE)					
Compression and rarefaction (Pressure variation and cavitation)	20 KHz 50-60 KHz	11	✓ Time efficiency ✓ Less solvent Consumption ✓ Cost-effective ✓ Improved yield ✓ Huge possibility of industrial scale-up & Automated process	✓ Energy input required ✓ Can cause damage to integral structure due to pressure variation	Rodrigues et al., 2015; Kadam et al., 2015; Garcia-Vaquero et al. (2017); Shi, Yan, Cheong, and Liu (2018)
Enzyme-aided extraction (EAE)					
Breakdown of glycosidic linkage and other interior bonds	_	50–70	✓ Time efficiency ✓ High catalytic efficiency & specificity ✓ Enzymes used are eco-friendly, non-toxic and food grade level ✓ High yield ✓ High chance for industrial scale up	✓ Limited due to its high price	(Rodrigues et al., 2015; Charoensiddhi et al., 2015; 2016; Okolie et al., 2017; Sanjeewa et al., 2017); Praveen, Parvathy, Jayabalan, & Balasubramanian, 2019

Table 6
Benefits and limitations of different seaweed polysaccharide purification techniques.

Polysaccharide purification technique	Benefits	Limitations	References
Ion exchange chromatography	✓ Change of pH and salt concentration ✓ High selectivity & resolution ✓ Scale-up and scale-down ✓ Cheap maintenance	✓ High equipment cost ✓ Stability & reproducibility	Rieman & Walton et al. (2013); (Acikara, 2013); Imbs et al. (2016)
Affinity chromatography	✓ High specificity ✓ High degree of purity ✓ Reproducibility	✓ Expensive ligands ✓ Leakage of ligands ✓ Limited lifetime ✓ Relatively low productivity	Dunlap (2013); Hahn et al. (2016)
Size exclusion chromatography	✓ Simplicity, reliability & versatility ✓ Ease of scale up ✓ Less analysis time ✓ Polydisperse samples	✓ Excess operating cost ✓ Pre-filtration of sample ✓ Low resolution ✓ Low sample handling	Hahn et al. (2016)
Membrane filtration	✓ Ease operation ✓ Design flexibility ✓ Ease scale-up ✓ Desalting	✓ Membrane fouling ✓ Expensive membranes ✓ Low sensitivity	Hjelland et al. (2012); Patel et al. (2013); Marcati et al. (2014); Xu et al. (2017)

chromatography is best suited and widely used. Fucoidan, the most available brown seaweed polysaccharide is positively charged. The anionic charge of fucoidan is due to the presence of sulfated ester groups embedded in the backbone composed of carbohydrates. Elution is done either by stepwise (Cong et al., 2016) or salt (NaCl) gradient (Dinesh et al., 2016; Imbs et al., 2016; Wang, Wang, Yun, Zhang, & Zhang, 2012). Fucoidan fractions of different molecular weight can be purified by anion exchange chromatography based on the degree of sulfate content. The high salt concentration is required for eluting heavily sulfated fucoidan fraction to enhance the resin interaction stronger. Anion exchange chromatography used for purifying fucoidan fractions of seaweeds with a distinct structural and chemical composition (Geng et al., 2018; Hahn et al., 2012).

4.1.2. Affinity chromatography

Affinity chromatography is a chromatographic method for separating the biological mixture. It works on the principle of high and specific interaction seen between antigen and antibody, enzyme and substrate, receptors and proteins. The interaction is due to ionic, hydrophobic, hydrogen and disulfide bond linkage. The specific interaction between the desired molecule and the ligand attached to the chromatographic column matrix assist purifying the biological compounds (Dunlap, 2013). In protein purification, dye affinity chromatography is used so that the polysaccharide from the crude extract gets attached to the dye and is eluted (Janson, 2012). For polysaccharide purification like fucoidan, lectins were utilized to effectively retrieve fucoidan from the crude extract. Fucose from fucoidan binds to lectin and this specific interaction is used for purification. Sulfate in the fucoidan can hinder and interrupt the binding of fucose subunits by interacting with lectin. Donor-acceptor domain complex is formed between the anionic sulphated polysaccharides and the cationic toluidine and methylene blue dyes. Amino derived sepabeads interaction with the toluidine blue dye provides the development of dye affinity chromatography which donates better and promising results for eluting highly purified fucoidan (95%) from the brown seaweeds (Hahn et al., 2016).

4.1.3. Size exclusion chromatography

Size exclusion chromatography (SEC) or molecular sieve chromatography is a separation method of eluting desired molecules ina solution mixture, based on their size and molecular weight by passing them through physically, chemically stable and inert porous matrix. Size exclusion chromatography is commonly applied for eluting large macromolecular compounds like polysaccharides, proteins, etc. Unlike Ion exchange chromatography, the buffer concentration does not have any impact in the case of SEC. Size exclusion chromatography can be utilized directly after any purification techniques using a buffer that is suited to the molecule in terms of purification and preservation (Mori & Barth., 2013). Previously reported studies described the utilization of certain criteria and Size exclusion chromatography conditions for different polysaccharide purification. Most frequently using columns for polysaccharide purification are PL aquagel OH, Sepharose CL-6B, Sephacryl S-300 and Superdex 200 (Cong et al., 2016; Wang et al., 2012). Columns that are found to be successfully connected are TSK (G4000, G3000) SW-XL (Anastyuk, Imbs, Shevchenko, Dmitrenok, & Zvyagintseva, 2012). Laminarins and fucoidans of brown seaweed polysaccharides were successfully purified in different fractions based on their molecular weight. Compound with higher salt concentration can be purified and desalted by size exclusion chromatography (Hahn et al., 2016).

4.2. Membrane filtration

Other than the chromatographic techniques, novel techniques like membrane filtration were used for polysaccharide purification. Membrane filtration method helps in purifying molecular compounds based on their molecular weight. The desired sample mixture placed in a membrane with ranging molecular weight cut off (MWCO) subjected to dialysis for effective removal of salt and other contaminants (Anastyuk et al., 2010). Hjelland, Andersen, and Yang (2012) described the utilization of MWCO membranes for purifying brown seaweed polysaccharide compounds like fucoidan and laminarin. Membrane filtration technique found application in purifying extracellular polysaccharides of microbes like bacteria (Wingender, Neu, & Flemming, 2012), soluble polysaccharides from plants (Wan, Prudente, & Sathivel, 2012) and microalgae (Chen et al., 2011; Marcati et al., 2014).

Membrane filtration techniques have several advantages like large-scale industrial purification and automated setup (Patel et al., 2013). This technique includes microfiltration, ultrafiltration, reverse osmosis, and nanofiltration for fractionation of marine algae (Xu et al., 2017) Membrane fouling is the term that hinders industries to apply this purification technique. It also leads to low performance and resolution, more energy input and frequent replacement of membranes (Marcati et al., 2014). Tangential flow filtration, sequential ultrafiltration and decreased MWCO diafiltration techniques were proposed to overcome the issue of membrane fouling (Marcati et al., 2014). The overall benefits and limitations of various polysaccharide purification techniques were presented in Table 6.

5. Prebiotic concept

Gibson and Roberfroid (1995) introduced the concept of prebiotics which has been redefined as, “ingredient that is selectively fermented, which allows certain changes in composition as well as the activity of

gastrointestinal microbes and which are potentially beneficial for host and health". The three basic criteria for considering it as a prebiotic substance are non-digestibility, selectivity and fermentability (Roberfroid, 2008; Raposo et al., 2016). Some examples of prebiotic polysaccharides are inulin, oligofructose, galacto oligosaccharides, lactulose, mushrooms, chicory roots and seaweeds (Kolida & Gibson, 2008; Moumita et al., 2017; Praveen, Parvathy, Jayabalan, & Balasubramanian, 2019). The prebiotic oligosaccharides enhance the growth of beneficial bacteria like *Lactobacillus, Bifidobacterium* and decrease the harmful bacteria like *Helicobacter, Salmonella* and others (CK Rajendran, Okolie, Udenigwe, & Mason, 2017). These prebiotics interacts with beneficial gut microbes leads to the production of SCFA which in turn generates mucin production, direct interaction with immune cells, decreased cell permeability against pathogens, improved health of gut epithelial cells (Rooks and Garrett, 2016). Marine polysaccharides and their byproducts (SCFA) mitigate metabolic disorders like altering the enteroendocrine hormone secretion and blood glucose levels by cellular signal pathways (Wang et al., 2018). Rico et al. (2018) assessed the bioactivities of seaweeds which species could diminish the cardiometabolic risk factors of Metabolic syndrome (MetS) and showed that *H.elongata* reduces LPS-induced inflammation and triglyceride accumulation.

5.1. Prebiotic oligosaccharides

Carbohydrates that are resistant and non-digestible to digesting hydrolytic enzymes are considered as prebiotics or short-chain carbohydrates. Prebiotic oligosaccharides have a degree of polymerization (DP) of two and are soluble in 80% ethanol (De Sousa, dos Santos, & Sgarbieri, 2011). Some prebiotic oligosaccharides like chicory insulin have a DP of 60 (Tanabe, Nakamura, & Oku, 2014). Carbohydrate conferred as prebiotic only if it satisfies the following criteria (Sridevi, Sumathi, Guru Prasad, & Kumar, 2014). i) It should not be absorbed or be digested in the upper part of the gastrointestinal tract. ii) Should be digested only in the colon region of the large intestine by potentially beneficial bacteria like *Lactobacillus and Bifidobacterium*. iii) Should be a selective substrate/carbon source for beneficial bacteria so as to induce an increase in their growth. iv) Should promote optimistic effect by removal of Ca, Mg, Fe, and other excessed trace elements. v) Should regulate the level of other invading pathogens in large intestine thereby reducing the risk of infection and colon cancer.

The low molecular weight polysaccharides which come in the DP of two to nine (2–9) and monomers in the range of 8–20. Because of their low degree of polymerization, the fermentation of these dietary fibers became easier for the gut microbiota to release end products like SCFA (Moreno, Corzo, Montilla, Villamiel, & Olano, 2017). To obtain these polysaccharides with a low degree of polymerization, techniques like acid hydrolysis and ultrasound was utilized. Acid hydrolysis does not find their significance except neutral sugars rich polysaccharides such as fucoidan, galactan, and carrageenan. Acid hydrolysis method cannot break several glycosidic bonds which hinders their application and pave way for other low molecular weight derivatives (Geng et al., 2018). Most commonly used acids were orthophosphoric acid, hydrochloric acid, and trifluoroacetic acid. Phosphoric acid was used commonly and found to be suitable for degrading higher molecular weight polysaccharides. HCl and trifluoroacetic acid are found unsuitable for degradation in some cases. HCl was used to hydrolyze agarose or galactose bonds (Sun, Wang, Shi, & Ma, 2009).

Free radical degradation was attempted by regulating temperature and time duration of the process. Hydrogen peroxide and copper salts were utilized to avoid breakage of the ring structure. Using this technique fucoidans with the low molecular weight of 7–8 kDa was isolated (Nardella et al., 1996). Zhou et al. (2004) reported λ carrageenan (*Chondrus ocellatus*) of low molecular weight 9–15 kDa are found to have more immune modulatory and anti-tumour activity rather than the normal size.

5.2. Physiognomies of prebiotic dietary fibers

5.2.1. Non-digestibility

A prebiotic substance should be indigestible by the digesting enzymes in the upper gastrointestinal tract in order to reach the colonic microbes as a selective substrate as discussed earlier in section 5.1. The characteristic of non-digestibility can be verified by examining the compound resistance to hydrolysis by acid and enzyme under in-vitro condition. Hu et al. (2006) in his report mentioned that agarose derived oligosaccharides showed resistance to amylolytic enzymes and remained stable even after incubating 24 h with the enzymes. The whole experiment was performed through electrophoresis analysis. Galactoside (glycerol) from red seaweed *Porphyra yezoensis* remains indigestible by the digesting enzymes (salivary, pancreatic, gastric and other intestinal enzymes). Galactoside from the red seaweed was also found to be a fermentable compound (Muraoka et al., 2008). It was noted in rats that the red seaweed polysaccharide galactoside was not adsorbed along with the small intestinal segments. Deville, Damas, Forget, Dandrifosse, and Peulen (2004) in his report discussed that the brown seaweed polysaccharide laminarin remains undigested after incubating them with HCl and digesting enzymes under in-vitro conditions. Glycoside bonds of certain dietary prebiotics are non-digestible by hydrolytic enzymes because of the inbuilt configuration of anomeric (C1, C2) carbon atoms. Digestibility and fermentability of *Ascophyllum nodusum* in simulated digestion model produces short-chain fatty acids confirmed the uphold ratio of Bacteroidetes to Firmicutes. There was an increase in growth of *Bacteroides ovatus* and further breaking down of fucoidan (Chen et al., 2018).

5.2.2. Fermentability

Another characteristic that the substance should hold in order to consider them as prebiotic is the gut microbe fermentation (Gibson & Roberfroid, 2008). The fermentation characteristic can be studied under in vitro conditions by incubating the compound with the pure and isolated culture of potentially beneficial bacteria's like *Lactobacillus and Bifidobacteria*. The same test should be carried out with pathogenic organisms like *Enterococcus, Vibrio cholerae* etc. Carbohydrates that find their path to cecum acts as a selective substrate for fermentation ends up in the release of SCFA (Boler & Fahey, 2012). SCFA are anions that have 1 to 6 carbon atoms produced by bacterial prebiotic fermentation (Ganapathy, Thangaraju, Prasad, Martin, & Singh, 2013). It is evident by in-vitro studies that SCFA induce bacterial growth and activity (Mussatto & Mancilha, 2007).

SCFA are produced in the large intestine after bacterial breakdown and fermentation of the dietary fibers. SCFA are the products formed after fermentation involves acetic acid, lactic acid, propionic acid, uronic acid and butyric acid along with methane gas, carbon dioxide and hydrogen gas (Wang et al., 2017). These fermented products induce several physiological effects in the human gastrointestinal system. There is an assumption that water-soluble dietary fibers are highly fermentable. Alginates are fermentable, and 65% of them are processed and metabolized into SCFA (Michell et al., 1996). It was reported that certain aqueous soluble dietary fibers namely fucoidan and cellulose are not fermented easily (Fujii, 1992). *Ulva lactuca* have high soluble fiber content, but it showed a modest rate of fermentation in rats (Andrieux et al., 1998). A prebiotic compound as an active substitute for carbon source is used and is inoculated with the pure culture to estimate the growth rate at a particular time interval. Hu et al. (2006) in his study reported that polysaccharides like agarose derived Neoagaro-Oligosaccharides (NAOS) were fermented by beneficial microbes and not by pathogen like *Enterococcus*. Fructo oligo saccharide an accepted prebiotic compound was used as a standard to compare the growth rate by colony forming unit. Polysaccharide extract of red seaweed along with the small protein content was fermented by the beneficial *Bifidobacteria* and other intestinal strains (Muraoka et al., 2008). Galactoside was studied for fermentation with more than 15

bacterial strains and positive results were obtained. It was also fermented by potential pathogens like *Clostridium, Bacteroides* and not by *Enterococcus* (Muraoka et al., 2008). Palanisamy, Vinosha, Marudhupandi, Rajasekar, and Prabhu (2017) studied that fucoidan from *S.asperum* has bioactivities like antioxidant and antibacterial properties which are right inclined to the concentration of fucoidan present the seaweeds which could be utilized for the development of antibacterial drugs in future.

5.2.3. Pathogen inhibition potential

Prebiotics that had been ingested should be a specific substrate for only beneficial microbes. They should not act as a substrate for pathogens that causes deadly diseases. As a consequence, the biomass of significantly potential microbes will be higher than the pathogens. Non-digestible oligosaccharides exhibit the potency to prevent binding of the invading pathogen on the epithelial cell surface (Quintero-Villegas et al., 2013). Several toxins releasing pathogens like *Salmonella, Campylobacter jejuni, Vibrio cholera and Clostridium* cause diseases by growing inside the GIT and start invading tissues of the host (Jain, Gupta, & Jain, 2014). Toxins can result in producing nausea, diarrhoea, vomiting and other disorders by disrupting intestinal mucosa (Wittke, Banavara, & Munoz, 2014). By the mechanism of adherence, bacteria adhere themselves to the intestinal surface and are not eliminated by natural host displacement processes like peristalsis and acid excretion (Gourbeyre, Denery, & Bodinier, 2011). The pathogen inhibition ability of the non-digestible oligosaccharides found application in the treatment of gastro-related diseases and disorders (Lozano et al., 2016). Potential prebiotics prevented the existence and development of causative pathogens of foodborne diseases such as *Salmonella* and *E.coli* in pigs (Tran, Everaert, & Bindelle, 2018).

5.3. Macroalgal dietary fiber as prebiotics

Many researchers provided substantial results that dietary fibers have sway over gut microbial growth and fermentation. Macroalgae though comprise a splendid amount of carbohydrate that ranges from 25 to 70% by their dry weight, these polysaccharides mostly retain as undigested nature in gastrointestinal tract and exhibit as dietary fibers (Okolie et al., 2017). Dietary fibers are the outlined skeletal residues of a plant cell that are impervious to enzymatic hydrolysis. Prosky et al. (1988) reported that dietary fibers are of two types namely soluble and insoluble fibers that are shown in Fig. 3. Dietary fibers can eliminate toxic substances and inhibit their mobility by binding to them. Soluble fibers regulate and maintain blood glucose and cholesterol (Raposo et al., 2016). Soluble fibers without being absorbed can pass through and reach the colon. Digestion is slowed down because of their viscous property. Sometimes, soluble fibers can decrease the nutrient availability and absorption, because the nutrients adhere themselves to the soluble fibers. Insoluble fibers enhance the mobility of compounds found in the digestive tract and promote bulking of stool and help to overcome constipation and other stomach irregularity (O' Sullivan et al., 2010).

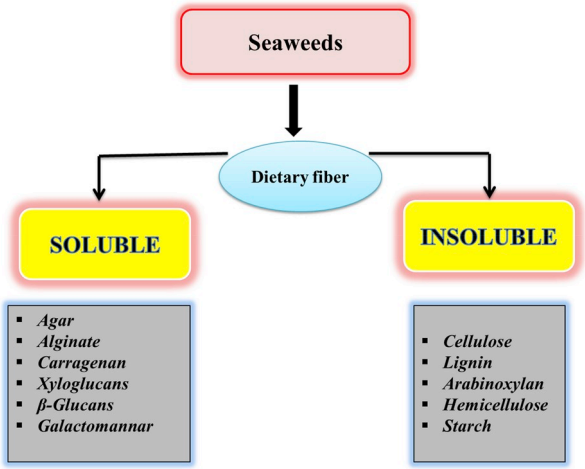

Fig. 3. Classification of soluble and insoluble dietary fibers among seaweeds.

5.3.1. Dietary fiber and its systemic effects

Dietary fiber in seaweeds exhibit several characteristics like fermentability, dispersibility, and viscosity in water, adsorb or binding capacity and their ability to bulk. These characteristics showed local and systemic effects in the gastrointestinal tract (Davidson & MC Donald, 1998; Schneeman, 1998). The local effects revealed by bowel, that can be mentioned are decreased the mobility of the bowel contents, homogenous mixing of the gastric contents, altered diffusion and enhancement in bile acid and other bound compounds excretion, improved microbial biomass and metabolic products. The systemic effects showed are decreased digestion rate and less adherence/absorption of lipids and carbohydrates. Due to the less adherent capacity of the lipids cholesterol level is regulated and maintained.

It was reported that *Undaria* and *Porphyra* polysaccharides decreased the level of enzymes that assist the conversion of pro-to carcinogens in rats (Gudiel-Urbano & Goñi, 2002). *Ascophyllum* oligosaccharides increased the microbial biomass of *Lactobacillus and E. coli* in pigs (Dierick, Ovyn, & De Smet, 2009). Polysaccharides of the brown algae *Laminaria* enhanced the fermented metabolic products SCFA and ammonia level in the colon of pigs (Lynch, Sweeney, Callan, O'Sullivan, & O'Doherty, 2010). In human, it was reported that alginates had increased the population of beneficial gut microbiota (Terada, Hara, & Mitsuoka, 1995). The low molecular weight polysaccharides of the red algae *Gelidium* reduced the level of putrefactive compounds and microorganisms, thereby showed a positive result on increasing the beneficial microorganisms and production of SCFA (Wang, Han, Hu, Li, & Yu, 2006).

Gelidium polysaccharides exhibited the property of improving the level of *Bifidobacterium*, acetic acid and propionic acids (Ramnani et al., 2012). In rats, it was reported that the oligosaccharides of seaweed *Chondrus* enhanced the histomorphological property of the colon, improved the immune system defence mechanism by increased production of immunoglobulin IgA and IgG (Liu et al., 2015). The biomass of the spirulina showed reduced pathogen and detrimental bacteria like *P. vulgaris, B. subtilis, and B. pumulis*. The biomass content of *Isochryis* induced microbial biomass improvement of lactic acid bacteria in rats (Nuno et al., 2013). Many recent in-vitro studies showed systemic effects of the dietary fibers from the polysaccharides of the marine seaweeds. Polysaccharides from marine seaweeds such as Chlorophyta, Rhodophyta, Phaeophyta have a prebiotic effect on intestinal microbes and stimulate an immune response that is summarized in Table 7.

6. Probiotics

Probiotics are live microbes which tend to restore the healthy gut microbiota and improves beneficial functions by increase the proportion of healthy gut bacteria through cross-feeding. The most commonly utilized microbes were *Lactobacilli* and *Bifidobacteria*, genera. These probiotic microbes consume prebiotics as diet source to produce short chain fatty acids (SCFA) which in turn stimulates immune responses. Recently probiotics are taken in the form of fermented dairy products like curd, cheese, etc. Commensal bacteria like *E.coli* assists in the production of Vitamin K2 keep checking for bad bacteria like *Enterococcus fecalis* whichcause illness (Daniluk, 2018).

6.1. Predominant probiotics in the gut

Probiotics along with prebiotics lead to a symbiotic physiological effect on the host organisms. Probiotics are significantly beneficial

Table 7
Prebiotic effect & immune response stimulation of seaweed polysaccharide.

Compound	Source	Expt.	Prebiotic effect	Immune response	References
Brown seaweeds					
β glucans	*L. digitata*	*In vitro*	↑*Bifidobacteria* ↑ SCFA ↓pH	↑ TNF-α in human	Zhao and cheung (2011); Miyanishi, Iwamoto, Watanabe, and Oda (2003)
Fucoidan	*L. japonica* *F. vesiculosis* *U. pinnatifida*	*In vitro*	↑Beneficial bacteria, ↑SCFA ↓pH ↓*Enterobacteria*	↑TNF-α, IL-12, IL-6, MMP-9, Phagocytosis ↑lysozyme activity, nitrous oxide, dentritic cell ↓anti-inflammatory cytokines IL- 4,5,13.	Kong, Dong, Gao, and Jiang (2016); Cong et al. (2016)
Laminarin	*L. digitata,* *L. hyperborean*	*In vivo*	↑Acidic mucin production in wistar rats	↑pro-inflammatory cytokines (IL-1, IL-8, TLR-2) ↓TNF-α, nitrite level	Okolie et al. (2017)
Alginate	Purchased (Nuotai, Shangai-China)	*In vitro*	↓*Enterococcus* in gut of pigs	↑pro-inflammatory cytokines (IL-1β, IL-6, IL-12 nitrous oxide and TNF-α) in RAW 264.7 cell line	Wang et al. (2006); Xu et al. (2014)
	L. japonica	*In vivo*	↑ *Lactobacillus*& *Bifidobacteria* in rats	↑Immunological activity of intestinal cells	
Laminarian + Fucoidan	*L. hyperborean*	*In vivo*	↑*Lactobacillus* ↓diarrhoea	↑TNF a, IL-1a, IFN g, IL 4, IL 6	Lynch et al. (2010); Dinesh et al. (2016)
Brown Polysaccharides	*E. radiata,* *A. nodosum* *S. japonica*	*In vitro*	↑Beneficial bacteria & SCFA	Interact with TLR-2 and TLR-4 to activate NF-κB	Makarenkova et al. (2012); Charoensiddhi, Conlon, Vuaran, Franco, and Zhang (2016); Geng et al. (2018)
Green seaweed					
Ulvan	*Ulva lactuca*	*In vitro*	↑Beneficial bacteria & SCFA	Improve wound repair Increased growth promoters to induce intestinal epidermal growth	O' Sullivan et al. (2010)
Red seaweeds					
Carrageenan	*S. gaudichaudii,* *C. crispus*	*In vitro*	↑ *Bifidobacterium spp.* ↓*C. perfringens*	↑ innate immune genes ↓ host infection rate	Liu et al. (2014); Kulshreshtha et al. (2014)
Ï,κ- carrageenan	*E. spinosum*	*In vivo*	↑Beneficial bacteria & SCFA	↑ IL-8, BCL-10 Production Induce apoptosis, cancer prevention Inhibit cell proliferation	Borthakur, Bhattacharyya, Dudeja, and Tobacman (2007, 2012)
Polysaccharides extract	*Lithothamnion spp.*	*In vitro*	↓*Enterococcus*	Inhibit polyp formation ↑ IL-1β, IL-6 and TNF-α	Drew et al. (2014)
	L. calcareum	*In vitro*	Improved histo morphology of colon	Inhibit Ki67 antigen-a proliferation marker in human colon culture cell lines	Dame, Veerapaneni, Bhagavathula, Naik, and Varani (2011)
Agaran	*P. columbina*	*In vitro*	Improvement in gut microbiota ↑beneficial bacteria & SCFA	Induce IL-10 in spleenocyte Inhibits pro inflammatory cytokine IL-6, TNF- α	Cian, López-Posadas, Drago, de Medina, and Martínez-Augustin (2012)
	P. yezoensis	*In vivo*	↓Putrefactive compound and microorganism.	Inhibits pro-inflammatory cytokine IL-6, TNF- α In RAW 264.7 mouse macrophage Inhibits NO & ROS production	Isaka et al. (2015)
Sulfated Polysaccharides	*G. changii*	*In vitro*	↑Beneficial bacteria & SCFA	Inhibit expression of TNF- and IL-6 in U937 cells	Shu, Appleton, Zandi, and AbuBakar (2013)
	Gracillaria spp.	*In vivo*	↑Beneficial bacteria (*Bifidobacterium)* & SCFA	Inhibit inflammatory cell infiltration, release off inflammatory cytokines and lipid peroxidation	
Porphyran	*P. tenera*	*In vivo*	Improvement in gut microbiota	Inhibit hypersensitivity reaction, Decreased IgE in the serum of BALB/c mice	Ishihara, Oyamada, Matsushima, Murata, and Muraoka (2005); Imbs et al. (2016)
Polysaccharides extract	*L. muelleri*	*In vivo*	↑Beneficial bacteria & SCFA	Anti-inflammatory effect on GVHD and arthritis Reduce colonic inflammation	Aslam, Paruchuri, Bhagavathula, and Varani (2010,2012); Rezende et al. (2013); Costa et al. (2015)

(MMP-Matrix metalloproteinases, ↑- increase, ↓-Decrease, TNF- Tumor necrosis factor, TLR- Toll-like receptor, IL- Interleukin, PS- Polysaccharides).

microorganisms that show protective and barrier property against disease-causing pathogens in order to protect the host. *Bifidobacteria, Lactobacilli* contributes to modification and stimulation of immune responses by the non-specific resistance of the host to pathogens (Mumcu et al., 2014). *Bifidobacteria* and *Lactobacillus* shortened and prevented diarrhoea by several means of pathogenic agents by inducing immune responses (Liu et al., 2014). The list of probiotic microbes and its role in the host system are given in Table 8.

6.1.1. Lactobacillus

Lactobacillus species are potential gut microbes that are gram-positive, catalase negative and form non-spore rods. *Lactobacillus* does not involve in nitrate reduction. *Lactobacillus* species that are frequently examined and studied are *L. acidophilus, L. casei, L. fermentum, L. brevis, L. plantarum* and *L. salivarius* (He, Morita, & Ouwehand, 2006). The metabolic final product of *Lactobacilli* is the lactic acid which is formed by the breakdown of glucose (Slover et al., 2008). Lactic acid and other several byproducts hydrogen peroxide of *Lactobacillus* metabolism is found to be beneficial in controlling and regulating the invasion of other 27 potentially pathogenic bacteria. Other acids like acetic acid and succinic acid are also produced but in very small amounts.

6.1.2. Bacillus

Mostly common species that could be found among *Bacillus* microbes are *B. subtilis, B. licheniforms, B. cereus, B. clausil* and *B. coagulans. Bacillus* has several advantages that include the formation of heat stable spores and does not lose the effect on viability if it stored in a desiccator at room temperature (Cutting et al., 2011). They also can survive at

Table 8
List of probiotic microbes and its role in the host.

Beneficial Bacteria	Role in the Host	References
Bifidobacteria	✓ Regulate the level of other bacteria ✓ Modulate immune response ✓ Prevent tumour formation ✓ Produce vitamins ✓ Reduces the risk of human contaminated food diseases caused by campylobacter like *C. jejuni* and *C. coli.* ✓ Helps in treating acute diarrhoea. ✓ Regulate cholesterol metabolism and synthesis.	Gibson et al., 2004; Iyer et al., 2008; Mumcu et al., 2014; Daniluk et al. (2018).
Lactobacillus	✓ Produce vitamins and nutrients ✓ Boost immunity ✓ Protect against carcinogens ✓ Prevent growth of *Clostridium difficile* which sometimes can proliferate even after antibiotic administration ✓ Induced apoptosis of (THP-1), a monocytic carcinoma cell line ✓ Regulate gut epithelial homeostasis ✓ Helps in treating inflammatory bowel disease (IBD)	Slover et al., 2008; Cutting et al., 2011; Mumcu et al., 2014; Daniluk et al. (2018).

acidic (gastric) pH (Barbosa, Serra, La Ragione, Woodward, & Henriques, 2005) but this advantage applicable for only some species (Tuohy et al., 2007). *Bacillus* can boost the immune system and species like *Bacillus coagulans* helps overcoming respiratory distress and some species helps in digestion of cancer-causing substances, thus act as auxiliary microorganisms for cancer therapy.

6.1.3. Bifidobacteria

Bifidobacteria possess club-shaped, dense morphology and are characterized as gram-positive microbes forming non-spore rods. In a gut microbial ecosystem, *Bifidobacterium* ranges of about 25% and are contributed to carbohydrate digestion in the colon. Mostly examined species of *Bifidobacterium* are *B. infantis, B. longum* (colon), *B. dentium* (oral cavity), *B. adolescentis*. Pathogen colonization is inhibited by *Bifidobacteria* and found used for preventing infection and cancer and also regulates cholesterol metabolism and synthesis. Dairy industry on the basis of above-mentioned advantage recognized *Bifidobacteria* as probiotics (Gibson et al., 2004).

7. Immunomodulation and other benefits

Prebiotics helps to increase the level of beneficial microbes like *Lactobacillus* and *Bifidobacteria* thus decreasing the level of invading pathogens. Colon cancer is prevented by reducing putrefactive compounds. Butyrate that is produced acts as a protective manager and production of butyrate is mediated by the colonic microbiota. *Bifidobacteria* helps to pull downcast the promoters of a carcinogenic factor and reduced the genotoxins. Prebiotics promote the shift down of the biomarkers for cancer as a result proliferation of cancer cells can be regulated and controlled (Kasubuchi, Hasegawa, Hiramatsu, Ichimura, & Kimura, 2015). Various applications of prebiotic dietary fiber in the host system are shown in Fig. 4.

The immune modulatory behaviour of the prebiotics boosted the immune response by interaction with the probiotics present in the gut (Schley and Field et al., 2002). The prebiotic and probiotic interaction directly induce immune system activation and the gut microbial biomass plays a role in overcoming disease vulnerability (Hemarajata and Versalovic., 2013). The interaction of prebiotics with probiotics like *Lactobacillus* lead to the production of SCFA, alteration in mucin production and interaction of prebiotics with membrane receptors such as Toll-like receptor of immune cells commence immune stimulatory responses (Peshev & Van den Ende, 2014). Charoensiddhi et al. (2016) reported that prebiotics can vary the mechanism and action of the intestinal microbes by in-vitro technique analysis. Prebiotics play a vital role in bone and mineral metabolism of enhancing the bioavailability of minerals like calcium for the improved growth of bone (Whisner et al., 2018). Potentially beneficial microbial biomass of intestine includes *Lactobacillus* and *Bifidobacterium* strains which are stimulated by prebiotics to breakout immune response with beneficial modulations (Kong et al., 2016; Lynch et al., 2010). κ- Carrageenan of red seaweed polysaccharides stimulate macrophages leading to epithelial disruption of the intestine, the release of inflammatory cytokine production and cell death.

Kim et al. (2008) reported that fucoidan from brown seaweed *F. vesticulosus* enhanced the TNF-α and IL-2 production and assist in maturing the dendritic cells through activation of NFκB signals. Jin et al. (2014) in his study reported that fucoidan from *F. vesticulosus* aids in up-regulating the proinflammatory cytokines in-vivo in the spleen cells of mice and also assist in the enhancement of dendritic cell and antibody secretion. In a clinical trial, fucoidan on ingesting into the serum of Japanese volunteers who were administered with influenza vaccine boosted the antibody secretion (Negishi, Mori, Mori, & Yamori, 2013). Brown seaweed polysaccharide alginate enhances and induce the secretion of nitric oxide and nitric oxide synthesizing enzymes in a murine cell line, and also stimulated the TNF- α production without impacting NO and ROs secretion (Xu et al., 2014). Suzuki, Christensen, and Kitamura (2011) mentioned that mannuronate residue of alginate induces the immune response activity of gastric cells via Peyer's patch cells of mice. Ma et al. (2017) studied the increase in sulfate group of degraded sulphated polysaccharides (DSPs) improves scavenging activities and also repairs the subcellular organelles of HK-2 cell damage. Therefore, there was a decrease in lactate dehydrogenase production leads to a decrease in cell apoptosis, improves the integrity of mitochondrial membrane potential and lysosome.

Endogenous microbes interact with immune cells and induce lymphoid tissue to regulate the metabolic responses (Binns et al., 2013). Rijkers et al. (2010) described the three levels of probiotic action that occur in the gastrointestinal tract which are shown in Fig. 5. Interaction of probiotics with the pathogen and resulting in pathogen engulfing process called phagocytosis or endocytosis (Level 1). Improving the barrier function of the mucosal layer and enhance the systemic immune system and also localized cell and individual organ systems like liver and brain (Level 2). Toll-like receptors mediate the interaction of probiotics/pathogen with host cells. *L. reuteri* factors reduce NF-KB gene expression that induces apoptosis by enhancing mitogen-activated kinase (Iyer et al., 2008).

L. helveticus increases the production of calcineurin during fermentation of milk and secretes factors, promoted the dense colonization of mast cells and islets of goblet cells in the gastrointestinal tract of the mouse (Vinderola, Matar, & Perdigón, 2007). Superficial proteins are being announced as key factors that have a major significance in immunomodulation. For example, in the mice colonic mucosal *L. crispatus* (competent aggregation) modifies the expression of receptors for innate immune TLR-2 and TLR-4 over the surface layer of epithelial cells (Saulnier, Spinler, Gibson, & Versalovic, 2009; Voltan et al., 2007).

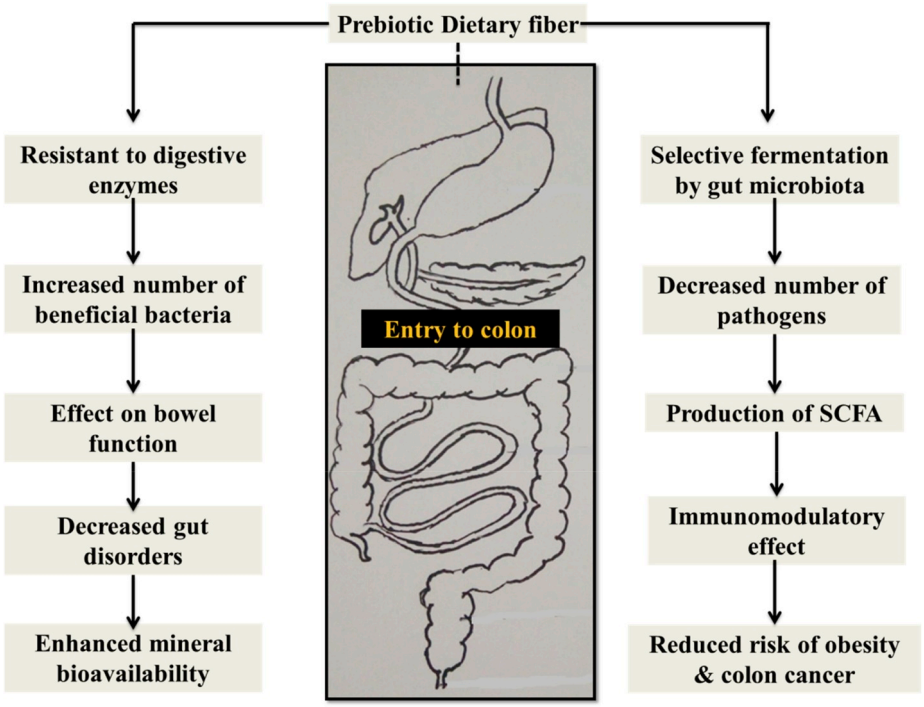

Fig. 4. Multiple applications of prebiotic dietary fiber in the host system.

7.1. Prebiotics and the gut system

Human GIT mucosal surface is of 200–300 m^2 and is populated with 10^{13-14} bacteria of more than 400 species (Hao & Lee, 2004). The colon is heavily populated with an equal balance of beneficial and harmful bacteria that performs several physiological functions. Example: (i) Metabolism and food digestion, (ii) Prevention and protection against pathogens (Tran et al., 2018). SCFA from bacterial fermentation of prebiotics increase the proliferation rate of normal colonic cells. SCFA can also alter the colonic cells by butyrate as a result, of action absorption, enhanced the action of the liver in lipid and glucose homeostasis (Tran et al., 2018). SCFA exhibit improved faecal release and secretion of intestinal hormones like glucagon-like peptide (GLP), GALT (Gut Associated Lymphoid Tissue) and improved the physiological and metabolic function of the central nervous system (CNS) (Delzenne, 2003). The role and the mechanism of prebiotics in the gut system are represented in Fig. 6.

7.2. Production of SCFA & its epigenetic metabolism

Prebiotics on fermentation by gut microbes harvest short-chain fatty acids like acetic, propionic and butyrate (Gibson & Roberfroid, 1995).

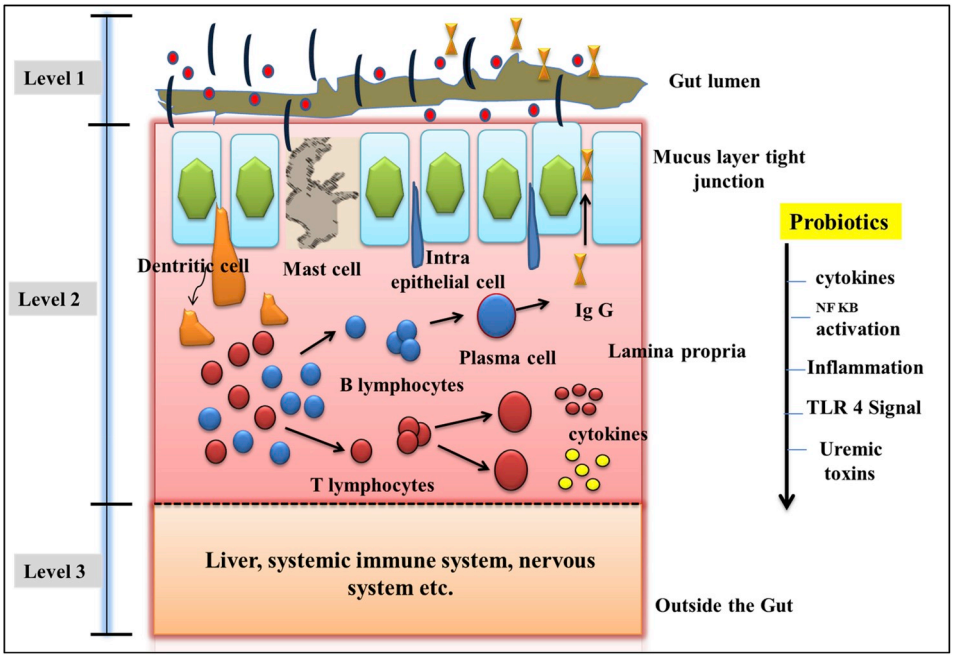

Fig. 5. Depiction of 3 levels of action of a probiotic in the GIT (Redrawn from Binns et al., 2013).

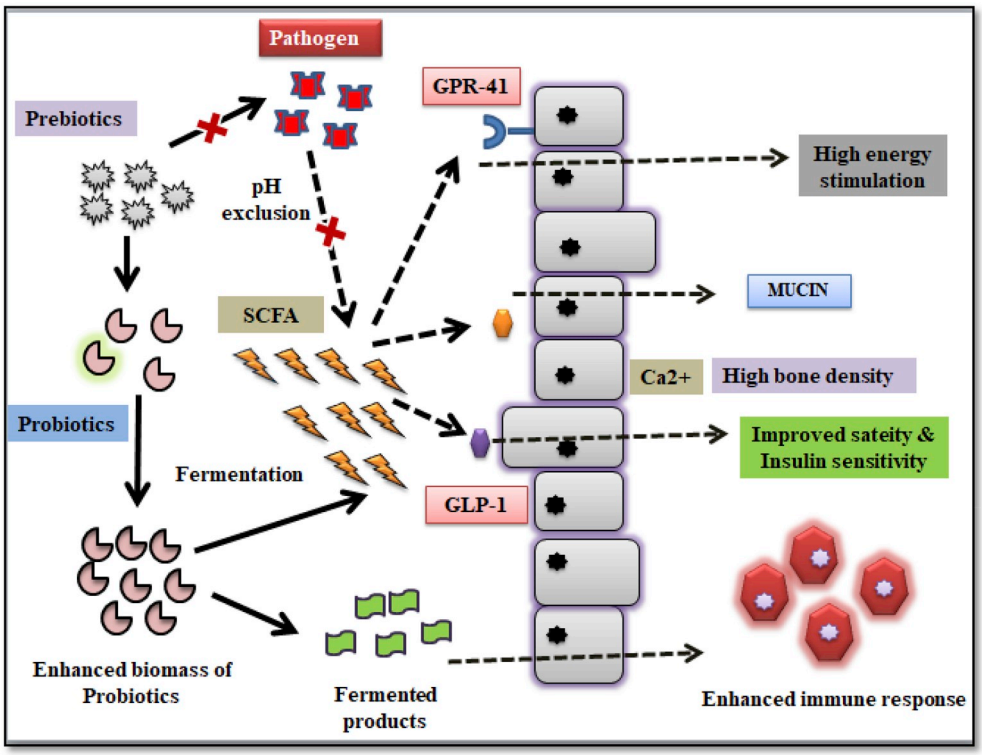

Fig. 6. Prebiotics and their mechanism in the gut system (Redrawn from Saulnier et al., 2009).

Enhanced production of natural killer cells was noted by ingesting SCFA orally on rats (Pratt, Tappenden, McBurney, & Field, 1996). Kim, Kang, Park, Yanagisawa, and Kim (2013) reported SCFA trigger activation of GPR 41 and 43, MAPK which regulate the function of transcription factors for increased production of cytokines.

It was proven that SCFA helps to reinstate the level of gut Treg pool or T regulatory cells which plays a vital role in preventing colitis. Treg pool maintains the homeostatic process in the gut and prevents inflammation by releasing of Foxp3 and amplifying CD_4 T cells. This mechanism is based on the genes Ffar2. Ffar2 is the expressed genes of the free fatty receptor that codes G protein-coupled receptor 43. Protein receptors and its expression are modulated by SCFA like acetate, butyrate, and propionate. Butyrate activation is weak when compared to the activation by acetate and other SCFA like propionate (Okolie et al., 2017). SCFA involve themselves in metabolisms like lipolysis, adipogenesis and other metabolic pathways by deactivating GPR43 genes in gut intestine parts of the rats (Correa-Olivera et al., 2016). SCFA helps to produce intestinal hormone peptides YY. Increase in SCFA production by means of dietary fiber can reduce the threat of obesity. SCFA also constrain the production of ghrelin to reduce the menace of obesity.

SCFA are also responsible for hindering the release of enzyme HDAC- histidine deacetylase. Thus they exert their role in anticancer activity by suppressing HDAC by secreting protein p21 which suppress the cyclin CB1. P21 is a cell cycle regulator and suppressor of cell-dependent enzyme CDK. Butyrate on binding with specific proteins namely SIN 3, p53, nuRD can suppress HDAC enzyme activity (Waldecker, Kautenburger, Daumann, Busch, & Schrenk, 2008). SCFA like acetic acid on the intravenous route of administration improved the production of antibodies, natural killer cell function and lymphocyte response in cancer patients (Pratt et al., 1996; Rooks et al., 2016). SCFA can directly influence IL10 activation and can prevent butyric acid inhibition over IL-2 production (Cavaglieri et al., 2003). The release of SCFA enhances the density and mass of bone by increased absorption of calcium a & b (Cieslik, Topolska, & Pisulewski, 2009). SCFA regulate the gut pH and decrease gastric disorders like diarrhoea dysentery and constipation (Cieslik et al., 2009). Prebiotics can generate antibodies that help in reducing fever and vomiting (Waligora et al., 2007). Ulcerative colitis, pouchitis, Crohn's disease has been prevented by the stimulated production of cytokines induced by the prebiotic effect (Lindsay et al., 2006).

7.3. Immune cell receptor binding and its action

Prebiotics directly bind and interact with the Toll-like receptors (TLRs) of the immune cells in order to provoke an immune response (Ale et al., 2011). TLRs are receptors that can identify pathogens and signal the NFκB. TLRs belong to the family PRR – Pattern Recognizing Receptor that recognizes the pattern of harmful pathogens. TLRs 2,5,7,8 are activated by the polysaccharide fructan which also activates the proteins of NOD2 domain- Nucleotide binding Oligomerisation domain. Already accepted prebiotics like inulin, fructoligosaccharides, galactooligosaccharides, mannan oligosaccharides stimulate immune activity in fish models (Akhter, Wu, Memon, & Mohsin, 2015). Polysaccharides of *L. japonica and F. evanescans* act as ligand so that they can interact with TLRs 2,4 to respond NFκB. κ- Carrageenan of red seaweed polysaccharides enhanced the release and production of TNF α, IL- 1 and IL-6 leading to cell death programming and epithelial electric resistance (Jiang, Wang, Chen, & Yan, 2013). Production of proinflammatory cytokines activates TLR and natural killer cells in order to protect the gut intestine epithelial layer. The increased production of TNF α, IL- 1 and IL-6 showed a significant effect on treating colon inflammation caused by dextran sodium sulfate injection (Bersudsky et al., 2014).

7.4. Alteration in mucin production mechanism

Mucins are the proteins that belong to glyco-conjugated high molecular weight protein family. They have the ability to form gel thus act as the main component in cell signalling of barrier formation in the intestine. Mucins can control mineral accumulation and formation of bone and can attach to the disease-causing pathogens as an active

participant of the immune system. MUC1 is a protein which on uncontrolled expression leads to cancer. Mucins possess hydrophobic domain which helps to adhere to the membrane (Okolie et al., 2017). Mucins are produced by the mucus layer. Mucins prevent pathogen mobilization across the epithelial layer by attaching to them (Schley and field et al., 2002). SCFA produced due to prebiotic fermentation of the gut microbes enhance the flourishment of epithelial cells of the intestine and exert their role in alternating the level of mucin production (Correa-Oliveira et al., 2016). The previous study reported SCFA like acetate and butyrate to enhance the secretion of mucin and enhance ATP secretion in the epithelial layer of cells (Barcelo et al., 2000).

8. Summary and perspectives

Seaweeds or marine macroalgae are efficient marine-derived prebiotic polysaccharide-rich food source that replaces existing nutrients or functional food ingredients for its huge industrial and therapeutic applications. The potential benefits of seaweed polysaccharides and dietary fibers were explored as prebiotics for formulating them as functional food ingredients along with probiotic microbes to exhibit therapeutic applications. For an efficient polysaccharide extraction, less energy and solvent utilization for higher yields should be followed. The development and advancement of seaweed polysaccharide extraction methods like conventional, microwave-aided, ultrasonication aided, enzyme-aided extractions and their impact on prebiotic behavior along with its membrane separation and chromatographic polysaccharide purification techniques were discussed in detail. The practical difficulties in a single method can be diminished through combining other extraction and purification techniques together could be the most effective strategy. The seaweed polysaccharides and their beneficial effect on gut microbes were reviewed along with their structural and functional relationship. The exhaustive literature survey revealed that the interaction of gut microbes and prebiotics leads to several metabolic mechanisms that impacts human health. Recently reported studies on prebiotics along with probiotics, directly or indirectly stimulate immune response with beneficial commensals. Clinical trials on a human being are limited in these prebiotic studies till date. Proper design and well planned human trials should be carried out to step out these studies to the next level. Successful clinical trial on a human being can put forward this dietary fiber based research could aid in realization of the potential impacts in the medicinal world. Deadly and chronic diseases like diabetes, cancer, obesity and others can be easily treated by less economically and extensively available seaweed dietary fibers along with appropriate alteration of gut microbes. The prebiotic studies on seaweeds should further be optimized in terms of parameters like dosage and duration. However, those reported studies paved the way to evaluate and discover other probiotic strains with significant host effect.

Managing a healthy gut is like managing a healthy body, since the human gut is being treated as a second brain nowadays. Gut, a non-thinking brain comprised of the bacterial ecosystem and neural network with more than 100 million neurons that is even higher than spinal cord neurons. Although the gut-brain connection is a dynamic complex system, it has serious influences on numerous physiological effects. Prebiotic and probiotic cultured food helps to maintain the second brain healthy with full of the vibrant and potential bacterial community.

Conflicts of interest

The authors declare no competing interest.

Acknowledgement

The authors acknowledge the Department of Science and Technology, India for funding the research under DST-WOS-B (Women Scientist Scheme – B category) *[SR/WOS-B/282/2016(G)]*. The authors thank the Department of Life Science and the Department of Biotechnology and Medical Engineering of National Institute of Technology Rourkela for providing the research facility.

References

Abdel-Fattah, A. F., & Hussein, M. M. (1970). Composition of some brown algae as influenced by seasonal variation. *Phytochemistry, 9*(4), 721–724.

Acikara, O. B. (2013). *Ion-Exchange Chromatography and Its Applications.* Column Chromatographyhttps://doi.org/10.5772/55744 Dean F. Martin and Barbara B. Martin, IntechOpen.

Akhter, N., Wu, B., Memon, A. M., & Mohsin, M. (2015). Probiotics and prebiotics associated with aquaculture: A review. *Fish & Shellfish Immunology, 45*(2), 733–741.

Al-Alawi, A. A., Al-Marhubi, I. M., Al-Belushi, M. S. M., & Soussi, B. (2011). Characterization of carrageenan extracted from *Hypnea bryoides* in Oman. *Marine Biotechnology, 13*(5), 893–899.

Ale, M. T., Mikkelsen, J. D., & Meyer, A. S. (2011). Important determinants for fucoidan bioactivity: A critical review of structure-function relations and extraction methods for fucose-containing sulfated polysaccharides from brown seaweeds. *Marine Drugs, 9*(10), 2106–2130.

Anantharaman, P., Parthiban, C., Saranya, C., Girija, K., Hemalatha, A., & Suresh, M. (2013). Biochemical composition of some selected seaweeds from Tuticorin coast. *Advances in Applied Science Research, 4*(3), 362–366.

Anastyuk, S. D., Imbs, T. I., Shevchenko, N. M., Dmitrenok, P. S., & Zvyagintseva, T. N. (2012). ESIMS analysis of fucoidan preparations from *Costaria costata*, extracted from alga at different life-stages. *Carbohydrate Polymers, 90*(2), 993–1002.

Anastyuk, S. D., Shevchenko, N. M., Nazarenko, E. L., Imbs, T. I., Gorbach, V. I., Dmitrenok, P. S., et al. (2010). Structural analysis of a highly sulfated fucan from the brown alga *Laminaria cichorioides* by tandem MALDI and ESI mass spectrometry. *Carbohydrate Research, 345*(15), 2206–2212.

Andrieux, C., Hibert, A., Houari, A. M., Bensaada, M., Popot, F., & Szylit, O. (1998). *Ulva lactuca* is poorly fermented but alters bacterial metabolism in rats inoculated with human faecal flora from methane and non-methane producers. *Journal of the Science of Food and Agriculture, 77*(1), 25–30.

Aslam, M. N., Bergin, I., Naik, M., Paruchuri, T., Hampton, A., Rehman, M., et al. (2012). A multimineral natural product from red marine algae reduces colon polyp formation in C57BL/6 mice. *Nutrition and Cancer, 64*(7), 1020–1028.

Aslam, M. N., Paruchuri, T., Bhagavathula, N., & Varani, J. (2010). A mineral-rich red algae extract inhibits polyp formation and inflammation in the gastrointestinal tract of mice on a high-fat diet. *Integrative Cancer Therapies, 9*(1), 93–99.

Badrinathan, S., Suneeva, S. C., Shiju, T. M., & Pragasam, V. (2011). Exploration of a novel hydroxyl radical scavenger from *Sargassum myriocystum*. *Journal of Medicinal Plants Research, 5*(10), 1997–2005.

Barbosa, M., Lopes, G., Andrade, P. B., & Valentão, P. (2019). Bioprospecting of Brown seaweeds for biotechnological applications: Phlorotannin actions in inflammation and allergy network. *Trends in Food Science & Technology, 86*, 153–171.

Barbosa, T. M., Serra, C. R., La Ragione, R. M., Woodward, M. J., & Henriques, A. O. (2005). Screening for *Bacillus* isolates in the broiler gastrointestinal tract. *Applied and Environmental Microbiology, 71*(2), 968–978.

Barcelo, A., Claustre, J., Moro, F., Chayvialle, J. A., Cuber, J. C., & Plaisancié, P. (2000). Mucin secretion is modulated by luminal factors in the isolated vascularly perfused rat colon. *Gut, 46*(2), 218–224.

Bersudsky, M., Luski, L., Fishman, D., White, R. M., Ziv-Sokolovskaya, N., Dotan, S., et al. (2014). Non-redundant properties of IL-1α and IL-1β during acute colon inflammation in mice. *Gut, 63*(4), 598–609.

Binns, N. (2013). *Probiotics, prebiotics and the gut microbiota.* ILSI Europe.

Boler, B. M. V., & Fahey, G. C. (2012). Prebiotics of plant and microbial origin. *Direct-fed microbials and prebiotics for animals* (pp. 13–26). New York, NY: Springer.

Borthakur, A., Bhattacharyya, S., Anbazhagan, A. N., Kumar, A., Dudeja, P. K., & Tobacman, J. K. (2012). Prolongation of carrageenan-induced inflammation in human colonic epithelial cells by activation of an NFκB-BCL10 loop. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1822*(8), 1300–1307.

Borthakur, A., Bhattacharyya, S., Dudeja, P. K., & Tobacman, J. K. (2007). Carrageenan induces interleukin-8 production through distinct Bcl10 pathway in normal human colonic epithelial cells. *American Journal of Physiology - Gastrointestinal and Liver Physiology, 292*(3), G829–G838.

Burtin, P. (2003). Nutritional value of seaweeds. *Electronic Journal of Environmental, Agricultural and Food Chemistry, 2*(4), 498–503.

Cavaglieri, C. R., Nishiyama, A., Fernandes, L. C., Curi, R., Miles, E. A., & Calder, P. C. (2003). Differential effects of short-chain fatty acids on proliferation and production of pro-and anti-inflammatory cytokines by cultured lymphocytes. *Life Sciences, 73*(13), 1683–1690.

Chakraborty, S., & Santra, S. C. (2008). Biochemical composition of eight benthic algae collected from Sunderban. *Indian Journal of Marine Sciences, 37*(3), 329–332.

Chan, J. C. C., Cheung, P. C. K., & Ang, P. O. (1997). Comparative studies on the effect of three drying methods on the nutritional composition of *seaweed Sargassum hemiphyllum (Turn.) C. Ag. Journal of Agricultural and Food Chemistry, 45*(8), 3056–3059.

Chandini, S. K., Ganesan, P., & Bhaskar, N. (2008). In vitro antioxidant activities of three selected brown seaweeds of India. *Food Chemistry, 107*(2), 707–713.

Chan, P. T., & Matanjun, P. (2017). Chemical composition and physicochemical properties of tropical red seaweed, *Gracilaria changii*. *Food Chemistry, 221*, 302–310.

Charoensiddhi, S., Conlon, M. A., Franco, C. M., & Zhang, W. (2017). The development of seaweed-derived bioactive compounds for use as prebiotics and nutraceuticals using

enzyme technologies. *Trends in Food Science & Technology, 70*, 20–*33*.
Charoensiddhi, S., Conlon, M. A., Vuaran, M. S., Franco, C. M., & Zhang, W. (2016). Impact of extraction processes on prebiotic potential of the brown seaweed *Ecklonia radiata* by in vitro human gut bacteria fermentation. *Journal of Functional Foods, 24*, 221–230.
Charoensiddhi, S., Franco, C., Su, P., & Zhang, W. (2015). Improved antioxidant activities of brown seaweed *Ecklonia radiata* extracts prepared by microwave-assisted enzymatic extraction. *Journal of Applied Phycology, 27*(5), 2049–2058.
Chen, C. S., Anaya, J. M., Zhang, S., Spurgin, J., Chuang, C. Y., Xu, C., et al. (2011). Effects of engineered nanoparticles on the assembly of exopolymeric substances from phytoplankton. *PLoS One, 6*(7), e21865.
Chen, L., Xu, W., Chen, D., Chen, G., Liu, J., Zeng, X., et al. (2018). Digestibility of sulfated polysaccharide from the brown seaweed *Ascophyllum nodosum* and its effect on the human gut microbiota in vitro. *International Journal of Biological Macromolecules, 112*, 1055–1061.
Chirapart, A., Praiboon, J., Puangsombat, P., Pattanapon, C., & Nunraksa, N. (2014). Chemical composition and ethanol production potential of Thai seaweed species. *Journal of Applied Phycology, 26*(2), 979–986.
Cian, R. E., López-Posadas, R., Drago, S. R., de Medina, F. S., & Martínez-Augustin, O. (2012). A *Porphyra columbina* hydrolysate upregulates IL-10 production in rat macrophages and lymphocytes through an NF-κB, and p38 and JNK dependent mechanism. *Food Chemistry, 134*(4), 1982–1990.
Cieslik, E., Topolska, K., & Pisulewski, P. M. (2009). Effect of inulin-type fructans on body weight gain and selected biochemical parameters at calcium hypoalimentation in rats. *Polish Journal of Food and Nutrition Sciences, 59*(2).
Cirik, Ş., Çetin, Z., Ak, İ., Cirik, S., & Göksan, T. (2010). Greenhouse cultivation of *Gracilaria verrucosa* (Hudson) Papenfuss and determination of chemical composition. *Turkish Journal of Fisheries and Aquatic Sciences, 10*(4), 559–564.
CK Rajendran, S. R., Okolie, C. L., Udenigwe, C. C., & Mason, B. (2017). Structural features underlying prebiotic activity of conventional and potential prebiotic oligosaccharides in food and health. *Journal of Food Biochemistry, 41*(5), e12389.
Clemente, J. C., Ursell, L. K., Parfrey, L. W., & Knight, R. (2012). The impact of the gut microbiota on human health: An integrative view. *Cell, 148*(6), 1258–1270.
Cong, Q., Chen, H., Liao, W., Xiao, F., Wang, P., Qin, Y., et al. (2016). Structural characterization and effect on anti-angiogenic activity of a fucoidan from *Sargassum fusiforme*. *Carbohydrate Polymers, 136*, 899–907.
Corrêa-Oliveira, R., Fachi, J. L., Vieira, A., Sato, F. T., & Vinolo, M. A. R. (2016). Regulation of immune cell function by short-chain fatty acids. *Clinical & translational immunology, 5*(4), e73.
Costa, V. V., Amaral, F. A., Coelho, F. M., Queiroz-Junior, C. M., Malagoli, B. G., Gomes, J. H. S., et al. (2015). *Lithothamnion muelleri* treatment ameliorates inflammatory and hypernociceptive responses in antigen-induced arthritis in mice. *PLoS One, 10*(3), e0118356.
Cui, Y., Liu, X., Li, S., Hao, L., Du, J., Gao, D., et al. (2018). Extraction, characterization and biological activity of sulfated polysaccharides from seaweed *Dictyopteris divaricata*. *International Journal of Biological Macromolecules, 117*, 256–263.
Cutting, S. M. (2011). Bacillus probiotics. *Food Microbiology, 28*(2), 214–220.
Dame, M. K., Veerapaneni, I., Bhagavathula, N., Naik, M., & Varani, J. (2011). Human colon tissue in organ culture: Calcium and multi-mineral-induced mucosal differentiation. *In Vitro Cellular & Developmental Biology Animal, 47*(1), 32–38.
Daniluk, U. (2018). Probiotics, the new approach for cancer prevention and/or potentialization of anti-cancer treatment? *Journal of Clinical & Experimental Ophthalmology, 2012*.
Davidson, M. H., & MC Donald, M. D. (1998). Fiber: Forms and functions. *Nutrition Research, 18*, 671–674.
Dawczynski, C., Schubert, R., & Jahreis, G. (2007). Amino acids, fatty acids, and dietary fibre in edible seaweed products. *Food Chemistry, 103*(3), 891–899.
Dawes, C. J. (1987). Physiological ecology of two species of *Sargassum* (fucales, phaeophyta) on the west coast of Florida. *Bulletin of Marine Science, 40*(2), 198–209.
Dawes, C. J. (1989). Physiological responses of brown seaweeds *Sargassum filipendula* and *S. pteropleuron* before and after transplanting on the west coast of Florida. *Journal of Coastal Research,* 693–700.
De Sousa, V. M. C., dos Santos, E. F., & Sgarbieri, V. C. (2011). The importance of prebiotics in functional foods and clinical practice. *Food and Nutrition Sciences, 2*(02), 133.
Delzenne, N. M. (2003). Oligosaccharides: State of the art. *Proceedings of the Nutrition Society, 62*(1), 177–182.
Deville, C., Damas, J., Forget, P., Dandrifosse, G., & Peulen, O. (2004). Laminarin in the dietary fibre concept. *Journal of the Science of Food and Agriculture, 84*(9), 1030–1038.
Dierick, N., Ovyn, A., & De Smet, S. (2009). Effect of feeding intact brown seaweed *Ascophyllum nodosum* on some digestive parameters and on iodine content in edible tissues in pigs. *Journal of the Science of Food and Agriculture, 89*(4), 584–594.
Dinesh, S., Menon, T., Hanna, L. E., Suresh, V., Sathuvan, M., & Manikannan, M. (2016). *In vitro* anti-HIV-1 activity of fucoidan from *Sargassum swartzii*. *International Journal of Biological Macromolecules, 82*, 83–88.
Drew, J. E., Farquharson, A. J., Mayer, C. D., Vase, H. F., Coates, P. J., Steele, R. J., et al. (2014). Predictive gene signatures: Molecular markers distinguishing colon adenomatous polyp and carcinoma. *PLoS One, 9*(11), e113071.
Dunlap, R. (Vol. Ed.), (2013). *Immobilized biochemicals and affinity chromatography: Vol. 42*Springer Science & Business Media.
Esteves, B. S., Taouil, A., & Suzuki, M. S. (2005). Nutrient composition of macroalgae and macrophytes of the Açu lagoon, Rio de Janeiro State, Brazil. *Acta Limnologica Brasiliensia, 17*(3), 233–244.
Fernández, P. V., Raffo, M. P., Alberghina, J., & Ciancia, M. (2015). Polysaccharides from the green seaweed *Codium decorticatum*. Structure and cell wall distribution. *Carbohydrate Polymers, 117*, 836–844.
Fitton, J. H., Stringer, D. N., & Karpiniec, S. S. (2015). Therapies from fucoidan: An update. *Marine Drugs, 13*(9), 5920–5946.
Fleurence, J. (1999). Seaweed proteins: Biochemical, nutritional aspects and potential uses. *Trends in Food Science & Technology, 10*(1), 25–28.
Fleury, N., & Lahaye, M. (1991). Chemical and physico-chemical characterisation of fibres from *Laminaria digitata* (kombu Breton): A physiological approach. *Journal of the Science of Food and Agriculture, 55*(3), 389–400.
Fujii, T. (1992). Fermentation of water-soluble polysaccharides of brown algae by human intestinal bacteria in vitro. *Nippon Suisan Gakkaishi, 58*, 147–152.
Ganapathy, V., Thangaraju, M., Prasad, P. D., Martin, P. M., & Singh, N. (2013). Transporters and receptors for short-chain fatty acids as the molecular link between colonic bacteria and the host. *Current Opinion in Pharmacology, 13*(6), 869–874.
Garcia-Vaquero, M., Rajauria, G., O'Doherty, J. V., & Sweeney, T. (2017). Polysaccharides from macroalgae: Recent advances, innovative technologies and challenges in extraction and purification. *Food Research International, 99*, 1011–1020.
Geng, L., Zhang, Q., Wang, J., Jin, W., Zhao, T., & Hu, W. (2018). Glucofucogalactan, a heterogeneous low-sulfated polysaccharide from *Saccharina japonica* and its bioactivity. *International Journal of Biological Macromolecules, 113*, 90–97.
Gibson, G. R. (2004). Fibre and effects on probiotics (the prebiotic concept). *Clinical Nutrition Supplements, 1*(2), 25–31.
Gibson, G. R., & Roberfroid, M. B. (1995). Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *Journal of Nutrition, 125*(6), 1401–1412.
Gourbeyre, P., Denery, S., & Bodinier, M. (2011). Probiotics, prebiotics, and synbiotics: Impact on the gut immune system and allergic reactions. *Journal of Leukocyte Biology, 89*(5), 685–695.
Gudiel-Urbano, M., & Goñi, I. (2002). Effect of edible seaweeds (*Undaria pinnatifida* and *Porphyra ternera*) on the metabolic activities of intestinal microflora in rats. *Nutrition Research, 22*(3), 323–331.
Hahn, T., Lang, S., Ulber, R., & Muffler, K. (2012). Novel procedures for the extraction of fucoidan from brown algae. *Process Biochemistry, 47*(12), 1691–1698.
Hahn, T., Zayed, A., Kovacheva, M., Stadtmüller, R., Lang, S., Muffler, K., et al. (2016). Dye affinity chromatography for fast and simple purification of fucoidan from marine brown algae. *Engineering in Life Science, 16*(1), 78–87.
Hao, W. L., & Lee, Y. K. (2004). Microflora of the gastrointestinal tract. *Public health microbiology* (pp. 491–502). Humana Press.
Haugan, J. A. (1994). Algal carotenoids 54. Carotenoids of brown algae (Phaeophyceae). *Biochemical Systematics and Ecology, 22*(1), 31–41.
Hemarajata, P., & Versalovic, J. (2013). Effects of probiotics on gut microbiota: Mechanisms of intestinal immunomodulation and neuromodulation. *Therapeutic Advances In Gastroenterology, 6*(1), 39–51.
He, F., Morita, H., & Ouwehand, A. C. (2006). *Bifidobacteria* and *Lactobacilli* exhibited different mitogenic activity on murine splenocytes. *International Journal of Probiotics and Prebiotics, 1*(1), 77.
Heo, S. J., Lee, G. W., Song, C. B., & Jeon, Y. J. (2003). Antioxidant activity of enzymatic extracts from brown seaweeds. *Algae, 18*(1), 71–81.
Hjelland, F., Andersen, A. H., & Yang, H. S. (2012). U.S. Patent Application No. 13/299, 615.
Hoagland, D. R., & Lieb, L. L. (1915). The complex carbohydrates and forms of sulphur in marine algae of the Pacific coast. *Journal of Biological Chemistry, 23*(1), 287–297.
Hu, B., Gong, Q., Wang, Y., Ma, Y., Li, J., & Yu, W. (2006). Prebiotic effects of neoagaro-oligosaccharides prepared by enzymatic hydrolysis of agarose. *Anaerobe, 12*(5–6), 260–266.
Hwang, E. S., Ki, K. N., & Chung, H. Y. (2013). Proximate composition, amino acid, mineral, and heavy metal content of dried laver. *Preventive Nutrition And Food Science, 18*(2), 139.
Imbs, T. I., Ermakova, S. P., Malyarenko, O. S., Isakov, V. V., & Zvyagintseva, T. N. (2016). Structural elucidation of polysaccharide fractions from the brown alga *Coccophora langsdorfii* and *in vitro* investigation of their anticancer activity. *Carbohydrate Polymers, 135*, 162–168.
Isaka, S., Cho, K., Nakazono, S., Abu, R., Ueno, M., Kim, D., et al. (2015). Antioxidant and anti-inflammatory activities of porphyran isolated from discolored nori (*Porphyra yezoensis*). *International Journal of Biological Macromolecules, 74*, 68–75.
Ishihara, K., Oyamada, C., Matsushima, R., Murata, M., & Muraoka, T. (2005). Inhibitory effect of porphyran, prepared from dried "Nori", on contact hypersensitivity in mice. *Bioscience Biotechnology & Biochemistry, 69*(10), 1824–1830.
Iyer, C., Kosters, A., Sethi, G., Kunnumakkara, A. B., Aggarwal, B. B., & Versalovic, J. (2008). Probiotic *Lactobacillus reuteri* promotes TNF-induced apoptosis in human myeloid leukemia-derived cells by modulation of NF-κB and MAPK signalling. *Cellular Microbiology, 10*(7), 1442–1452.
Jacobsen, C., Sørensen, A. D. M., Holdt, S. L., Akoh, C. C., & Hermund, D. B. (2019). Source, extraction, characterization, and applications of novel antioxidants from seaweed. *Annual Review Of Food Science And Technology, 10*, 541–568.
Jain, M., Gupta, K., & Jain, P. (2014). Significance of probiotics and prebiotics in health and nutrition. *Malaya Journal of Biosciences, 1*(3), 181–195.
Jang, J. S., Cho, Y., Jeong, G. T., & Kim, S. K. (2012). Optimization of saccharification and ethanol production by simultaneous saccharification and fermentation (SSF) from seaweed, *Saccharina japonica*. *Bioprocess and Biosystems Engineering, 35*(1–2), 11–18.
Janson, J. C. (Vol. Ed.), (2012). *Protein purification: Principles, high resolution methods, and applications: Vol. 151*John Wiley & Sons.
Jiang, Z., Hama, Y., Yamaguchi, K., & Oda, T. (2011). Inhibitory effect of sulphated polysaccharide porphyran on nitric oxide production in lipopolysaccharide-stimulated RAW264. 7 macrophages. *Journal of Biochemistry, 151*(1), 65–74.
Jiang, H. Y., Wang, F., Chen, H. M., & Yan, X. J. (2013). κ-carrageenan induces the disruption of intestinal epithelial Caco-2 monolayers by promoting the interaction between intestinal epithelial cells and immune cells. *Molecular Medicine Reports, 8*(6),

1635–1642.
Jin, J. O., Zhang, W., Du, J. Y., Wong, K. W., Oda, T., & Yu, Q. (2014). Fucoidan can function as an adjuvant *in vivo* to enhance dendritic cell maturation and function and promote antigen-specific T cell immune responses. *PLoS One, 9*(6), e99396.
Jin, W., Zhang, Q., Wang, J., & Zhang, W. (2013). A comparative study of the anticoagulant activities of eleven fucoidans. *Carbohydrate Polymers, 91*(1), 1–6.
Jung, K. A., Lim, S. R., Kim, Y., & Park, J. M. (2013). Potentials of macroalgae as feedstocks for biorefinery. *Bioresource Technology, 135*, 182–190.
Kadam, S. U., Tiwari, B. K., Smyth, T. J., & O'Donnell, C. P. (2015). Optimization of ultrasound assisted extraction of bioactive components from brown seaweed *Ascophyllum nodosum* using response surface methodology. *Ultrasonics Sonochemistry, 23*, 308–316.
Kalesh, N. S., & Muraleedharan, N. S. (2003). *Phycochemical distinctiveness of selected marine macrophytes of Kerala coastDoctoral dissertation*. Cochin University of science and technology.
Kang, J. Y., Khan, M. N. A., Park, N. H., Cho, J. Y., Lee, M. C., Fujii, H., et al. (2008). Antipyretic, analgesic, and anti-inflammatory activities of the seaweed *Sargassum fulvellum* and *Sargassum thunbergii* in mice. *Journal of Ethnopharmacology, 116*(1), 187–190.
Kasubuchi, M., Hasegawa, S., Hiramatsu, T., Ichimura, A., & Kimura, I. (2015). Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. *Nutrients, 7*(4), 2839–2849.
Kim, M. H., & Joo, H. G. (2008). Immunostimulatory effects of fucoidan on bone marrow-derived dendritic cells. *Immunology Letters, 115*, 138–143.
Kim, M. H., Kang, S. G., Park, J. H., Yanagisawa, M., & Kim, C. H. (2013). Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice. *Gastroenterology, 145*, 396–406.
Kim, N. J., Li, H., Jung, K., Chang, H. N., & Lee, P. C. (2011). Ethanol production from marine algal hydrolysates using *Escherichia coli KO11*. *Bioresource Technology, 102*(16), 7466–7469.
Kolida, S., & Gibson, G. R. (2008). *The prebiotic effect: Review of experimental and human data.* Boca Raton, FL, USA: CRC Press69–93.
Kong, Q., Dong, S., Gao, J., & Jiang, C. (2016). In vitro fermentation of sulfated polysaccharides from *E. prolifera* and *L. japonica* by human fecal microbiota. *International Journal of Biological Macromolecules, 91*, 867–871.
Kraan, S. (2013). Mass-cultivation of carbohydrate rich macroalgae, a possible solution for sustainable biofuel production. *Mitigation and Adaptation Strategies for Global Change, 18*(1), 27–46.
Kravchenko, A. O., Barabanova, A. B., Glazunov, V. P., Yakovleva, I. M., & Yermak, I. M. (2018). Seasonal variations in a polysaccharide composition of Far Eastern red seaweed *Ahnfeltiopsis flabelliformis* (Phyllophoraceae). *Journal of Applied Phycology, 30*(1), 535–545.
Kulshreshtha, G., Burlot, A. S., Marty, C., Critchley, A., Hafting, J., Bedoux, G., et al. (2015). Enzyme-assisted extraction of bioactive material from *Chondrus crispus* and *Codium fragile* and its effect on *Herpes simplex virus (HSV-1)*. *Marine Drugs, 13*(1), 558–580.
Kulshreshtha, G., Rathgeber, B., Stratton, G., Thomas, N., Evans, F., Critchley, A., et al. (2014). Feed supplementation with red seaweeds, *Chondrus crispus* and *Sarcodiotheca gaudichaudii*, affects performance, egg quality, and gut microbiota of layer hens. *Poultry Science, 93*(12), 2991–3001.
Kumar, S. (2013). *Potential of Sargassum wightii and Gracilaria verrucosa two important seaweeds as source of food and fuel through biorefinery approach*.
Kylin, H. (1913). Biochemistry of sea algae. *HZ Physiol. Chem, 83*(171197), 3.
Lahaye, M. (1991). Marine algae as sources of fibres: Determination of soluble and insoluble dietary fibre contents in some 'sea vegetables' *Journal of the Science of Food and Agriculture, 54*(4), 587–594.
Lim, S. J., & Aida, W. M. W. (2017). *Extraction of sulfated polysaccharides (fucoidan) from Brown seaweed.* Seaweed Polysaccharides.
Lindsay, J. O., Whelan, K., Stagg, A. J., Gobin, P., Al-Hassi, H. O., Rayment, N., et al. (2006). Clinical, microbiological, and immunological effects of fructo-oligosaccharide in patients with Crohn's disease. *Gut, 55*(3), 348–355.
Liu, J., Kandasamy, S., Zhang, J., Kirby, C. W., Karakach, T., Hafting, J., et al. (2015). Prebiotic effects of diet supplemented with the cultivated red seaweed *Chondrus crispus* or with fructo-oligo-saccharide on host immunity, colonic microbiota and gut microbial metabolites. *BMC Complementary and Alternative Medicine, 15*(1), 279.
Liu, Z., Lin, X., Huang, G., Zhang, W., Rao, P., & Ni, L. (2014). Prebiotic effects of almonds and almond skins on intestinal microbiota in healthy adult humans. *Anaerobe, 26*, 1–6.
Lozano, I., Wacyk, J. M., Carrasco, J., & Cortez-San Martín, M. A. (2016). Red macroalgae *Pyropia columbina* and *Gracilaria chilensis*: Sustainable feed additive in the *Salmo salar* diet and the evaluation of potential antiviral activity against infectious salmon anemia virus. *Journal of Applied Phycology, 28*(2), 1343–1351.
Lynch, M. B., Sweeney, T., Callan, J. J., O'Sullivan, J. T., & O'Doherty, J. V. (2010). The effect of dietary Laminaria-derived laminarin and fucoidan on nutrient digestibility, nitrogen utilisation, intestinal microflora and volatile fatty acid concentration in pigs. *Journal of the Science of Food and Agriculture, 90*(3), 430–437.
MacArtain, P., Gill, C. I., Brooks, M., Campbell, R., & Rowland, I. R. (2007). Nutritional value of edible seaweeds. *Nutrition Reviews, 65*(12), 535–543.
Mairh, O. P., Ohno, M., & Matsuoka, M. (1991). *Culture of brown alga Laminaria japonica (Phaeophyta, Laminariales) in warm waters of shikoku.* (Japan).
Makarenkova, I. D., Logunov, D. Y., Tukhvatulin, A. I., Semenova, I. B., Besednova, N. N., Zvyagintseva, T. N., et al. (2012). Interactions between sulfated polysaccharides from sea brown algae and toll-like receptors on HEK293 eukaryotic cells in vitro. *Bulletin of Experimental Biology and Medicine, 154*, 241–244.
Manivannan, K., Thirumaran, G., Devi, G. K., Hemalatha, A., & Anantharaman, P. (2008). Biochemical composition of seaweeds from Mandapam coastal regions along Southeast Coast of India. *American-Eurasian Journal of Botany, 1*(2), 32–37.
Marcati, A., Ursu, A. V., Laroche, C., Soanen, N., Marchal, L., Jubeau, S., et al. (2014). Extraction and fractionation of polysaccharides and B-phycoerythrin from the microalga *Porphyridium cruentum* by membrane technology. *Algal Research, 5*, 258–263.
Marinho-Soriano, E., & Bourret, E. (2003). Effects of season on the yield and quality of agar from *Gracilaria* species (Gracilariaceae, Rhodophyta). *Bioresource Technology, 90*(3), 329–333.
Marinho-Soriano, E., Fonseca, P. C., Carneiro, M. A. A., & Moreira, W. S. C. (2006). Seasonal variation in the chemical composition of two tropical seaweeds. *Bioresource Technology, 97*(18), 2402–2406.
Marrion, O., Fleurence, J., Schwertz, A., Guéant, J. L., Mamelouk, L., Ksouri, J., et al. (2005). Evaluation of protein *in vitro* digestibility of *Palmaria palmata* and *Gracilaria verrucosa*. *Journal of Applied Phycology, 17*, 99–102.
Ma, X. T., Sun, X. Y., Yu, K., Gui, B. S., Gui, Q., & Ouyang, J. M. (2017). *Effect of content of sulfate groups in seaweed polysaccharides on antioxidant activity and repair effect of subcellular organelles in injured HK-2 cells. Oxidative medicine and cellular longevity, 2017*.
Matanjun, P., Mohamed, S., Mustapha, N. M., & Muhammad, K. (2009). Nutrient content of tropical edible seaweeds, *Eucheuma cottonii, Caulerpa lentillifera* and *Sargassum polycystum*. *Journal of Applied Phycology, 21*(1), 75–80.
McDermid, K. J., & Stuercke, B. (2003). Nutritional composition of edible Hawaiian seaweeds. *Journal of Applied Phycology, 15*(6), 513–524.
McHugh, D. J. (2003). *A guide to the seaweed industry FAO Fisheries Technical Paper 441*. Rome: Food and Agriculture Organization of the United Nations.
Melo, M. R. S., Feitosa, J. P. A., Freitas, A. L. P., & De Paula, R. C. M. (2002). Isolation and characterization of soluble sulfated polysaccharide from the red seaweed *Gracilaria cornea*. *Carbohydrate Polymers, 49*(4), 491–498.
Michell, C., Lahaye, M., Bonnet, C., Mabeau, S., & Barry, J. L. (1996). *In vitro* fermentation by human faecal bacteria of total and purified dietary fibres from brown seaweeds. *British Journal of Nutrition, 75*(2), 263–280.
Miller, I. J. (1997). The chemotaxonomic significance of the water-soluble red algal polysaccharides. *Recent Research Development of Phytochemistry, 1*, 531–565.
MišurCoVá, L., KráčMar, S., KLeJduS, B., & VaCeK, J. (2010). Nitrogen content, dietary fiber, and digestibility in algal food products. *Czech Journal of Food Sciences, 28*(1), 27–35.
Miyanishi, N., Iwamoto, Y., Watanabe, E., & Oda, T. (2003). Induction of TNF-a production from human peripheral blood monocytes with b-1, 3-glucan oligomer prepared from laminarin with p-1, 3-glucanase from *Bacillus clausii NM- 1*. *Journal of Bioscience and Bioengineering, 95*, 192–195.
Moreno, F. J., Corzo, N., Montilla, A., Villamiel, M., & Olano, A. (2017). Current state and latest advances in the concept, production and functionality of prebiotic oligosaccharides. *Current Opinion in Food Science, 13*, 50–55.
Mori, S., & Barth, H. G. (2013). *Size exclusion chromatography*. Springer Science & Business Media.
Moumita, S., Goderska, K., Johnson, E. M., Das, B., Indira, D., Yadav, R., et al. (2017). Evaluation of the viability of free and encapsulated lactic acid bacteria using in-vitro gastro intestinal model and survivability studies of synbiotic microcapsules in dry food matrix during storage. *LWT-Food Science and Technology, 77*, 460–467.
Msuya, F. E., & Neori, A. (2002). *Ulva reticulata* and *Gracilaria crassa*: Macroalgae that can biofilter effluent from tidal fishponds in Tanzania. *Western Indian Ocean Journal of Marine Science, 1*(2), 117–*126*.
Mumcu, A., & Temiz, A. (2014). Effects of prebiotics on growth and acidifying activity of probiotic bacteria. *GIDA-Journal of Food, 39*(2), 71–77.
Murakami, K., Yamaguchi, Y., Noda, K., Fujii, T., Shinohara, N., Ushirokawa, T., et al. (2011). Seasonal variation in the chemical composition of a marine brown alga, *Sargassum horneri (Turner) C. Agardh*. *Journal of Food Composition and Analysis, 24*(2), 231–236.
Muraoka, T., Ishihara, K., Oyamada, C., Kunitake, H., Hirayama, I., & Kimura, T. (2008). Fermentation properties of low-quality red alga *Susabinori Porphyra yezoensis* by intestinal bacteria. *Bioscience Biotechnology & Biochemistry, 72*(7), 1731–1739.
Mussatto, S. I., & Mancilha, I. M. (2007). Non-digestible oligosaccharides: A review. *Carbohydrate Polymers, 68*(3), 587–597.
Nardella, A., Chaubet, F., Boisson-Vidal, C., Blondin, C., Durand, P., & Jozefonvicz, J. (1996). Anticoagulant low molecular weight fucans produced by radical process and ion exchange chromatography of high molecular weight fucans extracted from the brown seaweed *Ascophyllum nodosum*. *Carbohydrate Research, 289*, 201–208.
Negishi, H., Mori, M., Mori, H., & Yamori, Y. (2013). Supplementation of elderly Japanese men and women with fucoidan from seaweed increases immune responses to seasonal influenza vaccination. *Journal of Nutrition, 143*(11), 1794–1798.
Norziah, M. H., & Ching, C. Y. (2000). Nutritional composition of edible seaweed *Gracilaria changii*. *Food Chemistry, 68*(1), 69–76.
Nuno, K., Villarruel-López, A., Puebla-Pérez, A. M., Romero-Velarde, E., Puebla-Mora, A. G., & Ascencio, F. (2013). Effects of the marine microalgae *Isochrysis galbana* and *Nannochloropsis oculata* in diabetic rats. *Journal of Functional Foods, 5*(1), 106–115.
Okolie, C. L., CK Rajendran, S. R., Udenigwe, C. C., Aryee, A. N., & Mason, B. (2017). Prospects of brown seaweed polysaccharides (BSP) as prebiotics and potential immunomodulators. *Journal of Food Biochemistry, 41*(5), e12392.
Okolie, C. L., Mason, B., Mohan, A., Pitts, N., & Udenigwe, C. C. (2019). The comparative influence of novel extraction technologies on in vitro prebiotic-inducing chemical properties of fucoidan extracts from *Ascophyllum nodosum*. *Food Hydrocolloids, 90*, 462–471.
Ortiz, J., Uquiche, E., Robert, P., Romero, N., Quitral, V., & Llantén, C. (2009). Functional and nutritional value of the Chilean seaweeds *Codium fragile, Gracilaria chilensis* and *Macrocystis pyrifera*. *European Journal of Lipid Science and Technology, 111*, 320–327.
O'Sullivan, L., Murphy, B., McLoughlin, P., Duggan, P., Lawlor, P. G., Hughes, H., et al. (2010). Prebiotics from marine macroalgae for human and animal health

applications. *Marine Drugs, 8*(7), 2038–2064.
Palanisamy, S., Vinosha, M., Marudhupandi, T., Rajasekar, P., & Prabhu, N. M. (2017). *In vitro* antioxidant and antibacterial activity of sulfated polysaccharides isolated from *Spatoglossum asperum*. *Carbohydrate Polymers, 170*, 296–304.
Patara, L., Visbeck, M., Masina, S., Krahmann, G., & Vichi, M. (2011). Marine biogeochemical responses to the North Atlantic Oscillation in a coupled climate model. *Journal of Geophysical Research: Oceans, 116*(C7).
Patel, A. K., Laroche, C., Marcati, A., Ursu, A. V., Jubeau, S., Marchal, L., et al. (2013). Separation and fractionation of exopolysaccharides from *Porphyridium cruentum*. *Bioresource Technology, 145*, 345–350.
Peshev, D., & Van den Ende, W. (2014). Fructans: Prebiotics and immunomodulators. *Journal of Functional Foods, 8*, 348–357.
Ponce, N. M., Pujol, C. A., Damonte, E. B., Flores, M. L., & Stortz, C. A. (2003). Fucoidans from the brown seaweed *Adenocystis utricularis*: Extraction methods, antiviral activity and structural studies. *Carbohydrate Research, 338*(2), 153–165.
Prasad, P. D. (1986). A seasonal study of the red seaweeds *Solieria tenera* and three species of *Gracilaria* from Jamaica. *Hydrobiologia, 140*(2), 167.
Pratt, V. C., Tappenden, K. A., McBurney, M. I., & Field, C. J. (1996). Short-chain fatty acid-supplemented total parenteral nutrition improves nonspecific immunity after intestinal resection in rats. *Journal of Parenteral and Enteral Nutrition, 20*(4), 264–271.
Praveen, M. A., Parvathy, K. R. K., Jayabalan, R., & Balasubramanian, P. (2019). Dietary fiber from Indian edible seaweeds and its *in-vitro* prebiotic effect on the gut microbiota. *Food Hydrocolloids, 96*, 343–353.
Prince, J. S., & Daly, E. L. (1981). The ecology of *Sargassum pteropleuron Grunow* (phaeophyta, fucales) in the waters off South Florida. IV. Seasonal variation in mannitol, protein, ash and laminaran. *Phycologia, 20*(3), 232–241.
Prosky, L., Asp, N. G., Schweizer, T. F., DeVries, J. W., & Furda, I. (1988). Determination of insoluble, soluble, and total dietary fiber in foods and food products: Interlaboratory study. *Journal-Association of Official Analytical Chemists, 71*(5), 1017–1023.
Pushpamali, W. A., Nikapitiya, C., De Zoysa, M., Whang, I., Kim, S. J., & Lee, J. (2008). Isolation and purification of an anticoagulant from fermented red seaweed *Lomentaria catenata*. *Carbohydrate Polymers, 73*(2), 274–279.
Qasim, R. (1981). Biochemical studies on some seaweeds from Karachi coast. *Karachi University Journal of Science, 9*(1), 105–111.
Quintero-Villegas, M. I., Aam, B. B., Rupnow, J., Sørlie, M., Eijsink, V. G., & Hutkins, R. W. (2013). Adherence inhibition of enteropathogenic *Escherichia coli* by chitooligosaccharides with specific degrees of acetylation and polymerization. *Journal of Agricultural and Food Chemistry, 61*(11), 2748–2754.
Ramnani, P., Chitarrari, R., Tuohy, K., Grant, J., Hotchkiss, S., Philp, K., et al. (2012). *In vitro* fermentation and prebiotic potential of novel low molecular weight polysaccharides derived from agar and alginate seaweeds. *Anaerobe, 18*(1), 1–6.
Raposo, M. De J., de Morais, F., A. M. M. B, & de Morais, R. M. S. C. (2016). Emergent sources of prebiotics: Seaweeds and microalgae. *Marine Drugs, 14*(2), 27.
Ray, B., & Lahaye, M. (1996). Cell-wall polysaccharides from the marine green alga *Ulva rigida* (Ulvales, Chlorophyta)—NMR analysis of ulvan oligosaccharides. *Carbohydrate Research, 283*, 161–173.
Rezende, B. M., Bernardes, P. T., Resende, C. B., Arantes, R. M., Souza, D. G., Braga, F. C., et al. (2013). Lithothamnion muelleri controls inflammatory responses, target organ injury and lethality associated with graft-versus-host disease in mice. *Marine Drugs, 11*(7), 2595–2615.
Rico, D., Diana, A. B. M., Milton-Laskibar, I., Fernández-Quintela, A., Silván, J. M., Rai, D. K., et al. (2018). Characterization and *in vitro* evaluation of seaweed species as potential functional ingredients to ameliorate metabolic syndrome. *Journal of Functional Foods, 46*, 185–194.
Rieman, W., & Walton, H. F. (2013). *Ion exchange in analytical chemistry: International series of monographs in analytical chemistry*. Elsevier.
Rijkers, G. T., Bengmark, S., Enck, P., Haller, D., Herz, U., Kalliomaki, M., et al. (2010). Guidance for substantiating the evidence for beneficial effects of probiotics: Current status and recommendations for future research–3. *Journal of Nutrition, 140*(3), 671S–676S.
Rioux, L. E., Turgeon, S. L., & Beaulieu, M. (2007). Characterization of polysaccharides extracted from brown seaweeds. *Carbohydrate Polymers, 69*(3), 530–537.
Roberfroid, M. B. (2008). *Prebiotics: Concept, definition, criteria, methodologies, and products*. Boca Raton, FL, USA: CRC Press39–69.
Robic, A., Gaillard, C., Sassi, J. F., Lerat, Y., & Lahaye, M. (2009). Ultrastructure of ulvan: A polysaccharide from green seaweeds. *Biopolymers: Original Research on Biomolecules, 91*(8), 652–664.
Robledo, D., & Pelegrin, Y. F. (1997). Chemical and mineral composition of six potentially edible seaweed species of *Yucatan*. *Botanica Marina, 40*(1–6), 301–306.
Rodrigues, D., Sousa, S., Silva, A., Amorim, M., Pereira, L., Rocha-Santos, T. A., et al. (2015). Impact of enzyme-and ultrasound-assisted extraction methods on biological properties of red, brown, and green seaweeds from the central west coast of Portugal. *Journal of Agricultural and Food Chemistry, 63*(12), 3177–3188.
Rodriguez-Jasso, R. M., Mussatto, S. I., Pastrana, L., Aguilar, C. N., & Teixeira, J. A. (2011). Microwave-assisted extraction of sulfated polysaccharides (fucoidan) from brown seaweed. *Carbohydrate Polymers, 86*(3), 1137–1144.
Roesijadi, G., Jones, S. B., Snowden-Swan, L. J., & Zhu, Y. (2010). *Macroalgae as a biomass feedstock: A preliminary analysis (No. PNNL-19944)*. Richland, WA (United States): Pacific Northwest National Lab.(PNNL).
Rooks, M. G., & Garrett, W. S. (2016). Gut microbiota, metabolites and host immunity. *Nature Reviews Immunology, 16*(6), 341.
Routray, W., & Orsat, V. (2012). Microwave-assisted extraction of flavonoids: A review. *Food and Bioprocess Technology, 5*(2), 409–424.
Sánchez-Machado, D. I., López-Cervantes, J., Lopez-Hernandez, J., & Paseiro-Losada, P. (2004). Fatty acids, total lipid, protein and ash contents of processed edible seaweeds. *Food Chemistry, 85*(3), 439–444.
Sanjeewa, K. K. A., Fernando, I. P. S., Kim, E. A., Ahn, G., Jee, Y., & Jeon, Y. J. (2017). Anti-inflammatory activity of a sulfated polysaccharide isolated from an enzymatic digest of brown seaweed *Sargassum horneri* in RAW 264.7 cells. *Nutrition Research And Practice, 11*(1), 3–10.
Satpati, G. G., & Pal, R. (2011). Biochemical composition and lipid characterization of marine green alga *Ulva rigida* -a nutritional approach. *Journal of Algal Biomass Utilization, 2*(4), 10–13.
Saulnier, D. M., Spinler, J. K., Gibson, G. R., & Versalovic, J. (2009). Mechanisms of probiosis and prebiosis: Considerations for enhanced functional foods. *Current Opinion in Biotechnology, 20*(2), 135–141.
Schley, P. D., & Field, C. J. (2002). The immune-enhancing effects of dietary fibres and prebiotics. *British Journal of Nutrition, 87*(S2), S221–S230.
Schneeman, B. O. (1998). Dietary fiber and gastrointestinal functions. *Nutrition Research, 18*, 625–632.
Shi, F., Yan, X., Cheong, K. L., & Liu, Y. (2018). Extraction, purification, and characterization of polysaccharides from marine algae *Gracilaria lemaneiformis* with anti-tumor activity. *Process Biochemistry, 73*, 197–203.
Shu, M. H., Appleton, D., Zandi, K., & AbuBakar, S. (2013). Anti-inflammatory, gastroprotective and anti-ulcerogenic effects of red algae *Gracilaria changii* (Gracilariales, Rhodophyta) extract. *BMC Complementary and Alternative Medicine, 13*(1), 61.
Sinha, S., Astani, A., Ghosh, T., Schnitzler, P., & Ray, B. (2010). Polysaccharides from *Sargassum tenerrimum*: Structural features, chemical modification and anti-viral activity. *Phytochemistry, 71*(2–3), 235–242.
Slover, C. M., & Danziger, L. (2008). *Lactobacillus*: A review. *Clinical Microbiology Newsletter, 30*(4), 23–27.
Sridevi, V., Sumathi, V., Guru Prasad, M., & Kumar, M. S. (2014). Fructooligosaccharides-type prebiotic: A review. *Journal of Pharmacy Research, 8*, 321–330.
Suleria, H. A. R., Gobe, G., Masci, P., & Osborne, S. A. (2016). Marine bioactive compounds and health promoting perspectives; innovation pathways for drug discovery. *Trends in Food Science & Technology, 50*, 44–55.
Sun, L., Wang, C., Shi, Q., & Ma, C. (2009). Preparation of different molecular weight polysaccharides from *Porphyridium cruentum* and their antioxidant activities. *International Journal of Biological Macromolecules, 45*(1), 42–47.
Suzuki, S., Christensen, B. E., & Kitamura, S. (2011). Effect of mannuronate content and molecular weight of alginates on intestinal immunological activity through Peyer's patch cells of C3H/HeJ mice. *Carbohydrate Polymers, 83*(2), 629–634.
Tanabe, K., Nakamura, S., & Oku, T. (2014). Inaccuracy of AOAC method 2009.01 with amyloglucosidase for measuring non-digestible oligosaccharides and proposal for an improvement of the method. *Food Chemistry, 151*, 539–546.
Terada, A., Hara, H., & Mitsuoka, T. (1995). Effect of dietary alginate on the faecal microbiota and faecal metabolic activity in humans. *Microbial Ecology in Health and Disease, 8*(6), 259–266.
Tran, T. H. T., Everaert, N., & Bindelle, J. (2018). Review on the effects of potential prebiotics on controlling intestinal enteropathogens *Salmonella* and *Escherichia coli* in pig production. *Journal of Animal Physiology and Animal Nutrition, 102*(1), 17–32.
Tuohy, K. M., Pinart-Gilberga, M., Jones, M., Hoyles, L., McCartney, A. L., & Gibson, G. R. (2007). Survivability of a probiotic *Lactobacillus casei* in the gastrointestinal tract of healthy human volunteers and its impact on the faecal microflora. *Journal of Applied Microbiology, 102*(4), 1026–1032.
Vasconcelos, A., & Pomin, V. (2018). Marine carbohydrate-based compounds with medicinal properties. *Marine Drugs, 6*, 233.
Vázquez-Delfín, E., Robledo, D., & Freile-Pelegrín, Y. (2014). Microwave-assisted extraction of the carrageenan from *Hypnea musciformis* (cystocloniaceae, Rhodophyta). *Journal of Applied Phycology, 26*(2), 901–907.
Vinderola, G., Matar, C., & Perdigón, G. (2007). Milk fermentation products of *L. helveticus R389* activate calcineurin as a signal to promote gut mucosal immunity. *BMC Immunology, 8*(1), 19.
Voltan, S., Castagliuolo, I., Elli, M., Longo, S., Brun, P., D'Incà, R., et al. (2007). Aggregating phenotype in *Lactobacillus crispatus* determines intestinal colonization and TLR2 and TLR4 modulation in murine colonic mucosa. *Clinical and Vaccine Immunology, 14*(9), 1138–1148.
Waldecker, M., Kautenburger, T., Daumann, H., Busch, C., & Schrenk, D. (2008). Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. *The Journal of Nutritional Biochemistry, 19*(9), 587–593.
Waligora-Dupriet, A. J., Campeotto, F., Nicolis, I., Bonet, A., Soulaines, P., Dupont, C., et al. (2007). Effect of oligofructose supplementation on gut microflora and well-being in young children attending a day care centre. *International Journal of Food Microbiology, 113*(1), 108–113.
Wang, J., Chen, C., Yu, Z., He, Y., Yong, Q., & Newburg, D. S. (2017). Relative fermentation of oligosaccharides from human milk and plants by gut microbes. *European Food Research and Technology, 243*(1), 133–146.
Wang, Y., Han, F., Hu, B., Li, J., & Yu, W. (2006). *In vivo* prebiotic properties of alginate oligosaccharides prepared through enzymatic hydrolysis of alginate. *Nutrition Research, 26*(11), 597–603.
Wang, X., Wang, X., Jiang, H., Cai, C., Li, G., Hao, J., et al. (2018). Marine polysaccharides attenuate metabolic syndrome by fermentation products and altering gut microbiota: An overview. *Carbohydrate Polymers, 195*, 601–612.
Wang, J., Wang, F., Yun, H., Zhang, H., & Zhang, Q. (2012). Effect and mechanism of fucoidan derivatives from *Laminaria japonica* in experimental adenine-induced chronic kidney disease. *Journal of Ethnopharmacology, 139*(3), 807–813.
Wan, Y., Prudente, A., & Sathivel, S. (2012). Purification of soluble rice bran fiber using ultrafiltration technology. *LWT-Food Science and Technology, 46*(2), 574–579.
Wei, N., Quarterman, J., & Jin, Y. S. (2013). Marine macroalgae: An untapped resource for producing fuels and chemicals. *Trends in Biotechnology, 31*(2), 70–77.

Whisner, C. M., & Castillo, L. F. (2018). Prebiotics, bone and mineral metabolism. *Calcified Tissue International,* 1–37.
Wi, S. G., Kim, H. J., Mahadevan, S. A., Yang, D. J., & Bae, H. J. (2009). The potential value of the seaweed Ceylon moss (*Gelidium amansii*) as an alternative bioenergy resource. *Bioresource Technology, 100*(24), 6658–6660.
Wingender, J., Neu, T., & Flemming, H. (2012). *Microbial extracellular polymeric substances: Characterization, structure and function.* Springer Science & Business Media.
Wittke, A., Banavara, D., & Munoz, C. (2014). *U.S. Patent No. 8,648,036.* Washington, DC: U.S: Patent and Trademark Office.
Wong, K. H., & Cheung, P. C. (2000). Nutritional evaluation of some subtropical red and green seaweeds: Part I—proximate composition, amino acid profiles and some physico-chemical properties. *Food Chemistry, 71*(4), 475–482.
Wong, K., & Cheung, P. C. (2001). Influence of drying treatment on three Sargassum species. *Journal of Applied Phycology, 13*(1), 43–50.
Xu, S. Y., Huang, X., & Cheong, K. L. (2017). Recent advances in marine algae polysaccharides: Isolation, structure, and activities. *Marine Drugs, 15*(12), 388.
Xu, X., Wu, X., Wang, Q., Cai, N., Zhang, H., Jiang, Z., et al. (2014). Immunomodulatory effects of alginate oligosaccharides on murine macrophage RAW264.7 cells and their structure-activity relationships. *Journal of Agricultural and Food Chemistry, 62*, 3168–3176.
Yoshie, Y., Suzuki, T., Shirai, T., & Hirano, T. (1997). Analytical procedure and distribution of soluble and insoluble dietary fibers in seaweed foods. *Journal of the Tokyo University of Fisheries, 83*, 1–12.
Yuan, Y., & Macquarrie, D. (2015). Microwave assisted extraction of sulfated polysaccharides (fucoidan) from *Ascophyllum nodosum* and its antioxidant activity. *Carbohydrate Polymers, 129*, 101–107.
Zhao, j., & cheung, p. C. K. (2011). Fermentation of b-glucans derived from different sources by *Bifidobacteria*: Evaluation of their bifidogenic effect. *Journal of Agricultural and Food Chemistry, 59*, 5986–5992.
Zhou, G., Sun, Y., Xin, H., Zhang, Y., Li, Z., & Xu, Z. (2004). *In vivo* antitumor and immunomodulation activities of different molecular weight lambda-carrageenans from *Chondrus ocellatus*. *Pharmacological Research, 50*(1), 47–53.
Zubia, M., Payri, C. E., Deslandes, E., & Guezennec, J. (2003). Chemical composition of attached and drift specimens of *Sargassum mangarevense* and *Turbinaria ornate* (phaeophyta: Fucales) from tahiti, French polynesia. *Botanica Marina, 46*, 562–571.