CHAPTER

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SEAWEED-DERIVED β-GLUCAN AS POTENTIAL IMMUNE MODULATING AGENTS

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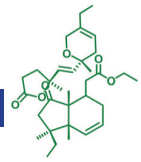
ABSTRACT

A significant portion of seaweeds or marine macroalgae consists of polysaccharides, displaying diverse properties and health benefits. Laminarin, also known as β-glucan, is a storage polysaccharide derived from brown algae. It has been recognized for its potential pharmacological effects, encompassing antioxidant, anti- anticancer, immunomodulatory and vaccine adjuvant properties. Laminarin, being biodegradable, biocompatible and minimally toxic, has been extensively explored as a functional material in various biomedical applications. This chapter summarizes laminarin's molecular characteristics *andelucidates* the mechanisms of action of the reported health benefits. As we decipher its molecular intricacies and immunomodulatory effects, further research promises to reveal new insights, enhancing our understanding of laminarin's potential in diverse fields.

Keywords: β-glucan, Laminarin, Brown algae, Immunomodulators, Storage polysaccharide

INTRODUCTION

The vast expanse of earth's surface encompassed by oceans that extend over approximately 75% harbours an extensive repository of natural marine organisms many of which remain relatively undiscovered. Within these, marine algae emerge as promising entities capable of addressing contemporary human needs. Seaweeds, or marine macroalgae, have captivated human fascination for centuries and have served as dietary cornerstones for coastal communities, notably in Japan, China, and Korea (Chakraborty, 2022). However, the utility of seaweeds transcends their nutritional contributions, as they emerge as source of diverse industrial products (Gora et al., 2018a). These include hydrocolloids such as agar, alginates, carrageenan, agricultural soil additives, animal feed supplements, and cosmetics. Moreover, the macroalgae emerge as reservoirs of bioactive and pharmaceutical compounds, complementing their appreciable nutritional qualities (Jiménez-Escrig et al., 2011). Recent decades have witnessed extensive scientific exploration into the immunomodulatory properties of seaweeds



(Gora et al., 2018b; Gora et al., 2018c), revealing bioactive components with promising therapeutic potential for health and disease management (Rehman et al., 2023; Bhuyan et al., 2023).Among the diverse array of seaweeds, the orders Laminariales, Fucales, and Dictyotales have been subject to exhaustive research, unveiling their intricate phytochemical properties. In addition to their rich polysaccharide content, these seaweeds boast other significant categories of metabolites including carotenoids, polyphloroglucinol phenolic compounds, and non-polar non-polyphenolic secondary metabolites such as terpenes. Different types of seaweeds are known to house distinct polysaccharides, each endowed with varying bioactive capabilities. For instance, the brown-seaweeds contain *laminarin*, alginates and fucoidans, while red seaweeds are abundant in galactans and carrageenans and green seaweeds exhibit ulvan polysaccharides.

BROWN SEAWEED POLYSACCHARIDES

Brown seaweed also known as Phaeophyceae thrives in marine waterswith certain species native to freshwater and brackish environments (Yao et al., 2023). The distinct brown hue of these algae is attributed to a carotenoid pigment called fucoxanthin, which suppresses other pigments. Their sizes vary widely, ranging from a few millimetres to approximately 70 meters, showcasing structural and compositional diversity among species within this algal class (Li et al., 2021). Brown algae seem to have evolved later than red algae, green algae, and terrestrial plants. No unicellular brown algae species have been identified, and their development into multicellular forms with plant-like structures occurred independently from other algae and plants. Nevertheless, brown algae share cell wall polysaccharides, such as cellulose with plants, sulphated fucans with animals, and alginate with bacteria. These macroalgae possess intricate and adaptable cell walls abundant in polysaccharides like alginate (also referred to as alginic acid and algin), fucoidan (also known as fucoidin and fucan), laminarin (also called laminaran), and cellulose. Additionally, they contain polyphenols, proteins, glycoproteins, phlorotannins (sulfated phenolic compounds), halogens such as iodine, and minerals like sodium, potassium, calcium, and magnesium. The proportions of these compounds differ among species and are greatly influenced by seasonal, environmental, and regional factors (Bhuyan et al., 2023). While alginate appears significant in most brown algae, laminarin and fucoidan are more prevalent in certain species, such as *Laminaria* spp. and *Fucus* spp. Free sugars like glucose, fructose, and sucrose are minimal in brown algae, as monomeric sugars swiftly convert into d-mannitol and polysaccharides. Glucose content, notably found in the β-glucan laminarin, fluctuates with seasons, primarily serving as a storage polysaccharide within the cells.

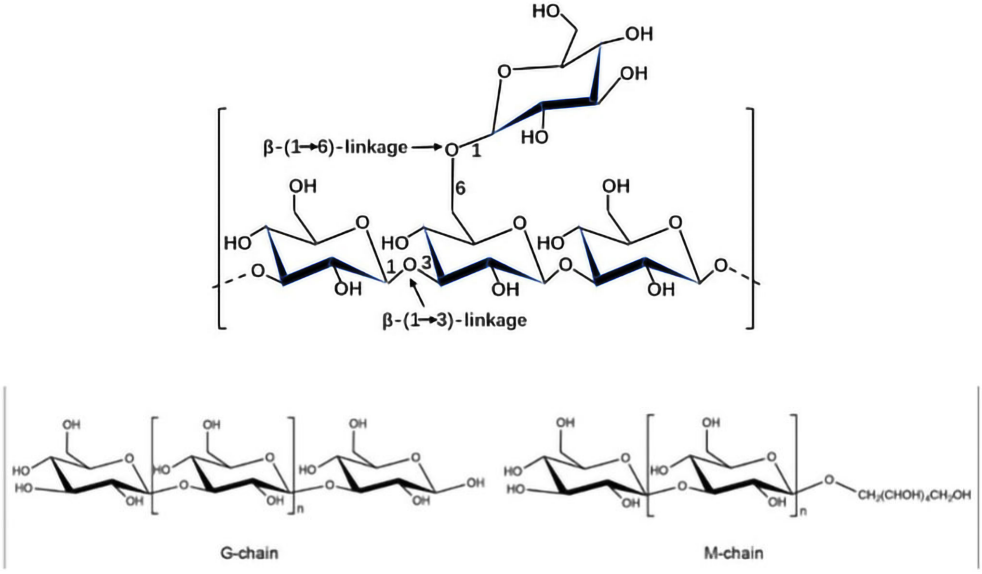
LAMINARIN OR BROWN SEAWEEDDERIVED *β--GLUCAN*

Laminarin, a polysaccharide present in brown algae, is gaining attention for its therapeutic potential and diverse applications (Karuppusamy et al., 2022). This polysaccharide is the predominant storage component in brown algae and has prompted extensive in vivo and in vitro research on the bioactivity of these glucans. It is being increasingly studied for its potential in functional food, nutraceuticals, and biomedical uses due to its biodegradable, biocompatible, and non-toxic nature. Laminarin, alongside laminarin-derived oligosaccharides, is anticipated to evoke similar health-enhancing responses in organisms as observed with other β-glucans (Bonfilm et al., 2017). These responses include antioxidant, anticoagulant, and antimutagenic activities. Moreover, specific anti-inflammatory and anti-cancer effects have been noted, primarily associated with β-1,3-(1,6)-glucans (Zargarzadeh et al., 2020). These glucans exhibit certain advantages over those found in other algae due to their low molecular complexity. This characteristic imparts various benefits to their biological activity, making them suitable for use in functional foods. Additionally, these glucans the ability to induce antibodies and possess potent immunostimulatory effects, influencing both innate and adaptive immunity. Studies also highlight laminarin's role as a dietary fiber and its ability to influence intestinal metabolism by affecting the pH and short-chain fatty acids (SCFAs) production in the tissue (Smith et al., 2011). This modulation potentially leads to enhanced immunity, better gut health, and disease resistance.

STRUCTURE OF LAMINARIN

Laminarin has a distinct structure composed of (1–3)- β-D-glucan with β (1–6)-linkages, branching comprising of 20–25 glucose units(Shin et al., 2009). Furthermore, it displays two distinct forms of chains – M chains (concluding with terminal 1-O-substituted D-mannitol residues) or G chains (ending with glucose residues) observed at the reducing end (Bonfilm et al., 2017). However, variations occur depending on species, potentially linked to differences in content, types (branch points or interchain), and spatial distribution of β-1,6-linkages. The ratio between β-1,6- and β-1,3-linkages within laminarin tends to fluctuate among species, ranging from predominantly β-1,3-linkages in Laminaria hyperborea to a moderate ratio of 1:7 in L. digitata, and to a higher ratio such as 1:3 or 2:3 in laminarin from *Eisenia bicyclis* (Read et al., 1996). Laminarin typically boasts an average molecular weight of around 5 kDa varying with the degrees of polymerization. Notably, compared to other seaweed polysaccharides, laminarin tends to exhibit a lower molecular weight. Moreover, environmental conditions play a significant role in shaping both the structure and biological functionalities of laminarin. Brown macroalgae typically contain approximately 350 mg/g of laminarin content (on a dry basis) (Jonson et al., 2020). However, this quantity can be affected by various factors including

algal species, harvesting season, geographic location, habitat, population age, and extraction method. Laminarin extraction has been performed across various brown macroalgal species like *L.digitata, Saccharina latissima, L. japonica, Ecklonia kurome,* and *E. bicyclis*. It has also been found, to a lesser extent, in species like *Ascophyllum, Fucus,* and *Undaria*, primarily sourced from Asian and European regions (Kadam et al., 2015). The solubility of different polysaccharides is influenced by the degree of branching, several species of Laminaria are water-insoluble and contain only linear β-1,3-linked residues, while water-soluble laminarin contain significant levels of β-1,6-linked branches.



Structure of laminarin (Chen et al., 2021)

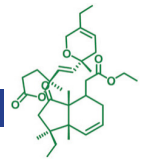
IMMUNOMODULATORY EFFECTS OF LAMINARIN

Enhancing host defence responses through the use of immunomodulators is regarded as one of the most promising therapeutic approaches. Recent investigations have revealed substantial immunomodulatory activity of laminarin derived from *Laminaria* spp. using both in vitro and in vivo approaches. The different immune modulatory effects of laminarin are listed in Table 1.The dietary β-glucans can cause either microbe-dependent or independent stimulation. In the case of microbe-independent stimulation, the glucans are directly recognized by immune receptors present on macrophages, neutrophils, dendritic cells and natural killer cells (NK) cells (Goodridge et al., 2009). Microbe-dependent stimulation occurs when indigestible

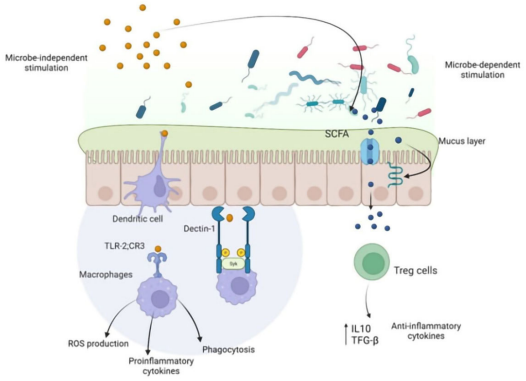
glucans are fermented by intestinal microbes, and the selective stimulation of beneficial microbes can indirectly have a significant role in the intestinal immune response (Raa et al., 2015).

Table 1. Different biologicalfunctions of laminarin

Function	Description	References
Activation of immune cells	Elevated the release of hydrogen peroxide, calcium, nitric oxide, monocyte chemotactic protein-1, vascular endothelial growth factor, leukaemia inhibitory factor, and granulocyte-colony stimulating factorin macrophages	Lee et al. (2012)
	Increased co-stimulatory molecule expression and pro-inflammatory cytokine production in spleen dendritic cells.	Song et al. (2017)
Anti-cancer effects	Expressionlevelofproteinsrelatedtoapoptosis,including death receptors (DR4, DR5), TNF-relatedapoptosis-inducing ligand (TRAIL), Fas-associated protein with death domain (FADD), caspase-8, caspase-3, Bid, and tBid was increased in human colon cancer cells	Ji et al. (2014)
	Treatment of mouse thymocytes with laminarin caused a substantial decrease in apoptotic cell death by about 2-fold and prolonged cell survival in culture by approximately 20%.	Kim et al. (2006)
Antioxidant activity	Increased the antioxidant levels of superoxide dismutase, glutathione peroxidase and catalase, while reduced malondialdehyde concentrations, induced a protective function against sepsis-induced oxidative damage and lipid peroxidation in rats.	Cheng et al. (2012)
	Acts as an antioxidant by scavenging free radicals and reducing oxidative stress, protecting immune cells from damage.	Sanjeewa et al. (2017)
	Significant reductions in hydroxyl radicals (•OH) and peroxynitrate (ONOO−) levels.Displayed the ability to scavenge mitochondrial O2•− generated by the administration of clinical drugs indomethacin or dabigatran.	Kurokawa et al. (2023)



Protection against infections	Supplementation with seaweed extract containing laminarin and fucoidan led to decreased faecal shedding of Salmonella typhimurium at day seven post-challenge, down-regulated the expression of pro-inflammatory cytokines (IL-6, IL-22, TNF-α, and Reg3-γ) and demonstrated the ability to balance bacterial flora and modulate the intestinal immune system.	Bouwhuis et al. (2017)
Vaccine adjuvant	Laminarin was conjugated with the diphtheria toxoid CRM197, a carrier protein used in glyco-conjugate bacterial vaccines. The Lam-CRM conjugate exhibited higher immunogenicity and provided protection as an immunoprophylactic vaccine against systemic and mucosal (vaginal) infections by *Candida albicans.* Lam-CRM–vaccinated mice were also protected against a lethal challenge with *Aspergillus fumigatus* conidia, with their serum inhibiting the growth of A. *fumigatus* hyphae.	Torosantucci et al. (2005)
	Laminarin was conjugated with β-mannan tetanus toxoid to form a tricomponent vaccine. Using a macrophage cell line binding and activation of the Dectin-1 signal transduction pathway by the β-glucan-containing vaccine was demonstrated. Treatment of immature bone marrow–derived dendritic cells (BMDCs) with the tricomponent vaccine caused activation of BMDCs through specific targeting and uptake by dendritic cells and released elevated levels of various cytokines TGF-β, IL-6. Immunizing mice with this vaccine yielded high titres of antibodiesas compared to other treatment groups.	Lipinski et al. (2013)



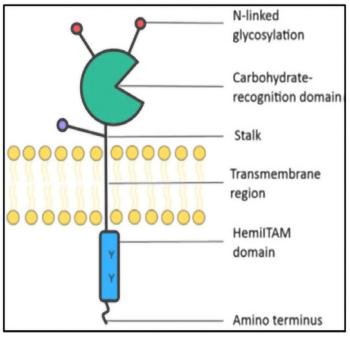
Possible immunomodulatory action of β-glucans

MICROBE-INDEPENDENT STIMULATION *BY β-GLUCAN*

Activation of immune response by β-glucan is associated with specific interaction with one or more immune receptors present on monocytes/macrophages, dendritic cells (DCs), neutrophils, and NK cells. The immune-modulatory action of β-glucan is generally studied with the activation of macrophages which has cell surface receptors called Pathogen recognition receptors (PRRs). PRRs can detect the non-self-molecules known as pathogen associated molecular patterns (PAMPs).

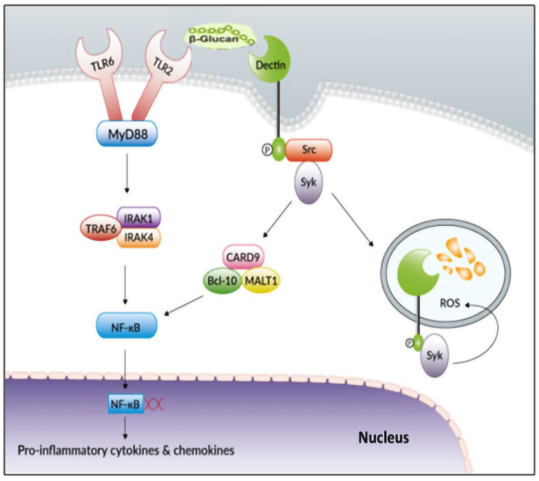
β-GLUCAN IMMUNE RECEPTORS

In mammals, Dectin-1 and Toll-like receptors are the major PRRs known for β-glucan binding inducing the signalling cascade and activate the immune system. The other receptors in mammals which are also involved for binding are complement receptor 3 (CR3), scavenge receptors (SR), and lactosylceramide (LacCer) (Brown and Gordon, 2005).



Structure of Dectin-1(Wagener et al., 2018)

Dectin-1 is an important phagocytic receptor for β-glucan recognition and mediates a massive oxidative burst activity after exposure. Dectin-1, also known as C-type Lectin domain family 7 member A (CLEC7A) is a Type II membrane receptor and is considered as the major and best described receptor for β-glucan binding, mainly present on macrophages and neutrophils. It has a single carbohydrate recognition domain (CRD), a short stalk, a transmembrane region and an intracellular cytoplasmic tail with oneimmunoreceptor tyrosine-based activation (ITAM)- motif (Goodridge et al., 2009). In the CRD, two aminoacids, tryptophan (W) and histidine (H) are separated by a third residue (WxH motif) and tyrosine(Y) residue is separated from histidine by four residues (WxHxxxxY). The tryptophan, histidine and tyrosine are arranged in a triangular fashion create a shallow hydrophobic groove where β-glucan binding occurs through hydrophobic interactions (Dulal et al., 2018). ITAM contain a single "LxxY" sequence, called hemi ITAM which upon β-glucan binding are phosphorylated by Src family kinase providing a docking site for syk (spleen tyrosine kinase) via binding of dual Src homology domains of syk (Goodridge et al., 2011). This is followed by association of syk with caspase associated recruitment domain protein (CARD9) resulting in the downstream signalling through B-cell lymphoma 10(BCL-10) and mucosa-associated lymphoid tissue lymphoma transcription protein (MALT1) complex to activate the transcription factor NF-kB. The activation of NF-kB results in the production of pro-inflammatory cytokine, chemokines and ligand phagocytosis. Dectin-1 signalling in neutrophils results in the production of reactive oxygen species (ROS). The Dectin-1 is reported to mediate most of the signals alone but may also act synergistically with TLR2 and TLR6 through MYD88 (Ozinsky et al., 2000). This may amplify the production of cytokines (TNF-α, IL-6) and down-regulate the production of IL-12 which can affect the adaptive immune response. β-glucan activated dectin-1 can also trigger Th1/Th17 and CTL responses (Wagener et al., 2018).



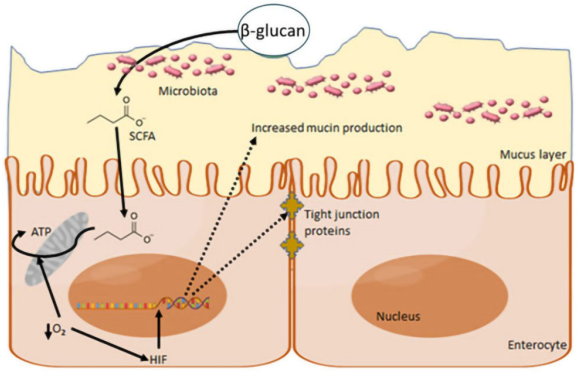
B-glucan mediated signalling pathway (Modified from Jin et al., 2018)

Complement receptor 3 (CR3), also known as membrane attack complex 1 is another β-glucan receptor mainly present on myeloid cells such as NK cells, DCs, macrophages and neutrophils. CR3 belongs to the family of β2-integrins with a heterodimeric protein of αMβ2 (CD11b/CD18) recognizing and binding to β-glucan through lectin site in αM(Xia et al.,1999a). Besides αM can recognize complement components and increase the uptake of opsonized -microparticles iC3b and C3b. β2 transmits signals of αM to Syk pathway which can result in CR3- mediated cytotoxicity (CR3-DCC) (Xia et al.,1999b).

Lactosylrceramide and scavenger receptors are expressed on the surface of both immune and non-immune cells like endothelial cells, alveolar epithelial cells and fibroblasts. Although it is reported that these receptors can recognize β-glucan, studies on the binding effect and immune cascade are not systematically investigated (Legentil et al., 2015).

MICROBE-DEPENDENT STIMULATION BY β-GLUCAN

Most β-glucan form complex structures that are stabilized by inter-chain hydrogen bonds and are therefore resistant to hydrolysis and are considered as dietary fibres (Deville et al.,2007). β-glucan are non-digestible polysaccharides which are fermented to a large extent in the intestine by the resident microbiota leading to the production of short chain fatty acids (SCFAs). These SCFAs are important in regulating the overall health of the host as they can diffuse across the intestinal epithelium and at the cellular level, are the main source of energy for epithelial cells (Venegas et al. 2019). Short chain fatty acids can have direct or indirect effects on processes such as cell proliferation, differentiation, and gene expression (Colgan et al. 2015). The SCFAs also promote the epithelial barrier function by promoting the stabilization of the hypoxia inducible factor (HIF). The conversion of polysaccharides to SCFAs is an oxidative process which consumes the oxygen in the intestinal mucosa. The reduction in the pO2 leads to proteosomal degradation of the proline hydroxylase enzyme. This in turn stabilizes the intracellular levels of the hypoxia inducible factors (HIF), transcription factors responsible for a variety of functions in the intestinal epithelial cells. One of the major functions of the HIF is the restitution of gut epithelial barrier function. The stabilized heterodimers of the HIF protein translocate across the epithelial membrane and bind the HIF responsive elements (HRE) in the genome. This binding, among other functions, leads to the expression of mucin proteins (Louis et al. 2006) and also increased expression of tight junction proteins (Glover et al. 2017), which eventually improves the gut epithelial barrier integrity. Therefore, an indirect function of the β-glucan may be maintenance of the intestinal barrier stability.



Restitution of gut epithelial barrier function by SCFAs produced by β-glucan

Laminarins have a multifaceted impact on gut health, beyond influencing mucin composition and the concentration of short-chain fatty acids (SCFAs), they affect bacteria in the gut by influencing adherence, translocation, and proliferation (Kuda et al., 2009). Interestingly, laminarins encourage the growth of Bifido bacterium, showcasing a potential prebiotic effect. Some studies indicate that laminarin promotes immune responses and could be valuable in inhibiting the production of putrefactive substances from undigested proteins (Nakata et al., 2016). In laboratory settings simulating the gut environment, 24-hour batch fermentations of laminarin led to increased populations of Bifidobacterium and Bacteroides, along with higher production of propionate and butyrate (Seong et al., 2019). However, conflicting findings exist—other research suggested that while laminarin might not be selectively fermented by *Lactobacillus* and *Bifido bacterium*, it could still alter the composition, secretion, and metabolism of mucosal linings in various parts of the intestine (jejunum, ileum, caecum, and colon), potentially guarding against bacterial translocation (Deville et al., 2007). Additionally, in rats, laminarin was observed to elevate the presence of *Clostridium* spp. and Parabacteroides distasonis (An et al., 2013).

CONCLUSION

In the vast expanse of earth's oceans, brown seaweeds, specifically Phaeophyceae, hold promise for various applications. Characterized by their unique brown hue, these algae offer diverse bioactive compounds. Laminarin, a polysaccharide stands out for its potential in functional foods and biomedical use due to its antioxidant, anti-inflammatory and anti-cancer effects. Notably, laminarin's effects extend to the gut, promoting the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus*. The exploration of laminarin opens avenues for health and wellness applications.

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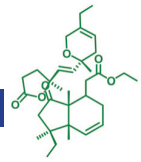

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