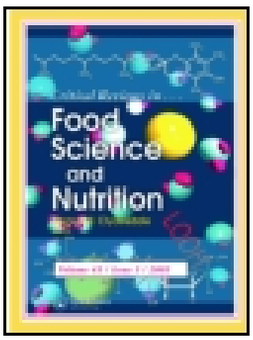

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Ravindra Pal Singh , Raja Bhaiyya , Kiran Khandare & Jagan Mohan Rao Tingirikari (2020): Macroalgal dietary glycans: potential source for human gut bacteria and enhancing immune system for better health, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1845605

To link to this article: https://doi.org/10.1080/10408398.2020.1845605

Published online: 16 Nov 2020.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1845605

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REVIEW

Macroalgal dietary glycans: potential source for human gut bacteria and enhancing immune system for better health

Ravindra Pal Singh[a], Raja Bhaiyya[a], Kiran Khandare[a], and Jagan Mohan Rao Tingirikari[b]

[a]Food and Nutritional Biotechnology Division, National Agri-Food Biotechnology Institute (NABI), Punjab, India; [b]Department of Biotechnology, National Institute of Technology Andhra Pradesh, Tadepalligudem, India

ABSTRACT

Macroalgae are the diverse group of photosynthetic algae found at the intertidal regions of oceans. Recent advances suggest that macroalgal derived glycans have tremendous potential to maintain gut microbiome and immune system. The human gut bacteria harbor unique arsenals for utilizing a variety of macroalgal glycans, and produce a variety of oligosaccharides *in vivo*. Those oligosaccharides interact with immune cell receptors, and also are available for microbial fermentation, thus play magnificent roles in balancing the gut homeostasis. However, this area of research is still in infancy condition in term to understand their molecular interactions. For wooing this area, we urge to emphasize more studies on mechanistic level sympathetic of depolymerizing marine dietary glycans by gut bacteria and elucidating molecular aspect of glycans to cell receptors interactions. This will invent new nutraceutical strategies to purposefully manipulate the microbial composition to improve health. Therefore, review focuses on the recent development of mechanistic understanding of human gut bacterial communities for utilizing macroalgal derived glycans. Recent trends of application of glycans in modulating immune system at mechanistic level and their available evidences are discussed.

KEYWORDS

Bacteria; biocomposites; immune system; macroalgae; polysaccharides utilization locus; polysaccharides

Introduction

Macroalgae subsidize significantly in total biomass produced in marine environment and contribute considerably in marine carbon chain for heterotrophic organisms over the globe (Becker et al. 2020). Macroalgae divide in to three major phyla, namely, chlorophyta (green), phaeophyta (brown), and rhodophyta (red) in which dietary fibers preserve either in cell wall components (such as carrageenan and alginate) or food storage materials (such as laminarin) (Xu, Huang, and Cheong 2017). Macroalgae as dietary fibers are consumed globally, such as wakame (Undaria) kombu (Laminaria), and nori (Porphyra) (Urbano and Goni 2002). Moreover, it is estimated that world population would cross 9 billion by the year 2050, and then macroalgal resources will play a major part in the food security. Given importance of the macroalgae in diverse industries including food ones, global market value of macroalgae is expected to touch US $21.11 billion by 2023 from US $14.08 billion in 2018 with a compound annual growth rate of 8.4% (Global market survey). These dietary fibers are complex in structures and contain variety of monosaccharides with diverse linkages, and majority of them have sulfate groups (Aguilar-Briseno et al. 2015; Gomez-Ordonez, Jimenez-Escrig, and Ruperez 2012; Vishchuk, Ermakova, and Zvyagintseva 2011; Yermak et al. 2017). These polysaccharides have been reported to have wide ranges of physiological and molecular functions such as antioxidant, antitumor, anti-viral, anti-diabetic, immunomodulatory, drug delivery vehicles, and prebiotic properties (Hwang et al. 2016; Singh and Reddy 2014; Yang et al. 2019; Yuan et al. 2006). Hence, they have wide applications in different areas including food, pharma and agricultural field.

In recent years, substantial advances have been made for comprehending the role of macroalgal poly- and oligosaccharides (collectively hereafter as glycans) for improving gut health in terms of modulating gut microbiota and their interaction with immune receptors. For instances, Pluvinage et al. (2018) demonstrated the molecular mechanism of utilizing agarose by the bacteria that is present in the human intestine (*Bacteroides uniformis* NP1). It has been found that glycan utilizing genes in *Bacteroides* occur in cluster, so called polysaccharide-utilization locus (PUL), which expresses all genes required for depolymerizing a glycan (Reeves, Wang, and Salyers 1997; Shipman, Berleman, and Salyers 2000; Shipman et al. 1999). In contrast, laminarin (1-3,1-6-β linked-D-glucan) binds with a pattern recognition receptor, dectin-1, that expresses on macrophages and dendritic cell lines (Xie et al. 2010). Upon binding, laminarin exerts a diverse array of bioactivities, including antitumor (Nakata et al. 2016), antioxidant activities (Choi, Kim, and Lee 2011), inhibition of apoptosis (Kim et al. 2006) and differentially modulates production of various cytokines (Smith et al. 2018). Similarly, in recent time, myriad of biological activities of glycans derived from other macroalgal sources are understood with their molecular actions. These biological activities

CONTACT Ravindra Pal Singh ravindrapal.1441@gmail.com Food and Nutritional Biotechnology Division, National Agri-Food Biotechnology Institute (NABI), SAS Nagar, Punjab, 140306, India.

are determined by chemical and physical properties of glycan including size, purity, solubility and bioavailability.

Intriguingly, oligosaccharides generated from macroalgae have displayed greater prebiotics potential as compared to their respective polysaccharides due to higher solubility and bioavailability (Fang et al. 2017; Park et al. 2016; Saigusa et al. 2015; Vera et al. 2011; Zhou et al. 2015). For instances, alginate-oligosaccharides (AOs) of degree of polymerization (DP) 2–5 or 2–7 were obtained from alginate using alginate lyase produced by *Pseudomonas* sp. HZJ 216 (Li et al. 2011), and *Cellulophaga* sp. NJ-1 (Zhu et al. 2016), respectively. Such generated oligosaccharides were previously used to promote growth of beneficial bacteria, such as *Bifidobacteria* and *Lactobacillus* and also found to be potent than plant derived fructo-oligosaccharides (Wang et al. 2006). The alginate lyase degrades alginate via β-elimination mechanism that produces unsaturated double bond at non-reducing end of sugars. Produced unsaturated AOs can show immunomodulatory activities by inducing reactive oxygen species (ROS), nitric oxide (NO), and tumor necrosis factor (TNF)-α production in murine macrophage RAW264.7 cells (Li, He, and Wang 2019), and anti-obesity effects in high-fat diet (HFD) mouse model (Xu et al. 2014). Although oligosaccharides can be obtained by physical, chemical and enzymatic methods, analysis of their composition and sequence are still challenging because of their intricacy in structures and monosaccharide heterogeneity (Lang et al. 2014). Therefore, we urge that future studies should first consider purification of defined DP with full understanding of structural properties and then evaluate biological activities in order to utilize them efficiently.

Despite having great benefit of oligosaccharides, it has been known that simple oligosaccharides are mainly digested in proximal gut and hardly reached to distal part (Duncan et al. 2003; Zoetendal et al. 2012). While, there are clear evidences that a number of microbial communities gradually increase in intestine, with highest number in distal gut (Hillman et al. 2017; Kastl et al. 2020). This understanding highlights that oligosaccharides should reach the distal part of the gut for promoting health benefits. Given the complexity of macroalgal glycans, they would be best fit for fulfilling this requirement. However, they are yet to be figure out this way.

In this review, we aim to highlight recent trends of usages of macroalgal glycans for modulating microbiome and immune system, and summaries their current understanding relates to molecular mechanisms.

Macroalgal glycan types and their structure

Macroalgal glycans, such as agar, alginate, carrageenan, and fucoidan, have a variety of physiological activities and are being used in agricultural, food and medical areas. Nevertheless, the usage of polysaccharides can be constrained by their low bioavailability, which depends on polysaccharides type and source of their production. On the other hand, their oligosaccharide counterparts have drawn increasing attention due to their excellent biological activities that arise due to good solubility and excellent bioavailability (Zhu et al. 2020). Overall, biological properties of macroalgal glycans vary based on sources, sulfate content and unsaturated glycan units (see below). Structural variation of the macroalgal glycans are as follows

Ulvan is a green macroalgal polysaccharide comprised of about 9%–36% of total cell wall component. The backbone structures of ulvan are highly diverse and often comprised of 1,4-linked α-L-rhamnopyranose, such as in edible *Ulva pertusa* (Tako et al. 2015). Diversity in ulvan structures could be attributed to the varies monosaccharide units, such as rhamnose, xylose, glucuronic and iduronic acids where rhamnose and xylose are linked with sulfate at 3 and 2 hydroxyl positions, respectively (Lahaye, Brunel, and Bonnin 1997; Lahaye and Robic 2007).

Fucoidans are sulfated polysaccharides produced mainly by brown macroalgae and marine invertebrates (sea cucumber or sea urchin) (Chizhov et al. 1999; Yu et al. 2014). This sulfated polysaccharide has complex structure comprising of α-L- fucopyranose with alternative glycoside linked by α-(1→3) and α -(1→4). The backbone structure is made of different monosaccharide sugars such as uronic acid, glucose, mannose, galactose, xylose, rhamnose, and arabinose with an average molecular weight (MW) of 10–950 kDa, such as in *Sargassum fusiforme* (Duarte et al. 2001). Half of the 3-linked residues can be substituted at C-4 position by a trifucoside units α -L-Fucp-(1→4)- α –L-Fucp- (1→3)- α -L-Fucp-(1→4)- (Bilan et al. 2006). Sulfate groups can be mainly observed at C-2 and sometimes at C-4 and C-3 positions of linked fucose residues with remaining hydroxyl groups can be randomly acetated (Bilan et al. 2002).

Laminarin is a non-sulfated polymer made of D-glucopyranose linked with β (1→3)- and β (1→6)-glucoside linkages, which predominately found in orders of *Laminariales*, and *Fucales* species as a storage material. The DP of laminarin is about 25 with a MW of up to 5000 Da (Alderkamp, van Rijssel, and Bolhuis 2007; Nelson and Lewis 1974). Laminarin is divided in to two types (G and M) based on the non-reducing sugar type. G and M types are ending with glucose and mannitol residue, respectively (Rioux, Turgeon, and Beaulieu 2010; Spicer et al. 2017).

Carrageenan is a group of linear sulfated polysaccharide belonging to red macroalgae, such as *Chondrus crispus*, *C. armatus*, *Tichocarpus crinitus, Gigartina*, and *Eucheuma* species (Barros et al. 2013; Ili Balqis et al. 2017; Jaballi et al. 2019). The backbone structure is comprised of linear chain of repeating units of β-3-D-galactopyranose and α-4-D-galactopyranose or 3,6-anhydro-α-D-galactopyranose with an average MW of 100–1000 kDa (Barros et al. 2013). Depending up on the macroalgal source, degree of sulfation and presence of 3, 6-anhydro-α- D galactose units, there are three main types of carrageenan, namely kappa (κ), iota (ι), and lambda (λ). Linkages in disaccharides units of each type is present as -(1→3)-β-D-galactopyranose-4-sulfate-(1→4)-3,6-anhydro-α-D-galactopyranose-(1→3)-, -(1→3)- β-D-galactopyranose-4-sulfate-(1→4)-3,6-anhydro-α-D-galactopyranose-2-sulfate-(1→3)-, and -(1→3)-β-D-galactopyranose-2-sulfate-(1→4)-α-D-galactopyranose-2,6-disulfate-(1→3) in κ, ι, and λ, respectively (Hilliou 2014; Janaswamy and Chandrasekaran 2001;

Jouanneau et al. 2010). κ, and ι, can form gel whilst λ does not form gel due to absence of 3,6-anhydro-α-D-galactopyranose unit. Carrageenan is considered as safe to use in functional foods and has been used as thickening, suspending and gelling agents (Aguilar et al. 2017).

Agar is the cell wall component and is mainly extracted from red macroalgae (Marinho-Soriano and Bourret 2005). Laboratory gelling agent, such as agar, is mainly extracted from *Gelidium;* however, it is often isolated from *Pterocladia, Petrocladiella*, *Gracilaria,* and *Hypnea* species (Li et al. 2008). Among the latter, about 50% of food grade agars extracted from *Gracilaria* species (Rocha et al. 2019). Agarose and agaropectin are the main fractions of agar, which are composed of repeating units of β-D- galactopyranose (GAL) and 3, 6-anhydro-α-L- galactopyranose (AHG). Although, 11 different disaccharide structures (agarobiose) were identified based on gender and environmental conditions of different species (Lahaye and Rochas 1991). These structures of agarobiose are closely related with porphyran whose structure is characterized by alternating 4-linked α–L-galactopyranose-6-sulfate (L6S) and 3-linked β-D-galactopyranose units (Morrice et al. 1983). In term of sulfate content, agarose is low in amounts as compared to agaropectin (Rochas, Lahaye, and Yaphe 1986).

Alginate is an anionic non-sulfated polysaccharide derived from brown algal cell wall such as *Laminaria hyperborean*, *Ascophyllum,* and *Macrocystis pyriform*. Alginate is a linear polymer made up of 1,4-linked β-D-mannuronic and 1,4 α-L-guluronic acids (both are epimer of C-5 position) residues arranged either in homogenous or heterogeneous patterns (Haug 1959). The content of homomeric and heteromeric composition depends on the source of alginate. Since glucuronic acid tends to bind strongly with calcium ions, majority of the alginate available for food and pharmaceutical applications are low in guluronic acid (Donati et al. 2005).

Recent understanding for utilization of macroalgal glycans by human gut bacteria

It is now widely accepted that nutraceutical strategies, such as prebiotics, exploit the host-diet-microbe concept to alter the gut microbiota for improving microbial composition of gut. Epidemiological data obtained from Japanese and Western diets suggest that consumption of macroalgae (5.3 g/day) in Japan decreased the incidence of chronic non-communicable diseases such as obesity, metabolic diabetes, cardiovascular disease, and inflammatory bowel disease (Chirumbolo and Bjorklund 2016; Kang et al. 2016). The total dietary fiber content in macroalgae varies from 20 to 60% (McDermid, Stuercke, and Haleakala 2005), which may provide an excellent source for promoting population with beneficial microbial communities including probiotics. A plenty of *in vitro* and *in vivo* studies have been carried on macroalgal glycans (poly- and oligo-saccharides) as carbon sources (Table 1). However, precise molecular mechanisms of majority of those studies have not been evaluated yet. It has been convincingly recognized that utilization of dietary fibers entirely relies on carbohydrate utilization potential or carbohydrates active enzymes (CAZymes) of gut microbial communities. Majority of glycan utilizing enzymes employed by human gut bacteria belongs to glycoside hydrolase and polysaccharide lyase families (El Kaoutari et al. 2013). In fact, it is reckoned that nutraceutical strategies for improving health of the gut would be highly benefited if we know which bacterium to be targeted and what glycan utilization arsenal they have. Therefore, we are hereby summarizing the latest understanding at precise mechanistic levels of utilization of macroalgal glycans by human gut bacteria.

It is known that genes required for digestion of a glycan is encoded in a cluster form, particularly in Gram-negative bacteria, in which they co-regulate upon sense of a specific glycan type. PUL was initially found in the human gut symbiont, *Bacteroides thetaiotaomicron* (Anderson and Salyers 1989). A typical PUL architecture represents genes homologous to susD (an oligosaccharide binding trans-membrane protein), susC (a TonB-dependent receptor that transports oligosaccharides in to periplasm), a large array of genes encoding several enzymes (which hydrolyze a glycan), genes for regulatory proteins and some with unknown function (Glenwright et al. 2017; Larsbrink et al. 2014). So far more than 13,500 PULs are known in *Bacteroides* (Lapebie et al. 2019). Each PUL is controlled by sensory protein known as the hybrid-two component systems (HTCSs) in *Bacteroides* (Sonnenburg et al. 2006). Expression of HTCS is activated by the specific size of oligosaccharide that enters in to periplasmic space and makes positive feedback until bacterial outer surface is sufficiently not saturated (Larsbrink et al. 2014).

Laminarin as dietary fiber concept was brought up by Deville et al. (2004), and their subsequent study found that laminarin does promote the growth of *Bacteroides*, *Bifidobacteria* and *Lactobacillus* genera among others and overall increases the concentration of short-chain fatty acids, SCFAs, (acetate, propionate and butyrate) (Deville et al. 2007; Lam et al. 2020). Given that nearly more than 20% genes of whole genome of *Bacteroides* are dedicated to carbohydrate utilization repertoire (Martens, Chiang, and Gordon 2008; Terrapon et al. 2015), *Bacteroides cellulosilyticus* WH2 (McNulty et al. 2013), and *Bacteroides uniformis* ATCC 8492 showed a significant growth on laminarin (Desai et al. 2016; Salyers, Palmer, and Wilkins 1977). Recently, molecular mechanism for utilization of laminarin was discovered in *Bacteroides uniformis* ATCC 8492 (Dejean et al. 2020). Study carried out with *B. uniformis* ATCC 8492 unveiled that PUL-encoded endo-acting glycoside hydrolases (GHs, GH158 and 16), and surface glycan-binding proteins (SGBPs) synchronize together to efficiently utilize laminarin at outer membrane surface, and then generate oligosaccharides by GH158 and 16, which are then internalized by SusCD complex in periplasmic space. In periplasmic space, exo-acting tailored GH3 converts the oligosaccharides into glucose before landing into cytoplasm. Newly identified GH158 family characterized to cleave curdlan (Helbert et al. 2019); however, the enzyme showed weaker activity. Further exploration on such enzyme would be useful for food industry to produce a large number of β-1-3-linked oligosaccharides from curdlan for promoting the growth of prebiotics

Table 1. Microbiome modulatory effect of macroalgal oligosaccharide.

Macroalgae polysaccharides	Bacterial modulating capacity	Reference
Agar and agar-oligosaccharides (AGOs)	Agar and agar-oligosaccharides mainly increased the population of *Bacteroides* whilst subtle changed in *Bifidobacteria*. *Bacteroides uniformis* L8 has the ability to significantly degrade AGOs, and *Bifidobacterium infantis* and *Bifidobacterium adolescentis* can utilize agarotriose among other AGOs.	Zhang et al. (2020) Li et al. (2014)
	AGOs improve the gut bacterial composition of microbiota by enriching the abundance of *Ruminococcaceae, Coprococcus, Roseburia,* and *Faecalibacterium.*	Han, Yang, et al. (2019)
Alginate and alginate oligosaccharides (AO_S)	A fraction CC2253 (64.64 kDa, an oligosaccharides fraction) increased the population of *Bifidobacteria* from $\log_{10}$ 8.06 to $\log_{10}$ 8.55 without changing other tested bacteria.	Ramnani et al. (2012)
	Alginate (100 kDa), mannuronic acid oligosaccharides (MO, 2.5 kDa),) and guluronic acid oligosaccharides (GO, 4 kDa) can increase population of *Bacteroides*, specifically, *B. ovatus*, *B. xylanisolvens*, and *B. thetaiotaomicron*. The GO generated the highest level of short-chain fatty acids (SCFAs).	Li, et al. (2016)
	The male Wistar rats fed with enzymatically produced AO_S (2.5%) for 2 weeks, increased 13 and 5-fold *Bifidobacterial* and *Lactobacilli* populations. Strikingly, AO_S stimulated the growths of *Bifidobacterium longum* SMU 27001 and *Bifidobacterium bifidum* ATCC 29521 more significantly in comparison with fructo-oligosaccharides.	Wang et al. (2006)
	AO_S can decrease the population of opportunistic pathogenic bacteria *Escherichia, Shigella,* and *Peptoniphilus*. However, degree of polymerization does impact this outcome.	Han, Yang, et al. (2019)
	The diet with 10 g alginate once a day for 2 weeks was given to eight healthy male volunteers that led to increase the levels of *Bifidobacteria* significantly as compared to the levels of *Enterobacteriaceae.*	Terada, Hara, and Mitsuoka (1995)
κ-carrageenan oligosaccharides (κ-CO_S)	*B. xylanisolvens* produces β-carrageenase, which degrades carraheptadecaose (DP17) and generates κ-CO_S having DP 2 to 7 after 144 h of incubation.	Li et al. (2017)
	κ-CO_S were prepared by simulating stomach condition *in vitro*, and two fractions (KO3 and KO6) having DP1, DP2, DP4, DP6, DP8, DP10 and DP12 were used for stimulating bacterial growth. Overall, larger DP ones were stimulated the growth of *Bifidobacteria* while all DPs stimulated growth of *Prevotella* and promoted SCFAs production.	Sun et al. (2019)
ï-carrageenan oligosaccharides (ï -CO_S)	Wanes population of facultative pathogenic bacteria, such as *Enterobacteria, Staphylococci,* and *Streptococci.*	Mallett et al. (1985)
Fucoidan	Promotes the growth of *Akkermansia muciniphila*, *Alloprevotella*, *Blautia, Bacteroides* and *Clostridiales* when C57BL/6J mice fed with 200 mg/kg fucoidan obtained from *Laminaria japonica* and *Ascophyllum nodosum*.	Shang, Shan, et al. (2018)
Laminarin	Stimulated the growth of *Bifidobacterium breve* ATCC 15700, *Lactobacilli* and *Bacteroides* at 1 % of carbon source.	Seong et al. (2019)
	High-fat diet with 1% laminarin leads to decrease in weight of the BALB/c mice and the abundance of *Bacteroides* and *Parabacteroides* significantly increased.	Nguyen et al. (2016)
Porphyran	Stimulates the growth of *Lactobacilli, B. bifidum*, and *Bacteroides* at 1 % carbon source.	
Ulvan	Stimulates the growth of *Bifidobacterium breve* ATCC 15700, *Lactobacillus plantarum* ATCC 10241, *B. thetaiotaomicron* ATCC 29148, *B. ovatus* ATCC 8483, and *B. uniformis* ATCC 8492 at 1 % of carbon source.	Seong et al. (2019)
	The Ulvan of *Ulva* at 1-2% content in yogurt enhance the growth and activity of prebiotic bacteria like *Lactobacillus acidophilus* and *Bifidobacterium* sp.	Shalaby and Amin (2019)

(Table 1). This exploration was carried out in our recent study that has clearly demonstrated that GH158 can cleave curdlan significantly when it is present in soluble form (Singh et al. 2020). The GH158 was used for generation of β-1-3-linked oligosaccharides that were found to be potent prebiotics. There are some reports which indicate that *Bifidobacteria* and *Lactobacillus* can grow on laminarin, but their utilizing arsenal is not clear yet (Lam et al. 2020).

The agar and porphyran (galactans) degrading enzymes that were identified in Japanese gut bacteria includes *Bacteroides plebeius* DSM 17135, a marine bacterium, *Zobellia galactanivorans* (Hehemann et al. 2010). Two proteins of porphyran utilization locus (POUL), Bp1689 (GH16-β-porphyranase) and Bp1670 (GH16-β-agarase) were previously thought to be unique to this bacterium among the human gut bacteria. However, this locus is also identified in other gut bacteria, such as *B. uniformis* JCM 13288^T (Singh et al. 2020). These genes are typically orchestra in PUL fashion with other endo-acting (two belonged to GH86A and B), exo-acting enzymes (two belonged to GH2 and a sulphatase) and SusCD complex, as shown in Figure 1. Further analysis of two, GH86A and B, GH86A was only active on porphyran and produced predominantly larger oligosaccharides as compared to Bp1689 (Hehemann et al. 2012). Given the generation of larger oligosaccharides, it remains to unveil whether or not those released oligosaccharides were involved in glycan cross feeding or only be used by *B. plebeius* DSM 17135 via action of Bp1689.

Hehemann et al. (2012), observed that *B. uniformis* NP1 and *B. thetaiotaomicron* VP1-3731 can utilize agarose and κ-carrageenan, respectively. Later, carrageenan and agarose degrading molecular mechanisms were reported in marine standard bacterium, *Z. galactanivorans* (Ficko-Blean et al., 2017), and human gut bacterium, *B. uniformis* NP1 (Pluvinage et al. 2018). Utilization potential of agarose and κ-carrageenan was also observed in *B. uniformis* L8 and *B. xylanisolvens* 38F6 isolated from human gut microbiota, respectively (Li et al. 2017). Mechanistic based agarose degradation in *B. uniformis* NP1 initially takes place at the outer surface of cell wall by the activity of GH16C and

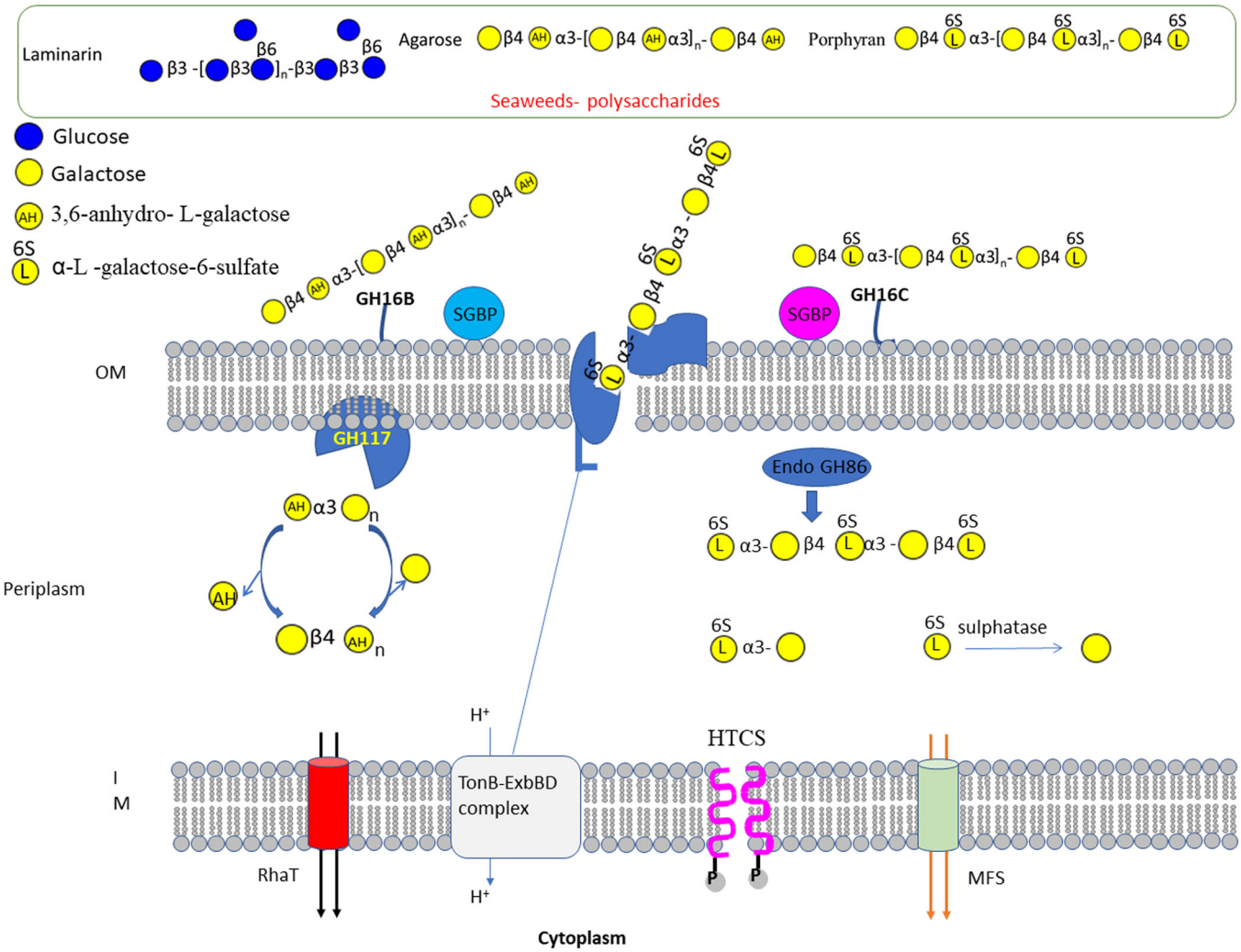

Figure 1. Initial depolymerization of porphyrin or agarose takes place at the outer surface of cell wall by the activity of GH16C and GH16B, respectively. These enzymes cleave the polymers from internally and generate a range of oligosaccharides, so called neoagarooligosaccharides (NAOS) that are internalized by orthologous SusCD complex. In the periplasmic space, NAOS can be further cleaved by two different pathway, (1) GH86 can convert NAOS in to neoagrobiose (AHG-α-1,3-GAL) or (2) can be depolymerized by in a cyclic fashion by the exo-acting GH117B–GH2C. Released AHG and GAL import in to cytoplasm by the RhaT and MFS proteins, respectively (Pluvinage et al. 2018).

GH16B, respectively (Pluvinage et al. 2018). These enzymes cleave the polymers internally and generate a range of oligosaccharides, so called neoagaro-oligosaccharides (NAOs) that are internalized by orthologous SusCD complex. In the periplasmic space, NAOs can be further cleaved by two different pathway, (1) GH86 can convert NAOs in to neoagrobiose (AHG-α-1, 3-GAL) or (2) can be depolymerized by in a cyclic fashion by the exo-acting GH117B–GH2C. Released AHG and GAL import in to cytoplasm by the RhaT and multi facilitator superfamily (MFS) proteins, respectively, as shown in Figure 1. However, it is yet to identify the length of oligosaccharides for this PUL that can activate regulatory protein (HTCS) to initiate PUL associated gene expression. Astonishing observation was obtained during the study where it was found that outer membrane tailored GH16 can capture NAOs that could be released by other microbes present in gut environment after cleavage of long chain polymers. Thus, the PUL can involve in glycan cross feeding. Released NAOs in gut environment may increase the abundance of *Firmicutes* and *Actinobacteria* and also reduce potential pathogenic bacteria, as mentioned in the Table 1 (Zhang et al. 2020). It should be explored through further studies.

During the hydrolysis of agar, agarose and carrageenan by enzymes releases the AHG which is not usual sugar, and requires certain unique enzymes to metabolize in conventional metabolic pathway (Pluvinage et al. 2018). Interestingly, *B. uniformis* NP1 contains five additional genes for expression of AHG dehydrogenase, AHG isomerase, ketodeoxygluconate kinase, galactose mutarotase and a RhaT-like sugar importer. Two genes AHG dehydrogenase and AHG isomerase show high sequence similarity (>64%) to the genes present in the marine bacterium *Vibrio* sp. EJY3, suggesting that agarose PUL in *B. uniformis* NP1 may be acquired by an *en bloc* horizontal gene transfer (HGT) event (Yun et al. 2015).

Enzymes required for utilizing uronic acid containing glycans (such as alginate) are referred as polysaccharide lyase (PL), belongs to 6, 7 and 17 PL families, which act on substrate via β-elimination mechanism and produce 4,5-unsaturated residue at non-reducing end (Lapebie et al. 2019). A careful examination on alginate utilization locus (AUL), and genes related to alginate degradation (α-L-guluronate or

β-mannuronate lyase) in human gut microbiota led to identification of exo-acting PL17_2 (mainly β-mannuronate lyase) colocalized with PL6_1 in AUL to grow on substrate (Mathieu et al. 2018). In human gut bacteria, two distinct type of PUL were observed, the one with PL17_2 and PL6_1, and independently PL6_1 to PL17_2 (Mathieu et al. 2018). This implies that it might have happened due to different HGT event where PL6 must be a common ancestor. Recently a polyM specific PL6 from the human gut microbe *Bacteroides cellulosilyticus* was identified that can generate unsaturated oligosaccharides having DPs 2 to 7 (Stender et al. 2019). Generated unsaturated oligosaccharides by PL action seem to be useful for promoting growth of probiotics strains belonging to *Bifidobacteria* and *Lactobacillus* species (Akiyama et al. 1992; Li, Li, et al. 2016) as mentioned in Table 1. However, further investigation is required to understand their utilization mechanism to handle them appropriately. Apparently, above mentioned specific nutrient utilization systems in *Bacteroides* clearly highlight that a bacterium harbors unique type of PUL to another one, most likely to maintain gut microbial homeostasis under diverse nutrient environmental conditions while reducing PUL redundancy. Furthermore, studies on glycan cross-feeding using different genera of gut bacteria would pave the way in contributing to gut health and wellbeing.

Acquisition of specific gene clusters from marine bacteria into human gut microbiota suggests that contaminated raw food material would have been sources for HGT event. It is also likely that regular diet containing macroalgal dietary glycan can enforce a selection pressure on certain gut bacteria to hold macroalgal dietary glycan utilization genes and such PUL become evolutionary conserved while transferring one generation to subsequent generation. For instances, analysis of Japanese gut microbiota suggests that the locus is transferred from mother to its baby and transmits within the closely related family members (Hehemann et al. 2010). Metagenomic survey across populations of different geographical areas, such as North America, Europe, China, and Japan, reveals that AUL of *B. uniformis* NP1 and POUL of *B. plebeius* DSM 17135 are highly abundant in Japanese population as compared to other metagenomic samples of North America, Europe and China (Pluvinage et al. 2018). Interestingly, AUL of *B. uniformis* NP1 was highly present in North America metagenomic samples when compared with Europe and China samples infers that mass movement of population and culture can affect HGT events. In other case, Dejean et al. (2020) has divided β-1-3 type locus in three different groups, namely *B. uniformis, B. thetaiotaomicron* and *B. fluxus*, in which *B. uniformis* is ubiquitously present across in European, North American and Asian population. Interestingly, these loci could not be detected in Hadza and Yanomami tribes, suggesting that they have high prevalence of *Prevotella* as compared to *Bacteroides* (De Filippo et al. 2010; Smits et al. 2017). Such scenario reflects that β-1-3 type locus is highly developed in industrialized human population. In order to get precise information about unique existence of these PULs in some *Bacteroides*, a significant study is required for underpinning adaptive genomic evolution under diverse lifestyle factors including contemporary diets.

On utilization of glycans by the gut microbiota, they produce several health promoting metabolites including SCFAs as mentioned in Table 1. Physiological functions of SCFAs are recently reported in our previous review (Singh 2019) and others (Alexander et al. 2019; Koh et al. 2016), hence ignored. In brief, SCFAs play an essential role in the communication between microbes and their associated host. It also plays a crucial role in host metabolic and immune functions (Parada Venegas et al. 2019). Nowadays, SCFAs are significantly assessed to understand their roles in protection against obesity and other metabolic diseases and inhibition of gut pathogens. Such as, propionate and formate decrease the pH of luman, which inhibits the growth of pH sensitive pathogenic bacteria, including *Salmonella* (Gomez-Garcia et al. 2019; Jacobson et al. 2018). Similarly in our recent study, we found that butyrate can inhibit quorum sensing system in *Clostridium perfringens* (Adachi et al. 2018), and induce production of mucin, which inhibits the bacterial adhesion (Jung et al. 2015). SCFAs are being screened for their importance in maintaining gut immune system during inflammatory bowel diseases (Ferrer-Picon et al. 2020; Russo et al. 2019). In recent time, we gained some understanding about how macroalgal glycans are utilized by human gut bacteria at mechanistic level. However, it is expected that more evidences on precise mechanism on utilization of macroalgal glycans by human gut bacteria will encourage more individuals from over the globe to take macroalgal glycans as one of the meal ingredients.

Immunomodulatory effect of macroalgal glycans

The ability of innate immune system is mediated by granulocyte cells, which serve as first line of defence. Glycans have been believed to stimulate immune response independent of T cells (Bohn and BeMiller 1995). Among all the cells, macrophages play a vital role in both innate and acquired immunity by activating pro/anti-inflammatory cytokines involved in boosting the host defence mechanism and regulating tumor development as well as controling inflammation. For instance, dectin-1, is a type II transmembrane protein receptor expressed on macrophages, neutrophils, dendritic cells and plays a major role in innate immunity by binding to β-1,3 and β-1,6 glucans (Adachi et al. 2004; Brown et al. 2003). Dectin-1 triggers the immune response by either phagocytosis or the production of proinflammatory factors as mentioned in Figure 2. It helps in releasing anti-cancer and anti-tumor mediators such as interleukin (IL)-12, IL-6, tumor necrosis factor (TNF)-α, and IL-10 by activating the Iκ-B kinase, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein (MAP) kinase pathway, signaling adaptor protein CARD9 and nuclear factor of activated T cells (Goodridge, Simmons, and Underhill 2007; Gross et al. 2006; Rogers et al. 2005). Blocking of the toll like receptor (TLR)-4 by glucans from *Ganoderma* (PS-G) suppressed the production of IL-12, p40 and IL-10, which indicate the

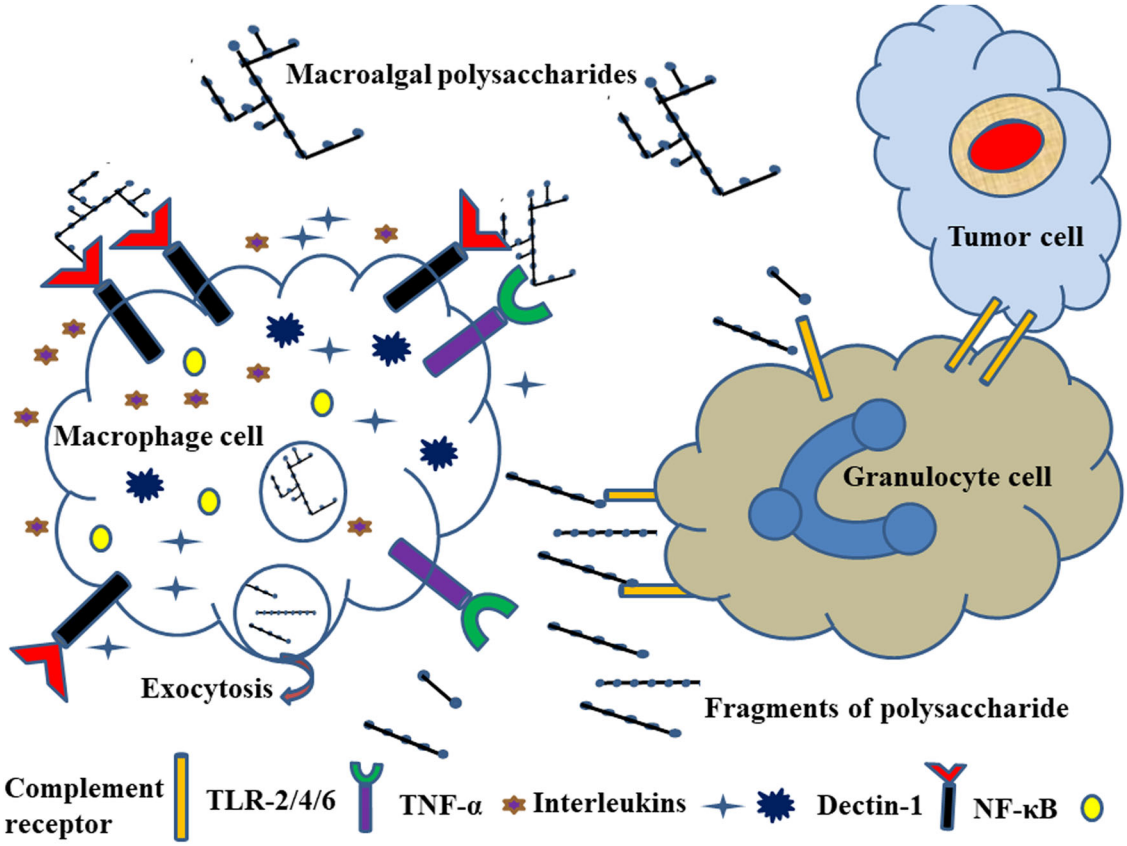

Figure 2. Dectin-1, and toll-like receptors (TLR) mediated activation of macrophages by binding of β-glucans (laminarin) followed by degradation of it by nitric oxide mechanism. Subsequent, degraded products of laminarin activate granulocytes in the presence of complement receptors. The cytoplasmic tail of dectin-1 contains an immunoreceptor (tyrosine-based activation motif) which signals through tyrosine kinase in association with TLR (Gantner et al. 2003; Herre et al. 2004; Taylor et al. 2002).

TLR-4 mediated activation of dendritic cells by β-glucans as shown in Figure 3.

Similarly, glycans from red macroalgal species such as *Porphyra yezoensis* and *Gracilaria verrucosa* displayed macrophage stimulating activity by binding the TLR-4, present on surface of macrophages under *in vitro* and *in vivo* conditions (Lee et al. 2009; Shin et al. 2011). While, fucoidan from *Undaria pinnatifida* was reported to stimulate cytokines (IL-6 and TNF-α), and chemokines (RANTES and monocyte chemoattractant protein) (Yoo et al. 2007). In case of κ-carrageenan isolated from red algae enhanced the production of TNF-α in mice leukocytes (Yuan et al. 2006). The TNF-α and IL-6 were induced by ulvan obtained from *Capsosiphon fulvescens* (Synytsya et al. 2015). Current understanding of these glycans in modulation of immune system has summarized below.

Ulvan

The immunomodulatory activity of ulvan greatly depends on the molecular structure and content of glucuronic acid, iduronic acid, xylose and sulfated rhamnose as well as differences in MW. In recent years, it was observed that a strong pro-inflammatory response can be triggered when RAW 264.7 cells were treated with ulvan (Tabarsa et al. 2018). Such as, the activation of the RAW 264.7 macrophages cells was enhanced with increasing in MW of ulvan derived from *Ulva pertusa* (Tabarsa et al. 2012). Desulfation of ulvan isolated from *U. rigida* has led to 50% decrease in activity of the RAW 264.7 cells (Leiro et al. 2007). Therefore, in the current scenario, it suggests that ulvan isolated from *U. pertusa*, *U. rigida*, *U. prolifera*, and *U. intestinalis* can modulate several biomarkers such as TNF-α, IL-1β, IL-4, IL-6, IL-10, IL-11, IL-12, and IL-13, and other enzymes, such as NO synthase (iNOS) and cyclooxygenase-2 (COX-2) (Kim et al. 2011; Tabarsa et al. 2018). Nevertheless, a defined molecular structure of ulvan that causes activation of macrophages is yet to be elusive.

Fucoidan

Fucoidans are excellent immune modulators that bind on TLR-4 of dendritic cells, macrophages and monocytes, and macrophage scavenging receptor (SR-AI). Thus, it activates pro/anti-inflammatory cytokines, helping in mounting immune response (Zhang et al. 2015). In particular, production of inflammatory cytokines was regulated by the presence of sulfate and acetyl groups of fucoidan (Choi et al. 2005). Although, binding of fucoidan with macrophage scavenging receptor AI (MSR-AI) is known since last 20 years (Hsu et al. 1998), only Segers et al. (2012) validated that fucoidans act as ligand molecule for MSR-AI to inhibit the production of NO, and show anti-inflammatory effect by inhibiting the migration of leukocytes to inflammatory tissues. The anti-inflammatory effect was due to inhibition of NF-κB, mitogen-activated protein kinase (MAPK) and Akt activation (Park, Han, et al. 2011). In contrast, Nakamura et al.

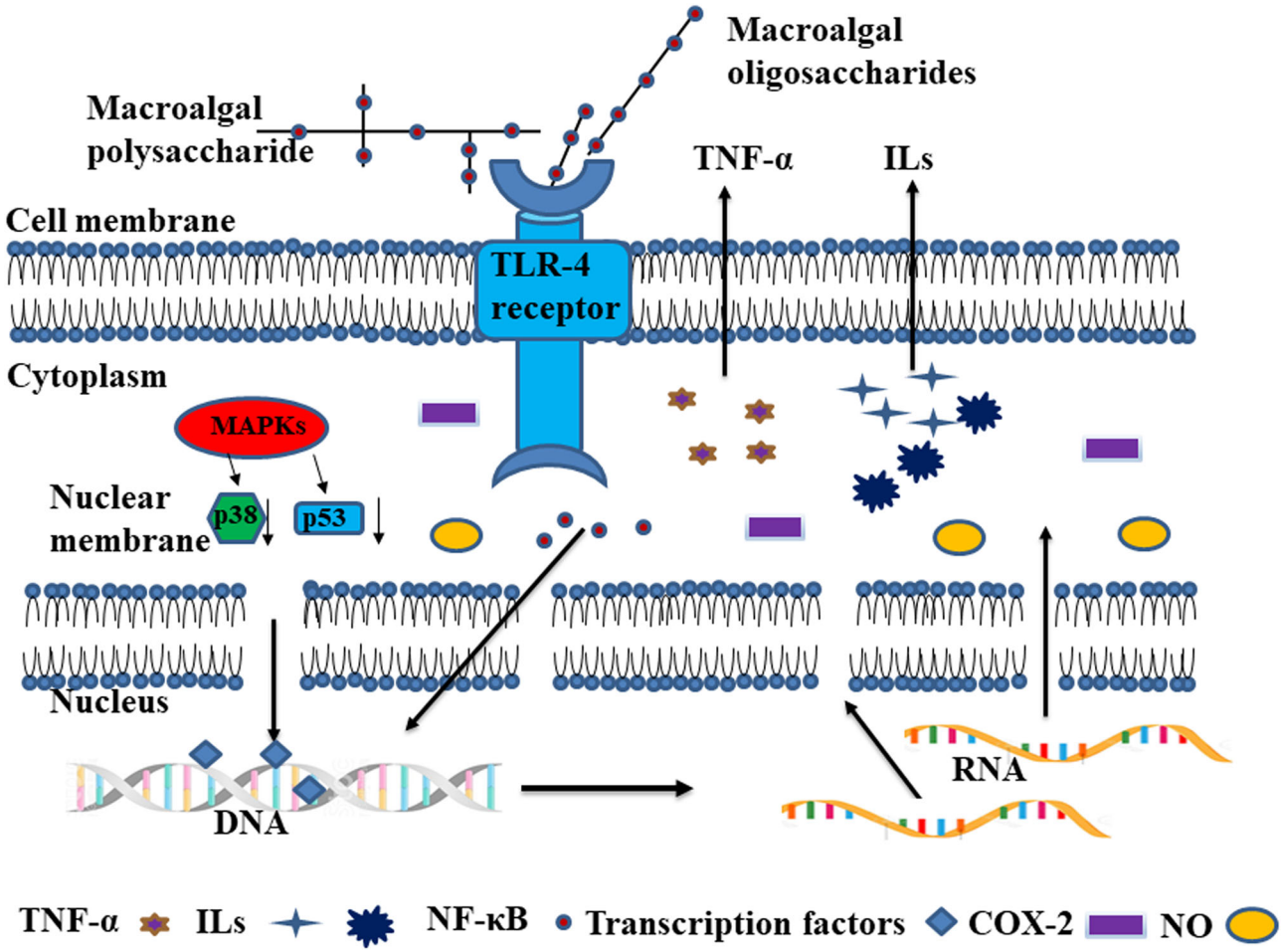

Figure 3. Toll-like receptor (TLR) mediated activation of macrophages by macroalgal glycans. Subsequent, it releases proinflammatory mediators such as tumor necrotic factor (TNF)-α, interleukins (IL), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), cyclooxygenase (COX)-2, and nitric oxide (NO). MAPK, mitogen-activated protein kinase.

(2006) reported that fucoidan regulates the signaling of MAPK—p38 and NF-κB—in the RAW264.7 cells by MSR-AI signaling (Table 2). Additionally, fucoidans are being used as adjuvant by up regulating CD40, 80, and 86 along with production of inflammatory markers, IL-6, IL-12 and TNF-α (Jin and Yu 2015; Jin et al. 2014). Thus, it helps in development of tumor vaccine and improving the (Th1/Th2) immune balance.

Fucoidan has been studied for its effect on breast cancer cell lines (4T1), in which it has ability to decrease the vascular endothelial growth factor (VEGF) expression, supressing the Bcl-2/BAX ratio and releasing of cytochrome-C, leading to apoptosis (Xue et al. 2012). Fucoidan isolated from *Padina boryana* consists of 1,4-linked-α-L-fucopyranose and 1,3-linked β-D-galactopyranose structure, which has the ability to exhibit the cytotoxic effect, and anti-colony forming effect on colorectal carcinoma cells, DLD-1 and HCT-116 (Usoltseva et al. 2018). However, degree of sulfation in fucoidan may affect the efficacy of anti-proliferative activity, as sulfated fucoidan isolated from *Cladosiphon okamuranus* was induced apoptosis by activating caspase-3 and caspase-5 (Teruya et al. 2007). Treatment of sulfated fucoidan has shown strong apoptosis and programmed cell death autophagy in human gastric adenocarcinoma cells (AGSs) (Park, Kim, et al. 2011). For example, a fucoidan fraction (ScF) obtained from brown macroalga *Saccharina cichorioides* has showed the anti-proliferative activity, and a supernatant fraction, obtained after 72 h of auto hydrolysis (1,3-linked-α-l-Fuc*p*-4-$OSO3^{-}$ repeating units with MW of 6 kDa), displayed most significant effect on colorectal carcinoma cells HT-29 among other fractions (Anastyuk et al. 2017). Possible molecular mechanism of macroalgal glycans for inhibiting cancer/anti-cancer properties are summarized below.

Fucoidan oligosaccharides (FOs) are being produced by either physical disruption, enzymatic or chemical treatment processes, which are reviewed elsewhere (Chen et al. 2012; Choi and Kim 2013; Daniel et al. 1999). FOs are generally made up of α −1, 3-L-fucose (Daniel et al. 1999) and are being explored for their anti-cancer/cytotoxicity effects. For instances, low MW fucoidan (5–30 kDa) with improved concentration showed significant cytotoxicity effect on MCF-7, AGS, and HepG-2 cancer cell lines under *in vitro* conditions as compared to fucoidan polysaccharide (Choi and Kim 2013). Hydrolyzed fucoidan from *Undaira pinnatifida* exhibited 38.3% more anti-cancer property as compared to native fucoidan due to desulfation of polysaccharide (Mak et al. 2014). It was reported that induction of tumor formation by the 12-O-tetradecanoylphorbol-13-acetate can be inhibited by both fucoidan poly and oligosaccharide generated by γ-treatment (Choi and Kim 2013). Administration of low MW FOs prevented arterial and parenchymal lesions occurring due to alloimmune injury (Kuznetsova et al. 2014). Thus, FOs can be efficiently used in

Table 2. Immunological properties of macroalgal polysaccharides.

Macroalgae polysaccharides	Immunological property	Reference
Alginate	Activation of macrophages, and lymphocytes to secrete IL-1β, IL-6, IL-8, IL-12 and TNF-α by NF-κB pathway under *in vitro* conditions.	Yang and Jones (2009)
κ-Carrageenan	Induce the expression of IL-10 and increases the levels of pro-inflammatory cytokines (IL-1β, IL-12, IFN-γ) under *in vitro* conditions.	Cunha and Grenha (2016)
	Induces both extrinsic and intrinsic apoptosis in human colon cancer as it shows generation of ROS, pro-apoptotic markers such as BAX and caspase-3 mRNA level induction, and cell cycle arrest in HCT116 cells under *in vitro* conditions.	Raman and Doble (2015)
	Reduces the tumor size and activated macrophage phagocytosis, serum TNF-α, IL-2 cytokine production, and increased NK cells in S180 murine sarcoma cells bearing mice under *in vivo* conditions.	Yuan et al. (2006).
λ-Carrageenan	Low level expression of cytokines IL-10, IL-6, and TNF-α in RAW 264.7 cells under *in vitro* conditions	Cicinskas et al. (2020)
	Administration of it could increase the secretion of IL17A and levels of TNF-α in *Mus musculus* skin melanoma (B16-F10), and mouse 4T1 breast tumor model models under *in vivo* conditions.	Luo et al. (2015)
β-Carrageenan	Expression of pro-inflammatory cytokines (IL-1β, IL-12, IFN-γ) in RAW 264.7 cells under *in vitro* conditions.	Cicinskas et al. (2020)
|-Carrageenan	Effectively blocked tumor cell (Wnt5b)-induced, β-catenin signaling, displayed anti-cancer effects under *in vitro* using human osteosarcoma cancer cells and *in vivo* conditions using tumor induced mice model.	Jin et al. (2017), Jin and Yu (2015), Jin et al. (2014)
Fucoidan	Regulation of p38, MAP kinases, NF-κB pathway in RAW 264.7 cells. It also produced NO, IL-6 and TNF-α in RAW 264.7 cells under *in vitro* conditions.	Nakamura et al. (2006),
	Fucoidan from *Undaria pinnatifida* and *Hizikia fusiforme* activated RAW264.7 cells by promoting the production of NO, TNF-α, and IL-6 under *in vitro* conditions. Fucoidan from *U. pinnatifida* induced cell death in human hepatocarcinoma cells (SMMC-7721) by enhancing the apoptosis mediated by increasing the BAX to Bcl2 ratio, production of ROS, damage of mitochondrial structure and activation of caspases.	Bi, Yu, et al. (2018), Jeong et al. (2015) Yang et al. (2013)
Laminarin	Expression of interleukin (IL-6 and IL-1β), TNF-α, in RAW 264.7 cells under *in vitro* conditions.	Lee et al. (2012)
	Strong agonist for dectin-1 in macrophages isolated from C57BL/6 mice under *in vitro* conditions.	Brown et al. (2002)
	In vivo studies conducted on normal and BALB/c mice clearly demonstrated that administration of laminarin increased the population of B, T, and macrophages cells in normal mice as compared to BALB mice.	Shang, Shih, et al. (2018)
	Dietary inclusion of 600 ppm of laminarin from *Laminaria digitate* significantly enhanced the expression of IL-6 and IL-8 in response to *ex vivo* LPS induced pigs.	Smith et al. (2011)
Ulvan	Activation of RAW 264.7 cells to releasing cytokines such as IL-1β IL-4, IL-6, IL-10, IL-11, IL-12, IL-13 and TNF-α under *in vitro* conditions.	Tabarsa et al. (2018), Tabarsa et al. (2012)
	The *U. lactuca* inhibited the cell growth of breast cancer cell line (MCF-7), and increased tumor suppresser gene (P53) and decreased anti-apoptotic marker (BCL-2) under *in vitro* conditions.	Ahmed and Ahmed (2014)
	The *U. lactuca* showed significant cytotoxic effect on hepatocellular carcinoma (HepG2), MCF7, and cervical cancer (Hela) cell lines with IC_{50} values of 29.67 ± 2.87, 25.09 ± 1.36 and 36.33 ± 3.84 µg/ml, respectively under *in vitro* conditions.	Thanh et al. (2016)

BAX, BCL2-associated X protein; FGF-2, fibroblast growth factor; IL, interleukin; NO, nitric oxide; LPS, lipopolysaccharide; Nrf-2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, reactive oxygen species; TNFα, tumor necrotic factor-α.

drug delivery system, anticancer, and as protective agent against alloimmune injury.

Laminarin

Laminarin-dectin-1 interaction is known to elicit the innate immune response (Brown et al. 2003; Brown et al. 2002). Chan, Chan, and Sze (2009), reported that once laminarin is detected by dectin-1 either in presence or absence of TLR-2/6 on macrophages and are subsequently internalized and processed in to smaller fragments, which are then released by exocytosis. The smaller fragments of laminarin thus released by exocytosis and are detected by complement receptor (CR)-3 present on granulocytes, dendritic cells, monocytes or macrophages itself to initiate the phagocytosis of monoclonal antibodies tagged tumor cells. These factors help in either phagocytosis or synthesis of proinflammatory chemokines (IL-8 and CCL-2), thus, are connected with cancer therapy (Smith et al. 2018). Dectin-1 in association with TLRs (2/4/6) has been reported to stimulate the NF-κB mediated activation of T cells (NFAT), and signal adaptor protein CARD9, which leads to the synthesis of certain cytokines, such as TNF-α, IL-6, 10, and 12 (Rogers et al. 2005). Lee et al. (2012) could not find significant effect of laminarin on TLR-2 expression. This is a contradictory finding to Rogers et al. (2005). This flaw can be explained by difference in MW of laminarin or presence of other contaminants along with test material as demonstrated by Smith et al. (2018). We urge that in future research some characterizations of examined material should be done prior to perform biological experiments.

Laminarin promoted the NK cells mediated cytotoxic effect by increasing the levels of IL-12, and IFN-γ in serum as compared to cyclophosphamide (immune suppressive agent) treated mice model (Zhu et al. 2019). Laminarin potentially supresses the proliferation and cell growth by G1 and G2-M phase cell cycle arrest via ErbB receptor suppression and phosphorylation of Akt in HT-29 colon cancer cells (Park et al. 2013). The ErbB receptor pathway and related proteins MAPK, PI3K/Akt and Src kinase have roles in cancer cell proliferation (Wee and Wang

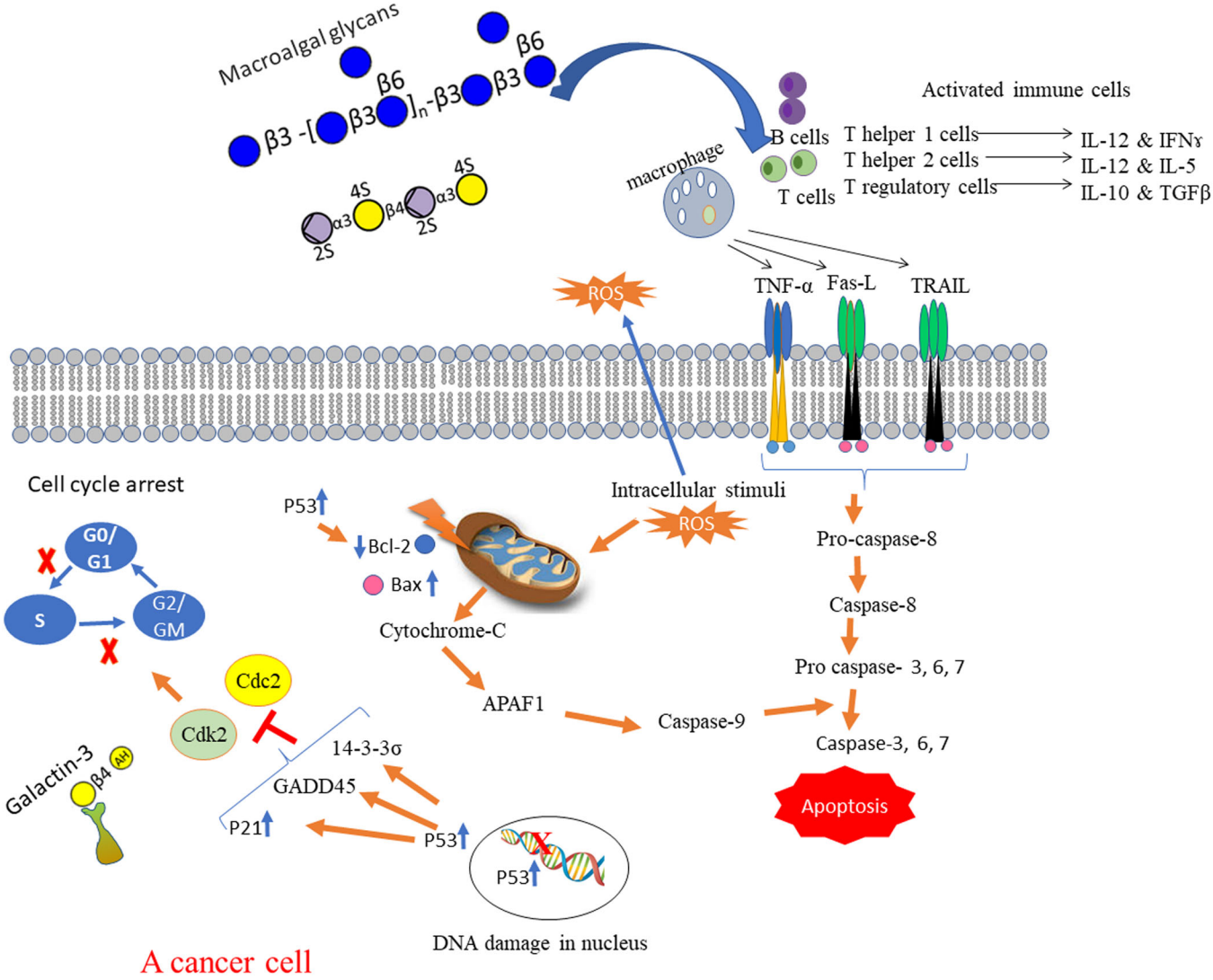

Figure 4. Macroalgal oligosaccharide mediated apoptosis in cancer cell lines by the activation of immune cells, or synthesis of reactive oxygen species (ROS), and other ligands such as tumor necrotic factor (TNF)-α, Fas (CD95 antigen), TNF-related apoptosis-inducing ligand (TRAIL). Macroalgal oligosaccharide controls the production in pro-apoptotic regulatory markers such as Bcl-2, Bcl-2 associated X protein (BAX) and down regulation of anti-apoptotic marker B-cell lymphoma (Bcl)-2. Releasing of cytochrome-C, apoptotic protease activating factor (APAF)-1 and caspases enzyme via mitochondrial membrane permeability cause the intrinsic apoptotic pathway activation. Cell cycle is arrest at different phases upon activation of P53. The P53 highly activates P21 that eventually causes apoptotic cell death (Chen 2016). Similar type of immune modulation activities by marine polysaccharide are also observed to induce phagocytosis and release of inflammatory cytokines, which eventually prohibit cancer cell development (Murad et al. 2016; Yuan et al. 2006).

2017). Laminarin isolated from *Laminaria digitata* induced anticancerous effect by activation of dendritic cells (DC), antigen specific T cells in the C57BL/6 rodents, and releases pro-inflammatory cytokines such as TNF-α, IL-12 and IL-6 in B16 melanoma cells (Song et al. 2017). Laminarin induces apoptosis via Fas pathway (Figure 4), which is a member of TNF-α family and blocks the insulin-like growth factor-I (IGF-1, has role in cancer development) receptor in human colon adenocarcinoma H29 cells (Park et al. 2012). Indeed, laminarin could be the best candidate for mitigating cancers, however we still need a defined structural molecule that can be taken further.

Carrageenan

Carrageenan is extensively used as stabilizing and thickening agents in food products. In addition, it displays anticoagulant, antitumor, and immunomodulatory activity in macrophages, lymphocytes, and NK-cells (Luo et al. 2015; Zhou et al. 2004). Carrageenan has ability to reduce the LPS-induced inflammatory response by interacting with TLR-4. In case of κ-carrageenan from *Callichirus armatus* partially inhibited the binding of LPS with TLR-4 and decreased the inflammatory response (Yermak et al. 2016). Studies conducted on λ-carrageenan using normal colonic epithelial cell (NCM460) and 10ScNCr/23 mouse macrophages (lack TLR-4 expression gene) by Bhattacharyya, Dudeja, and Tobacman (2008), and Borthakur et al. (2007) found that carrageenan induces inflammatory response by innate immunity mediated by Bcl10 (B-cell CLL/lymphoma 10) and up-regulates IL-8 secretion. Since a caspase-recruitment domain can be found in Bcl10, which is similar to NOD2/CARD15 (associated with genetic predisposition to Crohn's disease), is suggesting a relation between genetic and environmental etiologies associated with inflammatory bowel disease (Borthakur et al. 2007). Therefore, a diet rich in carrageenan may have clinical significance.

Kalitnik et al. (2017) and Sokolova et al. (2016) further investigated on the interaction between LPS and different carrageenans for induction of cytokines and cellular responses. Sokolova et al. (2016) observed that low contents of sulfate groups in carrageenan are able to interfere with LPS actions on TLR *in vitro,* which led to decrease in both intra- and inter-cellular activation of the neutrophils killing mechanisms. Concurrently, Kalitnik et al. (2017) concluded that pretreatment of murine peritoneal macrophages with κ/β-carrageenan increased the levels of anti-inflammatory cytokine (IL-10) and reduced pro-inflammatory cytokine (TNF-α) production as compared with control. Contrary, it was also reported that both κ/β types of carrageenan isolated from the red algae *Tichocarpus crinitus* induce pro-inflammatory cytokines (IFN-γ, IL-12, and IL-1β) with a higher efficacy for inducing IFN-γ production than LPS (Cicinskas et al. 2020). Such studies highlight that structures and most probably MW are influenced biological outcomes.

Studies conducted on *Mus musculus* skin melanoma (B16-F10), and 4T1 mice models by feeding λ-carrageenan stimulated the secretion of pro-inflammatory agents which triggered DCs, tumor-infiltrating M1 macrophages, and activated CD_4^+, and CD_8^+ T lymphocytes in spleen (Luo et al. 2015). Ovalbumin (OVA)-based λ-carrageenan showed efficient adjuvant effect, which meaningfully improved the production of anti-OVA antibody (Luo et al. 2015). Thus, λ-carrageenan can be efficiently used as adjuvant in cancer immunotherapy.

Perhaps, full understanding of molecular action of different carrageenans will pave the way for proper use. For examples, the commercial carrageenans (λ, κ, ï) were characterized for its purity and observed that they were contaminated with sugars such as dextrose and sucrose (McKim 2014). In order to evaluate the effect of sugar contaminants, McKim et al. (2015) have purified the commercial carrageenans (λ, κ, |) to remove the sugar contaminants and tested at different concentrations using TLR-4/MD-2/CD14/NF-κB/SEAP reporter constructed in a HEK293 cell lines. It was observed that none of the carrageenans (λ, κ, |) displayed agonist or antagonist activity with respect to TLR-4 signaling pathway and showed cytotoxic. However, it binds to serum proteins. The study clearly indicated that commercial carrageenans must be purified before performing the *in vitro* or *in vivo* experiments. It was also reported that carrageenans are devoid of lipid content, while LPS is comprised of lipid A, core oligosaccharide and O-side chain. In general lipid part of the LPS binds with TLR-4 receptor and helps in activation of macrophages (McKim et al. 2015). As a result, proinflammatory activity is more in LPS administered mice as compared to carrageenan fed mice (Cicinskas et al. 2020). Further research is necessary to relate the indirect action of λ, κ, | carrageenan in suppressing activity of pro-inflammatory cytokines and proof of action of above findings in animal model systems.

Carrageenan oligosaccharides (COs) are produced by chemical, enzymatic and physical degradation (Ghanbarzadeh, Golmoradizadeh, and Homaei 2018; Malfait and Van Cauwelaert 1990). The COs displayed cytotoxicity, anti-tumor and modulatory production of inflammatory markers (Table 3). For examples, the λ-COs displayed cytotoxic effect on human umbilical vein endothelial cells by stimulating the production of reactive oxygen species (ROS), which arrested the cell cycle at S and G2/M phases (Chen et al. 2009). They also actively regulate the expression of p53, BAX and down regulated the Bcl-2, thus initiating the caspases 9, and 3 mediated apoptosis (Figure 4). Oral administration of κ-COs (1.7 kDa), displayed anti-tumoral activity against sarcoma 180 tumor mouse (Haijin, Xiaolu, and Huashi 2003). κ-COs produced from *Kappaphycus striatum* reported to promote the macrophage phagocytosis, development of spleen lymphocytes, NK cell activation and enhanced the level of IL-2, TNF-α in 180 sarcoma bearing mice (Yuan et al. 2006). It was predicted that κ-COs could enhance the production of TNF-α, IL-2, and IL-6 involved in apoptosis of tumor cells (Xu et al. 2012). Anti-tumoral activity was reported to be higher in sulfated κ-COs as higher degree of sulfonation associated with it's the antitumoral activity (Hu et al. 2006). Indeed, a recent study performed on various κ, ι and λ-COs including the disaccharide-alditols and disaccharides (carrabioses) from different macroalgal extracts. It was observed that κ and ι-COs displayed cytotoxic effect by killing the LM2 tumor cells by apoptosis (Calvo et al. 2019). Strikingly, the study observed that sulfated κ/ι-carrabioses revealed higher cytotoxic effect than other COs and reduced metastatic ability under *in vitro* conditions. Additionally, Low molecular weight κ/β-COs (1.7 kDa) showed strong anti-inflammatory activity than its carrageenan polysaccharide (400 kDa) by producing cytokine IL-10 using human and mice blood cells under *in vivo* and *in vitro* conditions, regardless of concentration of κ/β-COs (Kalitnik et al. 2016).

Possible role of κ-COs in reducing neurodegenerative diseases was assayed by inhibiting the activity of microglial cells. A study observed that sulfated κ-COs can inhibit cell viability and induction of TNF-α by LPS-activated microglia cells (Yao et al. 2014). It was postulated that κ-COs spreads on microglial cells and prevent the binding of LPS on the surface where efficacy depends on sulfate content. Therefore, the COs can also be considered as a potential candidate for immunotherapy in various ways.

Alginate

Alginate has been extensively utilized in drug delivery and tissue engineering as other biomaterials. It was reported that alginate with high amount of mannuronic acid possess immuno-stimulating activity by inducing macrophages, which in turn helps in synthesis of cytokines and cytotoxic factors (Son et al. 2001). Sodium alginate has been reported to induce RAW264.7 cells to produce cytokines such as IL-1β, IL-6, IL-12 and TNF-α through NF-κB signaling pathway (Yang and Jones 2009). Given the activation of pro-inflammatory cytokines, it has postulated that sodium alginate works same way as LPS by inducing innate immune responses through NF-kB activation (Yang and Jones 2009). Lymphocytes when co-cultured with macrophages, it was observed that they assist macrophages to bind alginate hydrogel surfaces (Franz et al. 2011). Thus, both macrophages and lymphocytes stimulate the secretion of inflammatory mediators such as IL-1β, IL-6, IL-8, MCP-1, MIP-1β, ENA-78 and TNF-α, which help in activating

Table 3. Immunological properties of macroalgal oligosaccharides.

Macroalgae polysaccharides	Immunological property	Reference
Alginate monosaccharide	Down regulate the expression of TLR-2 and NF-κB gene expression under *in vivo* conditions.	Sharifi et al. (2017)
Alginate Oligosaccharides (AOs)	Suppress the T-helper cell development and secretion of IG-E by inducing IL-12 cytokine under *in vitro* conditions.	Yoshida et al. (2004)
	Down regulate the expression of TLR-2 and NF-κB gene expression under *in vivo* conditions.	Yoshida et al. (2004)
	Suppress the T-helper cell development and secretion of IG-E by inducing IL-12 cytokine under *in vitro* conditions.	Yamamoto et al. (2007)
	DP3-DP7 induced the synthesis of several cytokines such as TNF-α, granulocyte stimulating factor (GSF), and monocyte chemoattractant protein-1 (MCP-1) under *in vitro* conditions.	Xu et al. (2014)
AOs with degree of polymerization ranging from 3-6	Antitumor activity via suppression of prostate cancer cell proliferation and, induce the synthesis of cytokines in macrophages under *in vivo* conditions. AOs suppressed the proliferation of prostate cancer via Hippo/YAP pathway under *in vivo* conditions. It inhibited the expression of NF-κB and reduced the levels of p53 and p38. Whilst, increased the activation of Nrf-2 levels under *in vivo* conditions.	Chen et al. (2017) Han, Zhang, et al. (2019) Tusi et al. (2011)
Mannuronate oligosaccharides (M3-M7)	Secretion of TNF-α, granulocyte stimulating factor, monocyte chemoattractant protein-1 under *in vitro* conditions	Yamamoto et al. (2007)
Guluronate oligosaccharides (GOS)	Down regulating the expression of NO, ROS, and TNF-α in LPS induced RAW 264.7 macrophages cell lines by competitive binding of GOS to TLR-4 under *in vitro* conditions.	Iwamoto et al. (2005); Fang et al. (2017)
GOS	Production of ROS, TNF-α and decrease the expression levels of IL-1β, and IL-6 in osteosarcoma patients under *in vitro* conditions	Xu et al. (2014)
Agaro Oligosaccharides (AGOs)	Down regulate the secretion of NO and inflammatory cytokines (TNF-x, IL-1β, IL-6) under *in vitro* conditions.	Xu et al. (2018); Enoki et al. (2010)
AGOs (agarobiose, agarotetrose, and agarohexose)	Suppressed the levels of NO, prostaglandin E_2, TNF-α, interleukin-1β, and IL-6 in heme-oxygenase induced cells under *in vivo* conditions in mouse model.	Enoki et al. (2012)
AGOs	Suppressed the expression of COX-1, and increased the levels of 8-oxoguanine DNA-glycosylase-1 under *in vivo* conditions in high fat fed diet mouse model.	Bhattarai and Kashyap (2016)
Neo agaro oligosaccharides (NAOs-DP4)	Decreased the levels of NO, TNF-α, IL-6 in LPS induced macrophage cell lines. Down regulating the expression of MPAK and NF-κB pathways under *in vitro* conditions.	Wang et al. (2017)
NAOs (DP6)	Anti-tumor activity in *Mus musculus* skin melanoma (B16-F10) by binding to TLR-4 receptors of dendritic cells under *in vivo* conditions.	Hong et al. (2017)
κ-carrageenan oligosaccharides (COs)	Activation of NK cells, macrophages to produce inflammatory mediators such as IL-2, IL-6, TNF-α and promote apoptosis of tumor cells under *in vivo* conditions.	Yuan et al. (2006)
κ-carrageenan oligosaccharide and its desulfated derivatives	It inhibited the viability and levels of NO, TNF-α and IL-10 released by LPS-activated microglia cells in dose dependent manner under *in vitro* conditions.	Xu et al. (2012)
Fucoidan oligosaccharides (FOs)	Low molecular weight FOs prevented arterial and parenchymal lesions occurring in mice under *in vivo* conditions.	Kuznetsova et al. (2014)
	Low molecular weight FOs (7–38 kDa) generated by γ-irradiation showed higher cytotoxicity in cancer cells (AGS, MCF-7, and HepG-2), enhance the fibroblast growth factor (FGF-2) and tubular morphogenesis under *in vitro* conditions.	Choi and Kim (2013), Chabut et al. (2003)
	FOs produced by acid treatment (0.01 M sulfuric acid) displayed 38.3% more anticancer property than native polymer under *in vitro* conditions	Yang et al. (2013)
	A fraction contains monosaccharides α-L-Fuc*p*-4-OSO_3^-, α-L-Fuc*p*-2,4-di-OSO_3^- showed strong inhibition on colony formation of colorectal carcinoma cells HT-29.	Anastyuk et al. (2017)
	Low molecular weight Fucoidan (<10 kDa) from *Undaria pinnatifida* enhanced the release of NO, expression of iNOS, TNF-α and IL-6 in RAW264.7 cell lines. Also stimulated the activation of NF-κB and MAPK signaling pathways under *in vitro* conditions.	Bi, Yu, et al. (2018)

COX-1, cyclooxygenase 1; DP, degree of polymerization; HepG2, hepatocellular carcinoma; MCFF, human breast cancer; IL, interleukin; IgE, immunoglobulin E; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MPAK, mitogen-activated protein kinase; Nrf-2, nuclear factor erythroid 2-related factor 2; NO, nitic oxide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer cells; ROS, reactive oxygen species; TNFα, tumor necrotic factor α; TLR, toll-like receptor.

granulocytes (neutrophils, monocytes, T-lymphocytes and natural killer cells) (Chang et al. 2008; Paredes Juarez et al. 2014).

In recent times, roles of alginate have been suggested for treatment of osteoarthritis (Kerschenmeyer et al. 2017), type 1 diabetes and other hormone-deficient diseases via zwitterionically modified alginates (Liu et al. 2019). Particular, sulfated alginate has shown potent anti-inflammatory, anti-oxidant, and anti-immunogenic properties under *in vitro* conditions for treatment for osteoarthritis. Sulfated alginate has been reported to inhibit the activation of p38/MAPkinase and NF-κB expression in human chondrocytes (Arlov et al. 2017), and modulate macrophage polarization from M1 to M2 phases (Kerschenmeyer et al. 2017). Kerschenmeyer et al. (2017) observed that the degree of sulfonation in alginate is directly proportional to scavenge superoxide radicals and chelate metal ions in articular cartilage and produces IL-1β to stimulate inflammatory genes in human chondrocytes; whereas, low degree of sulfonation in alginate induces expression of pro-inflammatory markers (IL-6 and CXCL8) in the macrophages.

Alginate oligosaccharides (AOs) are produced by enzymatic and chemical hydrolysis of brown algal polysaccharides species such as *Laminaria*, *Ascophyllum, Macrocystis*, and *Fucales* (Chandıa, Matsuhiro, and Vásquez 2001; Chen et al. 2018; Iwamoto et al. 2003; Wong, Preston, and Schiller 2000). Immune modulatory activities through RAW264.7 cells depend on the composition and structural features of AOs. Such as, Iwamoto et al. (2005) used saturated

(sG3–sG9) and unsaturated guluronate (G3–G9), and saturated (sM3–sM9) and unsaturated mannuronate (M3–M9) oligomers to evaluate the effect on pro-inflammatory cytokines production from RAW264.7 cells. It was well identified that unsaturated G8 among guluronate, and unsaturated M7 among mannuronate oligomers resulted in significant production of IL-1α, IL-1β, and IL-6 via binding on TLR-2 and 4. Similar results were observed by the unsaturated guluronate oligosaccharide produced by enzymatic degradation (Xu et al. 2014). It was reported that ratios of M/G content influence the anti-tumor and anticancer properties. Such as, higher M/G ratio tends to show higher activity on pro-inflammatory cytokines production from RAW264.7 cells (Kurachi et al. 2005) and anticancer property (Belik et al. 2020), and guluronate rich alginate oligosaccharides have anti tumor property (Fujihara and Nagumo 1993). While, the current study of Han, Zhang, et al. (2019) suggests that the proliferation, migration and invasion of human prostate cancer cells can be suppressed by regardless of any M/G ratios via the Hippo/YAP pathway. Thus, ambiguity prevails between the roles of G and M oligosaccharides with functions of immune system (Table 3). It was proved that apart from guluronate and mannuronate content even sulfate derivatives of AOs contribute to the activation of macrophages by improving the solubility and increasing the charge density (Hu et al. 2004).

Immunomodulatory activity of AOs can be tested in different pathways. For examples, homo-oligomer administration of seleno-guluronate oligosaccharide in LPS activated RAW 264.7 cells resulted in preventing the expression of inflammatory mediators such as NO, prostaglandin E_2 (PGE_2), pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), inflammatory proteins (iNOS and COX-2). Thus, inhibiting the activation of NF-κB and MAPKs signaling pathways (Bi, Lai, et al. 2018). Sulfated (sulfation degree: 1.3) substituted AOs, having MW 3798 Da, induced tumor mitigation indirectly by modulating immune responses of the host at concentration of 100 μg/kg (Hu et al. 2004). Even, α-L-guluronic acid suppressed the expression of TLR-2, and NF-κB genes in patients suffering with variant immunodeficiency disorder (Sharifi et al. 2017).

Therefore, recent research related to alginate and alginate-derived oligosaccharides is predominantly focused on the anti-tumor and anti-cancer activities. In spite of identification of a variety of immunomodulatory activities based on M/G content and sulfation, the detailed research of their mechanism is inadequate, impeding further advance and utilization of AOs in treatment of cancer.

Agar oligosaccharides

In case of agar, majority of biological activity are reported with agar oligosaccharides (AGOs), which are produced by both enzymatic and chemical hydrolyzes methods (Chen et al. 2004; Chen et al. 2019). AGOs have been reported to inhibit the synthesis of NO and reduce the inflammation by inhibiting the production of inflammatory cytokines such as TNF-α, IL-1β, IL-6 (Table 3), and AGOs reduced the tumor cell proliferation by 48.7% in mice (Higashimura et al. 2013; Higashimura et al. 2014; Wang et al. 2004). AGOs increased the expression of hemeoxygenase-1 in the RAW264.7 cells, which in turn suppressed the T helper 17 mediated immune response, such as production of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) in LPS induced human monocytes and RAW264.7 cells (Enoki et al. 2010). Later study of same authors reported that AGOs such as agarobiose, agarotetrose, and agarohexose suppressed the tumor promotion on the two-stage mouse skin carcinogenesis model via inhibiting the levels of NO and PGE_2, which is one of crucial players in carcinogenesis (Enoki et al. 2012). AGOs increased anti-tumorigenic factor 8-oxoguanine DNA-glycosylase in high fat diet mice that leads to development of aberrant crypt foci (Bhattarai and Kashyap 2016).

Additionally, the AGOs have been reported to down regulate the expression of MAPK and NF-κB signaling pathway in LPS induced RAW264.7 cells (Wang et al. 2017). AGOs were separated individually and their effect was studied for tumor suppression in different cell lines. In the above studies, DP4 and DP6 reduced the production of TNF-α, IL-6, and NO in LPS induced RAW264.7 cells by binding competitively to TLR-4 (Wang et al. 2017). The DP6 of AGOs was reported for its antitumoral activity in B16F1 cell lines. This activity was mediated by the activation of dendritic cell via natural killer cell by TLR-4 receptor (Laffont, Seillet, and Guéry 2017).

Overall, these studies have clearly showed that functional properties of glycans derived from macroalgae rely on the degree of sulfation, glycoside linkages, and monosaccharide composition. There are some discrepancies arisen when some poly and oligosaccharides tested on different model organisms. Consequently, a lot of lacunae exist for defining role of specific glycan type with specific function. Resultant of those studies will help in management of different types of cancers, and regulation of immune system.

Possible mechanisms of macroalgal glycans in suppression of cancer

As aforementioned and summarized Tables 2 and 3, macroalgal glycans have been studied for their anticancer roles in recent years. Despite there are still several discrepancies on biological effects of different macroalgal glycans, possible overall mechanism can be postulated. Once glycan recognized by the receptors, several mechanisms can be triggered, which lead to programmed cell death. These mechanisms include generation of reactive oxygen species (ROS) through internal stimuli, eventually leading to cell cycle arrests and activation of pro-inflammatory receptor (Figure 4). Anti-apoptotic B-cell lymphoma-2 (Bcl-2) and Bcl-2 family proteins (Bcl-XL, Bcl-w, Mcl-1, Bfl1/A-1, and Bcl-B) overexpression hinder the cell death, thus blocking them can be considered as a major drug target in cancer therapy (Gheda, El-Sheekh, and Abou-Zeid 2018; Kang and Reynolds 2009). Extrinsic pathways of apoptosis initiate up on binding of external stimuli. For example, binding of glycans with receptors (such as Fas ligand domain and TNF-related apoptosis-

inducing ligand) induce the caspase cascade. Whereas, intrinsic pathways are mainly associate with mitochondrial response that includes production of ROS and cytotoxic factors, leading to modulation of BAX/Bcl-2 level and releasing of cytochrome (cyt)– C. These promotion initiate caspase cascade for modulation of apoptosis (Simon, Haj-Yehia, and Levi-Schaffer 2000; Zhang et al. 2008). BAX and Bcl-2 display main roles in controlling the effect of mitochondrial function and permeability, and releasing of Cyt-C cascade as mentioned in Figure 4 (Zhang et al. 2014). Bcl-2 is a large protein family that is expressed in nucleus and cytoplasm; however, the family is represented by BAX (promotes apoptosis- is mainly located in the cytoplasm). On the onset of DNA damage a tumor protein p53, a transcriptional activator, is overexpressed and regulates the expression of Mdm2 and other proteins involved in growth arrest (p21, Gadd45, and 14-3-3σ), DNA repair (p53R2) and apoptosis (BAX, Apaf-1, PUMA and NoxA) (Bertout et al. 2009). Macroalgae glycans contain galactose chain in their constituent that can be involved in inhibition of galactin-3 response. The galactin-3 is a member of the carbohydrate binding protein family and is β-galactoside-binding lectin. The lectin is mainly distributed in the cytoplasm; nevertheless, is often secreted onto the cell surface and transports into the nucleus. It assists in important biological functions including, apoptosis, cell growth, and inflammation (da Silva Filho et al. 2020). It has been understood that inhibition of galactin-3 is associated with suppression of cancer.

In cancer studies, it is now understood that inflammation and apoptosis are connected via NF-κB and TNF (Li, Liu, et al. 2016; Liu et al. 2017; Ting and Bertrand 2016). Recent studies have put macroalgal glycans in forefront for prevention of cancer. For instances, glycan extracted from *Sargassum wightii* induced cell death via ROS generation, followed by mitochondrial disruption and activation of caspase-3 and caspase-9 in human breast cancer cells MCF-7 and MDA-MB-231 (Vaikundamoorthy et al. 2018). The cell cycle check points are targeted using macroalgal glycans for treatment of cancer in some therapeutic studies (Murad et al. 2016; Xie et al. 2016). In that manner, laminarin and carrageenan can arrest cell cycle and promote apoptotic to battle with cancerous cells (Murad et al. 2016). Nevertheless, it is urging that precise molecular mechanism of macroalgal glycans in mitigating cancer incidence should be explored by taking well-defined structures of oligo- and polysaccharides.

Concluding remarks and future prospects

Recent findings have shown that the functional properties of macroalgal glycan rely on the monosaccharide composition, branching, structure, type of linkages and degree of sulfonation. Therefore, precise information about structure of glycan and their molecular interaction with gut microbiota or immune cells can lead to development of target-based nutraceutical products. Recently discovered mechanistic level understanding of glycan digestion let to know that how a complex architecture of a PUL of *Bacteroides* digests complex polysaccharides, though, their ecological roles in maintaining gut homeostasis is yet to be understood. Especially with oligosaccharides that can be released by the action of outer surface tailored enzymes of the PUL, which could have several health implications. Indeed, oligosaccharides of carrageenan, agar, agarose, and alginate have a huge range of profound impact on gut microbiota (Zhang et al. 2020), and pharmacological activities including anticancer, anti-inflammatory, antioxidative, and antiadhesive (reference herein).

Recent progress on elucidating the molecular interaction of polysaccharides and certain defined DPs of oligo-saccharides with immune receptors under *in vitro* and *in vivo* conditions, infer that we need more studies with well characterized structure of glycan. Studies with sulfated glycans have shown potential in perturbation of immune system without any serious safety concerns, hence, have attracted considerable attention globally. In fact, their biological attributes may also be relied on some other factors via various cellular pathways. It urges that future studies should involve defined DPs and well characterized sulfated glycans to elucidate the structure-activity relationship and molecular mechanisms involved in the immune function.

Acknowledgments

R. P. Singh would like to thank Department of Biotechnology, India for providing Ramalingaswami Re-entry Fellowship. Thanks to Manorma Negi who has helped with preparing Figure 4.

ORCID

Ravindra Pal Singh http://orcid.org/0000-0002-7765-6513

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