# Potential interest of gut microbial changes induced by non-digestible carbohydrates of wheat in the management of obesity and related disorders

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**Purpose of review**

The modulation of the gut microbiota by nutrients is of interest in order to reverse host metabolic alterations linked to gut microbiota dysbiosis. This review discusses how nondigestible carbohydrates (NDC) derived from wheat may constitute functional cereal food products in the management of obesity and diabetes, notably through modulation of gut microbiota.

**Recent findings**

Recent evidences highlighted that alterations in the composition of the gut microbiota participate in the development of obesity. Interesting nutrients that target specific gut microbes (prebiotics) are able to reverse host metabolic alterations linked to gut microbiota dysbiosis in obese individuals. Recent data suggest that NDC prepared from wheat represent a new class of nutrients exhibiting prebiotic properties.

**Summary**

Processing technologies of wheat grain lead to production of original NDC characterized by specific degree of polymerization and degree of substitution. Those characteristics condition the gut compartment where fermentation occurs, the changes of bacteria composition and the proportion of bacterial metabolites (i.e., short-chain fatty acids) released in the gut. Scientists may take into consideration a key question: could we help control obesity and type 2 diabetes through the modulation of gut bacterial metabolism and/or composition by wheat-derived NDC? This opens up an original area in nutrition research.

**Keywords**

arabinoxylan, microbiota, obesity, type 2 diabetes, wheat

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## Introduction

In most Western countries, cereals represent a major source of dietary fibers. Dietary fibers are one of the most important class of compounds in cereal grains related to positive health effects, and cereal products help reaching the recommended overall dietary fibers intake [1•,2]. Common wheat contains, on average, a highest level of dietary fiber reaching 11.5–18.3% of dry matter. Cereal products consumption has decreased dramatically over the last century [3]. In addition, cereals are consumed as more refined products than in the past. This phenomenon participates to the drop in daily fiber intake. In parallel, diabetes, obesity and cardiovascular diseases, clustered in the metabolic syndrome, have emerged as major health problems. An efficient approach in the prevention and treatment of this syndrome should involve lifestyle changes, including appropriate nutrition. On the basis of studies in animals and humans, it has been proposed that the intake of highly fermentable nondigestible carbohydrates (NDC) could be interesting nutrients prone to increase satiety to improve glucose tolerance, to lower hepatic and serum lipids, and even to control hypertension [1•,4,5]. The aim of this review is to highlight how wheat products containing NDC may constitute functional cereal foods in the management of obesity and diabetes, notably through modulation of gut microbiota.

## Prebiotic effect and obesity

The microbial community living within the mammalian host intestine reaches around 100 trillion of microorganisms harboring probably the most complex microbial ecosystem. It is becoming evident that the gut microbiota encodes a vast arsenal of gene products, which collectively provide a diverse range of biochemical and metabolic activities that complements the host eukaryotic


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genome [6••]. Recently, it has been proposed that alterations in the composition/activity of the gut microbiota (known as dysbiosis) participate in the development of obesity and its metabolic disorders [5,7•,8]. The changes in bacterial composition of obese versus lean persons, concern the bacterial phyla (decrease in Bacteroidetes, and/or an increase in Firmicutes), but also specific bacterial genera, such as, for example, a decrease in *Bifidobacterium* spp., or an increase in *Staphylococcus aureus*...) [7•,8,9]. Nobody knows exactly how those changes could contribute to the modifications of host energy storing and metabolism. In that context, the modulation of the gut microbiota by nutrients that counteract obesity-related dysbiosis, and thereby improve host health, would be interesting. This corresponds to the concept of prebiotic introduced by Gibson and Roberfroid [10] in 1995 and recently revisited to include the most recent development, leading to the definition: 'a dietary prebiotic is a selectively fermented ingredient that results in specific changes, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) for host health' [11]. The majority of the scientific data (both experimental and human) on prebiotic effects have been obtained using food ingredients/supplements belonging to two chemical groups, that are the inulin-type fructans and the galactooligosaccharides. These have, repeatedly, demonstrated the capacity to selectively stimulate the growth of bifidobacteria and, in some cases, lactobacilli leading to a significant change in gut microbiota composition [12,13]. We found that in prebiotic (inulin-type fructan)-treated mice, *Bifidobacterium* spp. significantly and positively correlated with improved glucose homeostasis and normalized obesity-related inflammation (decrease in endotoxemia and tissue or serum proinflammatory cytokines) [14]. Several mechanisms have been proposed in order to explain the positive effect of the prebiotic approach in obesity models. Among those hypotheses, the modulation of endocrine function (increase in the production of glucagon-like peptides, GLP-1 and GLP-2) occurs in prebiotic-fed animals is a phenomenon that contributes to the improvement of obesity and type 2 diabetes [5,15••]. A more recent study reported that prebiotic treatment allows a decrease in the expression of specific receptors implicated in adipocyte differentiation and/or increased adipocyte size, namely, the PPARγ and GPR43 [16,17]. Indeed, inulin-type fructans counteract GPR43 overexpression and PPARγ-related adipogenesis in the white adipose tissue of high fat-fed mice [18•].

Prebiotic properties leading to the improvement of obesity and related diseases have been mostly studied taking into account the inulin-type fructans as prebiotics [8,12]. In the next sections, we will assess the relevance of wheat-derived NDC as modulators of gut microbiota composition and activity, and we will try to relate those changes with the described effect of wheat grain on obesity and related disorders.

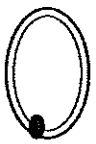
## Distribution of nondigestible carbohydrates present in wheat

Whole-grain cereals comprise three main fractions: the endosperm, the germ, and the bran (see schematic representation in Table 1) [2,19••,20–25]. The aleurone layer constitutes the outer layer of the endosperm but owing to its high adherence to the pericarp, it is found predominantly in the bran fractions after milling. The grain endosperm is composed mainly of starch – the digestibility of which will be affected by food processing (e.g., heating, drying, acid/enzymatic digestion) – and small amounts of proteins and B vitamins [24]. Germ, the smallest part of the grain, contains lipids, proteins, and some soluble carbohydrates, along with trace minerals, vitamins E and B, antioxidants, and phytonutrients. The bran is rich in nondigestible, mainly insoluble and poorly fermented, carbohydrates, B vitamins, and trace minerals [24]. The most important NDC present in wheat are the nonstarch polysaccharides, arabinoxylans representing 50% of dietary fibers, mixed-linkage β-glucan, fructans and cellulose [2,20]. In cereal botanical components, the majority of NDC generally occur in decreasing amounts from the outer pericarp to the endosperm, except arabinoxylans, which are a major component of endosperm cell wall materials (Table 1). Arabinoxylans are complex carbohydrates found in the cell walls of the starch endosperm and the aleurone layer and in pericarp tissues of cereals [19••]. Separation of specific fractions of NDC from cereal or cereal by-products, according to the knowledge of NDC distribution in cereal grains, could be achieved through processing technologies, such as milling, sieving, and debranning or pearling [25]. Of particular interest, hydrolysis of the highly polymerized arabinoxylans from bran, through wheat-associated endoxylanases or specific intestinal bacteria possessing arabinoxylan-degrading enzymes, leads to the formation of arabinoxylan oligosaccharides (AXOS). AXOS are characterized by their average degree of polymerization (avDP) and average degree of arabinose substitution (avDS) [26]. Another interesting NDC called wheat dextrin may be formed when wheat starch is processed by heating and treating with enzymes (amylase) [1•].

## Gut microbiota modulation by wheat nondigestible carbohydrates

First evidences demonstrating fermentation properties of wheat concerned studies assessing the ability of wheat fractions or wheat flours to produce short-chain fatty acids (SCFA) *in vivo* in rats and pigs or *in vitro* using human

**Table 1 Definition and distribution of nondigestible carbohydrates in wheat (% dry matter)**

| Schematic representation |  |  |  |  |
|---|---|---|---|---|
| Botanical components | Grain | Bran | Aleurone cells and germ | Starchy endosperm |
| Milling fractions | Wholemeal | Bran flour | Aleurone flour | White flour |
| Arabinoxylan [2,19••] | Carbohydrates consisting of β (1,4)-linked D-xylopyranosyl residues to which a-L-arabinofuranose units are linked as side chains. Some arabinoses can be substituted with ferulic acid. The degree of substitution refers to the arabinose moieties on the xylose backbone and is further also described as A/X ratio. | | | |
| | 4–9% | 12.7–22.1% | 60–70% | 1.4–2.8% |
| Fructan [20–22] | Carbohydrates of fructosyl units with or without one glucosyl unit. Wheat fructans contain both β (1,2) and β (6,2) linkages and have an avDP of up to 19 with a similar molecular weight distribution in the different fractions. Some fructooligosaccharides with an estimated DP of 5–7 in most whole grain whereas fructans in wheat flour have been reported to have a highest DP of 7–8 and ≥16. | | | |
| | 0.6–2.6% | 2.7–3.7% | 1.9% | 1.5–1.6% |
| β-Glucan [2,22,23] | Carbohydrates consisting of a linear homopolymer arranged in blocks of consecutive β (1,4)-linked d-glucose residues separated by single β (1,3)-linkages. The chain mainly consists of cellotriosyl (58–72%) and cellotetraosyl (20–34%) units; some cellulosic blocks having more than four residues | | | |
| | 0.5–1.4% | 1.4–1.8% | 0.9% | 0.3–0.4% |
| Resistant starch [24] | The starch consists of two main structural components, the amylose, which is essentially a linear polymer in which glucose residues are α -D-(1,4) linked, and amylopectin, which is a larger branched molecule with α -D-(1,4) and α -D-(1,6) linkages. Resistant starch is defined as that fraction of dietary starch, which escapes digestion in the small intestine; it is measured chemically as the difference between total starch obtained from homogenized and chemically treated sample and the digestible starch generated from nonhomogenized food samples by enzyme digestion. It is subdivided into four fractions: RS1, RS2, RS3, and RS4. | | | |
| | 16.4% | 1.1% | 0.8% (in germ) | |
| Cellulose [2,22] | Cellulose is a homopolymer of glucose linked by β-(1,4) linkages only | | | |
| | <5% | 8–10% | 3.9% | 0.5–0.6% |
| Galactooligosaccharides [20,25] | Galactooligosaccharides also called α-galactosides or raffinose family oligosaccharides (RFOs) are soluble low-molecular weight oligosaccharides, such as raffinose (trisaccharide), stachyose (a tetrasaccharide), verbascose (a pentasaccharide) and other oligosaccharides formed by α-(1,6)-galactosides linked to C-6 of the glucose moiety of sucrose. | | | |
| | Identified | Not determined | Identified (raffinose: 7.2% in germ) | Not determined |

avDP, average degree of polymerization; DP, degree of polymerization.

fecal material. Studies of Adam *et al.* [27] demonstrated that whole-wheat flours can strikingly affect cecal SCFA in rats, especially butyrate versus a control diet (wheat starch) [3]. Further, they investigated different milling fractions of wheat on digestive fermentations in Wistar rats. It appears that white flour rather promoted propionate-rich fermentations, whereas bran favored butyrate-rich fermentations. However, cecal SCFA pool was higher in whole flour and white flour than in bran fractions. More recently, opposite results were obtained in a study devoted to compare *in vitro* fermentation with pH change and SCFA production of native whole grain, bran and germ of wheat [24]. Indeed, wheat bran generated the lowest butyrate proportions. In addition, this study suggested that wheat germ NDC and whole-wheat grain were more fermentable than wheat bran NDC. Interestingly, *in vitro* fermentability using fresh human fecal material turned out to be higher in aleurone than in wheat bran, whereas proportions of the main SCFA were very similar [28]. In an experiment with pigs, fermentation in the large intestine of bread made from wheat aleurone flour produced higher butyrate than for bread made from whole-wheat grain [29]. Of interesting point of view, we demonstrated in a mice model of diet-induced obesity that wheat bran fractions (10% in the diet) increased bifidobacteria and lactobacilli in the cecal content, particularly in the aleurone-enriched bran fraction [21].

Besides effects of wheat grains and its milling fractions on gut microbiota and SCFA production, recent studies highlight modulation of gut microbiota by specific NDC prepared from wheat grain. Among fermentable NDC derived from wheat described above, only wheat arabinoxylans with its hydrolysis products AXOS and wheat dextrin were studied for their fermentability and their prebiotic potency.

### Wheat arabinoxylans and wheat arabinoxylan oligosaccharides

Fermentation of wheat arabinoxylans by human intestinal bacteria has been related to a slight increase in

propionic acid production [28]. Likewise, an increase in levels of acetate, propionate and butyrate were observed in feces of human volunteers that consumed arabinoxylan-enriched bread for about 3 weeks [30]. Similar effects on propionate production were observed in in-vivo studies with rats [31]. In a more recent study [32], the fermentation of arabinoxylan fractions characterized by different molecular masses was investigated *in vitro* using human fecal microflora and data showed a particularly high proportion of butyrate. In addition, the fermentation of these three arabinoxylan fractions was associated with proliferation of the bifidobacteria and lactobacilli [32]. In fact, arabinoxylans and AXOS represent a new class of candidate prebiotics. Recently, a prebiotic index was calculated for wheat arabinoxylans after its addition (1%) to a pH-controlled stirred anaerobic fermentation vessel [33]. This score was evaluated by an equation taking into account the number of bifidobacteria, lactobacilli, clostridia, bacteroides and total number of bacteria. It was shown that prebiotic index of arabinoxylans is comparable to other well established prebiotics (inulin-type fructan) and that prebiotic functionality of arabinoxylans was improved when the molecular mass decreases and also by pretreatment with xylanase leading to the formation of AXOS [32,33]. Another study [34] demonstrated that a bifidobacterial mixture and the fecal microbiota were able to utilize AXOS almost completely. However, bifidobacteria strains were able to utilize AXOS with differing strategies, as after the cleavage of l-arabinose, *Bifidobacterium adolescentis* consumed the xylooligosaccharide formed, whereas *B. longum* fermented the l-arabinose released; *B. breve* grew poorly with AXOS as substrate . Microbial metabolism and prebiotic potency of arabinoxylans and AXOS are well documented in several studies obtained by groups of Tom Van de Wiele, Kristin Verbeke and Jan Delcour. Grootaert *et al.* [26] made an overview of human intestinal bacteria that are involved in the breakdown of arabinoxylans in 2007. More recently, the prebiotic potential of AXOS (degree of polymerization = 15 and degree of arabinose substitution = 0.27) was compared with inulin in two simulators of the human intestinal microbial ecosystem [19••]. Microbial metabolism of both NDC and SCFA production was colon compartment specific, with ascending and transverse colon being the predominant site of inulin and AXOS degradation, respectively. Propionate levels increased in the transverse colon during AXOS supplementation. Furthermore, AXOS supplementation strongly decreased butyrate in the ascending colon, this in parallel with a decrease in *Roseburia* spp. and *bacteroides/Prevotella/Porphyromonas* levels [19••]. The structure–function relationships of these NDC with varying avDP and avDS were investigated *in vivo* in pigs for arabinoxylans[29] and in rats for AXOS [35]. Indeed, the AXOS with a low avDP (<3) resulted in increased colonic acetate and butyrate production and boosted bifidobacteria concentrations in the cecum. In contrast, an AXOS preparation with a higher avDP (61) neither increased colonic butyrate concentrations nor stimulated cecal bifidobacteria development. This study [35] suggests that the influence of the avDS was apparently limited and possibly overshadowed by that of the avDP.

### Wheat dextrin

Wheat dextrin is a soluble fiber that has been widely used in the food industry because it has a low viscosity and so has a good consistency when added to water, beverages or soft food [1•]. It is formed by heating wheat starch at high temperature, followed by enzymatic (amylase) treatment to form a resistant starch. One study [36] has compared in-vitro fermentability of wheat dextrin with that of inulin. Wheat dextrin exhibited a unique fermentation pattern and produced total SCFA concentrations similar to inulin in two separate in-vitro batch fermentation systems. Wheat dextrin produced SCFA gradually and completely over the 24-h period, in contrast to the rapid peaks and decline seen with inulin. Consumption of wheat dextrin led to a lower colonic pH, an increase in the fecal concentration of glucosidase, an increase in the beneficial lactobacilli population and a decrease in pathogenic *Clostridium perfringens*; in fact, increased glucosidase activity is considered beneficial to the host and is linked to substrate fermentation leading to more SCFA and lactic acid production [1•].

## Relevance of wheat nondigestible carbohydrates in the management of obesity and diabetes in human studies

Probably, due to the novelty of this concept, there are no data studies demonstrating the fact that modulation of gut microbiota through wheat NDC consumption is able to manage metabolic diseases associated with obesity. Nevertheless, examples from existing studies assessing the effects of wheat-derived NDC on parameters related to gut bacterial metabolism and/or in obesity and glucose homeostasis are provided in Table 2 [37–45,46••] and support this concept. Of particular interest, original studies revealed that AXOS prepared from wheat bran or resistant starch prepared from wheat starch (wheat dextrin) are able to undergo colic bacterial metabolism in humans reflected by measurement of fecal glucosidase activity, hydrogen breath test, p-cresol or $^{15}$N-excretion in urine or feces. However, it should be interesting to link effects of these wheat NDC on bacterial metabolism with parameters of obesity (body weight, hunger and satiety scores) and/or type II diabetes (glycemia, insulinemia ...). In the same way, correlations between positive health benefits concerning glycemic control of arabinoxylan fractions observed in healthy individuals as well as in diabetic population, and gut microbiota markers have not been investigated until now.

**Table 2 Gut microbiota modulation and/or metabolic effects after wheat-derived nondigestible carbohydrate consumption in humans**

| Wheat NDC | Study design | Delivery | Results | References |
|---|---|---|---|---|
| Wheat dextrin from wheat starch processing | 43 healthy individuals; a randomized, placebo-controlled, parallel, double-blind intervention | 30 or 45 g of the dextrin NUTRIOSE FB or 22.5 g of pure maltodextrin (glucidex 6) daily for 4–5 weeks. | ↓ Body weight ($P=0.07$) = hunger and satiety scores | [37] |
| Wheat dextrin from wheat starch processing | 20 healthy men; a randomized, placebo-controlled, multiple-dose, double-blind, combined cross-over and parallel intervention over 8 weeks | 10–30–60 g or 15–45–60 g of the dextrin NUTRIOSE FB or maltodextrin, each dose for 7 days. | ↑ Breath $H_2$ excretion; ↑ glucosidase activity in feces | [38,39] |
| AX from wheat-flour processing | 14 healthy individuals | Bread with 0–6–12 g AX three breakfasts on 3 days | ↓ Postprandial glycemia; improvement of insulin response | [40] |
| AX from wheat-flour processing | 15 patients with type II diabetes; randomized cross-over intervention | Bread and muffins with 14% AX for 5 weeks | ↑ Fecal output, ↓ fasting glycemia; ↓ glycemia and insulinemia 2 h post-OGTT = blood lipid, = fat mass, = blood pressure | [41] |
| AX from wheat-flour processing | 11 patients with impaired glucose tolerance; singled blind, controlled, cross-over intervention over 18 weeks | 15 g AX supplied daily via bread and powder for 6 weeks with a 6-week washout period | ↓ Fasting glycemia, ↓ serum triglycerides, ↓ apo A-1, =leptin, =adiponectin, =insulin, =resistin, =apo B, =NEFA; after LMCT: ↓ postprandial glycemia, ↓ triglyceridemia, ↓ insulin, ↓total ghrelin (=acylated ghrelin) | [42,43] |
| AX from wheat-flour processing | 15 healthy individuals; cross-over intervention | Breakfast with 0–6 g AX | =Postprandial glycemia; ↓ postprandial insulinemia ↑ postprandial total ghrelin | [44] |
| AXOS (avDP = 15, avDS = 0.26) from wheat bran processing | 20 healthy individuals; cross-over intervention | Test meal with 0–0.2–0.7–2.2–4.9 g AXOS | ↓ Urine $^{15}$N-excretion; ↑ fecal $^{15}$N-excretion = urinary p-cresol excretion; ↑ breath $H_2$ excretion | [45] |
| AXOS (avDP = 6, avDS = 0.26) from wheat bran processing | 20 healthy individuals; randomized, placebo-controlled cross-over intervention | 10 g AXOS or placebo (maltodextrin) daily for 3 weeks with a 4-week washout period | =Blood lipids; ↓ urinary p-cresol excretion; ↑ bifidobacteria | [46••] |

avDP, average degree of polymerization; avDS, average degree of substitution; AX, arabinoxylan; AXOS, arabinoxylan oligosaccharides; LMCT, liquid meal challenge test; NDC, nondigestible carbohydrate; NEFA, nonesterified fatty acids; OGTT, oral glucose tolerance test.

## Conclusion

Review of the evidence indicates that NDC present in wheat grain are important in concentration and are interesting colonic nutrients with prebiotic potency that could be relevant in the context of obesity and diabetes. Nevertheless, a number of questions on how and why the gut microbiota modulation by wheat NDC may be associated with improvement of obesity and diabetes will have to be answered. Regardless of the differences in bacterial metabolism performances following their avDP and avDS, a systematic approach is needed in order to identify the intrinsic and processing factors that could promote growth and/or metabolism of gut bacteria (bifidobacteria) *in vitro* and *in vivo*, on the one hand; and that could positively affect metabolic disorders associated to obesity, on the other hand. The possibility of isolating specific NDC from wheat such as wheat dextrin and AXOS through processing technologies (pearling, sieving), heating and/or enzymatic modifications look very promising nutrients.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 762).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This paper nicely presents that AXOS supplementation (10 g/day) is able to modulate gut microbiota composition in humans with a specific increase in fecal bifidobacteria and a reduction in proteolytic fermentation.