http://dx.doi.org/10.22037/afb.v%vi%i.20212

Review Article

APPLIED FOOD BIOTECHNOLOGY, 2018, 5 (3):121-130
Journal homepage: www.journals.sbmu.ac.ir/afb

pISSN: 2345-5357
eISSN: 2423-4214

Xylooligosaccharidesand Arabinoxylanoligosaccharides and Their Application as Prebiotics

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Abstract

Background and Objective: Xylooligosaccharides and arabinoxylanoligosaccharideshave been subject to nearly 30 years of in vitro and clinical trials, and advances in process technology have led to more widespread commercial availability. This review was conducted to examine xylooligosaccharidesand arabinoxylanoligosaccharidesas next generation prebiotics.

Results and Conclusion: Xylooligosaccharides and arabinoxylanoligosaccharides are based upon 5-carbon sugars, and their microbial utilization in the digestive tract is thus fundamentally different from prebiotics such as fructooligosaccharides, inulin, and resistant starch that are oligomers/polymers of 6-carbon sugars connected by α bonds. Five carbon sugars and oligosaccharides connected by β bonds are more narrowly utilized; xylooligos-accharides and arabinoxylanoligosaccharidesare especially effective for selective feeding of *Bifidobacteria*, although they can also be used by some strains of *Lactobacilli* and other bacteria. Clinical studies on xylooligosaccharides and arabinoxylanoligosacch-aridesreport beneficial impacts upon digestive health, management of blood sugars and lipids, beneficial modification of immune markers, and benefits for laxation. These outcomes have typically been observed at 1-4 grams per day, a lower dose than required for other prebiotics such as fructooligosaccharidesand inulin. The lower dose requirement for clinical efficacy also provides advantages in terms of product formulation and more options for delivery of a clinically beneficial dose to consumers.

Conflict of interest: The authors are the Chief Science Officer and Chief Nutrition Officer of Prenexus Health Inc.

Article Information

Article history:

Received	01 Feb 2016
Revised	22 Apr 2016
Accepted	27 Jun 2016

Keywords:
- *Bifidobacteria*
- Human clinical trials
- *Lactobacilli*
- Prebiotics
- Xylooligosaccharides

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1. Introduction

Prebiotics have been increasingly recognized for their ability to selectively promote the growth of beneficial bacteria, and provide health benefits. While the original focus had been on modulation of the microbiota in the digestive tract, more recently, opportunities to modify the microbiota of the skin, the oral cavity, and urogenital tract have been identified. The recently modified consensus definition for prebiotics from the International Scientific Association for Probiotics and Prebiotics reflects this broader sphere of influence[1].Critically, to satisfy the consensus definition for a prebiotic, the substrate must:

i) Selectively stimulate the growth of beneficial bacteria. It is not sufficient to modify the microbial community based upon the percentage of certain genera or species, as this could be accomplished with antimicrobial agents that are not substrates.

ii) Deliver a health benefit. In this regard, it is important to show, via human clinical trials, the ability of the prebiotic to promote health. It is also important to note that there are some newly identified compounds that may promote the growth of certain beneficial bacteria, but their health benefits have not yet been clearly documented.[1]

To date, the prebiotics market has been dominated by fructans, either inulin or fructooligosaccharides (FOS), although xylooligosaccharides (XOS) have been commercially available for nearly 30 years, mainly in southeast Asia, and galactooligosaccharides (GOS) enzymatically produced from lactose are also available commercially. This review focuses on clinical trials aimed at establishing the efficacy of XOS to maintain and enhance health. This review also includes arabino-

xylanoligosaccharides (AXOS), which are related to XOS, but contain side groups of arabinose on the XOS backbone. This review will also discuss the types of bacteria able to utilize XOS, based upon specific enzymes and carbohydrate transport systems. Differences in these transporters and enzyme systems between bacteria can account for variations in specificity between the various types of prebiotics, which all have different chemical and bonding structures.

XOS and AXOS are fundamentally different from FOS, inulin, and GOS. The latter are oligomers of 6-carbon sugars (glucose/fructose/galactose), whereas XOS and AXOS are oligomers of xylose and arabinose, which are 5-carbon sugars. These differences in chemical structure can affect the degree and rate of utilization of these oligosaccharides by beneficial and harmful bacteria, due to highly specific membrane transport systems and enzymes.

Prebiotics, including xylooligosaccharides, selectively stimulate the growth of specific *Bifidobacteria*(referred to as "B", below),*Lactobacilli*(referred to as "L" below), and other potentially beneficial bacteria. Growth of these beneficial bacteria may occur from direct utilization of the prebiotic substrate, and/or it may arise from cross-feeding, in which metabolites from so-called "primary degraders" feed certain beneficial bacteria. As shown in Figure 1, the growth of these beneficial bacteria can lead to a cascade of effects. *Bifidobacteria* and *Lactobacilli* tend to produce short chain fatty acids (SCFAs) such as acetic acid, propionic acid, and butyric acid, along with lactic acid, which collectively reduce the pH in the gastrointestinal tract, can act as substrates for other bacteria, and in some cases, can be absorbed into the bloodstream to provide other distal effects. In particular, acetate can be transported to the muscle and the brain, and may thus be responsible in part for some of the effects attributed to the "Gut-Brain Axis". Acetate also triggers hormones that are responsible for cholesterol production and regulate appetite. Propionate is transported to the liver, where it can play a role in regulation of blood glucose and cholesterol synthesis. Butyrate is a primary energy source for colonic epithelial cells, which impacts the production of colonocytes that have the potential to protect against colon cancer. The lower colonic pH created by these additional SCFAs also provides a more favorable environment for absorption of minerals such as calcium and magnesium, which are more soluble at a lower ph. The lower pH also creates a less favorable environment for the growth of bacteria responsible for protein fermentation, thus reducing the production of phenolics, ammonia and related compounds that are considered to have adverse health effects if present in excess.

In Vitro Fermentability Studies with XOS

An extensive number of in vitro studies have been undertaken to evaluate the fermentability of XOS, particularly in recent years when it has been possible to delve further into species and strain specific attributes. Okazaki et al. [2,3] conducted in vitro fermentations with *Bifidobacterium longum (B. longum), Bifidobacterium infantis (B. infantis),* and *Bifidobacterium adolescentis (B. adolescentis).*In particular, *B. adolescentis*was able to utilize xylobiose (DP2) and xylotriose (DP3). Hopkins [4]conducted growth trials using commercial XOS (DP2 – DP4, Suntory) and found that growth depended upon the strain of *Bifidobacteria*. Kontula [5]observed that among the strains they tested,*Lactobacillus plantarum*(*L. plantarum*) could utilize XOS, while *Lactobacillus rhamnosus* (*L. rhamnosus*) and *L. lactis* could not. Gullon [6] studied fermentability of *B. longum, B. adolescentis, B. breve* and *B. infantalis* with XOS (DP2-DP6) produced from rice husks. *B. adolescentis* was most readily able to use this substrate. Li et al. [7] conducted an extensive study of XOS utilization with 35 *Bifidobacterium* and 29 *Lactobacillus* strains. They noted that 86% of *Bifidobacterium* strains exhibited growth on XOS, even at a low dose, and 100% exhibited growth at a higher XOS dose. Select strains of *B. breve, B. animalis, B. infantis, B. longum, B. pseudocatenulatum,* and *B. catenulatum* all exhibited strong growth at low XOS doses, while higher XOS doses were typically needed to induce growth of*B. bifidum, B. thermophilum,* and *B. adolescentis.* In contrast, strains of *Lactobacillus* were able to use XOS, but less efficiently compared to *Bifidobacteria*. XOS led to growth of*L. brevis, L. casei, L. fermentum, L. rhamnosus GG, L. plantarum, and L. reuteri,* but growth was less robust compared to *Bifidobacteria.* There was no growth of the four strains of *L. acidophilus* and *L. gasseri* tested. Makelainen et al. [8] conducted a comprehensive study to compare the fermentability of various prebiotics and fiber sources by 12 strains of *Bifidobacteria*, 4 *Lactobacillus* strains, and 11 bacterial strains considered to be pathogenic, including *Clostridium* (*C.) difficile, C. perfringens, Staphylococcus (S.) aureus,* and *Escherichia (E.) coli* 0157:H7. They observed that most *B. lactis* strains were able to utilize XOS quite readily, and*B. adolescentis* also exhibited acceptable growth. They noted that *L. bulgaricus* and *L. acidophilus* NFCM grew on XOS, but only at about 30% of the rate of growth on glucose. Importantly, none of the pathogenic strains grew on XOS, whereas several of the pathogenic strains grew on galactooligosaccharides (GOS) and FOS. This is likely attributable to differences in the structure of the prebiotics (oligomers of C5 vs. C6 sugars), and the fact that the membrane transport systems and enzymes for FOS and GOS utilization are more broadly available throughout the microbial community.

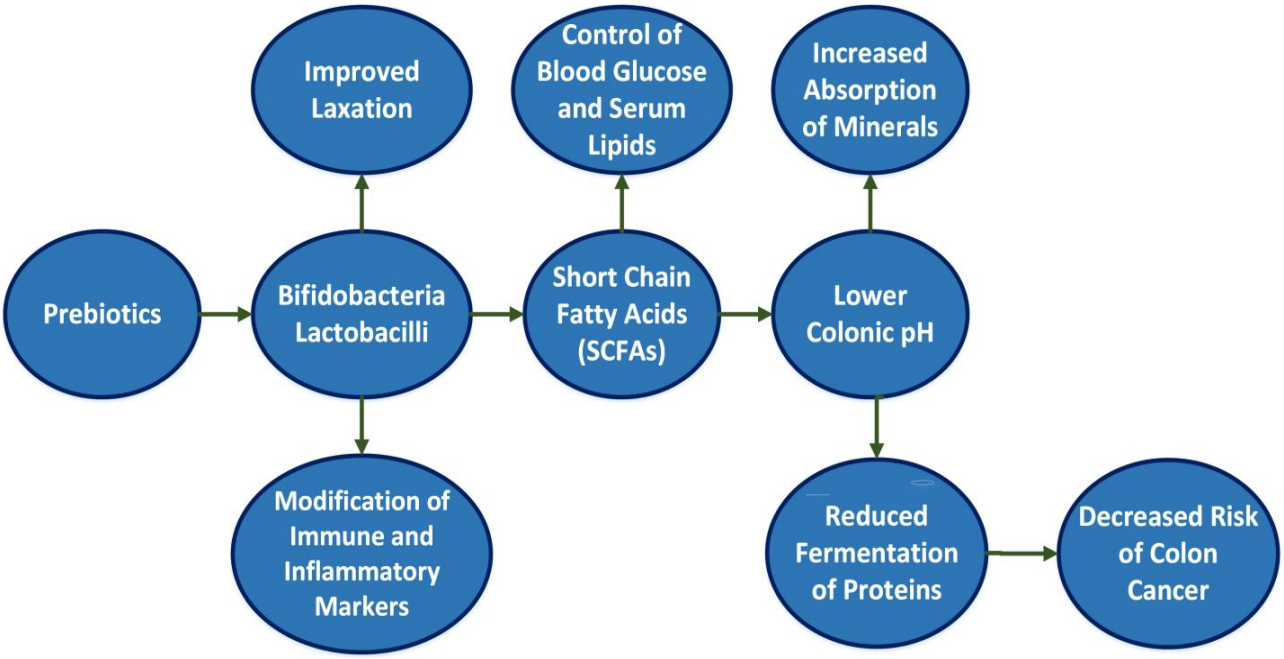

Figure 1. Impacts of Prebiotic Consumption

Ho et al. [9] examined the effect of degree of polymerization upon the fermentability of XOS produced from palm oil empty fruit bunches, including fractions with an average degree of polymerization (DP) of 4, 7, 14, 28, 44, and 64. This in vitro study examined growth in 3 separate mixed culturesfrom faecal stool samples, unlike the pure culture studies described above. Fluorescent in-situ hybridization (FISH) was used to enumerate genus-level changes in bacterial population. High DP fractions (average DP = 28, 44, 64)did not promote the growth of *Bifidobacteria*, whereas *Bifidobacteria* grew well on low DP fractions of XOS (average DP= 4-14). *In vivo*, high DP fractions may be hydrolyzed by *Bacteriodes* and *Prevotella* into lower DP XOS fractions that could be used by *Bifidobacteria*[10,11].

Ananieva et al.[12]used XOS and glucose to investigate the growth of lactic acid bacteria, comprising 2 strains of *L. plantarum*, 3 strains of*L. brevis*, and 4 strains of *L. sakei*. The authors observed no growth of the tested strains of *L. sakei*on XOS, whereas growth rates of the 2 *L. plantarum* strains and 1 of the 3 *L. brevis* strains were comparable on glucose and XOS.

Branching and substitutions on shorter chain XOS, e.g., with arabinan or ferulic acid, can influence selectivity for fermentation. Okazaki [2,3] found selectivity towards *Bifidobacteria*, whereas Van Laere [13] and Jaskari[14]observed that XOS produced from oat bran could also induce growth of *Lactobacillus acidophilus*, *Klebsiella*, *Clostridum spp*., and *Bacteriodes spp*. Arabinoxylans produced from wheat, with one or two arabino substitutions, were less amenable to fermentation by *Bifidobacteria* and *Bacteriodes*. Pastell et al.[15] compared fermentation of XOS and AXOS on single strains of *B. breve*, *B. longum*, and *B. adolescentis*, along with a mixed culture of faecal microbiota. They observed efficient growth of *B. adolescentis* on XOS and AXOS, but limited growth of this strain of *B. longum* on oligosaccharides, which instead preferred to grow on xylose and arabinose. Interestingly, growth of *B. adolescentis* was better on XOS than xylose, indicating intracellular transport of XOS, rather than extracellular hydrolysis of XOS to produce xylose for microbial fermentation. *B. breve* was able to grow on a more complex high viscosity XOS produced from rye flour.Kabel[16] and Ho et al. [9] also observed that XOS with acetyl substitutions could be fermented by selected*Bifidobacteria*. Ultimately, the ability of different species to use XOS of different degrees of polymerization or substitution depends upon the organism's inherent enzymes, including β-xylosidase, α-glucuronidase, acetylxylan-esterase, and α-L-arabinosidase.

Physicochemical Properties and Stability Parameters Affecting Use of XOS

Courtin et al. [17] evaluated various properties of FOS (DP5), XOS (DP3), and AXOS (DP15) -collectively, non-digestible oligosaccharides (NDOs) that could affect their utility as prebiotics and effectiveness in different food/beverage preparations. They observed that none of the NDOs underwent substantial degradation at pH 2, pH 3, or pH 7. Among the NDOs studied, XOSs were most

stable under acid conditions (most likely to be encountered in the gastrointestinal (GI) tract), but were more susceptible to degradation at alkaline pH. The glycosidic linkages in FOS were most sensitive to acidic conditions that would lead to early breakdown and subsequent digestion/fermentation in the GI tract. Rumpagaporn et al. [18]tested the stability of a 0.3% wt XOS solution at pH3 and pH7. They tested two variations - a native long chain arabinoxylan and a fraction that was hydrolyzed to lower DP using xylanase. They tested stability at 37^{o}C, 100^{o}C, and in a "pressure cooker" operating at 135^{o}C for 30 or 60 minutes. There was a small amount of hydrolysis of the higher DP XOS after treatment at 135C for 60 minutes, i.e., a shift to a lower DP. There was about 12% more of the lower DP XOS after 60 min at 135^{o}C and pH3. However, at pH 7, there was no degradation at 135^{o}C after 60 minutes. Collectively, these studies indicate that solutions of XOS and AXOS are stable at elevated temperatures and under a range of pH conditions. It is likely that a powdered/dry product would be stable at even higher temperatures. Their temperature and pH stability suggest that these prebiotic ingredients have good potential for use in food and beverage formulations, including juices and other products that may have a slightly acidic character.

Results from Human Trials

A large number of clinical trials have been published since XOS became commercially available nearly 30 years ago. Some recent trials have used AXOS, which typically includes >50% XOS. Table 1 summarizes these trials, including details regarding product and dose, patient population, study design, and key endpoints. Below we discuss some of the key trial results, including, where available, changes to the GI microbiome and clinical biomarkers of human health.

Impacts of XOS on laxation

Iino et al. [19] observed that 0.40 grams per day of XOS supplementation over 4 weeks in adult women increased the population of Bifidobacteria, while also improving abdominal conditions and stool frequency. Tateyama et al.[20]administered 4.2 grams per day XOS (Suntory) to pregnant women for 4 weeks, which led to reduced constipation, and improved/normalized stool consistency, with no adverse effects. Chung et al.[21] administered 4grams per day XOS for 3 weeks to seniors (> 65 years) without a recent history of GI disease. XOS supplementation increased the population of *Bifidobacteria* and faecal moisture, and reduced faecal pH. The product was well tolerated. Collectively, these trials point to improvements in laxation following consumption of XOS, at levels between 0.4 and 4.2 grams per day.

Impacts of XOS on regulation of lipids and blood glucose

Na and Kim [22]conducted a 28 day clinical trial in which either 1.4 or 2.8 grams per day of XOS was administered to healthy women. XOS intake at 2.8 grams per day reduced fecal pH after 14 days. Both groups experienced an increase in *Bifidobacteria* – after 14 days at 2.8 grams per day and 28 days at 1.4 grams per day. Serum triglyceride, cholesterol and glucose concentrations were significantly reduced in subjects taking 2.8 grams per day XOS. Sheu et al. [23] conducted a randomized, placebo-controlled study to assess the effect of XOS on subjects with type 2 diabetes. Patients were given 4grams per day Suntory 95P XOS (or a placebo) for 12 weeks. XOS reduced blood glucose, HbA1c, LDL, ox-LDL, apolipoprotein B, total cholesterol, and fructosamine. There was no impact on SCFAs. They collected data on GI symptoms, and no GI complaints were reported. Comparative literature indicated no effect of FOS on blood glucose or serum lipids in diabetics[24]. Yang et al. [25] administered 2.8 grams per day of a 70% XOS product to 13 healthy adults and 16 prediabetic adults over 8 weeks. They observed a tendency to reduce OGTT insulin in the prediabetic adults, along with lower levels of *Firmicutes*, a lower fecal pH, less excretion of cresol and acetate, and higher levels of butyrate in the stools. Childs et al. [26] observed that 8grams per day of XOS increased fasting HDL levels by 0.07 mm in healthy subjects; a 0.10 mm increase is associated with a 10% risk reduction in coronary heart disease.

Impacts of XOS on digestive health and microbiota

Kajihara et al. [27] administered 3grams per day of XOS orally for 2 weeks to patients with cirrhosis. They observed enhanced intestinal *Bifidobacteria* content and lower *Bacteriodes* content, with reduced levels of ammonia in the serum.

Finegold et al. [28] conducted a placebo-controlled trial in which 1.4grams per day or 2.8 grams per day of a 70% XOS product was administered for 8 weeks to healthy adults. They observed a statistically significant increase in the intestinal population of *Bifidobacteria* and *B. fragilis* at the 2.8 grams per day dose.

Childs et al. [26] conducted a clinical trial with 41 heathy subjects to assess the effects of XOS supplementation, either alone (8 grams per day) or in combination with the probiotic *Bifidobacterium animalis*. Supplementation with XOS alone statistically increased faecal *Bifidobacteria* counts and plasma HDL concentrations; the greatest increase in plasma HDL was noted from the XOS + probiotic combination. Both XOS and *B. animalis* individually altered concentrations of short chain fatty acids. The XOS was well tolerated, with no adverse effects reported.

Table 1. Summary of Clinical Trials Using XOS and AXOS

Study Authors	Product / Purity / Dose	Patient Population	Study Design and Duration	Control (Y/N)	Endpoints
Childs, C. et al.[26]	Longlive XOS (8grams per day) or XOS + with *B. lactis*	41 Healthy Adults	Randomized, double-blind, placebo-controlled, factorial cross-over study; 3 weeks dosing, with a 4 week washout between dosing periods	Yes	- IncreasedHDL levels by 0.07 mm (P = 0.005) • Increase of 0.10 mM is associated with 10% risk reduction in coronary artery disease - Increased# of bowel movements per day (P = 0.009) - Increased *Bifidobacteria* (P = 0.008) - Reduced IL-10 production (P = 0.049)
Chung,Y-C. et al.[21]	Suntory XOS95P, 4 grams per day	22 Healthy Adults (9 control, 13 XOS)	Randomized, placebo-controlled trial; includes a 1 week run-in, 3 weeks of dosing, and a 3 week washout	Yes	Statistically significant increase in fecal moisture (alleviates constipation) and fecal pH, with return to baseline post-washout (P < 0.05) - Statistically significant increase in *Bifidobacteria* content of the stool (P < 0.05)
Francois, I. et al.[21]	Fugeia wheat bran extract, 3grams per day, 10grams per day (comprised of 79% AXOS, which, in turn, consists of 49% XOS and 10% glucan)[1]	20 Healthy Adults	Double blind randomized placebo controlled cross-over trial; 3-week treatment periods interspersed with 2-week washout periods	Yes	- At 10grams per day: • Increased acetate, propionate, and butyrate (P = 0.009, P = 0.05, P = 0.001, respectively) • Reduced p-cresol (P = 0.039) • Lower fecal pH (P = 0.039) • Increased *Bifidobacteria* (P < 0.001) • Increased stool frequency (P = 0.258) • ReducedLDL (P = 0.168)
Na, M.H., and Kim, W.K.[22]	1.4 and 2.8 grams per day	14 Healthy Adults (7 per test group)	Randomized dose-dependent trial without a placebo; 4 weeks	Multiple dose study	- Reduced triglycerides, cholesterol and glucose in 2.8 grams per day group (all P < 0.05) - Increased *Bifidobacteria* content after 14 days (P < 0.05) - Increased lactic acid concentration (P < 0.05) While study lacked placebo, subjects saw effect of dose response over multiple doses
Cloetens, L. et al.[33]	AXOS, 10 grams per day (63% XOS, 17% arabinan, 12% glucan)	20 Healthy Adults	Randomized, placebo-controlled cross-over study; 3 weeks with AXOS or placebo, with 4-week washout between treatments	Yes	- Increased *Bifidobacteria* (P = 0.012) - Increased *B. adolescentis* (P = 0.013) - After 3 weeks, reduced urinary p-cresol (P = 0.011)
Finegold, S. et al.[28]	Longlive XOS; 1.4 or 2.8grams per day	32 Healthy Adults	Randomized double blind placebo-controlled trial; 2 week run-in period, followed by 8 weeks of treatment and a 2 week washout	Yes	- Statistically significant increase in *Bifidobacteria* (P = 0.007; 2.4 grams per day dose) and *B. fragilis* (P = 0.001; 2.4 grams per day dose) relative to placebo/baseline
Francois, I. et al.[34]	Fugeia Wheat Bran Extract, 5grams per day (comprised of 79% AXOS, which, in turn, consists of 49% XOS and 10% glucan)	29 Healthy Children	Double blind randomized placebo controlled cross-over trial; 3 weeks	Yes	- Increased *Bifidobacteria* (P = 0.069) - Reduced isovaleric and isobutyric acid (P < 0.01) - No impact on stool frequency or consistency
Kajihara, M. et al.[27]	3grams per day	14 Adults with Cirrhosis	Baseline data in patient population, followed by 2 weeks of dosing with 3grams per day of XOS	Patients were their own controls; baseline data collection	- Increased *Bifidobacteria* content - Reduced *Bacteriodes* - Reduced ammonia in serum (statistical data not presented)
Lecerf, J-M. et al.[31]	5 grams per day XOS (WitaXOS, 80% Pure); 1 gram per day XOS + 3grams per day inulin	60 Healthy Adults (20 in each of three groups: (i) XOS, (ii) XOS + inulin, (iii) placebo)	Randomized, placebo-controlled, doubled blind trial; 4 weeks	Yes	- Increased *Bifidobacteria* (P = 0.002) - Increased butyrate (P = 0.036) - Reduced cresol (P = 0.020), acetate (P = 0.011) and fecal pH (P = 0.033)
Walton, G. et al.[36]	180grams per day of Bread, with or without enrichment with 2.2g AXOS	40 Healthy Adults	Double-blind, randomized, placebo-controlled cross-over trial; five periods of 3 weeks each	Yes	- Increased *Bifidobacteria* relative to baseline (P = 0.0011) - Increased butyrate (P = 0.041) and propionate (P = 0.045) - Other results confounded by XOS/fructans in the placebo bread, which increased *Bifidobacteria*, short chain fatty acids, and bowel frequency relative to the baseline. The trend to further improve these characteristics via the AXOS-enriched bread were thus masked.

Study Authors	Product / Purity / Dose	Patient Population	Study Design and Duration	Control (Y/N)	Endpoints
Yang, J. et al.[25]	Longlive XOS (2.8 grams per day of 70% XOS; 2 grams of XOS per day)	13 Healthy Adults and 16 Prediabetic (Increased Risk of Diabetes) Adults	8 weeks	Yes	- Decreased *Firmicutes* - Attenuated changes in *Howardella*, *Slackia*, and *B. hydrogenotrophica* - Tendency to reduce OGTT insulin - No effect on blood glucose, triglycerides - Limited by small study numbers and lack of statistical analysis
Iino, T. et al.[19]	0.40 grams per day	40 Healthy Adults	4 Weeks	Yes	- Improved stool frequency ($P < 0.05$)
Sheu, W. et al.[23]	Suntory XOS (95P), 4grams per day	26 adults with type II diabetes (HBA1c between 7 and 10)	Randomized, double blind placebo-controlled trial; 8 weeks	Yes	- Statistically significant reduction in: • Blood glucose ($P < 0.05$) • (described as a point measurement of blood glucose, with the sample obtained after fasting) • LDL ($P < 0.01$) • Total cholesterol ($P < 0.01$) • HbA1c ($P < 0.05$) • Apolipoprotein B ($P < 0.05$)
Tateyama, I. et al.[20]	8g Suntory syrup, 4.2 grams per day	29 Adult Women (pregnant with constipation)	All received product, at the same dose, for 4 weeks	Data collected relative to a baseline condition	- Statistically significant increase in stool frequency and reduction in constipation - Improvement increased every week over the duration of treatment - Normalized stool consistency
Maki, K.C., et al. [30]	AXOS added to cereal, 2.2 grams per day or 4.8grams per day	65 healthy adults	Randomized, double blind, placebo-controlled cross-over trial; 3 weeks treatment with 2 weeks washout between treatments	Yes	- Dose-dependent increase in *Bifidobacteria* observed; statistically significant increase in the 4.8grams per day AXOS group ($P<0.001$) relative to the baseline and control - No statistically significant impact on fasting blood glucose, total cholesterol, HDL, or triglycerides -

Lin et al. [29] observed that subjects who consumed rice porridge supplemented with 1.2 grams per day of XOS for 6 weeks exhibited higher levels of faecal *Lactobacillus* spp. and *Bifidobacterium* spp., and lower levels of *C. perfringens* compared to subjects who consumed rice porridge without XOS. The lower levels of *C. perfringens* were attributed to suppression of growth by XOS. The authors concluded that XOS contributed to improvement of the "intestinal microbiota balance".

Collectively, these studies suggest beneficial impacts on the digestive system, including enhanced levels of Bifidobacteria and lactobacilli following consumption of XOS at doses from 1.2 to 8 grams per day. Several studies showed enhancement of *Bifidobacteria* at doses from 1.2 to 3 grams per day.

Impacts of XOS on immune markers

Childs et al. [26] observed changes in IL-4, IL-6, and IL-10 in 41 healthy adults that consumed either 8 grams per day of XOS or XOS in combination with *B. animalis*. The authors concluded that XOS could favorably modulate key markers of immune function.

Impacts of AXOS on laxation

Francois et al. [30] observed a mild increase in flatulence in subjects consuming an AXOS dose of 10 grams per day, along with improved constipation symptoms, but no change in bowel habits, in a 3-week placebo-controlled trial with 66 healthy adults. No changes were noted with the placebo or AXOS at 3 grams per day.

Lecerf et al. [31] observed more frequent stools and more liquid stools in healthy subjects consuming 1g AXOS + 3g inulin (from chicory root) over 4 weeks. Some adverse GI symptoms were noted, and attributed to the inulin component. Changes in bowel habits were not observed in subjects consuming the placebo (maltodextrin) or 5g AXOS (80% pure product from Witaxos DF3 SAS).

Impacts of AXOS on lipids and blood glucose

Maki et al. [32] noted a slight but statistically significant increase in LDL relative to the control in patients that consumed 4.4 grams per day of AXOS (but not different relative to the pre-trial baseline), in contrast to other studies that showed either no effect on lipids or an increase in HDL. The authors note that these inconsistencies may be due todifferences in the baseline lipid levels among the subject populations.

Impacts of AXOS on digestive health and microbiota

Cloetens et al. [33] administered either 10 grams per day AXOS (containing 63% XOS, 17% arabinan, and 12% glucan) or a placebo to healthy subjects for 3 weeks. Individuals receiving AXOS had higher levels of intestinal *Bifidobacteria* (especially *B.adolescentis*), and lower urinary excretion of p-cresol (indicating less protein fermentation), with no adverse gastrointestinal effects except a mild increase in flatulence. There was no impact on *Lactobacilli*. Various other clinical chemistry and haematological parameters, measured via blood or urine

samples, were unaffected by AXOS, confirming that AXOS has no toxicologically significant adverse impacts.

Francois et al. [30]observed increased *Bifidobacteria* levels in young and older (>50 years) subjects receiving 3 or 10 grams per day of AXOS from wheat bran for 3 weeks. They also observed reduced levels of p-cresol, increased faecal SCFA, and lower faecal pH. There were no clinically relevant adverse effects associated with AXOS consumption; blood samples of 44 safety-related clinical parameters were unchanged. A follow-on trial by Francois et al. [34]in 29 healthy children noted increased Bifidobacteria levels and reduced excretion of isovaleric acid and isobuytric acid after consuming 5grams per day of AXOS for 3 weeks.

Lecerf et al. [31]observed that consumption of 5g AXOS by healthy subjects over 4 weeks statistically increased the population of *Bifidobacteria*, increasedbutyrate concentration, and increased activities of α- and β-glucuronidase (typical of bacteria that produce more butyrate). Concentrations of acetate and cresol decreased, along with faecal pH. The higher butyrate concentration and lower faecal pH have been associated with a lower risk of colon cancer, and α- and β-glucuronidase are suggested to enzymatically convert pro-carcinogenic compounds, alleviating their impact in the digestive tract. The AXOS product was well tolerated.

Maki et al. [32]reported data on healthy patients that consumed a cereal enriched with 2.2 grams per day or 4.4 grams per day of AXOS over 3 weeks. They observed a statistically significant, dose-dependent increase in Bifidobacteria content in stool samples, but populations of other bacteria, including Lactobacilli, were unaffected. No changes were noted in faecal pH, acetic acid, lactic acid, propionic acid, blood glucose or ammonia levels. Butyric acid levels decreased slightly (contrary to expectations and in contrast with other studies). The cereals containing the AXOS were well tolerated.

Collectively, these data point to bifidogenic effects and digestive health benefits following AXOS administration at does from 2.2 to 10 grams per day.

Impacts of AXOS on immune markers

Lecerf et al. [31] observed a reduction in lipopolysaccharide concentrations in the blood of healthy subjects receiving 1g AXOS + 3g inulin (from chicory root) over 4 weeks. The pro-inflammatory effects of a high-fat diet were also attenuated, as demonstrated via changes in measurements of IL-1β̦TNF̃α̦ IL-10 and IL-13.

Comparison to other prebiotics

Collectively, *in vivo* data indicate that xylooligosaccharides can deliver a bifidogenic effect and health benefits at a lower dose than other prebiotics such fructooligosaccharides and inulin. The lower dose requirement is likely attributable to the greater selectivity of XOS towards *Bifidobacteria*, due to their 5-carbon structure and the presence of unique enzymes, transporters and binding domains in many *Bifidobacteria* that allow xylooligosaccharides to be used efficiently [35]. In contrast, fructooligosaccharides, either as short chain FOS, longer-chain oligofructose, or inulin, are comprised of 6-carbon sugars that are more readily fermented by a broader spectrum of bacteria, and in a mixed microbial community, these substrates must be shared, which would reduce their availability to feed *Bifidobacteria* and *lactobacilli*. Six-carbon sugars are also readily utilized by methanogens, which may contribute to issues with tolerance to FOS and inulin at high doses.

Conclusion

XOS prebiotics have been commercially available since the 1980s, and have been the subject of many in vitro and clinical studies. More recently, AXOS prebioticshave been developed and clinically evaluated. XOS and AXOS are based upon 5-carbon sugars, and their metabolism in the digestive tract is thus fundamentally different from other prebiotics, such as FOS, inulin, and resistant starch, which are structures of 6-carbon sugars. Five carbon sugars are more narrowly utilized; most importantly, Bifidobacteria have the cell transport systems and enzymes to use XOS and AXOS, meaning that these substrates will be more selective towards these beneficial bacteria. Clinical studies report beneficial impacts upon digestive health, management of blood sugars and lipids, beneficial modification of immune markers, and benefits for laxation. Furthermore, these outcomes have typically been observed at lower doses than required for other prebiotics such as FOS and inulin. XOS and AXOS are also better tolerated than FOS and inulin, likely due to the lower dose and selective fermentation of these 5-carbon prebiotics. The lower dose requirement also provides advantages in terms of product formulation and more options for delivery of a clinically beneficial dose to consumers.

Acknowledgements

We gratefully acknowledge Allison Simmonds for her assistance in formatting and editing the manuscript.

Conflict of Interest

The co-authors of this paper are co-founders of a company that aims to isolate bioactive compounds, including prebiotics, from cane.

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http://dx.doi.org/10.22037/afb.v%vi%i.20212

Review Article

APPLIED FOOD BIOTECHNOLOGY, 2018, 5 (3): 121-130
Journal homepage: www.journals.sbmu.ac.ir/afb

pISSN: 2345-5357
eISSN: 2423-4214

گزیلواولیگوساکاریدها و آرابینوگزیلان اولیگوساکاریدها و کاربردشان به‌عنوان زیست یار

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چکیده

سابقه و هدف: گزیلواولیگوساکاریدها و آرابینوگزیلان اولیگوساکاریدها حدود 30 سال موضوع مورد مطالعه در شرایط برون تنی و مطالعات بالینی بوده است، و پیشرفت‌های فناوری فرایند به دسترسی‌های گسترده تجاری بیشتری منجر شده است. این مقاله مروری گزیلواولیگوساکاریدها و آرابینوگزیلان اولیگوساکاریدها را به‌عنوان نسل بعدی زیست‌یارها مورد بررسی قرار می‌دهد.

یافته‌ها و نتیجه‌گیری: گزیلواولیگوساکاریدها و آرابینوگزیلان اولیگوساکاریدها اسکلت قندهای 5 کربنی می‌باشند، و مصرف آنها توسط ریزاندامگان‌ها در مجرای گوارش اساسا با کمک زیست‌یارهایی (prebiotic) مانند فروکتواولیگوساکاریدها، اینولین، و نشاسته مقاوم، که اولیگومر یا بسپار قندهای 6 کربنی (oligomers/polymers of 6-carbon sugars) با پیوند آلفا متفاوت هستند. قندهای 5 کربنی و اولیگوساکاریدها با پیوند بتا مصرف محدودتری دارند؛ گزیلواولیگوساکاریدها و آرابینوگزیلان اولیگوساکاریدها برای خوراک‌دهی *بیفیدوباکتری‌ها* به‌طور کارایی اختصاصی می باشند، اگرچه می توانند توسط برخی گونه‌های *لاکتوباسیلوس* و سایر باکتری‌ها مورد استفاده قرار گیرند. مطالعات بالینی انجام شده روی گزیلواولیگوساکاریدها و آرابینوگزیلان اولیگوساکاریدها اثرات مفید بر سلامت هضم، کنترل چربی و قند خون، اصلاح مفید نشانگرهای ایمنی، مزیت ملین بودن را گزارش کرده‌اند. این نتایج به‌خصوص هنگام استفاده از 1 تا 4 گرم در روز، میزانی کمتر از مقدار مورد نیاز برای سایر کمک زیست‌یارهایی مانند فروکتواولیگوساکاریدها و اینولین، مشاهده شد. مقدار کمتر مورد نیاز برای اثربخشی بالینی مطلوبیت‌هایی به جهت فرموله‌کردن فرآورده و امکانات بیشتر حمل و نقل میزان لازم برای اثر بخشی بالینی برای مصرف کنندگان را به‌همراه دارد.

تعارض منافع: نویسندگان اعلام می‌کنندکه هیچ تعارض منافعی وجود ندارد.

تاریخچه مقاله

دریافت 01 فوریه 2018
داوری 22 آپریل 2018
پذیرش 27 ژوئن 2018

واژگان کلیدی

- بیفیدوباکترها
- مطالعات بالینی انسانی
- *لاکتوباسیلوس*
- کمک زیست‌یار
- گزیلواولیگوساکاریدها

***نویسنده مسئول**

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