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Opinion paper

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 fibers, 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 development, we elaborate the steps required to propose dietary guidelines related to dietary fibers, taking into account their interaction with the gut microbiota.

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 recommendation 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 harbouring the gut microbiota. Therefore, this Opinion Paper focuses on the results of studies performed with prebiotic fibers studied in the MyNewGut project —namely arabinoxylo-oligosaccharides (AXOS)- and outlines recommendations for an in-depth understanding of gut microbiota-fibers 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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List of abbreviations

ANGPTL4	angiopoietin-related protein 4
AX	arabinoxylans
AXOS	arabinoxylo-oligosaccharides
BCFA	branched-chain fatty acids
DF	dietary fiber
EFSA	European Food Safety Authority
EU	European Union
FDA	United States Food & Drug Administration
FOS	fructo-oligosaccharides
GLP-1	glucagon-like peptide-1
GOS	galacto-oligosaccharides
HMOs	human milk oligosaccharides
IL	interleukin
ITF	inulin-type fructans
ISAPP	International Scientific Association for Probiotics and Prebiotics
LPL	lipoprotein lipase
LPS	lipopolysaccharide
MU	monomeric units
NSP	non-starch polysaccharides
PYY	peptide YY
RO	resistant oligosaccharides
RS	resistant starch
SCFA	short-chain fatty acids
WBE	wheat bran extract

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 have 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 $\geq$ 10); (ii) resistant oligosaccharides (RO) (MU 3–9); and (iii) resistant starch (RS) (MU $\geq$ 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 $\geq$ 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 to health must be proven. In this sense, the fermentation-related criteria were chosen as primary end-points for a range of oligosaccharidic fibers, such as FOS (including inulins), GOS and other resistant oligosaccharides (i.e., isomalto-oligosaccharides, resistant maltodextrins, polydextrose). 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 $\geq$ 3). Nutrition facts information related on 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

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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 the 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 Probiotics and Prebiotics (ISAPP) panel lastly updated the definition of a prebiotic as a "substrate that is selectively utilized by host microorganisms conferring a health benefit" [16]. This definition expands 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 prebiotics 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 ingredients/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 potential 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 potential 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 vegetables, 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 *Faecalibacterium 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-

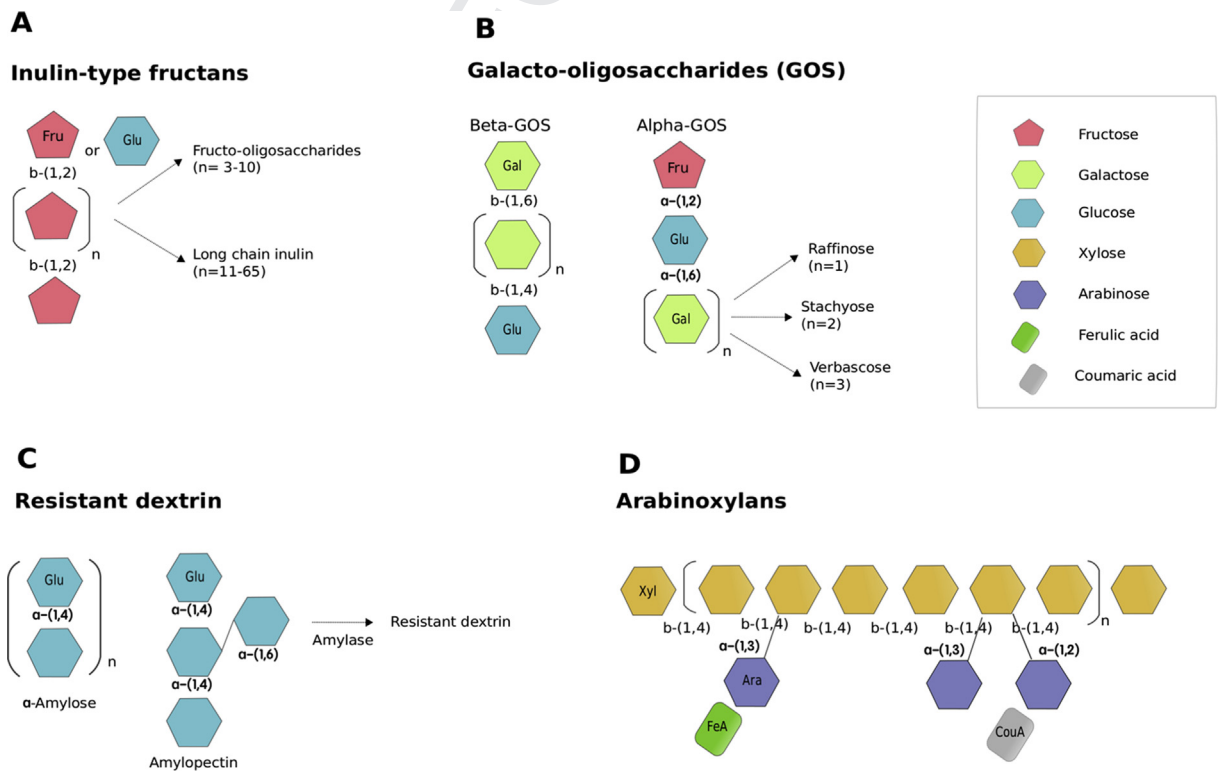

Fig. 1. Schematic representation of the structure of A) inulin-type fructans, B) galacto-oligosaccharides (GOS), C) resistant dextrin, and D) arabinoxylans (Note that p-coumaric acid is present only in stems of grasses, not in grain).

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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-glucosidic bonds) or α-galactosides, such as raffinose (trisaccharide), stachyose (tetrasaccharide), and verbascose (pentasaccharide) (Fig. 1B). Even though there 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 at high temperature followed by enzymatic (amylase) 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 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 modulating the intestinal microbiota. Using two distinct *in vitro* models for the human gut, Van den Abbeele 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 *Bacteroides longum* and propionate production, inulin increased *Bacteroides 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 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 H_2 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 arabinoxylo-oligosaccharides (AXOS) reporting effects on metabolic parameters.

Reference	Study design	Fiber treatment	Placebo treatment	Dose	Time	Study population	Size, n	Outcome
[43]	Single blind	Bread with low or high AX-rich fiber content	Control bread without AXs-rich fiber	0.6 or 12 g	3 d	Healthy individuals (5 men and 9 women) Aged 32.0 ± 6.6 BMI 22.7 ± 4.3	14	↓ postprandial glycaemia, improvement in the insulin response
[44]	Cross-over	AX-bread and muffins	Bread and muffins non supplemented	14–17 g	5 wk	Type 2 diabetes patients (6 male, 9 female) Aged 60 ± 2.0 BMI 28.1 ± 0.9	15	↓ fasting glycaemia, ↓ glycaemia and insulinaemia 2 h post OGTT
[45]	Cross-over	Bread rolls with AX	Bread rolls non supplemented	6 g	Acute	Healthy individuals (6 men and 9 women) Aged 26.4 ± 2.6 BMI 22.9 ± 27	15	=postprandial glycaemia, ↓ postprandial insulinaemia
[46,47]	Single blind, cross-over	Bread rolls with AX, and AX in powder	Isocaloric bread rolls and powder without AX	15 g	6 wk	Overweight individuals with insulin resistance (4 men and 7 women) Aged 55.5 ± 6.2 BMI 30.1 ± 5.7	11	↓ fasting glucose, ↓ TG ↓ apolipoprotein A-1 =insulin, adiponectin, leptin. After a liquid meal challenge test: ↓postprandial glycaemia,↓insulin, ↓TG, ↓total plasma ghrelin
[48]	Cross-over	Crude AXOS	Maltodextrin	10 g[a]	3 wk	Healthy individuals (6 men and 14 women) Aged 24.0 ± 5.0 BMI 20.9 ± 2.3	20	↑Bifidobacteria ↓urinary p-cresol excretion =total cholesterol, HDL, LDL, and TG
[49]	Double blind, cross-over	RTEC with AXOS	Ready-to-eat cereal containing no AXOS	2.2 or 4.8 g	3 wk	Healthy individuals Men and women Aged not specified BMI not specified	55	=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*,
[50]	Double blind, cross-over	Non-carbonated soft drinks with wheat bran extract rich in AXOS	Non-carbonated soft drinks non supplemented	2.4 or 8 g	3 wk	Healthy individuals (33 man and 30 women) Aged 42 ± 17 BMI 23.2 ± 3.2	63	↑Bifidobacteria, ↑SCFA =total cholesterol, HDL, LDL, and TG ↓*p*-cresol
[51]	Cross-over	Semolina porridge with AX, RK, or AXRK	Semolina porridge non supplemented	3.5 g (AX) 4.7 g (RK) 4.4 g (AXRK)	Acute	Individuals with MeS (8 men and 7 women) Aged 63.5 ± 5.0 BMI 31.3 ± 2.7	15	AXRK: ↓acute glucose, insulin, feeling of hunger AXRK and AX: ↑plasma butyrate and acetate
[52]	Cross-over	Bread with AX, BG, or RK	Wheat bread non supplemented	7.1 g (AX) 2.6 g (BG) 6.1 g (RK)	Acute	Individuals with MeS (7 men and 8 women) Aged 62.8 ± 4.2 BMI 31.1 ± 3.2	15	BG and RK: ↓ postprandial glucose RK: ↓insulin and GIP vs the other breads. BG: ↓insulin more than AX AX, BG and RK: ↑satiety feeling
[53]	Double blind, cross-over	Trial 1 and 2: RTEC with AXOS or RTEC with intact AXOS from flax	Trial 1 and 2: low-fiber RTEC (≠ E content) Trial 2: low-fiber RTEC (isocaloric)	15 g	Acute	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	30 (trial 1) 36 (trial 2)	AXOS and flax: ↑ postprandial GLP-1 and PYY vs LF-iso =appetite response,
[54]	Double blind, cross-over	Bread with AX-enriched white flour	Bread with refined white flour	3.2 g	Acute	Healthy individuals (6 men and 18 women) Aged 34.5 ± 12.5 BMI 22.1 ± 2.5	24	↓ postprandial glucose

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Table 1 (*continued*)

Reference	Study design	Fiber treatment	Placebo treatment	Dose	Time	Study population	Size, n	Outcome
[55]	Cross-over	White bread with AXOS + RS, high content of AXOS, or high content of RS	White bread non supplemented	8.9 (AXOS + RS) 18.4 (high AXOS)	Acute	Healthy individuals (9 men and 10 women) Aged 23.0 ± 0.4 BMI 22.2 ± 0.4	19	↓ glucose dose-dependently High AXOS improved insulin sensitivity ↑ Breath H_2 concentration and circulating SCFA in both breads with AXOS.
[56]	Double blind	AX in powder	Maltodextrin	7.5 or 15 g	6 w	Obese and overweight (25 men and 22 women) Aged 48.0 ± 1.6 BMI 31.0 ± 2.4	47	↑ Occludin expression in 7.5 AX group in colonic biopsies ↑ Claudin-3 and -4 in 15 AX group in colonic biopsies ↑ Microbiota diversity, ↑ SCFA, acetate, propionate, butyrate =intestinal permeability and tight function expression =no changes in metabolic markers

AX, arabinoxylans; AXOS, arabinoxylo-oligosaccharides; AXRK, arabinoxylans + rye kernels; BMI, body mass index; d, days; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; LF, low-fiber; OGTT, oral glucose tolerance test; PYY, peptide YY; RS, resistant starch; RTEC, ready-to-eat cereal; RK, rye kernels; SCFA, short chain fatty acids; wk, weeks; BG, β-glucan; "=" means no significant changes *versus* control.

[a] The fiber treatment is named "crude AXOS" but the dose applies to the pure AXOS.

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]. An 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]. All 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 thermophylic 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* and *Lactobacillus*, and on the other

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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*, *Roseburia* spp., and *Bifidobacterium* [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*. Besides, novel insight tying the endocrine function and the gut barrier was proposed to explain the anti-obesigenic 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 *Butyricicoccus* [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 it 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 synergic 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 symbiont *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 that 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 ITF modulate the enteroendocrine function by increasing the number of L cells in the proximal colon of rats or mice. This increase was associated to 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 ITF, 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, other study also evaluating AXOS reported no differences in markers of the gut barrier function despite AXOS promoted barrier-protecting bacteria, such as *Butyricicoccus* [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 angiopoietin-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

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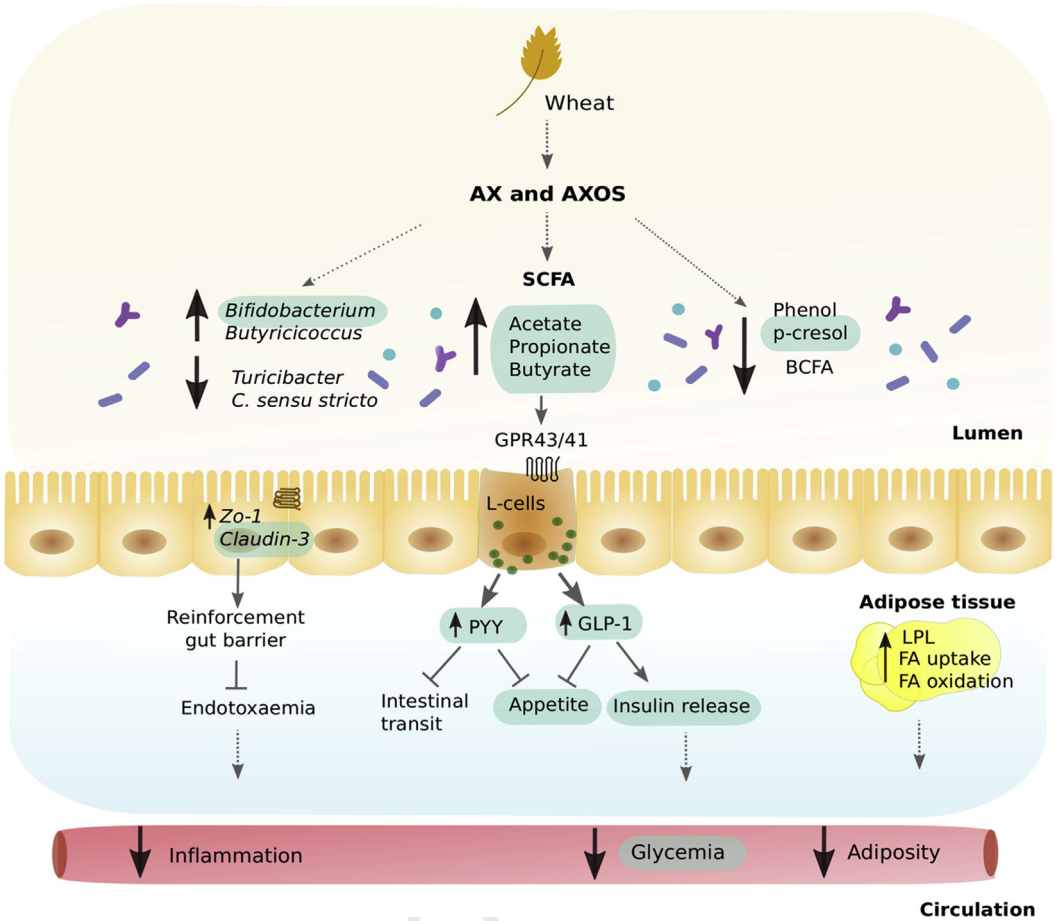

Fig. 2. Mechanisms evoked to understand the biological effect of arabinoxylans (AX) and arabinoxylo-oligosaccharides (AXOS) in the context of obesity. In animal models of diet induced-obesity, AX and/or AXOS produce changes in the taxonomy of the intestinal microbiota and its activity (production of bacterial metabolites). At the intestinal level, these changes are associated with a reinforcement of the intestinal barrier and with stimulation of the enteroendocrine system to produce hormones that regulate appetite and homeostasis of glucose. In the adipose tissue, AX and/or AXOS influence the regulation of lipid metabolism which ultimately reduces the development of adiposity. The observations that have been confirmed in intervention studies with humans appears labeled in blue. FA, fatty acid; GLP-1, glucagon-like peptide-1; LPL, lipoprotein lipase; PYY, peptide YY; Zo-1, Zonula occludens.

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

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Table 2
Recommendation for daily dietary (DF) intake adapted from Lockyer et al. [103].

Reference	Region	Recommendation	Issuing body
[104]	EU	25 g/day for adults 2 g/MJ for children from the age of one year	EFSA
[105]	UK	30 g/day for adults 15 g/day (age 2–5) 20 g/day (age 5–11) 25 g/day (age 11–16) 30 g/day (age 16–18)	UK's SACN
[106]	Nordic countries	25–35 g for adults	The Nordic Council of Ministers
[107]	US	33.6 g for men 28 g for women (14 g/1000 kcal)	USDA
[108]	Australia and New Zealand	30 g for men 25 g for women	NHMRC

EFSA: European Food Safety Authority; EU, European Union; FSAI, Food Safety Authority of Ireland; NHMRC, National Health and Medical Research Council; SACN, Scientific Advisory Committee on Nutrition; UK, United Kingdom; USDA, United States Department of Agriculture.

(positive or negative) relate to specific metabolites or microbial components in humans has to be established in the future. The task is not easy, in particular, because appropriate (and consensual) 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 microbiota 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 report 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 authors (NMD, MO, AMN, MB, LK, TML, AB-P, MR-P, VG-C, DB, YS, JWvdK) contributed to discussion, editing and approval of the final manuscript.

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