Plant Foods Hum Nutr (2016) 71:123–128
DOI 10.1007/s11130-016-0547-4

ORIGINAL PAPER

Feruloylated Oligosaccharides from Maize Bran Modulated the Gut Microbiota in Rats

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Published online: 10 May 2016
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Abstract Corn bran is a byproduct produced from corn milling; it is rich in ferulic acid and hemicellulose. In this research, the effects of feruloylated oligosaccharides (FOs) from maize bran on the microbial diversity and profiles in rat feces were investigated through 16S rRNA sequencing. FOs significantly increased bacterial richness and diversity compared with the control and xylooligosaccharides (XOS) alone. In comparison with the control group and the group administrated with XOS, FOs orally administered at 300 mg/kg increased OTU in feces by 57.0 and 24.8 %, and Chao value by 93.4 and 37.6 %, respectively. FOs also influenced obesity- and diabetes-associated bacteria. Oral administration of FOs at 300 mg/kg decreased the ratio of *Firmicutes* to *Bacteroidetes* from 477.7:1 to 55.1:1; greatly increased the reads of bacteria that were previously found resistant against diabetes in rats, such as *Actinobacteria*, *Bacteroides*, and *Lactobacillus*; whereas decreased diabetes-prone bacteria, such as *Clostridium* and *Firmicutes*.

Juanying Ou and Junqing Huang contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s11130-016-0547-4) contains supplementary material, which is available to authorized users.

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Keywords Feruloylated oligosaccharide · Microbiota · Obesity · Diabetes

Abbreviations

ACE	Abundance-based coverage estimator
Chao	Chao estimator
FA	Ferulic acid
FOs	Feruloylated oligosaccharides
OTU	Operational taxonomic units
XOS	Xylooligosaccharides

Introduction

The human gut is the natural habitat for large and dynamic bacterial communities; gut microflora primarily salvage energy and absorbable nutrients, exert trophic effects on intestinal epithelia and on immune structure and function, and protect the colonized host against invasion by alien microbes [1]. Gut microflora are also associated with certain pathological disorders, such as colon cancer, inflammatory bowel diseases, or even obesity, diabetes, and hepatic encephalopathy [2, 3].

Functional oligosaccharides promote normal flora proliferation and pathogen suppression in the gastrointestinal tract, and show protection against hypercholesterolaemia, hyperglycaemia and intestinal disorders [4]. Feruloylated oligosaccharides (FOs) are a kind of functional foods derived from arabinoxylans; in which, ferulic acid (FA) is esterified to L-arabinofuranosyl side chain of oligosaccharides, and possess the physiological functions of both FA and oligosaccharides [5, 6].

Different from pure oligosaccharides, FOs still release FA after fermentation by gut microorganisms [7], which exhibits antimicrobial activity against various microorganisms [8]. The

FA released in the colon can be absorbed in the body, where it exerts various physiological functions as free FA, including anticarcinogenic effect in the colon [9–11]. Similar to oligosaccharides, FOs can selectively stimulate the growth of *Bifidobacterium* and *Lactobacilli* in *in vitro* studies [12]. They also increase the growth of *Lactobacilli* and *Bifidobacteria* in cow fecal cultures [2, 13].

Whether and how these FOs influence the growth of gut microbiota *in vivo* are unknown. In this research, we aimed to investigate the effect of FOs prepared from maize bran (with highest content of FA among lignocellulosic materials) on the profiles of stool microbiota in rats using xylooligosaccharides (XOS) without bound FA as a control, which is derived from xylan and has been proven with beneficial effect on gut health [14].

Materials and Methods

Materials FA was purchased from Sigma–Aldrich Company (St. Louis, MO, USA). Xylose, arabinose, galactose, glucose, mannose, and fucose were purchased from Aladdin Reagents Database Inc. (Shanghai, China), XOS (92 %) from Shandong Longlive Bio-Technology Co., Ltd. (Dezhou, Shandong Province, China), with xylobiose, xylotriose, and xylotetranose content 36.3, 31.8 and 27.9 g/100 g, respectively.

FOs were prepared in accordance with our previous method [15]. The separated FOs used for animal test had an average polymerization degree of 4.5 and moisture content 3.7 %, which contained two feruloylated oligosaccharides (feruloylated arabinose and 5-*O*-FA-α-L-arabinose-1,3-xylose), with the content of bound FA, free FA, xylose, arabinose, and galactose at 46.8, 2.4, 564.3, 284.6, and 129 mg/g, respectively.

Animal Groups and Experimental Design Sprague–Dawley male rats weighing 160–170 g were obtained from the Experimental Animal Center of Guangdong Province (Guangzhou, China). The animals with three rats *per* cage were acclimatized for seven days in an environmentally controlled room maintained at 21 ± 2 °C with a 12 h light–dark cycle. The animals were divided into five groups ($n = 9$). Group 1 received normal feed. Groups 2, 3, 4, and 5 received normal feed and intragastrically administrated with 300 mg/kg body weight (bw)/day (d) XOS, 300 mg/kg bw/d XOS + 12 mg/kg bw/d FA, 300 mg/kg bw/d FOs, and 600 mg/kg bw/d FOs, respectively. Five weeks later, fresh feces were collected and stored at -80 °C until analysis.

Fecal Bacterial DNA Extraction, 16S rRNA Gene PCR Amplification and Sequencing The fecal bacterial DNA of each sample was extracted using TIAN amp Stool DNA kit (Tiangen, Beijing, China) in accordance with the manufacturer's instructions. The V4 hypervariable domain of 16S rRNA gene were PCR amplified from microbial genome DNA which were harvested from fecal samples; the primers forward S-D-Bact-0564-a-S-15 (5'-AYTGGGYDTAAAGNG-3') and reverse S-D-Bact-0785-b-A-18 (5'-TACNVGGGTATCTAATCC-3') were designed according to Klindworth et al. [16]. PCR reactions contained 5–100 ng of DNA template, 1 × GoTaq Green Master Mix (Promega, Madison, WI, USA), 1 mM $MgCl_2$, and 2 pmol each primer. The following thermal cycling conditions were used: initial denaturation at 94 °C for 3 min; 35 cycles at 94 °C for 45 s, 50 °C for 60 s, and 72 °C for 90 s; and a final extension at 72 °C for 10 min. Amplicons were purified using the Qiaquick 96 kit (Qiagen, Hilden, Germany) and quantified using PicoGreen dsDNA reagent (Invitrogen, Grand Island, NY, USA) in accordance with the manufacturers' instructions. Purified libraries were sequenced on the Illumina GAIIx platform from KangChen Bio-Tech (Shanghai, China).

The bacterial sequence reads were compared to a reference database of known 16S rRNA genes obtained from the Ribosomal Database Project (RDP). The bacterial sequences were assigned taxonomically on the basis of the RDP classifiers. Rarefaction curves, Shannon indices, and Chao nonparametric richness estimators were determined using the mothur package [17]. The microbial community structures in different samples were compared using FastUniFrac on the basis of the phylogenetic relationships between representative reads (OTUs) from different samples [17].

Determination of FA, Reducing Sugars, Total Sugars, Monosaccharide Composition and Feruloylated Oligosaccharides in FOs Bound FA was determined using HPLC as we previously described [15, 18]. Reducing sugars were determined using DNS method, and total sugars were determined using DNS method after the FOs were acid-hydrolyzed by 1 M H_2SO_4 at 100 °C for 3 h according to the method used by van den Borne et al. [19]. Monosaccharides in FOs were determined by gas chromatography–mass spectrometry (GC–MS) according to Sun et al. [20]. The species of feruloylated oligosaccharides were determined according to Yao et al. [15].

Results and Discussion

Body Weight and Growth No differences for growth feature between the treatments were observed. Feeding XOS and FOs did not significantly change the body weight of rats compared with the control at early days (Fig. S1). However, the body weight of the group fed with FOs at a dose of 300 mg/kg was lower than the other treatments after day 12, and the body weight of the group fed with XOS was higher than the other treatments after day 17 (Fig. S1).

Table 1 OTU and different estimator parameters for alpha diversity in the feces of rats after oral administration of FOs for five weeks

	OTU[a]	Chao	ACE	Shannon	Simpson
Control	879 ± 24a[b]	1889 ± 113a	3413 ± 33a	1.23 ± 0.08a	0.45 ± 0.02c
XOS[b]	1106 ± 50b	2654 ± 167b	3923 ± 135b	2.08 ± 0.13b	0.24 ± 0.01a
XOS + FA	1279 ± 115b	3496 ± 133c	4484 ± 210e	2.41 ± 0.02c	0.26 ± 0.05a
FOs (300 mg/kg)	1380 ± 22c	3653 ± 90c	5508 ± 81c	2.49 ± 0.05c	0.25 ± 0.02a
FOs (600 mg/kg)	1387 ± 11c	3645 ± 154c	6484 ± 266d	2.41 ± 0.07c	0.27 ± 0.02b

[a] *ACE* abundance-based coverage estimator, *Chao* Chao estimator, *FA* ferulic acid, *FOs* feruloylated oligosaccharides, *OTU* operational taxonomic units, *XOS* xylooligosaccharides

[b] Values (means ± SD, $n = 9$) with different letters within a column are significantly different at the 5 % level

Microbial Diversity in Rat Feces after five Weeks of Oral FOs Administration In the alpha diversity analysis, Chao and OTUs are two important parameters to estimate the richness and the total number of species in ecology [17]. Table 1 lists the diversity indices for feces microbiota. OTU results indicated that FOs administration significantly influenced the feces microbiota in rats. Chao, ACE, Shannon, and Simpson diversity indices were calculated to estimate the number of unobserved species in the different treatments (Table 1). Chao was highly correlated with but much lower than ACE in all treatments (Table 1). Compared with XOS alone, FOs or XOS combined with FA increased bacterial richness (Chao value) in rat feces. Similarly, Shannon estimator of bacterial diversity were higher and Simpson estimator was lower in the FOs or XOS + FA treatment than in the XOS treatment alone, further confirmed that feeding rats with FOs increased bacterial diversity in the gut of rats.

XOS showed superior prebiotic activity to fructooligosaccharides and other oligosaccharides [14]. The results in this research indicated that feruloylated oligosaccharides showed even higher prebiotic activity than XOS, indicating their prebiotic potential.

FOs Altered Microbiota Profiles in Rat Feces *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* are the dominant bacteria detected in rat feces (Table 2). Feeding rats with FOs significantly increased *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* but slightly decreased *Firmicutes*; however, feeding rats with higher FOs doses significantly decreased *Actinobacteria* compared with feeding rats with lower FOs doses (Table 2). The growth stimulatory effect of FOs or XOS combined with FA for *Bacteroidetes* was much higher than that of XOS alone, but a converse effect was observed for *Proteobacteria* (Table 2). *Acidobacteria*, *Cyanobacteria*, *Deferribacteres*, *Planctomycetes*, *Tenericutes*, and *Verrucomicrobia* were also identified as minor bacterial groups in rat feces (Table 2). In the *Firmicutes*, the dominant genera were *Lactobacillus* and *Clostridia* (Table 3). FOs significantly increased *Lactobacillus* and *Ruminococcus* but significantly decreased *Clostridia* in rat feces (Table 3). Compared with the control, feeding rats with FOs at level of 300 and 600 mg/kg increased *Lactobacillus* by 53.5 and 87.2 %, but decreased *Clostridia* by 40.1 and 66.4 %, respectively. FOs also influenced the number of reads for *Enterococcus* and *Streptococcus* but only slightly affected

Table 2 Number of reads assigned to each phylum level identified in the feces of rats

	Control	XOS[a]	XOS + FA	FOs (300 mg/kg)	FOs (600 mg/kg)
Acidobacteria	2 ± 0a[b]	6 ± 2c	3 ± 1b	10 ± 3d	7 ± 3cd
Actinobacteria	244 ± 38a	949 ± 66c	1003 ± 99c	1321 ± 176d	370 ± 13b
Bacteroidetes	201 ± 14a	431 ± 2b	1224 ± 139c	1579 ± 133d	1685 ± 136e
Cyanobacteria	1 ± 1a	2 ± 1a	7 ± 4b	2 ± 1a	1 ± 1a
Deferribacteres	2 ± 1a	8 ± 2c	8 ± 2c	5 ± 1b	3 ± 1a
Firmicutes ($\times 10^4$)	9.60 ± 0.21c	8.51 ± 0.44a	8.82 ± 0.75b	8.70 ± 0.22b	8.69 ± 0.41b
Deferribacteres	3 ± 2a	20 ± 3d	14 ± 2c	7 ± 2b	3 ± 1a
Planctomycetes	0a	5 ± 2c	0a	3 ± 1b	1 ± 1a
Proteobacteria	1371 ± 143a	3084 ± 237d	3805 ± 331e	2506 ± 30c	1434 ± 211b
Tenericutes	0a	4 ± 1c	2 ± 1b	13 ± 4d	25 ± 5e
Verrucomicrobia	5 ± 2b	3 ± 1a	2 ± 1a	3 ± 1a	5 ± 1b
Cyanobacteria	1 ± 1b	2 ± 1b	0a	2 ± 1b	0a

[a] *FA* ferulic acid, *FOs* feruloylated oligosaccharides, *XOS* xylooligosaccharides

[b] Values (means ± SD, $n = 9$) with different letters within a line are significantly different at the 5 % level

Table 3 Number of reads assigned to each genus level of *Firmicutes* identified in the feces of rats

	Control	XOS[a]	XOS + FA	FOs (300 mg/kg)	FOs (600 mg/kg)
Enterococcus	40 ± 2e[b]	32 ± 4d	23 ± 1c	17 ± 3b	11 ± 1a
Lactobacillus	21,533 ± 1773a	33,056 ± 2694b	34,179 ± 3009b	33,054 ± 2563b	40,309 ± 2743c
Lactococcus	4 ± 2a	404 ± 41d	305 ± 28c	16 ± 2b	5 ± 2a
Streptococcus	343 ± 32b	387 ± 54c	45 ± 14a	535 ± 18d	552 ± 27e
Clostridia	47,417 ± 1670e	45,932 ± 165d	23,958 ± 2032b	28,384 ± 919c	15,951 ± 897a
Papillibacter	16 ± 3a	30 ± 5b	74 ± 12d	48 ± 9c	19 ± 2a
Ruminococcus	34 ± 5a	262 ± 43b	536 ± 17d	492 ± 41c	240 ± 11b
Turicibacter	632 ± 17c	541 ± 29b	68 ± 3a	546 ± 42b	657 ± 38c

[a] *FA* ferulic acid, *FOs* feruloylated oligosaccharides, *XOS* xylooligosaccharides

[b] Values (means ± SD, $n = 9$) with different letters within a line are significantly different at the 5 % level

Lactococcus and *Turicibacter* (Table 3). Table 4 shows the effect of feeding rats with FOs on *Bacteroidetes*, *Acidobacteria*, and *Proteobacteria*. FOs influenced the growth of most bacteria but only slightly affected *Bifidobacterium*, another probiotics existing in the colon (Table 4).

FOs and Obesity-Associated Bacteria Obesity is a chronic disease that causes morbidity, mortality, and reduction of life quality; this disease was proved to be associated with gut microbiome [2, 21]. Turnbaugh et al. [3] found that microbiota in the distal gut of obese mice has a greater relative abundance of *Firmicutes* and lower relative abundance of *Bacteroidetes* compared with that in the distal gut of lean mice. In the present research, FOs administration significantly increased the relative abundance of *Bacteroidetes* while significantly decreased the relative abundance of *Firmicutes* (Table 2). The ratio of the number of reads of *Firmicutes* to that of *Bacteroidetes* decreased from 477.7:1 in the control to 55.1:1 and 51.5:1 in the 300 and 600 mg/kg FOs treatments, respectively; the ratio for the rats fed by 300 mg/kg XOS was 197.4:1. From the alteration view of obesity-associated microbiota, FOs may play a potential role in body weight control and show superiority to XOS.

FOs and Diabetes-Associated Bacteria Diabetes is a chronic disease that is becoming a major public health burden worldwide [22]. Our previous research [23] indicated that FOs

Table 4 Number of reads assigned to each genus of *Bacteroidetes*, *Acidobacteria*, and *Proteobacteria* identified in rat feces

		Control	XOS[a]	XOS + FA	FOs (300 mg/kg)	FOs (600 mg/kg)
Bacteroidetes	*Bacteroides*	1 ± 1a[b]	1 ± 1a	29 ± 5c	22 ± 1b	50 ± 7d
	Prevotella	75 ± 5bc	58 ± 8a	78 ± 6c	70 ± 7b	53 ± 6a
	Odoribacter	0 ± 0a	1 ± 1b	3 ± 1c	2 ± 1b	1 ± 1b
	Parabacteroides	2 ± 1a	2 ± 1a	5 ± 2b	23 ± 2c	32 ± 3d
	Alistipes	1 ± 1a	4 ± 1b	76 ± 8c	77 ± 5c	88 ± 5d
Acidobacteria	*Bifidobacterium*	15 ± 1c	27 ± 3d	6 ± 1a	6 ± 1a	12 ± 2b
	Eggerthella	218 ± 27a	908 ± 43c	999 ± 25d	1092 ± 91d	368 ± 4b
	Collinsella	4 ± 2b	18 ± 4d	7 ± 4c	6 ± 2c	1 ± 1a
Proteobacteria	*Brevundimonas*	3 ± 2a	27 ± 4d	12 ± 2b	34 ± 3e	16 ± 2c
	Bosea	18 ± 6a	135 ± 8e	51 ± 4b	117 ± 17d	76 ± 2c
	Rhizobium	0 ± 0a	1 ± 1b	3 ± 1c	2 ± 1b	1 ± 1b
	Desulfovibrionaceae	146 ± 12a	232 ± 23b	605 ± 33d	555 ± 20c	258 ± 23b
	Helicobacter	18 ± 4a	143 ± 12c	136 ± 15c	36 ± 4b	35 ± 4b
	Acinetobacter	15 ± 4b	22 ± 3c	21 ± 5c	20 ± 2c	10 ± 1a
	Psychrobacter	3 ± 2a	15 ± 4bc	12 ± 2b	20 ± 2d	16 ± 2c
	Pseudomonas	24 ± 3b	81 ± 5d	12 ± 2a	42 ± 4c	22 ± 3b

[a] *FA* ferulic acid, *FOs* feruloylated oligosaccharides, *XOS* xylooligosaccharides

[b] Values (means ± SD, $n = 9$) with different letters within a line are significantly different at the 5 % level

prepared from wheat bran mitigate diabetes syndrome in alloxan -induced diabetic rats. In addition, colon microbiota has been proven an amazingly rich source of novel immunomodulatory molecules and is associated with diabetes [24].

Murri et al. [25] compared the gut microorganisms in the healthy and diabetic children. They found that in the children with diabetes, the bacterial number of *Actinobacteria*, *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and the ratio of *Firmicutes* to *Bacteroidetes* were all decreased, while the quantity of *Firmicutes* significantly increased with respect to healthy children. Moreover, *Clostridium* correlated positively and significantly with the plasma glucose level in the diabetes group. In our present research, compared with the control, FOs at levels of 300 and 600 mg/kg were found to increase *Actinobacteria* (by 4.41 and 0.52 times), *Bacteroides* (by 7.86 and 8.38 times), and the ratio of *Bacteroidetes* to *Firmicutes* as shown in Table 2, and *Lactobacillus* (by 58.7 and 87.2 %) as shown in Table 3. However, they significantly decreased *Clostridium* (by 40.1 and 66.4 %) and *Firmicutes* (by 9.3 and 9.53 %) as shown in Table 2 and Table 3. These results suggest that FOs prepared from maize bran may prevent or protect against diabetes by modulating the growth of diabetes-related bacteria in the colon.

This research investigated the effect of functional ingredient of FOs on gut microbiota in normal rats. The results indicated that FOs exhibited higher prebiotic capacity than XOS. In order to get full information of this kind of functional food, future investigation needs to be carried out in diseased models, such as diabetic or obese animal models.

Conclusion

Oral administration of FOs significantly increased bacterial richness and diversity in the feces of rats compared with the control and XOS, a structure-similar oligosaccharide to FOs without bound FA. Feeding rats with FOs at level of 300 mg/kg bw/day increased OTUs by 57.0 % compared with the control, and by 24.8 % compared with the rats administrated with the same dose of XOS. FOs significantly altered the obesity-associated and diabetes-associated bacteria. Oral administration of 300 mg/kg FOs decreased ratio of *Firmicutes* to *Bacteroidetes* from 477.7:1 to 55.1:1, increased diabetes-resistant bacteria, such as *Actinobacteria*, *Bacteroides*, *Lactobacillus* by 4.41, 9.84 times, and 58.7 %, respectively; whereas decreased diabetes-prone bacteria, such as *Clostridium* and *Firmicutes* by 40.1 % and 9.3 % respectively. It can be assumed that FOs is a kind of functional ingredient superior to XOS for gut health.

Acknowledgments This work was supported by Fundamental Research Funds for the Central Universities (NO. 21615483) and the National Science Foundation of China (31371745). We also appreciate Guangzhou Gene Denovo Co. (Guangzhou, China) for helping us to carry out 16S rRNA gene sequencing.

Compliance with Ethical Standards

Animal Study We have animal studies in this research. However, we only collect fresh feces from the rats.

Conflict of Interest The authors declare no conflicting or financial disclosures.

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