Chapter 15

Pectic Oligosaccharides and Other Emerging Prebiotics

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Additional information is available at the end of the chapter

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Abstract

A prebiotic is a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health. The most widely accepted prebiotics are lactulose, inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and the human milk oligosaccharides (HMO). However, there is a growing list of potential prebiotics although the evidence for these, especially in humans, is not as well established as for FOS and GOS. Some of them are already commercialized but others such as polydextrose (PDX), pectic oligosaccharides (POS), bacterial exopolysaccharides (EPS), polysaccharides derived from algae and sugar alcohols are still in the early stages of development. This chapter summarizes the scientific literature regarding the manufacture and the evaluation of the properties of this group "emerging prebiotics".

Keywords: emerging prebiotics, pectic oligosaccharides, polydextrose, algae-derived oligosaccharides, bacterial exopolysaccharides, sugar alcohols

1. Introduction

The consumption of prebiotics is being specially considered as a good health-improving strategy; they have been recently defined as "nondigestible compounds that through its metabolization by microorganisms in the gut, modulate the composition and/or the activity of the gut microbiota, thus conferring physiological benefit effects on the host health" [1].

The microbial communities that inhabit the human intestinal tract constitute a complex association, comprising more than 1000 species and around 10^{14} microorganisms, mainly anaerobic (>99.9%). **Figure 1** shows the human gastrointestinal tract, indicating the different

levels of microorganisms and the main bacterial groups. Along the jejunum, and particularly in the ileum, there is a gradual increase in the number and diversity of bacteria, and finally, the majority of gastrointestinal microbes are housed in the colon [2].

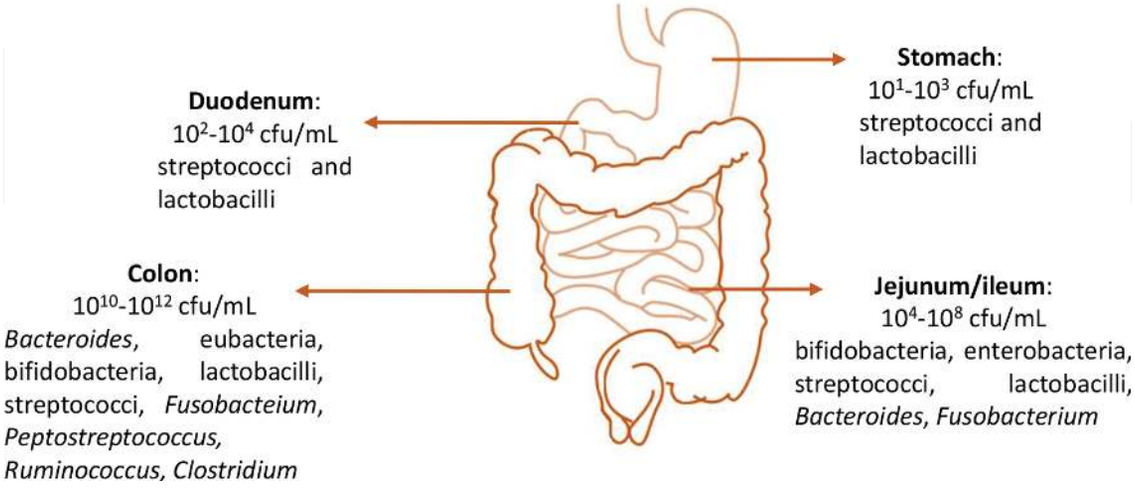

Figure 1. The human gastrointestinal tract (CFU, colony-forming units).

However, scientific works on this field suggest that the gut microbiota is not only a simply collection of microorganisms, but also reflects an interrelationship between the different groups that might work together for the benefit of the host [2]. In addition, the microbiota also establishes a close symbiosis with the host: humans provide the nutrients and the appropriate conditions for its development, and it performs three essential primary functions: metabolic, trophic, and defensive [3]. In fact, there is a long list of pathologies which are linked to the alteration of the gut microbiota, including hepatic encephalopathy, diarrhea, diabetes, obesity, colon cancer, IBS, IBD, gastrointestinal infections, and necrotizing enterocolitis [4, 5].

The composition of the gut microbiota is influenced by a variety of factors that include: (i) the microbial species which are acquired at birth, (ii) host genetics, (iii) age [6–8], (iv) diseases and antibiotic usage [9, 10], (v) the stress [11], and (vi) the diet. In fact, the diet is probably the most important factor and several studies are focused on the modulation of the gut microbiota by the consumption of functional foods, such as prebiotics [12–14].

For considering a food ingredient as a prebiotic, it must fulfill the following requirements [15]: (i) it cannot be hydrolyzed or absorbed in the upper gastrointestinal tract, (ii) it has to encourage the development of beneficial bacteria such as bifidobacteria and lactobacilli, and (iii) it must induce beneficial physiological effects on the host health, so that well-conducted human trials are required.

In addition to the generally identified as beneficial bacteria (bifidobacteria, lactobacilli, and even, eubacteria), a recent review by Hill et al. [16] indicates that the species *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, and others such as *Roseburia* spp. and *Eubacterium hallii*, which could be useful to alleviate gut inflammation, to induce and regulate of the immune system or to improve the intestinal barrier function.

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The most widely accepted prebiotics are lactulose, inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and the human milk oligosaccharides (HMO). However, there is a growing list of potential prebiotics and some of them are already commercialized and others, like polydextrose (PDX), pectic oligosaccharides (POS), bacterial exopolysaccharides (EPS), polysaccharides derived from algae and sugar alcohols that are still in the early stages of study [15]. This chapter summarizes the scientific literature regarding the manufacture and evaluation of this group of emerging prebiotics.

2. Pectic oligosaccharides (POS)

POS have been recently classified as emerging prebiotics and their potential is currently being evaluated.

2.1. Raw materials for POS production

POS are oligosaccharides that can be obtained by partial hydrolysis of pectins, which are heteropolysaccharides with a highly complex structure.

Pectins are mainly made up by a backbone of galacturonic acid units (GalA) connected by α-(1,4) links that can be randomly acetylated at the O-2 and/or O-3 positions and methylated at C-6. This fraction is known as "smooth region," and it is occasionally interrupted by the "hairy region," where side chains, formed by a variety of neutral sugars, can be found. **Figure 2** shows the major structural fragments of pectin:

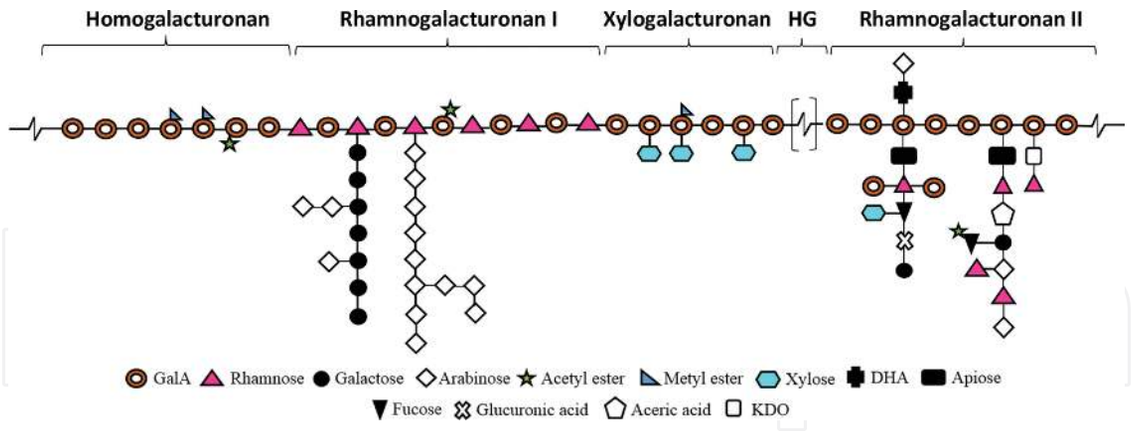

Figure 2. Simplified structure of pectin.

a. Homogalacturonan (HG). HG is a linear polymer consisting of a chain with an estimated length of 72–100 GalA units that represent, approximately, 60% of the total pectin [17]. Acetylation and methylation degrees (DA and DM, respectively) vary according to the origin and the development stage of the plant [18].

b. Xylogalacturonan (XG). XG is a chain of GalA residues partially substituted by D-xylose residues connected by β-(1,3) links at C-3 and/or C-2 positions.

c. Rhamnogalacturonan I (RG-I). It represents up to 7–14% of the pectins [19] and contains alternating units of α-(1,4)-galacturonosyl and α-(1,2)-rhamnosyl. In many cases, rhamnose residues show side chains as substituents on the O-4 position, made up of arabinan and/ or arabinogalactan I and II, although lower concentrations of xylose or glucose can be also found [18].

d. Rhamnogalacturonan II (RG-II). RGII is a region characterized by a length of 7–9 GalA units, where complex branches made up of 12 types of monosaccharides (as a maximum) can exist, including some minority monomers such as apiose, fucose, acetic acid, DHA, or KDO [20].

Pectin has a great number of applications including its use as ingredient for medicaments for treating gastrointestinal disorders, diabetes, high blood pressure, or hypercholesterolemia [21–23].

Currently, citrus pulp and apple pomace are the major sources of pectin, but this polymer can also be found in other agro-products such as sugar beet pulp [24].

2.2. Manufacture and purification

Several methods have been used for POS production from both agro-industrial byproducts and purified pectins, including partial enzymatic hydrolysis, acid hydrolysis, hydrothermal treatments, dynamic high-pressure microfluidization, or photochemical reaction in media containing TiO_2 [24].

Chemical methods include the acidic or basic hydrolysis of α and β-glucosidic links of the principal chains of HG, RG-I, and RG-II and their side chains. These methodologies include hydrothermal treatments and processes where external acids are added. In both cases, hydronium ions act as catalytic species [24]. A variety of raw materials such as orange albedo, apple pulp, or deesterified beet pulp have been treated to obtain POS, using acids such as HNO_3, HCl, or TFA [24], although alkalis (KOH) can also be employed [25]. POS mixtures have been obtained from lemon and orange peel wastes [26–28], dried apple pomace [29], sugar beet pulp [30], or alperujo [31] using stainless steel reactors, whereas Sato et al. [32] employed both a batch and a continuous tubular flow reactor to produce arabinooligosaccharides (AraOS) and feruloylated AraOS from beet fiber.

As an alternative, pectin-degrading enzymes constitute a group of enzymes that catalyze the degradation of the pectic polymers in plant cells. Although pectins have a complex structure, they can be modified by diverse enzymes, including hydrolases, lyases, and esterases [33].

Several raw materials with different characteristics have been enzymatically treated, such as bergamot peel [34], gum tragacanth [35, 36], ginseng pectin [37], orange peel wastes [38], lemon peel wastes [39], sugar beet [40, 41], apple pectin [42], or medicinal herbs [43].

Both mono-active and commercial mixtures can be used for pectin depolymerization; however, mono-active enzymes target only specific structures, causing the release of more defined oligosaccharides than when commercial enzyme mixtures or chemical treatments are employed [44]. Mixture of several preparations have been widely employed for POS produc-

tion [38, 41, 45–48]. A comparable yield respect to acidic treatments can be achieved using enzyme preparations [42].

In addition, enzymes can be also advantageous for the alteration of the methylation or acetylation degree of the polymer [44].

On the other hand, chemical and enzymatic hydrolysis have been combined to depolymerize pectin [49] or to obtain different pectin fractions, such as POS and neutral and acidic xylooligosaccharides [31]. Other technologies that have been combined are enzymatic and microwave-assisted alkaline extraction [48], hydrothermal and acid treatment for polygalacturonic acid hydrolysis [50], subcritical water and ultrasonic-assisted treatments [51].

Finally, physical technologies (for instance, the dynamic high-pressure microfluidization under acidic conditions) have been emerged as innovative [52].

After production, purification stages are usually needed to obtain a product suitable to be used as food ingredient. The most common purification technique is the membrane filtration. A process involving diafiltration followed by concentration was performed by Gómez et al. [26] to purify pectic oligosaccharides from autohydrolysis liquors obtained from lemon peel wastes, yielding a refined product with about 98 wt% of oligomers which contained oligogalacturonides (with DP in the range of 2–18) and AraOS (with DP in the range of 2–8). A similar approach was performed by Gómez et al. [27] achieving a refined final product containing 90% of the target product, where there were identified AraOS (DP 3–21), GalOS (DP 5–12), and OGalA (DP 2–12), with variable DM and also long-chain products.

Rubio-Senent et al. [53] isolated fractions (MW > 3 kDa) which were rich in pectic material from an alperujo aqueous hydrolysate by ultrafiltration thought 3 kDa regenerated cellulose.

Ultrafiltration and diafiltration (50 kDa cut-off) were employed by Sulek et al. [54] to isolate AraOS, which were further fractionated into a stirred membrane reactor equipped with a 1 kDa MWCO.

This methodology has also been employed to sequentially fractionate oligosaccharides by its molecular weight [55].

Other alternatives were also used in this field; Lama-Muñoz et al. [31] fractionated and purified neutral and POS by adsorption XAD chromatography (Amberlite XAD-16 resin), and the gel Sephadex G-75 was selected by Lee et al. [56] to purify POS from Korean Citrus Hallabong peels.

2.3. Prebiotic potential of POS

POS have been suggested as a new class of prebiotics, which are capable of exerting a number of health-promoting effects, including [24] stimulation of apoptosis in human colonic adenocarcinoma cells, potential for cardiovascular protection *in vivo*, reduction of damage by heavy metals, antiobesity effects, antitoxic, antiinfection, antibacterial, and antioxidant properties.

The main derived products from the intestinal bacterial fermentation of POS, as well as from other dietary fiber, are the SCFA (acetate, propionate, and butyrate). SCFA exert several beneficial effects including: (i) a key role in the prevention and treatment of the metabolic syndrome, bowel disorders, and cancer [57–59]; (ii) protection against diet-induced obesity and regulation of the gut hormones [60]; or (iii) a positive effect on the treatment of ulcerative colitis, Crohn's disease, and antibiotic-associated diarrhea and obesity [61–63]. Particularly, butyrate is the major energy source for the colonocytes, propionate has a role in gluconeogenesis processes, and acetate is used for the lipogenesis [64].

The following paragraphs summarize the results derived from the recent *in vitro* and *in vivo* studies carried out employing POS as substrate:

a) In vitro assays

Citrus peel wastes and sugar beet pulp were subjected to hydrothermal treatment and the resulting liquors refined by membrane filtration. The final POS mixtures were then fermented by human fecal samples leading to an increase of the bacterial population of up to eight different groups. Specifically, POS from sugar beet pulp showed the highest bifidogenic potential and the maximum SCFA concentration. Meanwhile, the largest increase in *Lactobacillus* population was observed using POS from orange peel wastes as a carbon source, whereas the best results for other bacterial groups such as *Eubacterium*, *Faecalibacterium*, or *Roseburia* were observed for POS from lemon peels wastes [27, 65]. In the same way, POS derived from sugar beet (enriched in AraOS) were used as substrates in *in vitro* fermentation assays of POS leading to increases in bifidobacteria populations (which preferred low molecular weight fractions) without stimulating the growth of *Clostridium* [66–68]. In a recent study with POS from sugar beet pulp containing GalOS, AraOS, and mixtures of acidic oligosaccharides (mainly made up of RG and HG oligosaccharides), no a clear bifidogenic effect was observed, whereas important increases of *Faecalibacterium* were reported. Moreover, the SCFA concentrations were found higher in experiments with POS than with FOS [69].

Regarding apple pectin, a variety of works were reported concluding that POS might be an interesting prebiotic candidate with slightly improved physiological properties if they are compared to commercial ones. In this context, Gulfi et al. [70] indicated that pectin hairy regions from ripe apples revealed to be a very readily fermentable substrate for human colonic bacteria, showing a substantial impact on pH and SCFA production. Suzuki et al. [71] found that AraOS from apple pectin, especially those that consist of more than three units, are more selectively utilized by *Bifidobacterium adolescentis*, *B. longum*, and *Bacteroides vulgatus* than FOS and XOS. Meanwhile, Chen et al. [52] reported the ability of apple-derived POS for promoting the bifidobacteria and lactobacilli growth and for decreasing numbers of bacteroides and clostridia, whereas the fermentation of refined POS mixture from apple pomace with human feces resulted in an increase in the populations of *Bifidobacterium*, *Eubacterium rectale* and *Lactobacillus*, but also of *Clostridium* and *Bacteroides* [72].

Some authors as Mandalari et al. [12] employed other types of pectin sources, demonstrating that almond seeds, which contain arabinose-rich pectin, exhibited potential for their use as a novel sources of prebiotics, increasing the populations of bifidobacteria and *Eubacterium rectale*

with the subsequent increase in butyrate concentrations. Guevara-Arauza et al. [73] observed that POS from nopal act as prebiotics, reducing putrefactive ammonium production, increasing SCFA production, and sustaining bifidogenic effects over longer periods of time.

In addition, in order to elucidate structure–function relationships in POS, Onumpai et al. [74] compared the fermentation properties of pectin fractions and their parent pectins using a pH-controlled fecal fermentation system. All of the tested carbohydrates increased the populations of bacteroides, but just galactan- and arabinan-derived oligosaccharides increased the bifidobacteria counts. On the other hand, methylated oligogalacturonides, compared to the parent polysaccharide and to other pectic fractions, caused a significant increase in the *Faecalibacterium prausnitzii* populations [74].

b) In vivo assays

Despite the advances in *in vitro* models, the *in vivo* studies involving the use of animals and especially of humans provide the best models for studying the changes in the microbiota populations. However, they often require specialist facilities and are both expensive and time-consuming, limiting the number of this type of assays [75].

Jiao et al. [76] demonstrated that water-soluble oligosaccharides isolated from Panax ginseng significantly inhibited tumor growth in mice by enhancing their immune system. In this last year, native intact (TrPP) and modified, low molecular weight (MTrPP) forms of pectic polysaccharides isolated from turmeric were evaluated for ulcer-preventive potentials in *in vivo* rat models. MTrPP was rich in galacturonic acid (687 mg/g; TrPP-544 mg/g) and galactose (52.9%; TrPP-21.7%) from HG and RG-I containing galactan. The results suggested that MTrPP possess significantly improved ulcer-preventive properties than TrPP (inhibiting ulcer scores up to 85%), revealing that the fine structural features of pectin are crucial in delivering its therapeutic benefits against gastric ulcer [77].

Regarding the clinical assays, Fanaro et al. [78] observed increased counts of bifidobacteria and lactobacilli by the administration of POS as a component of infant formulae. Similarly, Magne et al. [79] detected increased proportions of bifidobacteria in the mixture GOS/FOS/POS respect to the mixture GOS/FOS, as well as the proportions of *Bacteroides* and *Clostridium coccoides* decreased. Moreover, the use of neutral and acidic oligosaccharides to preterm infants (mixtures of POS, GOS and FOS) showed a trend toward a lower incidence of serious endogenous infection and serious infectious episodes [80]. Finally, the intake of POS in a mixture with short-chain GOS and long-chain FOS by volunteers who were in the earlier stages of HIV-1 infection, resulted in the modulation of gut microbiota by increasing the bifidobacteria numbers and by decreasing the counts of pathogens [81].

3. Polydextrose (PDX)

3.1. Structure and manufacture

PDX is an artificial highly branched polysaccharide synthesized conventionally by random polycondensation of glucose with sorbitol and a food grade acid (e.g., citric acid) as catalyst, at a high temperature and under partial vacuum [82]. Recently, other methods have been explored as the synthesis by microwave irradiation [83]. PDX is composed of a mixture of glucose oligomers, with an average degree of polymerization (DP) of 12, ranging from DP 2–120 [84, 85] and contains all different combinations of α- and β-(1,2), (1,3), (1,4), and (1,6) glycosidic linkages, but α-(1,6) linkages are predominant [85, 86]. PDX is regarded as a resistant polysaccharide [87] and it is widely used in the food industry as a low-energy bulking agent (1 kcal/g) and as a sugar or fat replacer [86].

3.2. Prebiotic effects

Due to its complex structure and to the nature of its glycosidic bonds, PDX is resistant to mammalian digestive enzymes in the upper gastrointestinal tract. For this reason, PDX reaches the colon intact where it is partially fermented by gut microbiota, stimulating selectively target bacterial groups [84, 85, 88]. These two characteristics, indigestibility and selective fermentability, support that the PDX has been identified as a source of prebiotic fiber with several health-promoting effects [89], including:

- Improvement of the bowel function, by promoting the growth of beneficial bacteria (e.g., bifidobacteria and lactobacilli) while preventing the growth of harmful ones (such as clostridia and bacteroides), decrease of fecal pH and increase of the residual concentration of short chain fatty acids (SCFA) [88].
- Reduction of the risk of colon cancer development [88, 90].
- Modulation of the lipid metabolism, decreasing the total cholesterol and LDL cholesterol and increasing HDL cholesterol [84].
- Prevention of the adhesion of opportunistic pathogens related with meningitis and sepsis in neonates [91].
- Anti-inflammatory action [92] and positive effects on canine osteoarthritis [93].
- Reduction of the symptoms of human atopic eczema [94].
- Improvement of the absorption of magnesium, calcium and iron [95–97]. The studies related to the biological and prebiotics effects of PDX (observed *in vivo, in vitro* and human intervention assays) are summarized in **Table 1**.

Biological and prebiotic effects	Study type	References
Proliferation of *Lactobacillus* and *Bifidobacterium* species and decreases in *Bacteroides* species. Increases in concentrations of SCFA. Improvement of the bowel function and inhibition of the excessive glucose absorption in the small intestine	C.I.	[98]
Increases in *Ruminococcus intestinalis* and *Clostridium* clusters I, II, and IV that are butyrate-producing. Decreases in fecal water genotoxicity	C.I.	[88]

Biological and prebiotic effects	Study type	References
Reduction of LDL cholesterol and total cholesterol	C.I.	[99]
Infants fed with formulas with PDX had softer stools (similar to breastfed infants) in comparison with those who receive unsupplemented formulas	C.I.	[100]
Increases in bifidobacteria and stools weight. Decreased in fecal ammonia, phenol, indoles and BCFA (isobutyrate, isovalerate, and valerate)	C.I.	[101]
Reduction of the orofecal transit time, and improvement of stool consistency in persons suffering from constipation	C.I.	[102]
Increases in *Faecalibacterium prausnitzii* numbers	C.I.	[103]
Reduction in fecal pH and improvement of stool consistency	C.I.	[104]
Supplementation with GOS–polydextrose and *Lactobacillus rhamnosus* GG in preterm infants reduces the risk of rhinovirus infections in infants	C.I.	[105]
The intake of yogurt with polydextrose, *B. lactis* HN019, *and L. acidophilus* NCFM® improved constipation	C.I.	[106]
Reduction of the production of biogenic amines and BCFA in rats. Improvement of the immune function	A.S.	[107]
Increases in defecation without diarrhea	C.I.	[108]
Increases in populations of bifidobacteria with a similar pattern with breastfed infants	C.I.	[109]
Increases in the number of bifidobacteria and selective stimulation of *Bifidobacterium infantis* compared with other carbohydrates tested	*in vitro*	[110]
Increases in bifidobacteria and lactobacilli and SCFA production	*in vitro*	[111]
Increases in the concentration of acetate and propionate and reduction of BCFA concentration.	*in vitro* (C.M.)	[112]
Increases in the production of fecal SCFA, especially acetate and propionate, and decreased fecal indole	A.S. (dogs)	[113]
Reduction of the expression of mucosal COX-2 (closely related to the colorectal cancer)	A.S. (pigs)	[114]
Increases in the content of ileal lactobacilli and in the levels of propionic and lactic acid. Reduction of cytokine expression	A.S. (pigs)	[89]
Reduction of chronic visceral hypersensitivity in rats exposed to early-life painful stimulus	A.S. (rats)	[115]
Improved calcium absorption in postmenopausal rats	A.S. (rats)	[116]
Ability to inhibit adherence of *C. sakazakii* to gastrointestinal epithelial cells	*in vitro*	[91]
Positive effect in canine osteoarthritis	A.S. (dogs)	[93]
Reduction of symptoms of allergen-induced dermatitis	A.S.(mice)	[94]
Stimulation of apoptosis in colon cancer cells	*in vitro* (C.M.)	[90]

A.S., animal study; C.I., clinical intervention; C.M., colonic model.

Table 1. Results obtained in studies carried out using polydextrose as substrate.

4. Algae-derived oligosaccharides

4.1. Structure, sources, and production

Seaweeds are a source of bioactive compounds like sulphated polysaccharides, proteins, polyunsaturated fatty acids (PUFA), and polyphenols with potential beneficial health effects, such as antibacterial [115], anti-inflammatory [116, 117], antioxidant [118–120], antitumoral [121, 122], anticoagulant [123] antiadhesive [116], and apoptotic activities [124, 125] among others. The major polysaccharides which can be found in seaweeds are alginates, laminarins, fucans and cellulose in brown seaweeds, ulvan in green seaweeds, and agars and carrageenans in red seaweeds. Several extraction methods of bioactive sulphated polysaccharides from seaweeds have been investigated in recent years, including: diluted acid extraction [126, 127], hydrothermal processing [128], microwave-assisted extraction [129–131], ultrasound-assisted extraction [132], enzyme-assisted extraction [132, 133], or pressurized liquid extraction [134].

4.2. Prebiotic properties

In the last decade, seaweed polysaccharides have been considered as dietary fibers and have attracted much interest because of their potential use as prebiotics [135, 136]. In this sense,

several studies have reported that seaweed polysaccharides resist the digestion in the upper of gastrointestinal tract, support the growth of lactic acid bacteria, reduce of harmful bacteria as well as modulate the intestinal metabolism through their effects on pH and SCFA concentration [137].

To date, several studies *in vitro* and *in vivo* were carried out to evaluate the potential prebiotic effects of seaweed polysaccharides. **Table 2** summarizes the results obtained. No human trials have been conducted yet using this type of substrates.

Product or seaweed	Biological and prebiotic effects	Study type	References
Chondrus crispus and Sarcodiotheca gaudichaudii	Increases in the numbers of *Bif. longum* and *Streptococcus salivarius* and reduction in the populations of *C. perfringens*. Increases in SCFAs concentration and i-butyric acid.	A.S. (hens)	[140]
Laminarin	Increases in the levels of SCFAs	*In vitro* (HGM)	[137]
Laminarin	Variations of mucus composition in jejunum, ileum, cecum, and colon	A.S. (rats)	[137]
Ascophyllum nodosum	Reduction in populations of *Escherichia coli*	*In vitro* (PGM)	[141]
Carrageenans	Increases in cecal moisture and in concentrations of acetic and propionic acid. Reduction in the levels of triglycerides and total cholesterol	A.S. (rats)	[142]
Alginate oligosaccharides	Increases in numbers of fecal *bifidobacteria* and *lactobacilli* and reduced counts of *bacteroides* respect to the FOS	A.S. (rats)	[143]
Alginate oligosaccharides	Stimulation of the growth of *Bifidobacterium bifidum* ATCC 29521 and *Bifidobacterium longum* SMU 27001	*In vitro*	[143]
Saccharina latissima	Increases in the concentrations of acetic and propionic acids	A.S (rats)	[144]
Laminarin and fucoidan	Reduction in the populations of *Enterobacteria* and increases in the populations of *Lactobacilli*	A.S. (pigs)	[145]
Porphyran	Increases in the content of propionic acid in the cecum. Decreases in the number of *Clostridium coccoides*.	A.S. (mice)	[146]
Carrageenan	Increases in the populations of *Bif. breve* and reduction in the populations of *Clostridium septicum* and *Streptococcus neumoniae*. Increases in the concentrations of SCFAs and immunoglobulin levels	A.S. (rats)	[147]
Fucoidan and laminarin	Increases in the counts of *Lactobacillus* and *Bifidobacterium* in the ileum	A.S. (piglet)	[148]
Low MW polysaccharides from agar and alginate	Increases in the number of *bifidobacteria*. No effect on the populations of *Lactobacilli, Bacteroides, Eubacterium rectale/C. coccoides*, and *C. histolyticum*	*In vitro* (HGM)	[149]
Fucoidan	Stimulation of apoptosis in HT-29 and HCT116 human colon cancer cells	*In vitro*	[150]
Himanthalia elongata	Increases in the acetic, propionic, and butyric acids concentrations. Improvement of the lipid profile	A.S. (rats)	[151]
Fucoidan	Inhibition of the adhesion of *Helicobacter pylori* to the gastric mucous	*In vitro*	[152]
C. crispus	Enhancement of the host immunity and reduction of the infection by *Pseudomonas aeruginosa*	*In vitro*	[153]

A.S., animal study; C.I., clinical intervention; C.M., colonic model; HGM, human gut microbiota; PGM, pig gut microbiota.

Table 2. Results obtained in studies carried out using polysaccharides and oligosaccharides derived from algae as substrates.

5. Bacterial exopolisaccharides

5.1. Structure, sources, and production

Bacteria can produce polysaccharides that usually play a protective role against environment pressures. As these polymers are excreted into the extracellular surrounding, they are known as EPS. They can occur in two forms (capsules or biofilm) [150, 151] and are classified in two groups according to their composition:

- homo-EPSs made up of a single type of monosaccharide such as fructans, α-D-glucans, β-D-glucans, dextran, curdlan, alternan, mutan, reuteran, or levan [152–154].

- hetero-EPSs composed of different types of monosaccharides, mainly D-glucose, D-galactose, L-rhamnose, and their derivatives, such as xanthan, gellan, alginate, hyaluronan, succinoglycan, kefiran, emulsan, galactoPol, or FucoPol [152–154]. The heteropolysaccharides are the most abundant bacterial EPSs.

The critical factors for maximum EPSs production are carbon and nitrogen sources, mineral requirements, oxygen and aeration rate, temperature and pH [155], among others. Sugars are the most commonly carbon sources used for the production of bacterial EPSs. However, cheaper substrates, such as agro-food or industrial wastes and byproducts are suitable carbon sources for EPSs production [153]. EPSs synthesis is generally favored by the presence of the carbon source in excess, and the production of most bacterial EPSs occurs under aerobic conditions [153].

On the other hand, the methods for EPSs extraction have a crucial influence as their physicochemical properties could be affected by the isolation and purification techniques [154]. It can be carried out by two methods: (i) by solvent precipitation when they are in slim form and (ii) by alkaline extraction prior centrifugation and alcohol precipitation when they are in form of capsule. The recovery is performed by solvent precipitation [155].

5.2. Biological properties

The EPSs have been proved to have functional roles in human or animal health including immunomodulatory properties, antiviral, antioxidant, antimutagenecity, antihypertensive, antiulcer, and antitumor activities, and have also been used as food additives for texture improvement, as gelling agents or emulsifiers [152, 155, 156]. Moreover, EPSs may induce other positive physiological responses including lower cholesterol levels, reduced formation of pathogenic biofilms, modulation of adhesion to epithelial cells, and increased levels of bifidobacteria, showing a prebiotic potential [157].

The use of bacterial EPSs as prebiotic substrates has been scarcely investigated [151]. **Table 3** shows the results from some *in vitro* and *in vivo* assays that have explored the prebiotic potential of this kind of substrates. Up to date, not human interventions with bacterial EPSs have been carried out.

EPS type	Producer strain	Biological and prebiotic effects	Study type	References
Levan	*Lactobacillus sanfranciscensis* LTH1729, *Lactobacillus sanfranciscensis* LTH2590	Bifidogenic effect; enhanced growth *Eubacterium biforme*	*In vitro* (HGM)	[162]
EPS (type not identified)	*Weissella cibaria A2, Weeissella confusa A9, Lactobacillus plantarum A3 and Pediococcus.pentosaceus 5S4*	High resistance to gastric and intestinal digestions, enhancement of growth of *Bifibacterium bifidum* and some growth in case of *B. longum, B. adolescentis*, and *Lb. acidophilus*	*In vitro* (pure cultures)	[155]
EPS (type not identified)	*Weissella cibaria A2*	Enhanced growth of *Bifidobacterium* and *Lactobacillus /Enterococcus* groups, reduction of numbers of *Clostrida*. Increase in SCFA concentrations (acetate, propionate, butyrate)	*In vitro* (HGM)	[155]
EPS (type not identified)	*B. animalis, B. pseudocatenultum, B. longum*	Increases in SCFA concentration and moderate bifidogenic effect	*In vitro* (HGM)	[163]
Fructan	*Lactobacillus sanfranciscensis* TMW 1.392	Metabolized by *B. breve, B. bifidum, B. adolescentis*, and *B. infantis*	*In vitro* (pure cultures)	[164]

EPS type	Producer strain	Biological and prebiotic effects	Study type	References
Dextran	*Leuconostoc mesenteroides* NRRL B-1426	Low digestibility by simulated human gastric juice, high resistance to digestion by human a-amylases, stimulated the growth of *B. animalis, B. infantis, Lb. acidophilus*	*In vitro* (pure cultures)	[165]
Reuteran	*Lb. reuteri* TMW 1.656	Contribution to the prevention of enterotoxigenic *E. coli* adhesion to the intestinal mucosa	*In vivo* (weanling piglets)	[166]
EPS (type not identified)	*B. bifidum* WBIN03	Significant inhibition of enterobacteria, enterococci, and *Bacteroides fragilis*; significant enhancement of the amount of *Lactobacillus* and total anaerobes	*In vivo* (mice)	[167]

HGM, human gut microbiota.

Table 3. Results obtained in studies carried out using bacterial exopolysaccharides as substrates.

6. Sugar alcohols

6.1. Definition and production

Sugar alcohols are low digestible carbohydrates that are hydrogenated, which means that there is an alcohol group (>CH–OH) in place of the carbonyl group (>C=O) in the aldose and ketose moieties of mono-, di-, oligo- and polysaccharides [162]. They can be classified into three groups: (i) hydrogenated monosaccharides (erythritol, xylitol, sorbitol, manitol); (ii) hydrogenated disaccharides (lactitol, isomalt, maltitol), and (iii) hydrogenated polysaccharides (hydrogenated starch hydrolysates (HSHs), polyglycitols) [163].

Sugar alcohols occur naturally in certain fruits and vegetables, and some of them are even generated by the human body. However, huge amounts of sugar alcohols are manufactured for the food industry (**Table 4**) where they are used as replacers in foodstuffs performing functions such as flavor enhancer, humectant, sweetener, anticaking agent, bulking agent, glazing agent, stabilizer, thickener, emulsifier, and sequestrant [166].

Sugar alcohol	Natural source	Synthesis
Erythritol	Vegetables, fruits (melons, peaches, mushrooms, fermented foods (wine, beer, sake, soy sauce)	Fermentation of glucose using yeasts or lactic acid bacteria
Xylitol	Fruits, vegetables, berries, oats, mushrooms	Metal catalyzed hydrogenation of D-xylose Biotechnological production from corn cobs, waste of sugarcane, and other fibers using yeasts
Sorbitol	Apples, pears, apricots, nectarines, prunes, dates, raisins	Catalytic hydrogenation of glucose or dextrose using Ni catalyst at high T[a]. Electrochemical reduction of dextrose at pH>7
Mannitol	Fruits, vegetables, brown seaweeds, wine	Fermentative process using lactic acid bacteria
Isomalt	–	Enzymatic transglucosidation of sucrose into maltulose and further hydrogenation
Lactitol	–	Catalytic hydrogenation of lactose using Raney nickel as catalyst
Maltitol	–	Catalytic hydrogenation of maltose or very high maltose glucose syrup
Polyglycitols/ HSHs	–	Partial hydrolysis of starch (from corn, potato or wheat) resulting in dextrins that undergoes subsequent hydrogenation

Table 4. Natural sources and industrial synthesis of sugar alcohols [170, 171]

6.2. Biological properties

Sugar alcohols are characterized by their lower blood glucose response, and they can be metabolized without insulin [166]. Although they are structurally similar to sugars, their nutritional value is lower than them because they are only partially absorbed by the body, and the absorbed portions are either poorly metabolized (e.g., erythritol) or excreted via the urinary tract. The unabsorbed polyols are partially fermented in the colon, and they can modulate beneficially the gut microbiota acting as prebiotics [109, 162]. **Table 5** lists the results obtained in several studies that have been carried out with sugar alcohols.

Sugar alcohol	Biological and prebiotic effects	Study type	References
Erythritol	Not change on bacterial population dynamics but significant increase in acetate	*In vitro* (human gut microbiota)	[113]
Sorbitol	Favors growth of autochthonous *Lactobacillus* species and increases colonic production of butyrate	*In vivo* (in rat)	[174]
Mannitol	Modification of large intestine fermentation to produce more butyrate and propionate	*In vivo* (in rat and pig model)	[175]
	Promotion of absorption and retention of Ca and Mg	*In vivo* (in rat)	[176]
	Lowering effect on body fat accumulation and reduction of the level of serum triglycerides	*in vivo* (in rat)	[177]
Isomalt	Significant increase in *bifidobacteria* and increase in butyrate, acetate and propionate	*In vitro* (human gut microbiota)	[113]
Lactitol	Ability to reduce circulating levels of NH3 and toxic microbial substances, the clinical utility of which is the treatment of hepatic encephalopathy	C.I.	[178]
	Reduction of levels of plasma endotoxin in chronic viral hepatitis through improving intestinal microbiota	C.I.	[179]
	Significant increases in counts of *Bifidobacterium* and both propionic and butyric acids and significant reduction of fecal pH with a consumption of 10 g/d	C.I.	[180]
	Fermentation by pure cultures of *Bifidobacterium lactis* Bi-07, *Lactobacillus acidophilus* NCFM, *Lactobacillis paracasei* Lpc-37, *Lactobacillus rhamnosus* HN001	*In vitro* (pure cultures)	[181]
	Increase fecal numbers of *L. acidophilus* NCFM. No significant changes in SCFA and fecal concentrations of spermicine and PGE2	C.I.	[182]
	Significant increase in *bifidobacteria* and increases in butyrate, acetate and propionate	*In vitro* (human gut microbiota)	[113]
Maltitol	Significant increase in *bifidobacteria*, minor increase in *Lactobacillus/enterococci*, and increases in major SCFA (acetate, propionate, and butyrate)	*In vitro* (human gut microbiota)	[113]
	Significant increases in *bifidobacteria, lactobacilli, clostridium histolyticum/perfringens* populations, *bacteroides, Fusobacterium prausnitzii, E. rectal, R. flavefaciens, Atopobium, R. bromii*, and in major SCFA (acetate, propionate, and butyrate)	C.I.	[183]

C.I., clinical intervention.

Table 5. Biological and prebiotic effects of sugar alcohols.

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