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Nutritional interest of dietary fiber and prebiotics in obesity: Lessons from the MyNewGut consortium

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SUMMARY

The aim of EU project MyNewGut is to contribute to future public health-related recommendations supported by new insight in gut microbiome and nutrition-host relationship. In this Opinion Paper, we first revisit the concept of dietary fiber, taking into account their interaction with the gut microbiota. This paper also summarizes the main effects of dietary fibers with prebiotic properties in intervention studies in humans, with a particular emphasis on the effects of arabinoxylans and arabinoxylo-oligosaccharides on metabolic alterations associated with obesity. Based on the existing state of the art and future developments, we elaborate the steps required to propose dietary guidelines related to dietary fibers, taking into account their interaction with the gut microbiota.

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1. Introduction

One of the goals of the MyNewGut consortium is to generate scientific knowledge that helps to take into account microbiota-nutrients interactions to establish dietary recommendations as part of healthy lifestyles. Within this framework, the MyNewGut consortium has recently worked on a set of Opinion Papers founded on the project results and the latest advances in the field [1].

Regarding the role of dietary fiber (DF), recent reviews outline the benefits of ancestral diets and high fiber diets to maintain a rich and diverse gut microbiome and related health benefits [2]. In light of those data, some studies propose that DF intake would at least reach 50 g/day, whereas the current recommendations are around 30 g per day in the adult [3]. Despite the common characteristic of being non-digestible in the human small intestine, the DF is widely different in composition, structure and the way they are feeding the bacteria haboring the gut microbiota. Therefore, this Opinion Paper focuses on the results of studies performed with prebiotic fibers studied in the MyNewGut project—namely arabinoxyl-o-oligosaccharides (AXOS)—and outlines recommendations for an in-depth understanding of gut microbiota-fiber interactions in health and diseases. This is preceded by an outline of recent developments in the definition of DF, including the approval by authorities of health benefits of added fiber ingredients in foods, as well as criteria to be taken into account when evaluating the health effect of DF.

2. Background: the concept of dietary fiber

Over the years, the definition of DF, analytical methods and their effects on health and disease have been widely discussed. As indicated in the recent review by Stephen et al., a fair degree of uniformity currently exists in the definition of fiber, the method

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used for analysis and the recommended amounts for consumption [4]. Gut microbiota related health benefits are not yet included in the current dietary and public health recommendations but, as indicated in this Opinion Paper, significant advances have been made to have clarifications about the physiological effects of DF to be taken into account for future recommendations [5,6].

The definition issued after the Codex Alimentarius in 2008 has a fair degree of uniformity [4,7]. DF is made up of carbohydrate polymers with three or more monomeric units (MU), which are neither digested nor absorbed in the human intestine and includes: (i) non-starch polysaccharides (NSP) from fruits, vegetables, cereals and tubers whether intrinsic or extracted, chemically, physically and/or enzymatically modified or synthetic (MU ≥ 10); (ii) resistant oligosaccharides (RO) (MU 3–9); and (iii) resistant starch (RS) (MU ≥ 10). The Codex definition includes polymers with at least 10 monomeric units (MU) but leaves to national authorities the decision on whether or not to include carbohydrates with an MU number of 3–9. The European Union (EU) and other countries with an own fiber definition, e.g. the USA, Canada, China, Australia/New Zealand and, Japan include carbohydrates with MU ≥ 3 [4–6]. When extracted, chemically, physically and/or enzymatically modified or synthetic, generally accepted scientific evidence of benefits for health must be demonstrated to consider the polymer as DF. Most definitions also include ‘associated substances’, which are non-carbohydrate such as lignin and substances, which are present in cell walls linked to polysaccharides and quantified as DF by the accepted analytical methods.

These views are reflected in dietary recommendations worldwide, where only consumption of DF naturally present in food is emphasized, whereas there’s still no reference to added, non-digested carbohydrate polymers, due to the limited body of evidence of benefits to health of these fibers. For instance, the European Food Safety Authority (EFSA), the United States Food & Drug Administration (FDA), and Health Canada approved health claims for a limited number of DF, including both some of the naturally present fibers and some added fibers, indicating that the criteria for approval of a health claim are considerably more strict than the criteria for getting approval as DF as was recently obtained in the USA and Canada for a wide range of added fibers.

Regarding the benefits for health, Codex states that DF generally present one or more of the following properties: (i) decrease intestinal transit time, increase stools bulk; (ii) fermentation by colonic microbiota; (iii) reduce blood total and/or LDL cholesterol levels; and (iv) reduce post-prandial blood glucose and/or insulin levels. These, or similar criteria, were included in the EU Directive 2008/100/EC and applied, in recent years, for evaluating the benefits to health of a wide range of fiber ingredients by Health Canada’s Food Directorate [6,8] and the FDA [5]. Both, Health Canada and the FDA concluded that, for most current commercially available DF, sufficient scientific evidence is available for including them in the list of compounds that can be officially considered as DF. The approved fibers include: (i) NSP including cellulose, hemicelluloses (i.e., arabinoxylans (AX)), mannans, pectins, and other hydrocolloids (i.e., gums, mucilages, β-glucans), inulin and fructans; (ii) RO including fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS); and (iii) RS [4]. Probably the list of approved fibers will grow further when studies provide evidence for new health benefits.

Regarding the role of colonic fermentation in attributing health benefits to fiber, there are some differences among countries. Health Canada requires “providing energy-yielding metabolites through colonic fermentation” emphasizing the production of short-chain fatty acids (SCFA). While colonic fermentation is not currently a physiological effect of fibers approved by FDA, fermentation-related criteria that apply are (i) “increasing mineral absorption” associated to the increased solubility and bioavailability through the production of SCFA, and (ii) “reducing energy intake” related to colonic fermentation of fibers. However, still, some discrepancies exist concerning the real contribution of SCFA as energy providers and/or as regulators of energy homeostasis. For each approved fiber, the primary benefit of health must be proven. In this sense, the fermentation-related criteria were chosen as primary end-points for a range of oligosaccharic fibers, such as FOS (including inulins), GOS and other resistant oligosaccharides (i.e., isomalt-oligosaccharides, resistant maltodextrins, poly-dextrose). In EU, the evaluation is different, and the recognition of DF is case by case performed based on analytical criteria, through the widely accepted AOAC2009.01 standard method, or a similar approved method (taking into account the Codex definition and the EU definition with the MU ≥ 3). Nutrition facts information related to DF can then be put on product labels.

Contrary to the still widely accepted view that soluble fibers are fermentable and insoluble fibers are non-fermentable, almost all types of DF are fermentable, entirely or to some degree [4]. The difference is that some fibers are rapidly fermented by the colonic microbiota, whereas others are fermented more slowly, and in some instances to a limited extent. Although a classification according to the fermentability is difficult to establish since the evaluation has not been performed systematically for all DF, a few broad statements can be made. Soluble RO (but not viscous) are highly fermentable in the colon. Among insoluble NSP, the fermentability varies depending on the cereal and the tissue of the cell wall from which it is extracted. For instance, in maize, the bran is very poorly degraded compared to wheat bran [9]. At the same time...
time, within the wheat bran the fermentability is also different on
the different tissues that constitute it and the milling settings [10].
In the aleurone layer, which represents approximately 40–50% of
the wheat bran, there are AX and β-glucan [11]. These are well
degraded when exposed to in vitro fermentation; however, other
tissues also composing the wheat bran are not fermented
although they contain a large amount of AX, cellulose, and lignins
[12,13].

3. Dietary fibers with prebiotic properties

The term prebiotic, first introduced by Gibson & Roberfroid
(1995) was initially defined as “a non-digestible food ingredient
that beneficially affects the host by selectively stimulating the
growth and/or activity of one or a limited number of bacteria in the
colon, and thus improves host health” [14]. Tempting to classify
microorganisms as beneficial or detrimental is complicated since
the invasive or pathogenic properties of the bacteria depend on the
whole microbial ecosystem and host gut homeostasis. In 2015, it
was proposed an extension to the term prebiotic to “non-digestible
compounds that, through their metabolism by microorganisms in
the gut, modulate the composition and/or activity of the gut
microbiota, thus, conferring a beneficial physiological effect on the
host” [15]. In 2017, the International Scientific Association for Pro-
biotics and Prebiotics (ISAPP) panel lastly updated the de-

definition of a prebiotic as a “substrate that is selectively utilized by host mi-
croorganisms conferring a health benefit” [16]. This definition ex-

pands the concept of prebiotics to possibly include non-
carbohydrate substances, applications to body sites other than
the gastrointestinal tract, and diverse categories other than food.
The requirement for selective microbiota-mediated mechanisms
was retained and, beneficial health effects must be documented for
a substance to be considered a prebiotic.

Next, we summarize the main reported effects of some pre-
biotics in intervention studies in humans. Note that currently and
mostly for historical reasons, the majority of the scientific data
related to prebiotic effects have been obtained using food ingredi-
ents/supplements belonging to the chemical groups known as
inulin-type fructans (ITF) and GOS [14,17–20]. Besides, for the last
10 years, additional data have been obtained concerning the po-
tential of other DF to modulate the gut microbiome. One example is
the AX extracted from wheat bran and the hydrolysis product of AX
so-called AXOS. The latter was the compound chosen by the
MyNewGut consortium to explore its prebiotic properties as a po-
tential intervention strategy to combat obesity. Consequently, the
effects of AX and AXOS in the context of obesity are discussed in
more detail throughout this Opinion Paper.

3.1. Inulin-type fructans (ITF)

ITF are oligomers or polymers of fructose whose schematic
representation appears in Fig. 1A. ITF are present in various vege-
tables, but can also be isolated from non-edible plant sources
(like chicory roots) or synthesized from saccharose. Fructans have
repeatedly demonstrated the capacity to selectively stimulate
certain bacteria like Bifidobacteria, and besides, new analytical
tools allow to demonstrate that additional changes in microbiota
occur when feeding oligosaccharides. The ITF feeding provide
changes in microbiota that can be related to changes in biomarkers
related to health. For example, double-blind, randomized, cross-
over intervention showed that the treatment with ITF, but not
the placebo, caused an increase in Bifidobacterium spp. and Faec-

callibacterium prausnitzii, and that both bacteria were negatively
correlated with the seric levels of lipopolysaccharide (LPS) [21]. A
more recent study assessed in healthy subjects the effect of ITF
supplementation throughout a double-blind, randomized, cross-

![Fig. 1. Schematic representation of the structure of A) inulin-type fructans, B) galacto-oligosaccharides (GOS), C) resistant dextrin, and D) arabinoxylans (Note that p-coumaric acid
is present only in stems of grasses, not in grain).]
over intervention combining ecosystem-wide microbiome and metabolome profiling techniques [22]. This study demonstrated that the effect of ITF supplementation on the fecal microbiota is mainly restricted to changes in *Anaerostipes, Bilophila* and, *Bifidobacterium* and concluding that ITF quite selectively influences the growth of a limited number of gut bacteria [22]. Furthermore, these authors found first indications that the observed reduction in *Bilophila*, a genus containing known pathobionts, is associated with enhanced host well-being assessed by physical discomfort and treatment satisfaction scores [22]; A second study, also published in 2017, described the beneficial effects of oligofructose-enriched inulin in children with overweight or obesity [23]. This study is relevant for public health since excess weight in childhood tends to persist into adulthood and is an early risk factor for obesity-associated morbidity and mortality [24]. Oligofructose-enriched inulin increased *Bifidobacterium* spp. numbers and significantly reduced body weight z-score, percent body fat, and serum level of interleukin (IL)-6 in children with overweight or obesity [23].

### 3.2. Galacto-oligosaccharides (GOS)

GOS are β-galactosides (terminal glucose and remaining galactose units linked together by β-glicosidic bonds) or α-galactosides, such as raffinose (trisaccharide), stachyose (tetrasaccharide), and verbascose (pentasaccharide) (Fig. 1B). Even though there are many studies related to human milk oligosaccharides (HMOs) and their influence in the infant health [25], still is limited the number of studies reporting beneficial metabolic effects of GOS in the adult population. The available evidence shows, for example, that the supplementation with a GOS to healthy elderly volunteers decreased systemic and fecal pro-inflammatory markers associated with increases in *Bifidobacterium* spp., *Lactobacillus-Enterococcus* spp, and the *C. coccoides—E. rectale* group numbers, together with reductions in *Bacteroides* spp., *E. coli*, and *Desulfovibrio* spp. [26]. Another intervention study, but in this case enrolling overweight participants, showed that the supplementation with GOS improved insulin and lipid homeostasis and attenuated low-grade systemic inflammation [27]. In contrast, a more recent study in overweight or obese prediabetic subjects confirmed that the supplementation of GOS increased *Bifidobacterium* spp. abundance, as previously reported in healthy elderly volunteers, but was not associated with significant changes in insulin sensitivity or metabolic parameters [28].

#### 3.3. Resistant dextrin

Wheat dextrin is a soluble fiber widely being used in the food industry because of its low viscosity and good consistency when added to water, beverages or soft food. Wheat dextrin is a glucose polymer derived from wheat or maize starch and formed by heating a polymer derived from wheat or maize starch and formed by heating at high temperature followed by enzymatic (amylace) treatment to form a resistant starch (Fig. 1C). One study comparing the *in vitro* fermentability of wheat dextrin with that of inulin showed that wheat dextrin exhibited a unique fermentation pattern and produced total SCFA concentrations similar to inulin [29]. Several *in vitro* and *in vivo* studies (in rats and humans) have been undertaken to explore the potential prebiotic effects of wheat dextrin. Resistant dextrin has shown to increase lactobacilli and bifidobacteria, and reduce *Clostridium perfringens* when administered to healthy volunteers [30]. In another study with 40 female subjects, resistant dextrin supplementation not only increased Bacteroides, the predominant beneficial saccharolytic genus of a “normal” gut microbiota, but also decreased the numbers of pathogenic bacteria [31]. Interestingly, resistant dextrin supplementation can also modulate inflammation and improve insulin resistance in women with type 2 diabetes [32]. However, additional studies are needed to determine whether the effect of resistant dextrin on the improvement in glucose homeostasis is linked to gut microbiota modulation.

### 3.4. Arabinoxylans (AX)

AX consists of a linear chain of residues of xylose to which units of arabinoses can be linked and whose degree of substitution is described as A/X ratio (Fig. 1D) [33], Besides, in grain, ferulic acid can be attached to AX, whereas in stems of grasses, but not in grain, the bond of p-coumaric acid to AX has been also documented [34], As explained above, aleurone is part of the bran. About 25% of AX are found in the starchy endosperm, 25% in aleurone and the remaining 50% are found in the other outer tissues of the grain [35]. Most AX in wheat bran are water-insoluble because of ferulic acid residues establishing crosslinks between AX and adjacent units of lignin [36]. AX are selectively degraded in the colon by intestinal bacteria expressing xylanases and arabinofuranosidases and represent a new class of prebiotics [37–39]. Until now, only a few studies investigated whether wheat-derived AX could have beneficial effects on host health (by modulation of the intestinal microbiota). Using two distinct *in vitro* models for the human gut, Van den Abbeel et al. have shown that a specific concentrate of water-extractable long chain AX and the well-established prebiotic inulin may be complementary as they both induced specific fermentation patterns within the intestinal microbiota with specific potential health benefits [40]. While AX specifically increased *Bifidobacterium longum* and propionate production, inulin increased *Bifidobacterium adolescentis* (among other bifidobacteria) and butyrate levels. Future research should establish how widespread these specific microbial responses to AX and ITF in human subjects. They suggest that AX seem to fulfill the requirements to be considered a promising prebiotic compound and that they might confer beneficial health effects through gut microbiota modulation, potentially in a more specific and potent manner as compared to inulin [40]. AXOS are hydrolysis products of AX and are characterized by their lower average degree of polymerization and their average degree of arabinose substitution [36,41]. Because of pre-hydrolysis, they are highly soluble and rapidly fermentable as shown in *in vitro* experiments [42]. Many interventions studies with humans, enrolling healthy subjects or subjects with overweight or metabolic syndrome, have assessed the effects of wheat-derived AX or AXOS on metabolic parameters [43–56] (Table 1). The most consistent observation across studies is related to an improvement in the glucose homeostasis. For instance, one study in healthy young adults showed that white bread enriched with a high content of AXOS (18.4 g) has the potential to beneficially influence overnight glycemic regulation and gut fermentation (measured as the increase in breath H2 and circulating SCFA) [55]. The latter observation was in agreement with another previous study that reported the same effect, but in which the prebiotic potential of AXOS was not linked to the host metabolism [57]. Additional studies are needed to determine whether the effect of wheat-derived AX or AXOS improvement in glucose homeostasis is linked to gut microbiota modulation. With this aim, the influence of AXOS-rich wheat bran extract (WBE) in overweight individuals on gut microbiota and metabolic risk markers has been studied by the MyNewGut consortium in a randomized cross-over trial (NCT02215343). This study is the first analyzing the effects of AXOS intake on gut microbiota composition by 16S rRNA sequencing in human. The main results demonstrated that AXOS exhibit the characteristic bifidogenic effect and promote the increase of a wide variety of butyrate producers [58].
Table 1
Summary of the intervention studies performed in humans with arabinoxylans (AX) and arabinoxyl-o-oligosaccharides (AXOS) reporting effects on metabolic parameters.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Fiber treatment</th>
<th>Placebo treatment</th>
<th>Dose</th>
<th>Time</th>
<th>Study population</th>
<th>Size, n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[43]</td>
<td>Single blind</td>
<td>Bread with low or high AX-rich fiber content</td>
<td>Control bread without AXs-rich fiber</td>
<td>0.6 or 12 g</td>
<td>3 d</td>
<td>Healthy individuals (5 men and 9 women)</td>
<td>14</td>
<td>↓ postprandial glycaemia, improvement in the insulin response</td>
</tr>
<tr>
<td>[44]</td>
<td>Cross-over</td>
<td>AX-bread and muffins</td>
<td>Bread and muffins non supplemented</td>
<td>14–17 g</td>
<td>5 wk</td>
<td>Type 2 diabetes patients (6 male, 9 female)</td>
<td>15</td>
<td>↓ fasting glycaemia, ↓ glycaemia and insulinaemia 2 h post OGTT</td>
</tr>
<tr>
<td>[45]</td>
<td>Cross-over</td>
<td>Bread rolls with AX</td>
<td>Bread rolls non supplemented</td>
<td>6 g</td>
<td>Acute</td>
<td>Healthy individuals (6 men and 9 women)</td>
<td>15</td>
<td>↓ postprandial glycaemia, ↓ postprandial insulinaemia</td>
</tr>
<tr>
<td>[46,47]</td>
<td>Single blind, cross-over</td>
<td>Bread rolls with AX, and AX in powder</td>
<td>Isocaloric bread rolls and powder without AX</td>
<td>15 g</td>
<td>6 wk</td>
<td>Overweight individuals with insulin resistance (4 men and 7 women)</td>
<td>11</td>
<td>↓ fasting glycaemia, ↓ TG ↓ apolipoprotein A-1 ↓ insulin, adiponectin, leptin. After a liquid meal challenge test: ↓ postprandial glycaemia, ↓ insulina, ↓ TG, ↓ total plasma ghrelin ↓ Bifidobacteria ↓ urinary p-cresol excretion —total cholesterol, HDL, LDL, and TG</td>
</tr>
<tr>
<td>[48]</td>
<td>Cross-over</td>
<td>Crude AXOS</td>
<td>Maltodextrin</td>
<td>10 g</td>
<td>3 wk</td>
<td>Healthy individuals (6 men and 14 women)</td>
<td>20</td>
<td>↓ fasting glycaemia, ↓ fasting insulinaemia (2.2 g vs control), ↓ Bifidobacteria, ↓ butyric acid —total bacteria, Bacteroides, Lactobacillus spp., —C. coccoides, Clostridium clusters I and II, F. prausnitzii, ↑ Bifidobacteria, ↑ SCFA —total cholesterol, HDL, LDL, and TG</td>
</tr>
<tr>
<td>[49]</td>
<td>Double blind, cross-over</td>
<td>RTEC with AXOS</td>
<td>Ready-to-eat cereal containing no AXOS</td>
<td>2.2 or 4.8 g</td>
<td>3 wk</td>
<td>Healthy individuals Men and women</td>
<td>55</td>
<td>↓ fasting glycaemia, ↓ fasting insulinaemia (2.2 g vs control), ↓ Bifidobacteria, ↓ butyric acid —total bacteria, Bacteroides, Lactobacillus spp., —C. coccoides, Clostridium clusters I and II, F. prausnitzii, ↑ Bifidobacteria, ↑ SCFA —total cholesterol, HDL, LDL, and TG</td>
</tr>
<tr>
<td>[50]</td>
<td>Double blind, cross-over</td>
<td>Non-carbonated soft drinks with wheat bran extract rich in AXOS</td>
<td>Non-carbonated soft drinks non supplemented</td>
<td>2.4 or 8 g</td>
<td>3 wk</td>
<td>Healthy individuals (33 man and 30 women)</td>
<td>63</td>
<td>↓ Bifidobacteria, ↑ SCFA —total cholesterol, HDL, LDL, and TG</td>
</tr>
<tr>
<td>[51]</td>
<td>Cross-over</td>
<td>Semolina porridge with AX, RK, or AXRK</td>
<td>Semolina porridge non supplemented</td>
<td>3.5 g (AX), 4.7 g (RK), 4.4 g (AXRK)</td>
<td>Acute</td>
<td>Individuals with MeS (8 men and 7 women)</td>
<td>15</td>
<td>↓ AXRK ↓ acute glucose, insulin, feeling of hunger ↓ AXRK and AX ↓ plasma butyrate and acetate</td>
</tr>
<tr>
<td>[52]</td>
<td>Cross-over</td>
<td>Bread with AX, BG, or RK</td>
<td>Wheat bread non supplemented</td>
<td>7.1 g (AX), 2.6 g (BG), 6.1 g (RK)</td>
<td>Acute</td>
<td>Individuals with MeS (7 men and 8 women)</td>
<td>15</td>
<td>↓ BG and RK ↓ ↓ postprandial glucose ↓ ↓ insulin and GIP vs the other breads, BG: ↓ insulin more than AX, AX, BG, and RK; ↑ satiety feeling ↓ AXOS and flax; ↑ postprandial GLP-1 and PYY vs LF-iso —appetite response,</td>
</tr>
<tr>
<td>[53]</td>
<td>Double blind, cross-over</td>
<td>Trial 1 and 2: RTEC with AXOS or RTEC with intact AXOS from flax</td>
<td>Trial 1 and 2: low-fiber RTEC (≠ E content) Trial 2: low-fiber RTEC (isoscaloric)</td>
<td>15 g</td>
<td>Acute</td>
<td>Overweight women Trial 1: Aged 22.5 ± 0.6 BMI 27.0 ± 0.3, Trial 2: Aged 24.3 ± 0.5 BMI 27.4 ± 0.3 Healthy individuals (6 men and 18 women)</td>
<td>30 (trial 1) 36 (trial 2)</td>
<td>↓ postprandial glucose</td>
</tr>
<tr>
<td>[54]</td>
<td>Double blind, cross-over</td>
<td>Bread with AX-enriched white flour</td>
<td>Bread with refined white flour</td>
<td>3.2 g</td>
<td>Acute</td>
<td>Healthy individuals (6 men and 18 women)</td>
<td>24</td>
<td>↓ postprandial glucose</td>
</tr>
</tbody>
</table>
4. Relevance of DF with prebiotic properties in the management of obesity and related metabolic diseases in human studies: focus on AX and AXOS

Obesity and related metabolic disorders is a context taken into account by EFSA when evaluating the interest of DF on weight maintenance, fiber intake and satiety [59]. The EFSA concluded that an increased intake of DF, both from naturally fiber-rich foods and added fiber or fiber supplements, has been shown to be related to improved weight maintenance in adults and sustained weight reduction in overweight subjects [59]. However, the effect of different sources or types of DF on body weight management in the context of obesity is poorly documented [60,61]. Increased satiety results from eating certain viscous types of DF, whereas the impact of such DF on energy intake or body weight, at least in the short term, can be inconsistent [62]. Among the factors associated with those effects, changes in lifestyle (i.e., higher levels of physical activity) can contribute. Some properties of high fiber diets, such as the replacement of high-energy foods, can also be involved in the improvement of glucose regulation and body weight [63].

Although there is strong epidemiologic evidence that DF intake is protective against overweight and obesity, a few studies demonstrate the fact that modulation of gut microbiota through DF consumption can manage metabolic diseases associated with obesity. Numerous studies have described the effect of prebiotics feeding (mostly 5–10% wt/wt food) on the evolution of body weight and fat mass in experimental animal models [20]. In studies of rodent models (lean, genetic or nutritional induced obese mice or rats), the decrease in fat mass following feeding with ingredients showing a prebiotic effect was associated with a reduction of food/energy intake [20,64]. The decrease in food/energy intake is not observed when ITF prebiotics are substituted by non-fermentable DF (microcrystalline cellulose), suggesting that at least the colonic fermentation plays a role in the modulation of food intake [65,66]. The decrease in food intake associated with prebiotics feeding in animals might be linked to the modulation of gastrointestinal peptides involved in the regulation of food intake. This particular finding, consisting in the promotion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), has been confirmed in healthy human subjects resulting in changes in appetite sensations [67], even if the dose of prebiotics given to humans is far below the one given to rodents (around 50 times higher in mice compared to humans).

Indeed, some studies suggest that DF with prebiotic potency improves anthropometric and metabolic outcomes in overweight and obese adults, thereby indicating that supplementation may improve health in these individuals [68]. However, the interpretation of these findings warrants caution because of the considerable between-study heterogeneity, for instance, the variability concerning the duration of the intervention. There is less report related to AX and wheat DF derivatives than reviews focusing on ITF, but the available epidemiological data describe that a high DF intake, mainly from whole-grain products, reduces the risk of obesity and type 2 diabetes mellitus [69]. This lead us to select this type of DF and to unravel the potential mechanism linking the changes in microbiota and AX/wheat DF intake, with a focus on obesity and related metabolic disorders.

5. Focus on mechanistic DF studies performed in the context of MyNewGut

5.1. Mechanism of action of AXOS in preclinical animal models of obesity

The use of animal models is crucial to evaluate the mechanism by which the change in the gut microbiota driven by prebiotics may influence obesity-related diseases [70]. Throughout this section, we discuss the studies performed in animal models of diet-induced obesity supplemented either with AX, AXOS, and wheat bran as it constitutes the starting material. It is essential to keep in mind that as described above, AX represent the most abundant DF in wheat bran and that AX can then be hydrolyzed to produce AXOS [36,71]. The production of AXOS in situ from fiber-rich bread has been described when a mixture of xylanases comprising at least one thermophilic xylanase is added to the dough [72].

Regarding the potential effects of AX and AXOS, the first pieces of evidence were obtained using the raw materials used for the extraction, namely wheat bran crude fraction or the aleurone-enriched fraction [12,73]. The supplementation with one of these two wheat bran fractions in the high-fat diet (HFD)-fed mice showed, on one hand, that aleurone-enriched increased the numbers of Bifidobacterium spp. and Lactobacillus spp., and on the
other hand, that the crude fraction decreased IL-6 in the plasma [73]. Any of the two fractions affected the body weight, adiposity, glucose or lipid metabolism [73]. Later on, another study supplementing the HFD with AX showed that, whereas the HFD induced the expression of genes mediating fatty acid uptake, fatty acid oxidation and, inflammation, the supplementation with AX prevented the HFD-induce adiposity, body weight gain and insulin resistance [74]. These beneficial effects were accompanied by increases in Bacteroides–Prevotella spp., Roseburia spp., and Bifidobacterium spp. [74]. Next, the prebiotic potency of AXOS was tested in HFD-fed mice during eight weeks [75]. The authors observed an anti-obesogenic effect associated with a bloom in the genus Bifidobacterium spp.. Besides, novel insight tying the endococrine function and the gut barrier was proposed to explain the anti-obesogenic effects of AXOS [75]. The differential effect between the crude wheat bran and AXOS has been confirmed in one recent study [76]. AXOS was more efficient to reduce body weight gain, and adiposity than the two fractions of wheat bran with different particle size tested in parallel [76]. Besides and for the first time, the sequencing of the 16S rRNA gene showed that the microbial changes induced by AXOS in mice are profound and go beyond the bifidogenic effect and also confirmed in the mentioned one [76]. AXOS also increased in barrier-protecting bacteria like Butyrivibrio coccoides [76–78] and wholly blunted taxa related to bacteria associated with colitis and inflammatory disorders, such as Turicibacter and Clostridium sensu stricto [76]. The latter study represents an approach in which AXOS is administered together in an enriched–fat diet to test its preventive effects [76]. Besides, recently, AXOS has shown beneficial effects when administered after the pre-treatment of 4 weeks with an obesogenic diet [79]. In the MyNewGut project, we have explored the potential synergetic or complementary effects of different DF utilized by indigenous intestinal human bacteria that can constitute the next generation of probiotics. In this context, AXOS was also proven to be the best fiber to stimulate the in vitro growth of the symbiotic Bacteroides uniformis CECT 7771 along with up-regulation of the expression of genes involved in AXOS metabolism [80]. Ongoing animal trials also demonstrate that the combination of B. uniformis CECT 7771 and AXOS reduces body weight gain and fat mass to a greater extent that the bacterial strain or the fiber alone (unpublished data). All in all, AXOS could be a promising novel nutritional strategy to reduce the metabolic consequences of a regimen rich in fat. However, human intervention studies are warranted.

Preclinical models have pointed to several mechanisms to explain the link between the anti-obesity effect of AX and/or AXOS and the changes in the gut microbiota, and interestingly, some of these observations have been confirmed in intervention studies with humans (Fig. 2). These include: (i) the modulation of entero-endocrine function; (ii) the regulation of the lipid metabolism; and (iii) the generation of SCFA. Initially, it was shown that IFT modulate the enteroendocrine function by increasing the number of L cells in the proximal colon of rats or mice. This increase was associated with the secretion of different peptides – GLP-1, GLP-2, and PYY - with critical roles in the control of gut barrier, appetite, and glucose homeostasis [52,65,81–84]. Similarly to what was shown for IFT, AXOS also can increase the level of circulating GLP-1 and PYY [75]. Moreover, AXOS supplementation upregulated the expression of the tight junction proteins Zo-1 and Claudin 3, an effect that might explain the decrease in LPS concentration and the protection from metabolic related-metabolic alterations [75,85]. However, another study also evaluating AXOS reported no differences in markers of the gut barrier function despite AXOS promoted barrier-protecting bacteria, such as Butyrivibrio coccoides [76]. Finally, the prebiotic-induced changes in the gut microbiota may also influence the expression of host genes involved in the control of fatty acid absorption, oxidation, and storage [86–88]. In the subcutaneous adipose tissue, the administration of AXOS caused a down-regulation of pathways involved in adipocyte differentiation, fatty acid uptake, fatty acid oxidation, that were up-regulated by the HFD [74]. Among the markers down-regulated by AXOS, it should be highlighted the expression of lipoprotein lipase (LPL) [74]. LPL is a specific enzyme which catalyzes the release of fatty acids from circulating triacylglycerol and lipoproteins in the muscle and the adipose tissue, and which activity is inhibited by the fasting-induced adipose factor (Fiaf, also known as angioptien-related protein 4 (ANGPTL4)) [89]. The suppression of Fiaf has been proposed as the critical piece for the microbiota-induced deposition of triglycerides in adipocytes [23]. However, to the best of our knowledge, to date, no mechanistic studies have been performed confirming this hypothesis.

5.2. Do bacterial metabolites mediate the beneficial effects of AXOS?

As described above, AXOS are metabolized by the gut microbiota resulting in the production of bacterial metabolites that are considered as crucial intermediates between the microbiota and the host. Therefore, it can be hypothesized that some of the effects of AXOS might be mediated by a modulation of the metabolic activity of the gut microbiota. AXOS are generally considered to promote saccharolytic fermentation, leading to increased production of SCFA. Indeed, consumption of bread containing AXOS increased fecal and plasmatic SCFA in healthy humans, notably with an increased acetate, propionate and butyrate in healthy adults [50], or only in butyrate [56,90] SCFA are accepted to be crucial executors of diet-based microbial influence on the host health [91]. However, some studies did not observe an alteration of SCFA production after supplementation with AX-rich WBE [92,93], or even have reported reductions in butyrate [49]. These discrepancies could be related to different degrees of polymerization of AX that determines the gut segment where AXOS is fermented. Low degree of polymerization could induce a proximal AXOS fermentation and absorption of SCFA, resulting in a lack of apparently increased concentration in feces [92].

Besides SCFA, the gut microbiota can produce branched-chain fatty acids (BCFA) from the degradation of branched-chain amino acids, and p-cresol or indole from aromatic amino acids [94]. In healthy subjects, AXOS (or AX-rich WBE) reduced the fecal concentration of the gut microbiota-derived BCFA and the urinary excretion of p-cresol [72,92,93]. In obesity, there is also a decrease in BCFA content in the serum [95] and adipose tissue biopsies [96]. These changes might have physiological relevance since the in vitro exposure of adipocytes to two BCFA (isobutyric acid and isovaleric acid) influences adipocyte lipid and glucose metabolism [97]. Thus, the significance of the reduction of BCFA observed after the intake of AXOS or AX-rich WBE awaits to be investigated. Regarding the effects of derivatives from aromatic amino acids, it has been described that p-cresol has toxic effects for the intestinal epithelium [98], and consequently, low concentration of this metabolite is generally considered as beneficial for gut health. It can be hypothesized that AXOS-induced reduction of p-cresol production might have beneficial effects for gut barrier function in the context of obesity. One study in chronic kidney disease patients found that AXOS slightly decreased plasma trimethylamine-N-oxide [99], this bacterial
metabolite being implicated in cardiovascular disease progression [100]. Although this finding should be confirmed in obese subjects, the AX-induced reduction of trimethylamine-N-oxide could contribute to the beneficial metabolic effects of AXOS.

Interestingly, some inter-individual differences have been observed regarding the AX-induced modulation of the metabolic activity of the gut microbiota [92]. However, the features of the gut microbiota of AXOS responders remain to be determined. Importantly, metabolization by the gut microbiota of ferulic acid associated with AXOS might also result in the production of bacterial bioactive metabolites that could underlie AXOS metabolic effects [101]. In conclusion, there is strong evidence that AX modulates the metabolic activity of the gut microbiota. However, these data should be confirmed in obese subjects, and the relative contribution of the bacterial metabolites to the beneficial effects of AXOS should be further investigated. The full integration of metagenomic, metabolomics and lipidomic data derived from subjects enrolled into the MyNewGut 4-week AXOS intervention also proves that the consumption of this DF changed the gut microbiome gene functions and host-microbe related metabolites with potential impact on glucose homeostasis. Moreover, the activation of specific microbial metabolic circuits in particular gut microbes strongly indicates that sustained consumption of AXOS in time would be central for maintenance of metabolic health in humans [102].

6. DF with prebiotic properties: outcomes and needs to progress with dietary guidelines and innovation in human nutrition

In this last section, we aim to address the following question: can we elaborate dietary recommendations of DF taking into account their interaction with the gut microbiota? The current dietary recommendations refer to a certain amount of total DF to be eaten in g per day or per 1000 kcal intake. The discrepancy between fiber solubility and fermentability, the proportion of soluble versus insoluble DF does not appear as essential to take into account when establishing dietary recommendations by the corresponding authorities (Table 2).

The concept of “modulation of gut microbiota activity and/or composition by prebiotic DF” is interesting, but it is rather difficult to establish at which doses a prebiotic DF must be ingested to change the gut microbiota significantly, and how it is related to health effect. For some prebiotic DF, some bacteria (i.e., Bifidobacteria for inulin-type fructans) appear as “biomarkers” of the microbial response rather than as a key player in the health effects, that are merely not attributable to single species. Most intervention studies with prebiotic DF have been conducted with “purified” or isolated DF, at relatively high doses (around 20 g for most studies) and we do not know if those prebiotic DF present in a natural food matrix will modulate the gut microbiota. How health outcomes
(positive or negative) relate to specific metabolites or microbial components in humans has to be established in the future. The task not be easy, in particular, because appropriate (and consensus) quantitative and qualitative analysis of DF are missing in most food composition tables, but also because dealing with microbiota complexity, requires that the scientists involved in this domain agree on the adequate methodology to assess human gut micro-
biota fermentation and microbiome assessment. Besides, the setting of dietary recommendation should take into account the problems of discomfort linked to the consumption of DF. For instance, a mild increase in flatulence has been reported in studies testing a dose of 10 g per day of AXOS [48], but in lower doses (2.2 or 4.8) no effect was noticed [49]. Consequently, the balance between tolerance and the positive impact on the microbiota is an issue that the future dietary recommendation should also tackle. In conclusion, upon the data obtained in the MyNewGut project and recent publications in the field, we could progress in the evaluation of the fiber sources that beneficially impact specific components of the gut microbiota and metabolism and contribute to discovering new players and mechanisms of action that could support specific health-outcomes.

Duality of interest

CSIC has received research funding from LNC and Vision Global.

Conflicts of interest

None declared.

Contribution statement

NMD, MO, AMN, MB, and JWvdK wrote the manuscript. NMD coordinated the work. MO prepared the tables and figures. All au-
thors (NMD, MO, AMN, MB, LK, TML, AB-P, MR-P, VG-C, DB, VS, JWvdK) contributed to discussion, editing and approval of the final manuscript.

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