TITLE

A comprehensive review on the impact of β-glucan metabolism by *Bacteroides* and *Bifidobacterium* species as members of the gut microbiota.

Running title: β-glucan metabolism by *Bacteroides* and *Bifidobacterium* species.

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ABSTRACT

β-glucans are polysaccharides which can be obtained from different sources, and which have been described as potential prebiotics. The beneficial effects associated with β-glucan intake are that they reduce energy intake, lower cholesterol levels and support the immune system. Nevertheless, the mechanism(s) of action underpinning these health effects related to β-glucans are still unclear, and the precise impact of β-glucans on the gut microbiota has been subject to debate and revision. In this review, we summarize the most recent advances involving structurally different types of β-glucans as fermentable substrates for Bacteroidetes (mainly *Bacteroides*) and *Bifidobacterium* species as glycan degraders. *Bacteroides* is one of the most abundant bacterial components of the human gut microbiota, while bifidobacteria are widely employed as a probiotic ingredient. Both are generalist glycan degraders capable of using a wide range of substrates: *Bacteroides spp*. are specialized as primary degraders in the metabolism of complex carbohydrates, whereas *Bifidobacterium spp.* more commonly metabolize smaller glycans, in particular oligosaccharides, sometimes through syntrophic interactions with *Bacteroides spp.*, in which they act as secondary degraders.

Keywords: β-glucans; *Bacteroides*; *Bifidobacterium*; Syntrophic interactions; metabolism; Carbohydrate active enzymes.

1. Introduction

β-Glucans are complex polysaccharides composed of D-glucopyranosyl residues that are linked through β-bonds. These ubiquitous polymers are present in cells walls of yeast, fungi, seaweed, bacteria and cereals, such as wheat, oat and barley [1, 2]. The macromolecular structure of β-glucans is different according to the extraction source. For instance, cereal β-glucans have a backbone of single β(1,3)-bonds separating short sections of β(1,4)-bonds, while seaweed β-glucans typically consist of a β(1,3)-linkage backbone with single β(1,6) branching points, in which the resulting side chain contains β(1,3)-linkages (Fig. 1). Additionally, mushroom-derived β-glucans typically represent polymers composed of β(1,6)-linked branches from a β(1,3) backbone, while bacterial β-glucans simply consist of a linear β(1,3) backbone (Fig. 1) [3-6].

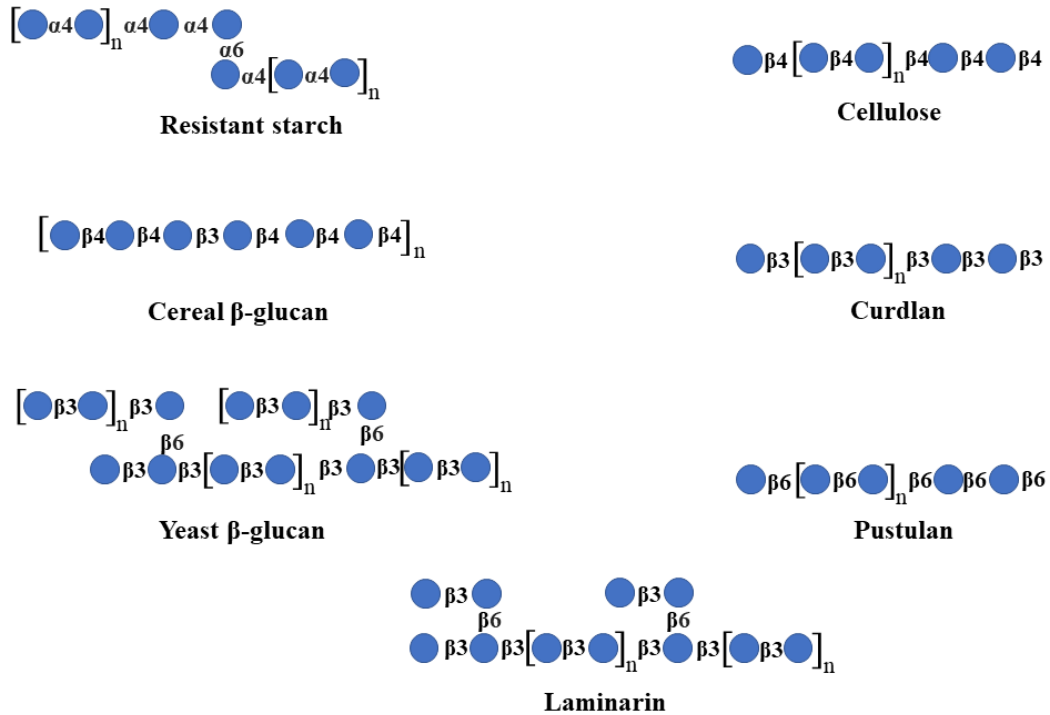

Fig. 1. Structure of different types of alpha- (resistant starch) and β-glucans. The sources of β-glucans are varied: cereals, brown algae (Laminarin), *Saccharomyces cerevisiae* (yeast), Fungi *Lasallia pustulata* (Pustulan), bacteria, e.g. *Alcaligenes faecalis* (Curdlan), and plants (cellulose) [5].

β-glucans can be modified by physical, chemical and biological methods, which affect their primary structure, spatial conformations and bioactivity. In fact, modification and transformation of β-glucans may not only improve their biological functionalities in the human gut, but also their applications as a prebiotic [7-9]). Such processed β-glucans have been reported to (*i*) reduce glucose and cholesterol blood levels, (*ii*) promote production of short chain fatty acids (SCFAs), which may act as important modulators of host immune function, (*iii*) decrease energy intake, and (*iv*) lower obesity, diabetes and cardiovascular risk [10-16]. Moreover, several studies have underlined a wide range of interesting properties of β-glucans, such as anticancer effects [17-20], immunomodulatory abilities [21], anti-inflammatory activities [22], or their role as potential adjuvants for vaccine delivery and efficacy [23] or as delivery vehicles for probiotics [24].

The focus of this review is on outlining various metabolic routes described for structurally different dietary β-glucans by human gut *Bacteroides* and *Bifidobacterium spp.* in order to clarify the various effects these polysaccharides may have on the abundance and metabolic activity of mentioned gut commensals. Understanding glycan metabolism is fundamental to determine how polysaccharides shape the microbial gut communities, as well as its associated health effects. In addition, this understanding will facilitate the development of nutraceutical-based strategies to increase the content of specific beneficial bacteria.

The gut and its associated Human Gut Microbiota (HGM) together form a recently considered novel organ of the human body that impacts on human health in a variety of ways [25, 26]. The HGM in Western populations represents a complex microcosm of

trillions of microorganisms, with Bacteroidetes and Firmicutes being the most dominant phyla, and Actinobacteria, Proteobacteria and Verrucomicrobia being less abundant components (Fig. 2) [27, 28]. Nonetheless, such minor components may still represent important ecological players in the complexity of HGM, especially for the metabolic interactions they offer to members of the Bacteroidetes and Firmicutes phyla. For example, *Akkermansia muciniphila* (which belongs to the Verrucomicrobia phylum) has recently been shown to represent a human gut commensal that supports host health [29, 30]. The relative abundance of *Akkermansia muciniphila* has been inversely correlated with obesity, diabetes, cardiometabolic diseases and low-grade inflammation, highlighting its potential as a probiotic to support human health and well-being [29, 30].

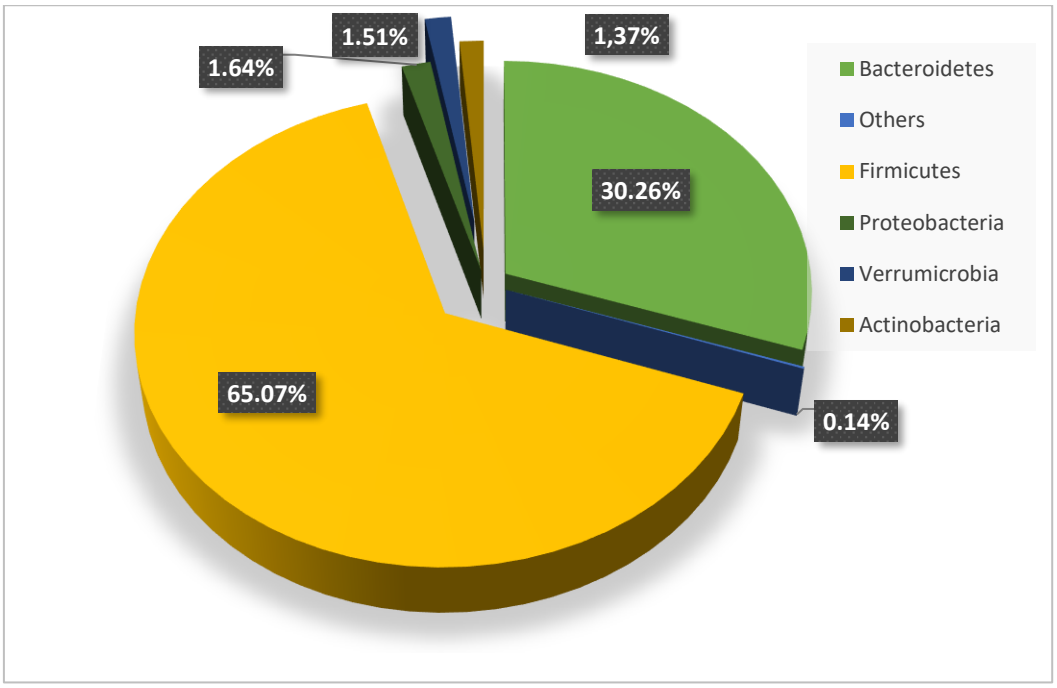

Fig. 2. Distribution of major bacterial phyla population according to their relative abundance in the human gut [28].

Bacteroides is the main genus within the Bacteroidetes phylum, though recent metagenome studies have indicated that four distinct *Prevotella* clades in this phylum have been underrepresented in Western populations [31]. Most *Bacteroides* members

are common gut commensals, though they can act as opportunistic pathogens under certain conditions, an example of this being *Bacteroides fragilis* [32, 33]. *Bacteroides* are widespread in different natural niches and human populations and possess a wide range of mechanisms to adapt to and persist in various competitive environments [31, 34-37]. *Bacteroides* species are widely known for their role as primary glycan degraders since their genomes contain a relatively high number of genes (when compared to other members of the gut microbiota) encoding carbohydrate active enzymes, such as glycoside hydrolases (GHs) and polysaccharide lyases (PLs) [38, 39]. For this reason, they are able to access a broad range of complex carbohydrate substrates [40]. Some members, such as *Bacteroides thetaiotaomicron* (289 GHs and 23 PLs) or *Bacteroides cellulosilyticus* (431 GHs and 30 PLs), dedicate around 18% of their genome content to carbohydrate metabolism, thereby reflecting their huge metabolic capacity and versatility to use this type of carbon and energy source [41, 42]. Carbohydrate active enzymes or CAZYmes are classified into different families according to protein sequence similarities, which means that they commonly elicit related activities. Therefore, enzymes belonging to the same family have a similar protein sequence, a conserved catalytic apparatus and similar quaternary structure [42-44].

Bacteroides genomes harbour polysaccharide utilization loci (PULs), which are clusters of genes involved in the detection and digestion of a specific polysaccharide. To date, all sequenced *Bacteroides* genomes contain PULs, which typically encode surface glycan binding proteins (SGBPs), enzymes for carbohydrate degradation (GHs and PLs), TonB-dependent transporters (TBDT) and sensors/regulators [43]. Polysaccharide breakdown usually begins at the cell surface by a GH or PL, which degrades the complex intact polysaccharide into oligosaccharides. These released oligosaccharides

are then transported by the *Bacteroides* species into the periplasm by SusC-like TBDT proteins [45], although they may also be utilized by other bacteria as substrates through *cross-feeding*, a common phenomenon observed for complex polysaccharides or cofactors [38, 39, 46-48]. In the periplasm, several exo- and endo-glycosidases are responsible for further hydrolysis of the internalized oligosaccharides, and this degradation commonly releases a signal molecule (typically a di-/tri-/tetrasaccharide), which binds to the sensor/regulator, thereby triggering transcriptional induction of the corresponding PUL. The final step of this degradative process involves the incorporation of monosaccharides into the cytoplasm where they are channelled into central carbon catabolism. This general PUL model was first described for starch metabolism by *Bacteroides thetaiotaomicron* [49, 50] and was the first to describe how *Bacteroides* species carried out starch degradation [51-53]. The corresponding PUL, designated *sus*, is composed of eight genes, *sus*RABCDEFG, whose encoded proteins constitute a complex and cell envelope-associated apparatus highly specialized in starch catabolism [51-53]. The SusC/D complex is predominantly responsible for starch binding with SusE and SusF being involved in increasing the efficiency of the binding process [51-53]. SusG generates internal hydrolytic cuts in the bound starch, releasing oligosaccharides that are transported into the periplasmic compartment by SusC [51-53]. Here, SusA and SusB, both glycoside hydrolases, degrade these malto-oligosaccharides to glucose, which is then transported into the cytosol [51-53]. Transcriptional regulation of the whole process is accomplished by SusR in response to starch availability [51-53]. A schematic representation of this starch degradation process is shown in Fig. 3.

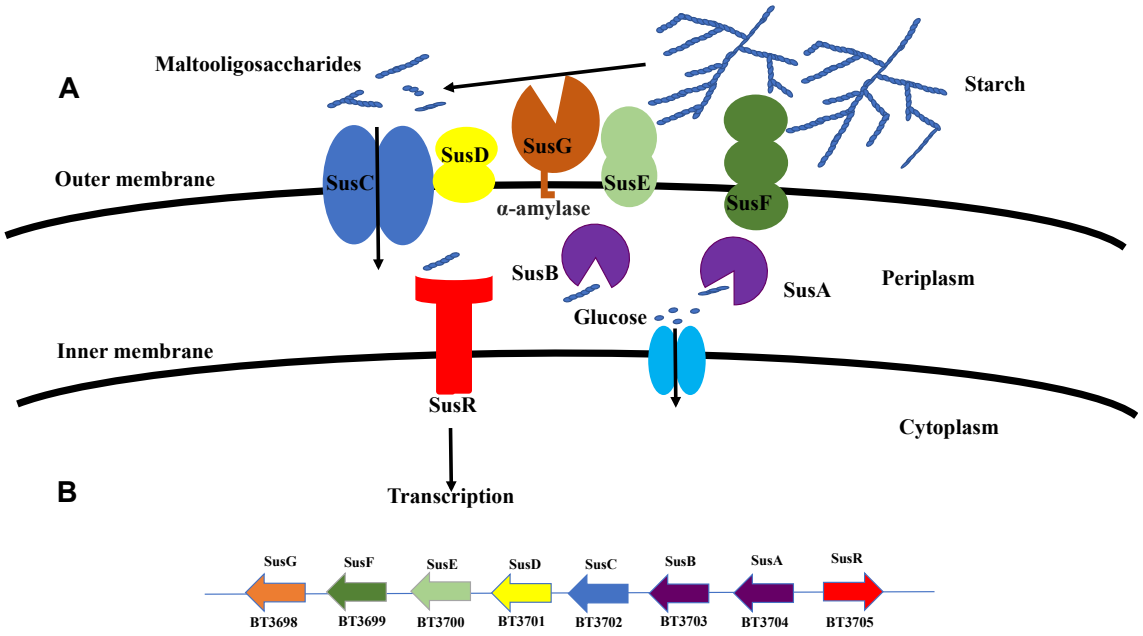

Fig. 3. A. Cartoon representation of starch utilization system model in *Bacteroides thetaiotaomicron VPI-5482* [51, 54]. The hydrolytic degradation of complex intact polysaccharide is initiated at the outside surface of the cell by SusG (alpha-amylase), thereby generating oligosaccharides. These oligosaccharides are incorporated into the periplasm by binding and import proteins (facilitated by the SusC/SusD pair), which allows further degradation to glucose by other glycoside hydrolases (SusA and SusB) and which generates a signal molecule for the regulator (SusR), causing transcriptional activation of the entire PUL. **B.** Genomic content of the PUL for starch metabolism in *Bacteroides thetaiotaomicron VPI-5482* [51, 54].

Bifidobacterium is a genus belonging to the Actinobacteria phylum whose species occupy several ecological niches, since they may be isolated from waste water, the oral cavity and the gastrointestinal tract of humans and other mammals [55, 56]. Some species are commonly identified in adults, such as *Bifidobacterium adolescentis* and *Bifidobacterium pseudocatenulatum*, while *Bifidobacterium bifidum*, *Bifidobacterium breve*, and *Bifidobacterium longum* subsp. *infantis*, are typically isolated from faecal samples of breast-fed infants [57, 58]. Various studies have demonstrated the positive

health impact or probiotic effect of certain bifidobacterial species/strains, such as those belonging to *Bifidobacterium breve*, *Bifidobacterium longum* or *Bifidobacterium bifidum* [24, 59]. In the context of this review, it should be noted that certain bifidobacteria have been reported to ferment laminarin, curdlan or oat β-glucan [60].

Also bifidobacteria contain gene clusters, each of which being dedicated to the metabolism of a specific poly/oligosaccharide [61]. These clusters encode ABC transporters (most frequently observed), permeases or proton symporters to facilitate transport of mono-/oligo-saccharides, such as fucosyllactose, fucose or galactooligosaccharides, into the cytoplasm. Once internalized, intracellular glycoside hydrolases degrade these oligosaccharides into monosaccharides and/or channel these hexoses or pentoses into the central carbohydrate metabolic pathway for energy generation (Fig. 4) [62].

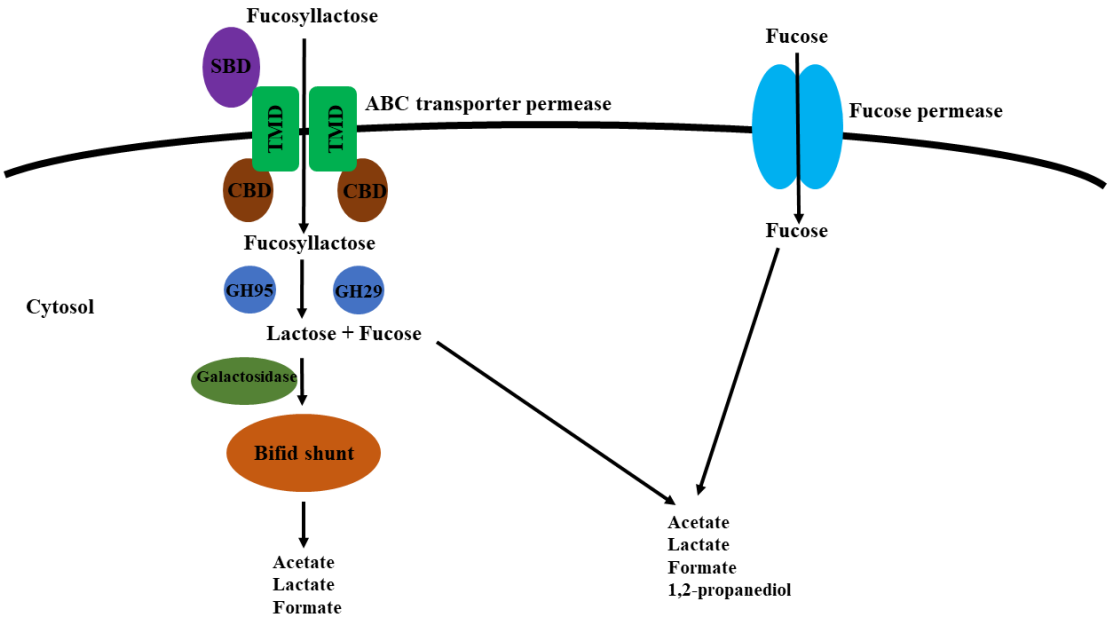

Fig. 4. Schematic representation of the fucose and fucosyllactose utilization system in *Bifidobacterium kashiwanohense* [62]. Fucosyllactose is incorporated into the cytoplasm by an ABC transporter permease with a sugar binding domain (SBD), transmembrane domain (TMD)

178 and an ATP-hydrolysing cytosolic domain (CBD). Once in the cytoplasm, a fucosidase (GH95
179 or GH29) and a β-galactosidase break the oligosaccharide into fucose, galactose and glucose,
180 which are then further channelled into the central carbohydrate metabolic pathways, i.e. the
181 bifid shunt, or in the case of fucose into a separate metabolic pathway. The monomer fucose is
182 imported into the cytoplasm by means of a fucose permease after which it enters the fucose
183 metabolic pathway [62].
184
185 *Bifidobacterium* is unique in using a specialized central metabolic carbohydrate route,
186 called the "bifid shunt", which employs a number of key enzymes, such as fructose-6-
187 phosphoketolase, being considered a key taxonomic marker for the Bifidobacteriaceae
188 family [61, 63, 64]. The bifid shunt is used by *Bifidobacterium* for the metabolism of
189 hexoses and pentoses, and theoretically can produce more ATP molecules per molecule
190 of glucose than alternative carbohydrate fermentation strategies used by lactic acid
191 bacteria or *Bacteroides* species [65]. This unique bifidobacterial pathway lacks the
192 enzymes aldolase, which is characteristic of glycolysis, and glucose-6-phosphate
193 dehydrogenase, typical of hexosemonophosphate pathways [61, 63, 64]. However,
194 monosaccharide fermentation in bifidobacteria is characterized by fructose-6-phosphate
195 phosphoketolase, from which the pathway obtained its name as the phosphoketolase
196 route or "bifid shunt" [61, 63, 64].
197
198 **2. Cereal β-glucans**
199 Cereals are the most common and widespread source of β-glucan in the human diet and
200 their chemical structures are usually described as homoglucopolysaccharides with a
201 backbone of single β(1,3)-bonds separating short sections of β(1,4)bonds [1, 2]. Due to
202 the large variety of existing cereals, we will focus our review on β-glucans isolated from
203 oat, barley and wheat.

One particular utilization locus was identified in *Bacteroides ovatus* ATCC 8483 (Bovatus_02740-Bovatus_02745) when this strain metabolizes barley-derived, mixed-linkage β-glucans (MLG, Fig. 5) [66, 67]. This locus encodes a GH16 *endo*-β-glucanase ($BoGH16_{MLG}$) which hydrolyses β(1,4)-linkages that are preceded by a β(1,3)-linked glucosyl residue, and a GH3 *exo*-β-glucosidase that digests the oligosaccharides released by $BoGH16_{MLG}$ to glucose. This PUL also encodes two Surface Glycan Binding Proteins (SGBPs), a $SusD_{MLG}$-like homolog and $BoSGBP_{MLG}$. The $SusD_{MLG}$-like homolog is essential for growth of *Bacteroides ovatus ATCC8483* on barley β-glucan because it incorporates the oligosaccharides originated by $BoGH16_{MLG}$ into the periplasm. In contrast, $BoSGBP_{MLG}$ is not essential for growth though it may assist in oligosaccharide scavenging. PULs homologous to the Bovatus_02740-Bovatus_02745 PUL of *Bacteroides ovatus* are present in the genomes of *Bacteroides xylanosolvens* XB1A and *Bacteroides uniformis* ATCC 8492, which highlights the apparent prevalence of PULs dedicated to β-glucan metabolism among *Bacteroides* species [66, 67].

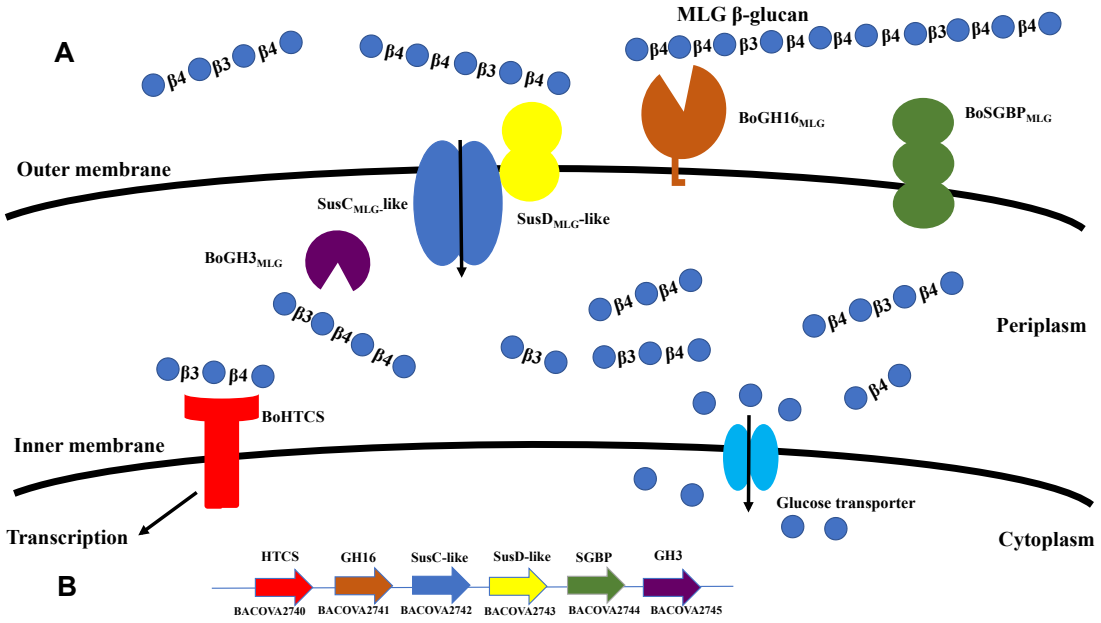

Fig. 5. A. Example of the mixed-linkage glycan (MLG) utilization locus in *Bacteroides ovatus* ATCC 8483 [67]. In a similar way to starch metabolism, mixed linkage β-glucan is first degraded outside the cell by a cell surface-associated GH16 ($BoGH16_{MLG}$), which generates oligosaccharides. The SusC/SusD-like pair incorporates these oligosaccharides into the periplasm, where a GH3 (β-glucosidase, $BoGH3_{MLG}$) degrades these internalized oligosaccharides into glucose monomers, which are then internalized into the cytoplasm. **B.** Genomic content of the MLG PUL in *Bacteroides ovatus* ATCC 8483 [66, 67].

2.1. Oat β-glucans

The effect of oat β-glucan ingestion has been shown to be associated with a modest increase in bacterial richness (yet decreasing the *Bacteroides* population) in both ileal effluent and faecal samples when compared with intake of cellulose or carboxymethylcellulose (Table 1) [68]. Also, the effect was viscosity-dependent, since low-viscosity oat β-glucan reduces the relative abundance of *Bacteroides* to a higher degree when compared to high-viscosity oat β-glucan. Moreover, the same decreasing

effect was observed in a similar study where oat β-glucan was compared with pectin, inulin and arabinoxylan (Table 1) [69].

However, in a subsequent study in BALB/c mice, oat β-glucan ingestion decreased bacterial biodiversity yet caused an increase in the relative abundance of the phylum Bacteroidetes compared with the control and with a mixture oat β-glucan-cellulose. In addition, *Bacteroides* was found as the dominant genus in the colon and it was associated with a higher concentration of beneficial short chain fatty acids (SCFAs), such as propionate and acetate (Table 1) [70]. The increase in *Bacteroides* populations was also reported by Carlson *et al.* using Oatwell (oat-bran containing 28% oat β-glucan, Table 1) [71].

Additionally, different studies have demonstrated the effect of oat β-glucans in *Bifidobacterium* (Table 2). Wu et al. found that *Bifidobacterium* content was decreased by the dietary supplementation with oat β-glucans [72]. Nevertheless, an *in vitro* fermentation study by Ji-lin et al. showed *Bifidobacterium longum* BB536 as a good degrader of raw and hydrolysed oat β-glucans hydrolysates, with preference for the hydrolysed fractions (Table 2) [73]. Another study concluded that the addition of β-glucan to yogurt increased survival of *Bifidobacterium longum* R0175 (Table 2) [74]. Furthermore, *Bifidobacterium* abundance was demonstrated to increase significantly in rats fed with oat whole meal or oat β-glucan compared with a control group, with rats exhibiting a higher growth rate when fed on pure oat β-glucan (Table 2) [75].

2.2. Barley β-glucans

Supplementation with barley β-glucan in rats with low or high-fat diet increased the production of SCFAs, reduced inflammation and cholesterol levels, and lowered the abundance of *Bacteroides fragilis* NCTC 9343 in the caecum (Table 1) [76]. Additionally, in a study with polypectomyced patients (patients having colorectal polyps), no significance difference was observed during a 90-day feeding intervention using 3 g/day of barley β-glucan. Nevertheless, two weeks after cessation of the treatment, the abundance of the genus *Bacteroides* was found to be significantly decreased (Table 1) [77]. A similar negative correlation was observed in hypercholesterolemic rats fed with a medium molecular weight (530 kDa) barley β-glucan diet (Table 1) [78]. However, the application of 3 g/day of this medium molecular weight barley β-glucan in hypercholesterolemic human patients increased the relative abundance of Bacteroidetes, while that of Firmicutes was decreased. Interestingly, no significant differences were observed when patients received 3 g/d or 5 g/d of low molecular weight barley β-glucan. These findings therefore suggest that the promoting effect of Bacteroidetes abundance by barley β-glucan is molecular weight-dependent (Table 1) [79]. In addition, *Bacteroides ovatus* ATCC 8483 prioritizes the use of barley β-glucan in a mixture with pectin, xyloglucan and arabinoxylan, being able to use this substrate when it was the only carbon source in the medium, with higher growth rates than *Bifidobacterium longum* subsp. *longum*, *Megasphaera elsdenii*, and *Ruminococcus gnavus*, but lower than *Veillonella parvula* (Table 1) [80].

In *Bifidobacterium*, the bifidogenic effect of barley β-glucan supplementation in food/feed has been described in various publications. For instance, Arora et al. discovered that C57BL/6 mice, when maintained on a high fat diet containing 10 % barley β-glucan during 8 weeks, showed a lower body weight gain and also an increase

in relative abundance of *Bifidobacterium* in both faecal and caecal samples (Table 2) [81]. Similar results were found in rats fed on a low fat diet supplemented with barley β-glucan for 25 days [76] and, in a similar way, in other murine trials (Table 2) [82].

2.3. Wheat β-glucans

In obese subjects with an unhealthy dietary behaviour, wheat β-glucan was correlated with a relative abundance increase in members belonging to the Bacteroidetes phylum and *Bacteroides* genus. It was also suggested that *Bacteroides* reduces the levels of inflammatory markers TNF-α and IL-6, and that it plays a role in reducing pathologies associated with inflammation (Table 1) [83]. In a similar study, *Bacteroides cellulosilyticus*, *Bacteroides ovatus* and *Bacteroides stercoris* were described as predominantly wheat-bran β-glucan degraders, while *Bacteroides uniformis*, *Bacteroides dorei* and *Bacteroides eggertii* were enriched in β-glucans derived from wheat-lumen, so apparently not all *Bacteroides* species exhibit the same glycan utilization behaviour (Table 1) [84]. The authors showed differences in the structure and composition of wheat bran and lumen, suggesting that these differences explain the different metabolic capabilities [84]. Nevertheless, the use of whole grains instead of extracted β-glucan requires further studies for wheat.

2.4. Mix of different cereals

A dietary intervention using 3 g/d of durum wheat flour and whole-grain barley pasta for 2 months did not reveal any significant differences in the microbiota composition of the subjects (Table 1) [85]. However, in another trial with wheat bran and barley in Japanese adults, a positive interaction was observed when both cereals were combined, causing an increase in relative abundance of the genus *Bacteroides* and other butyrate-

producing species (Table 1) [86]. Differences in the microbiota composition of distinct human populations as a result of varying diets and life styles may explain these apparently conflicting findings [87-89].

Regarding *Bifidobacterium*, Shen et al. carried out a comparative study of the prebiotic efficacy of oat and barley β-glucan in rats. The study resulted in an increase in *Bifidobacterium* abundance using either of these cereals, with a more pronounced effect for oat β-glucan [90].

3. Seaweed β-glucans

Seaweeds are potential prebiotics rich in three polysaccharides depending on the seaweed source, being either brown, green or red algae. In brown algae, fucoidan, alginate and laminarin have been shown to act as antioxidant, cognitive protective, anti-inflammatory, anti-angiogenic, anti-cancer, anti-viral, and anti-hyperglycemic agents, thus having very promising potential as a food additive and prebiotic [91, 92]. Laminarin (Fig. 1) is a glucose-based homopolysaccharide with a β(1,3) backbone and β(1,6) branches at a 3:1 ratio, being isolated from the brown algae species *Laminaria* and *Alaria*, representing almost a 50 % of algal dry matter. Laminarin is a type of β-glucan with special interest because of its proposed anticancer, antioxidant and immunomodulatory activities [93-95]. For instance, in a recent study, both native laminarin and its enzymatic digestion products inhibited cell transformation on SK-MEL-28 human melanoma and DLD-1 human colon cancer cells, where the maximum anticancer effect was shown to be correlated with a high level of branching [95].

Recently, a paper on β(1,3)-glucan metabolism by *Bacteroides* species, showed that *Bacteroides uniformis* ATCC 8492, *Bacteroides thetaiotaomicron* NLAE-zl-H207 and *Bacteroides fluxus* YIT 12057 have the ability to metabolize laminarin as a carbon source because of the defined PUL architecture where a GH158 is key in the release of oligosaccharides [96]. These authors described a putative β(1,3)-glucan utilization locus in *Bacteroides uniformis* ATCC 8492 (Fig. 6A and 6B, BACUNI_01484-BACUNI_01490) that encodes a TonB-dependent transporter (TBDT, SusC-like), two cell surface glycan-binding proteins (SusD-like and BuSGBP), three glycoside hydrolases (BuGH16, BuGH158 and BuGH3) and a hybrid two-component regulatory system (BuHTCS) (Fig. 6B). BuGH158 was described as a specific laminarinase, while BuGH16 was shown to be a broad-specificity *endo*-β(1,3)-glucanase with activity towards yeast β-glucan and mixed-linkage glucan from cereals. For its part, BuGH3 was described as a specific β(1,3) glucosidase which handles the hydrolysis products of BuGH158 and BuGH16. However, only BuSGBP was able to bind β-(1,3)-glucans (Fig. 6A). Despite the fact that homologous PULs active on β(1,3)-glucans have been detected in some species of *Bacteroides thetaiotaomicron* NLAE-zl-H207 and *Bacteroides fluxus* YIT 12057, the one described in *Bacteroides uniformis* ATCC 8492 was shown to be highly prevalent in the microbiome of humans, and unique with an ability to utilize three different types of β(1,3)-glucan, i.e. that from laminarin, curdlan and yeast.

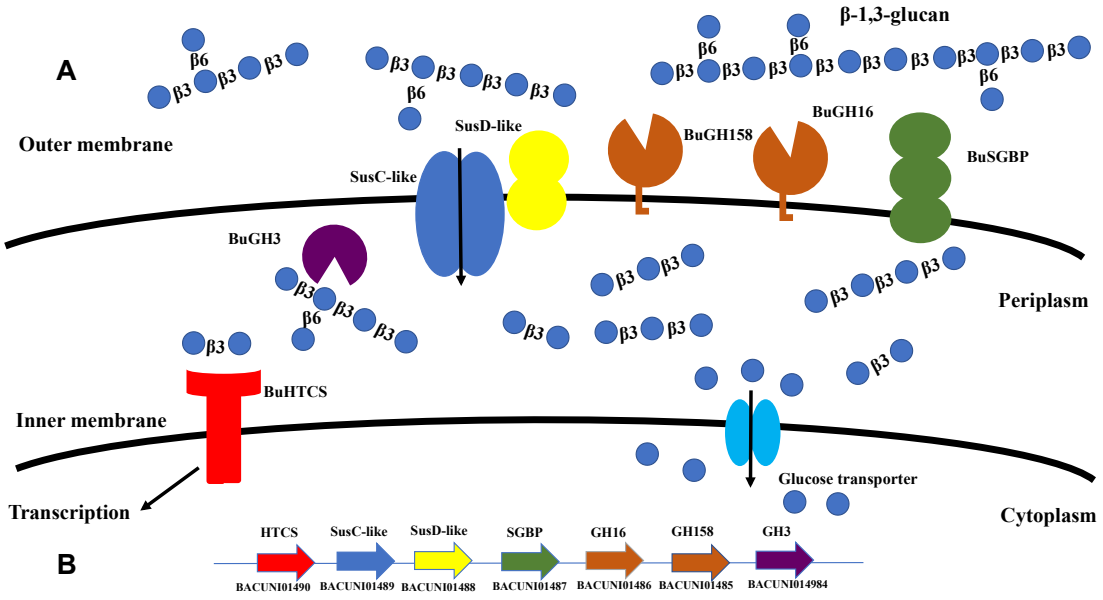

Fig. 6. A. Schematic representation of β(1,3)-glucan degradation by *Bacteroides uniformis* ATCC 8492 based in analogy with the starch utilization system [96]. **B.** Genomic content of the β(1,3)-glucan PUL in *Bacteroides uniformis* ATCC 8492 [96].

Although the main purpose of this review is the effect of β-glucans on selected elements of the HGM, laminarin has also been widely studied as a growth substrate for various marine *Bacteroides* species. An analysis of Bacteroidetes-fosmids from ocean regions showed that 4 out of 14 identified PULs were laminarin-specific, and were co-located with predicted β-glucosidase-encoding genes, thereby underscoring the role of laminarin as a common metabolic substrate for ocean-derived Bacteroidetes species [97].

At species level, the degradation of laminarin in the marine bacterium *Zobellia galactanivorans* has been described in different studies. Thomas et al. studied gene transcription in *Zobellia galactanivorans* Dsij^{T} when it grows on laminarin as its sole carbon source (Fig. 7) [98]. The authors determined that this marine polysaccharide induced the expression of the cluster ZOBELLIA_209 to ZOBELLIA_214, which is

predicted to encode two TonB-dependent receptors (ZOBELLIA_212 and ZOBELLIA _214) and their associated surface glycan-binding proteins (ZOBELLIA_211 and ZOBELLIA_213), respectively. These gene pairs are characteristic features of PUL clusters present in Bacteroidetes genomes [43]. In addition, this cluster encodes a predicted carbohydrate binding module family 4 (CBM4, ZOBELLIA_209), whose family has been characterized to bind to β(1,3)-glucan, β(1,3-1,4)-glucan, β(1,6)-glucan, xylan, and amorphous cellulose (CAZY database, http://www.cazy.org/; [99-102]). Therefore, this cluster is involved in the recognition, binding and incorporation of laminarin at the cellular surface of *Zobellia galactanivorans*, which has been used as a bacterial model to understand the algal carbon metabolism showing several adaptive treats to algal-associated life [103], representing a clear example for a genomic cluster dedicated to laminarin, Fig. 7.

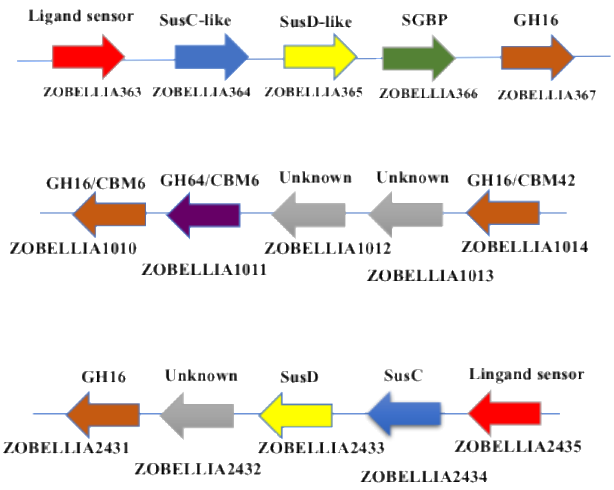

Fig. 7. Genomic composition of the laminarin PUL in *Zobellia galactinovorans* Dsij^T [103].

Another study showed that the incorporation of 2% of brown algae laminarin in feed for a rat trial decreased the relative abundance of the Bacteroidetes phylum in caecal

390 microbiota populations. Specifically, the ratio of identified clones, based on 16S rRNA
391 gene sequencing, of *Bacteroides capillosus* fell around 27 % compared to the control
392 (Table 1) [104]. By contrast, in a study with mice fed with a high fat diet as control and
393 comparing with a high fat + laminarin diet, the authors found that the diet without
394 laminarin led to an increase in Actinobacteria, whereas dietary supplementation with
395 laminarin witnessed an increase in the relative abundance of Bacteroidetes, especially
396 the genus *Bacteroides*, and a decrease in Firmicutes. Laminarin ingestion shifted the
397 microbiota at species level towards a higher energy metabolism, increasing the
398 *Bacteroides* species, and therefore increasing the number of carbohydrate active
399 enzymes. Laminarin also slowed weight gain in mice and decreased the bacterial
400 species diversity (Table 1) [105]. The same increase in Bacteroidetes/Firmicutes ratio
401 was observed in a recent study with albino mice (Table 1) [106] in which laminarin was
402 shown to be metabolized by *Bacteroides intestinalis* and *Bacteroides acidifaciens*,
403 producing succinate and acetate as end-products, which are precursors of the beneficial
404 short chain fatty acids (SCFAs) propionate and butyrate, respectively [107-109].

405

406 In contrast, several feeding studies have concluded that laminarin from *Laminaria*
407 *digitata* and *Laminaria hyperborea* does not affect the relative abundance of
408 *Bifidobacterium* in the gut microbiota [110, 111]. Nevertheless, Lynch et al. reported a
409 linear decrease in caecal *Bifidobacterium* in boars as a result of the addition of laminarin
410 from *Laminaria hyperborea* [112]. The above reports do highlight the need for further
411 in depth studies to thoroughly analyse the effect of laminarin on the HGM.

412

413 **4. Fungal β-glucans**

Fungal β-glucans are polymers composed of a β(1,6) or β(1,3) backbone, with a variable branching degree (Fig. 1). *Bacteroides* species have been reported as degraders of different types of fungal β-glucan. For example, when β-glucan from *Saccharomyces cerevisiae* (β-1,3-glucan with β-1,6-linked side chains) was administered to C57BL/6 mice, it was shown to cause a reduction in bacterial diversity, yet an increase in relative abundance of the phylum Bacteroidetes. This effect was accompanied with higher levels of SCFAs such as acetic, propionic and butyric acids [113]. Also, the positive correlation between an increase in Bacteroidetes and SCFA production was observed when mice with colorectal polyps were fed with a complex β-glucan-chitin complex (KytoZyme SA) [114].

As we stated in the seaweed β-glucan section, Dejean et al. showed the ability of certain *Bacteroides* species to metabolize β(1,3)-glucan from laminarin, yet also from yeast [96]. They showed that the same PUL was involved in the degradation of both of these β-glucan substrates (Fig. 6). In another study, β(1,3)-glucan from *Candida albicans* was shown to increase the relative abundance of the *Bacteroides* genus when mice were administered live or heat killed-*Candida* [115]. In addition, one particular PUL (BT3309-BT3314) from *Bacteroides thetaiotaomicron VPI-5182* has been associated with the degradation of fungal β(1,6)-glucan (pustulan, Fig. 8A and 8B), a common component of fungal cell walls of mushrooms and yeast [116]. BT3312 (GH30_3) represents an endo-β(1,6)-glucanase located at the cell surface accompanied by a SGBP (BT3313), a SusC-like (BT3310), a SusD-like (BT3311) and a β-glucosidase (GH3, BT3314). *Bacteroides thetaiotaomicron* employs a very efficient mechanism to fully metabolize pustulan as a carbon and energy source (Fig. 8A). The SGBP BT3313 binding protein starts the degradation process by recognising and binding the intact

polysaccharide at the cell surface of *Bacteroides thetaiotaomicron.* Following this, the BT3312 (GH30_3) enzyme cleaves the intact glycan into smaller glucooligosaccharides, which will then be internalized into the periplasm by the permease pair BT3310/BT3311 (SusC-like/SusD-like). In the periplasm, a GH3 enzyme (BT3314) will continue metabolism by degrading the internalized 1,6-glucooligosaccharides (Fig. 8A). BT3314 has been shown to exhibit a 30-fold higher activity for 1,6-glucobiose than for 1,3- or 1,4-glucobiose, and probably possesses two subsites into the active site, because of its similar activity on 1,6-glucobiose and 1,6-glucotriose [116]. The latter report postulated that the observed slow metabolism of 1,6-glucooligosaccharides in the periplasm of *Bacteroides thetaiotaomicron* may allow the persistence of a higher concentration of the "induced ligand" for BT3309 (HTCS or regulator of the PUL), enabling the locus to be up-regulated for an extended period of time for the use of pustulan as a carbon source by *Bacteroides thetaiotaomicron*. Comparative genome analysis with other species revealed that homologous PULs are located in the genomes of *Bacteroides uniformis* ATCC 8492, *Bacteroides ovatus* ATCC 8483 and *Bacteroides xylanosolvens* XB1A [116].

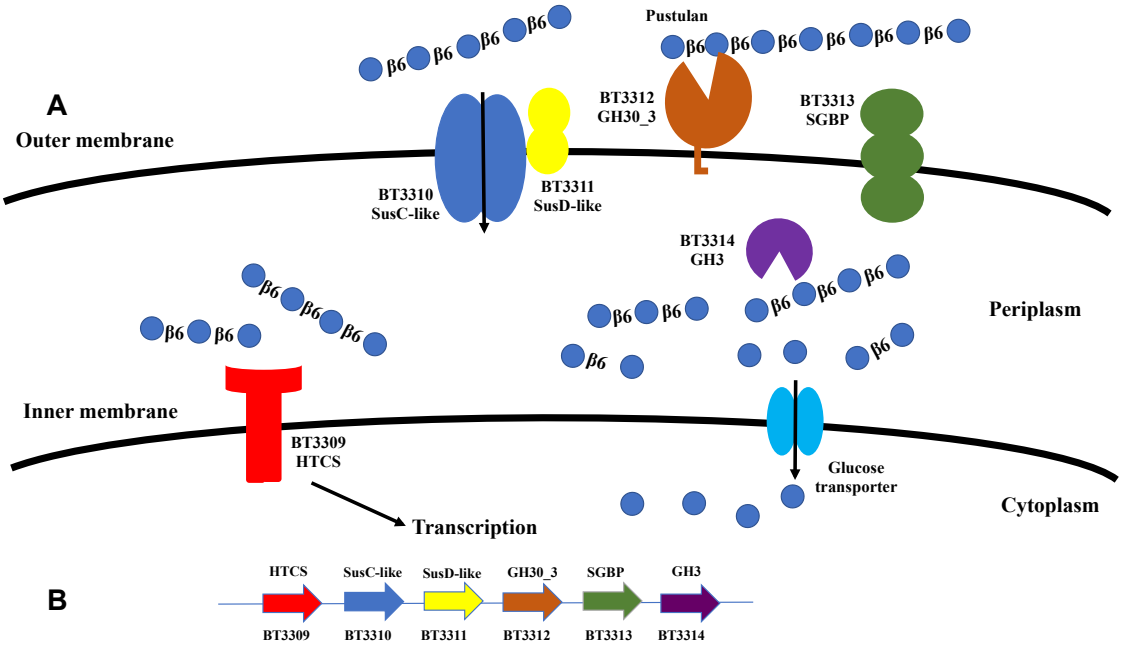

Fig. 8. A. Schematic of β-(1,6)-glucan (pustulan) degradation by *Bacteroides thetaiotaomicron* VPI-5482 [116]. This linear β-glucan is degraded by a GH30_3 in the surface of *Bacteroides thetaiotaomicron* and the resulted oligosaccharides are incorporated into the periplasm, where another GH3 (β-glucosidase) hydrolyses the smaller oligosaccharides into single glucose monomers. **B.** Genomic content of the pustulan PUL in *Bacteroides thetaiotaomicron* VPI-5482 [116].

Recent studies have addressed the role of fungal β-glucans in *Bifidobacterium.* For instance, Wang et al. studied the correlation between sulphated β-glucan from *Saccharomyces cerevisiae* and immune response [117]. Using immuno-suppressed chickens as a result of cyclophosphamide treatment, the addition of 0.4 g of yeast β-glucans per kilogram of chicken was shown to alleviate the immuno-suppression, affecting the concentration of cytokines and promoting the proliferation of *Bifidobacterium* [117]. Furthermore, supplementation with yeast β-glucans in Alzheimer-induced mice has been shown to cause an increase in the relative abundance of the genus *Bifidobacterium*, which was similar to that found in control mice [118]. Recently, in a macro study by Alessandri et al., the authors evaluated the growth ability of hundred bifidobacterial strains using glucan-chitin complex from *Aspergillus niger* as the only carbon source. All strains were shown to exhibit some, though mostly modest growth with *Bifidobacterium breve* and *Bifidobacterium bifidum* strains eliciting the highest levels of growth [119].

Zhao and Cheung showed that mushroom β-glucans elicit a prebiotic effect by enhancing growth of *Bifidobacterium longum* subsp. *infantis* [59]. These authors studied the proteomic profile of this catabolic process, showing that this bifidobacterial species expresses 17 proteins that may be linked to mushroom β-glucan degradation.

These proteins include ABC transporters of sugars, enolase and a phosphoenol phosphotransferase system. Among the 17 proteins, a predicted intracellular glucanase is highly expressed. The authors proposed a metabolic model for this degradation where (some parts of) the autoclaved polysaccharide (which is likely to cause hydrolysis of this glycan) is incorporated into the cytoplasm by ABC transport system and PTS (phosphotransferase system) proteins. After this incorporation, the intracellular glucanase breaks down the polysaccharide into glucose monomers, which are subsequently incorporated into the central fermentative pathway or "bifid shunt" [59].

Several papers have addressed the impact and metabolism of dietary plant glucosides, such as flavonoids and gingenosides, on bifidobacterial and *Bacteroides* metabolism [120-123]. However, very few studies have identified bifidobacterial β-glucosidases active on β-glucan. Pokusaeva et al. identified the *cldC* gene in *Bifidobacterium breve* UCC2003 to be involved in the metabolism of cellodextrins, which are β(1,4)-glucose hydrolysis products from cellulose (Fig. 1) [124]. The authors showed the ability of this bacterium to use cellobiose, cellotriose, cellotetraose and cellopentaose through the *cldEFGC* gene cluster with a higher preference for cellobiose. Disruption of the *cldC* gene resulted in the inability of *Bifidobacterium breve* UCC2003 to use these cellodextrins as a carbon source, confirming that this gene cluster is uniquely required for cellodextrin metabolism by this bacterium. It is reasonable to assume that these enzymes would be able to degrade MLG oligosaccharides in a similar way to cellodextrin oligosaccharides, though this hypothesis awaits experimental validation. Indeed, more studies are required to fully understand the impact of β-glucan oligosaccharide metabolism on proliferation of bifidobacterial species in the gut.

5. Conclusions

In this review we discussed recent publications that have studied the effect of β-glucans from different sources on microbiota changes pertaining to Bacteroidetes (mainly *Bacteroides* species) and *Bifidobacterium*. As previously reported, *Bacteroides* species possess an extensive ability for glycan degradation, due to the presence of PULs in their genomes [38, 39], allowing them to use different types of substrates and to occupy different niches and environments [31, 35, 36]. We have focussed our review on the most predominant types of β-glucans, clarifying the role of these polysaccharides as potential substrates for Bacteroidetes and *Bifidobacterium*, as important bacterial representatives of the adult gut microbiota [34]. Of a total of 16 studies involving fungal, seaweed and cereal β-glucans, 8 concluded that dietary inclusion of β-glucans causes an increase in the relative abundance of members of the Bacteroidetes phylum or *Bacteroides* genus, where some studies also highlight beneficial effects elicited by specific species (Table 1) [84, 106]. Nevertheless, 7 studies (6 with β-glucans from cereals and 1 from seaweed) revealed the opposite results, a negative effect on the relative abundance of Bacteroidetes or *Bacteroides*, and only one reported a 'no effect' conclusion (Table 1). The most significant disparity was found for cereal β-glucans [86]. In oat β-glucans, we found a similar number of studies with positive or negative correlations on the Bacteroidetes increase. In addition, for barley β-glucans, the number of studies published showing negative conclusions was higher than the published with positive correlations.

One would imagine that the same substrate should have equal consequences for a specific bacterial genus, so the variation in the results may be due to the utilization of different models, substrates and/or methodologies (Table 1) [79]. The results may differ

in a molecular weight-dependent manner even when using the same substrate. Furthermore, the utilization of different model systems (pigs, rats, mice or humans) is likely to play an important role in this variation, because of the distinct microbiota composition in each of these mammalian species (Table 1) [77-79, 82]. While it seems that the positive effects are very clear for fungal and seaweed β-glucans [88, 101, 102], the differences observed between the three types of β-glucans must be tested in more detail and further studies should be done for the three sources in order to clarify if the observed disparity in the experimental results is caused by the application of non-unique procedures, or, by contrast, if these correlations between the substrates and the degraders remain stable [77-79, 99-102]. Due to the increasing interest in β-glucans as potential prebiotics and their effect on human health, this work provides further avenues to understand the behaviour of β-glucan-fed HGM.

Very little is currently known about the molecular mechanism how *Bifidobacterium* degrade different β-glucan types. Only a small number of papers have established the prebiotic effect of cereal and fungal β-glucans, both through *in vitro* fermentations and by means of human trials. Strains from *Bifidobacterium breve*, *Bifidobacterium bifidum* and *Bifidobacterium longum* have been shown to be able to at least partially degrade fungal β-glucan-chitin complex [119]. These authors showed the transcriptional profile of *Bifidobacterium breve* 2L when using this complex substrate as a unique carbon source. Due to the complexity of β-glucan-chitin, the authors expect that other bacterial members of the gut microbiota community are involved in the complete metabolism of β-glucan-chitin through syntrophic interactions [119].

More mechanistic studies are needed to understand the size of oligosaccharides incorporated by bifidobacterial transporters. In addition, detailed structural mechanistic insights and substrate specificity studies of glucosidases and glucanases in *Bifidobacterium* species, when they act on several types of β-glucan, are required to expand our knowledge on the direct or indirect (through cross-feeding) use of these glycans as prebiotics. Finally, there is a clear knowledge gap regarding the cross-feeding process between different members of *Bacteroides* and *Bifidobacterium* and further studies are needed to shed light on the molecular details of such syntrophic interactions, a good example of this being the cross-feeding interactions involving dietary arabinogalactan [46]. Such studies will allow the rational design of nutraceutical strategies with the help of particular β-glucans as functional food ingredients, perhaps in combination with certain bifidobacterial species in so-called synbiotic formulations.

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Conflict of interest

The authors declare no conflict of interests.

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TABLE 1. Carbohydrate intake and intervention parameters for the intervention trials with *Bacteroides* genus influences.

Reference	Type of β-glucan	Duration	Organism	Analized parameters	Main Outcomes
[68]	Oat β-glucan	17 days	8 cross-bred Duroc-Landrace pigs	Bacterial populations, SCFAs levels	Oat β-glucan ingestion was associated with a reduction in *Bacteroides*
[69]	Oat β-glucan	12 hours of incubation	15 healthy humans	Bacterial populations, BCFAs and SCFAs fermentation	Oat β-glucan ingestion was associated with a reduction in *Bacteroides* and *Bifidobacterium*
[70]	Oat β-glucan	8 weeks	28 health male BALB/c mice,	Bacterial populations, SCFAs production, feed intake, body weight gain	Oat β-glucan decreased the bacterial biodiversity yet increased the relative abundance of the phylum Bacteroidetes. *Bacteroides* was found as the predominant genus in the colon and it was associated with a higher concentration of beneficial short chain fatty acids (SCFAs), such as propionate and acetate
[71]	Oatwell (28% oat β-glucan)	24 hours of incubation	3 healthy humans	Bacterial populations, SCFAs production	Oatwell was related to higher *Bacteroides* abundance and propionate concentration
[76]	Barley β-glucan	25 days	8 groups of 7 male Wistar rats	Bacterial populations, SCFAs production, feed intake, body gain, amino acid production, cholesterol levels	Barley β-glucan increased the production of SCFAs, reduced inflammation and cholesterol levels, and lowered the abundance of *Bacteroides fragilis* in the caecum
[77]	Barley β-glucan (125 g/day of bread with 3 g of barley β-glucan)	3 months	20 polictemized human patients	Bacterial populations, SCFAs concentration	No significance difference during the intervention. Nevertheless, two weeks after cessation of the treatment, *Bacteroides* genus was found significantly decreased
[78]	Low and medium molecular weight barley β-glucan	39 days	48 male Wistar rats	Bacterial populations, SCFAs concentration, Feed intake, body gain, plasma lipid	The ratio *Bacteroides/Prevotella* was reduced by low and medium molecular weight barley β-glucan

				levels	
[79]	Low and high molecular weight barley β-glucan	35 days	30 human subjects	Bacterial populations, CVD risk factors	High molecular weight barley β-glucan can significantly increase *Bacteroides* and reduce CVD risk
[80]	Barley β-glucan extracted from Glucagel™ and arabinoxylan, xyloglucan, glucan, and pectin.	48 hours of incubation	*Bacteroides ovatus* ATCC 8483T310 , *Bifidobacterium longum* subspecies *longum* ATCC 15707T, *Megasphaera elsdenii* DSM 20460T311 , *Ruminococcus gnavus* ATCC 29149T, and *Veillonella parvula* DSM 2008T	Bacterial growth	*Bacteroides ovatus* ATCC 8483T310 prioritizes the use of barley β-glucan before the other substrates, with higher growth rates than the other studies species except *Veillonella parvula*.
[83]	Whole wheat grains	8 weeks	68 human subjects	Bacterial populations, phenolic compounds levels glycaemia, plasma lipids, inflammatory markers and	Wheat β-glucan was correlated with an increase in Bacteroidetes phylum and *Bacteroides* genus. *Bacteroides* could reduce inflammatory markers TNF-α and IL-6 and plays a role in reducing pathologies associated with inflammation
[84]	Whole wheat grains	48 hours of incubation	10 health humans	Bacterial populations,	*Bacteroides cellulosilyticus, Bacteroides ovatus* and *Bacteroides stercoris* were described as predominantly wheat-bran β-glucan degraders, while *Bacteroides uniformis, Bacteroides dorei and Bacteroides eggertii* were enriched in the β-glucans from wheat-lumen, so not all *Bacteroides* present the same feed-responsive behaviour
[85]	durum wheat flour and whole-grain barley pasta	2 months	26 healthy humans	Bacterial populations, blood cholesterol, amino acid concentration, SCFAs levels	No clear change in the microbiota composition. Increase in 2-methyl-propanoic acid, acetic acid, butanoic

					(butyric) acid, and propanoic (propionic) acid
[86]	wheat bran and BarleyMax	4 weeks	60 healthy humans	Dietary Intake, Biochemical Analysis, Microbiota Composition, SCFA levels	Increase in *Bacteroides* genus, Higher SCFAs concentrations, especially butyric acid
[104]	Laminaran	2 weeks	18 male Wistar rats	Microbiota composition, body weight, carbohydrate levels, organic acids levels	Reduction in Bacteroidetes abundance. Laminaran also can reduce the levels of cecal putrefaction substances levels
[105]	Laminaran	6 weeks	18 female BALB/c mice	Bacterial population, carbohydrate active enzymes activity, body weight	Increase in relative abundance of Bacteroidetes phylum, especially the genus *Bacteroides*, and a decrease in the Firmicutes phylum. Laminarin ingestion shifted the microbiota at the species level towards a higher energy metabolism, and therefore increasing the number of carbohydrate active enzymes. Laminarin also slowed weight gain in mice and decreased the bacterial species diversity.
[106]	Laminaran	11-13 days	18 male ICR mice	Bacterial populations	*Bacteroides intestinalis* and *Bacteroides acidifaciens*, producing succinate and acetate, which are precursors of beneficial propionate and butyrate

TABLE 2. Carbohydrate intake and intervention parameters for the intervention trials with *Bifidobacterium* genus influences.

Reference	Type of β-glucan	Duration	Organism	Analized parameters	Main Outcomes
[72]	Oat β-glucan	25 days	32 weaned pigs	Bacterial populations, body weight, serum parameters	Oat β-glucan supplementation decreased *Bifidobacterium*
[73]	Oat β-glucan and its hydrolysates	1 week	3 male Sprague-Dawley rats	SCFA production, bacterial growth of different faecal microbiota	No significant differences with intact oat β-glucan However, the oat β-glucan hydrolysates OGH treatment evidently promoted the growth of *Bifidobacterium longum* BB536. The hydrolysates of oat *β*-glucan produced greater amounts of SCFA (mainly acetate, propionate and butyrate) with no significant difference in SCFA pattern when compared with oat *β*-glucan.
[74]	Oat β-glucan	35 days	Pure strains of *Bifidobacterium breve* R0070, *Bifidobacterium longum* R0175	Bacterial growth	These data indicate that the addition of beta-glucan to yogurt increased survival of *Bifidobacterium longum* R0175
[75]	Oat β-glucan	4 weeks	30 male SD rats	Food Intake, body Weight, ATPase activity, bacterial population	Oat β-glucan decreased glycaemia and insulin response while it increased ATPase activity and *Bifidobacterium* relative abundance
[81]	Glucagel™ (80% barley derived β-glucan)	8 weeks	36 C57BL/6 male mice	Body weight, food intake, tissue weights and adiposity Data, Gut microflora composition and SCFAs	Barley β-glucan attenuate weight gain and increase relative abundance of *Bifidobacterium* both in faeces and caecal contents over the 8 weeks of dietary intervention
[76]	Barley β-glucan	25 days	56 male Wistar rats	Cecal microbiota, SCFAs levels, cholesterol, TAG and inflammatory levels, feed intake, weight gain, caecal content, pH, tissue weight	Barley β-glucan was related with an increase in the abundance of *Bifidobacterium* and SCFA levels and a reduction in cholesterol levels and inflammatory markers
[82]	Barley β-glucan	8-12 weeks	male C57BL/6J mice (amount not given)	Bacterial populations, SCFAs production	Barley β-glucan suppressed appetite and improved insulin sensitivity. Furthermore, barley β-glucan increased the relative abundance of the genus *Bifidobacterium* and SCFA production