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The effect of polydextrose on fecal bulk and bowel function in mildly constipated healthy adults: a double-blind, placebo controlled study

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ABSTRACT

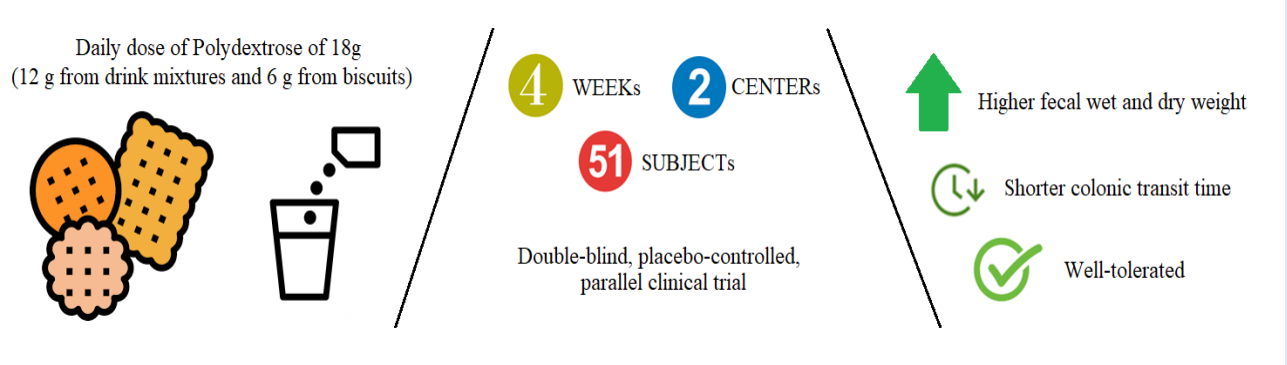
Background: Polydextrose (PDX) (8-30g/day) increases fecal bulk and consistency, helping to ease stool passage. However, the results of its effect on defecation frequency and colonic transit have been discordant, and most focused on either healthy or highly constipated adults, leaving the question on if and how PDX could also aid mildly constipated individuals partially unanswered.

Material and Methods: We investigated the effects of PDX consumption by healthy subjects experiencing one or more symptoms of mild constipation on fecal bulk, defecation frequency, stool consistency, ease of stool passage, and total colonic transit time to further characterize and generate additional evidence regarding the potential beneficial effects of this fibre. 51 subjects participated in a 4-week, two-center, randomized, double-blind, placebo-controlled, parallel study testing a control (CON) and a PDX treatment (18 g/d included in biscuits and drink mixtures) (registered on clinicaltrials.gov with the identifier" NCT05309837").

Results: Consumption of PDX resulted in 120.7 g and 25.7 g higher fecal wet and dry weight, respectively ($p < 0.05$). Colonic transit time was ~4 h shorter in the PDX group: although this difference did not reach significance ($p > 0.05$) as it was underpowered to detect a significant difference for this secondary outcome, this result still carries a physiological importance. Consumption of PDX was well-tolerated, with some PDX volunteers reporting more mild flatulence ($p < 0.05$).

Conclusion: All in all, our study adds new evidence on how a moderate (18g) daily intake of PDX could increase fecal bulking and potentially shorten colonic transit time, making this ingredient a good candidate to be used to reformulate packaged goods by replacing caloric carbohydrates with lower caloric content, enriching food items easily consumed to enhance fibre intake and support bowel function.

KEYWORDS: polydextrose; PDX; constipation; bowel function; clinical trial gut health; fibre



INTRODUCTION

Constipation represents an important public health concern with an estimated prevalence in the general population from 0.7% to 79% (median 16%) worldwide [1,2]. The more characteristic symptoms are infrequent stools, difficult hard stool passage with pain and stiffness, feeling of incomplete evacuation with relative abdominal discomfort and bloating [3]. Inclusion of more fibre in the diet is one of the most important interventions to manage this problem, endorsed by several international guidelines [4]. Indeed, meta-analyses and comprehensive reviews have highlighted how increasing soluble fibre intake is beneficial to patients. A need for further clinical trials to better assess their effective benefits and potential adverse effects, is however evident [5-8]. There is a wish to further confirm that certain soluble fibres express beneficial effects on bowel function parameters in both constipated and healthy subjects [9]. This follows several research papers that have shown the health benefits of dietary fibre, e.g., in favour of cardiovascular health, lowering spikes in blood glucose, helping with weight management and promoting gut health [10]. However, average fiber intakes are well-below the recommended amounts globally [4]. While traditional sources of fibres (e.g, whole grains, fruits, and vegetables) are highly encouraged, added fibres are also important contributors to fibre intakes and positive health outcomes. A recent dietary modelling study suggested that fibre fortification could notably increase the population's fibre intake and have a significant reduction in risk of type II diabetes and cardiovascular problems in the next 10 years [11].

Among commercially available ingredients, polydextrose (PDX) is a soluble, non-absorbed and partially fermentable fibre, with only 1 kcal/g and high gastrointestinal tolerance that has been widely used in

many countries as a bulking and texturing agent. It is a safe ingredient, confirmed in both short and long terms, which has been used in a variety of prepared foods for over two decades as also confirmed by the European Food Safety Authority (EFSA) in a recent re-evaluation [12-14]. In the EU, health claims on PDX, when employed to replace sugars, have also been authorized, relating to the contribution of the maintenance of tooth mineralization, and induction of a lower blood glucose rise [15,16]. Physiological health benefits attributed to PDX include aiding glucose management [17,18], increasing satiety, reducing voluntary energy intake at a subsequent meal [19,20], supporting the growth of beneficial gut bacteria [21-24] and overall health status [25-27]. Several studies have reported the effects of PDX doses of 8-30 g on increasing fecal bulk and consistency, softening stools, and leading to easier passage [9, 28-30]. However, findings on the effect of PDX on defecation frequency have been inconclusive [9, 28-32]. Similarly, data on the effects of PDX on transit time are rather limited and have provided mixed results so far [28, 30, 33-35]. More recent studies have confirmed a role for PDX in dosages of 12 g per day in increasing the number of bowel movements [36], but not in improving gut transit time at doses of 8-12 g [37]. Most of the above-mentioned studies have mainly focused on either healthy or highly constipated adults, leaving the question of if and how PDX could also aid mildly constipated healthy individuals partially unanswered.

Patient reported outcomes (PROs) have been developed as valid and reliable measurements for both clinical and research applications to several functional disorders, including gastrointestinal ones, such as the validated gastrointestinal quality of life index (GIQLI) [38-40]. At the same time, both regulatory and scientific bodies globally have referred to more quantitative traits (e.g., fecal weight) as appropriate bowel function markers to substantiate health claims related to the gastrointestinal tract [41,42]. For this reason, the purpose of this study was to substantiate a potential digestive health claim on PDX for a regulatory submission, we chose to investigate the effect of PDX consumption (18 g / day) on fecal bulking in a subset of the healthy population which might experience one or more symptoms of mild constipation. Indeed, an increase in fecal bulk has been positively evaluated by EFSA as fibre contributes to the maintenance of normal defecation, and dietary reference values for dietary fibre in mixed diets have been established on the basis of maintaining normal bowel function in relation to normal defecation [41]. The secondary purpose of this research was to explore other bowel function parameters including defecation frequency, stool consistency, total colonic transit time, and gastrointestinal tolerability, to further characterize and generate additional evidence regarding the potential beneficial effects attributed to this fibre.

MATERIALS AND METHODS

Study conduct: The study was conducted according to the Declaration of Helsinki, and the protocol was approved by Research Ethics Committee of Hospital District of Northern Savo (Finland) and the regional ethical review board in Uppsala (Sweden) (Project identification code: TALI “4010”). Signed written informed consent was obtained from all subjects at Visit 1, before any protocol specific procedures were carried out. The study was conducted at two Foodfiles, a Clinical Research Organization (CRO), study sites located in Finland and Sweden. The recruitment of study subjects started at the end of the year 2012 and continued until the end of May 2013. The original purpose of this research was to substantiate digestive health claims on PDX. Being a proprietary study initially used for a regulatory submission, for confidentiality reasons it could not be published at the time of execution but can now, as its main purpose had been served. Even though this is

an older study, this investigation still holds significance and addresses a current gap in the literature, i.e., the exploration of bowel function effects in mildly constipated healthy subjects, as most similar published studies either focused on heavily constipated or healthy individuals. The study was registered on clinicaltrials.gov with the identifier"NCT05309837".

Subjects: Participants were recruited online, via public advertisements and direct mailing in the areas of Northern Savo (Kuopio, Finland) and Uppsala (Sweden). The first inclusion criterium regarded the definition of mildly constipated healthy adults. As the study was intended as a regulatory submission, the aim was not to focus on patients diagnosed by functional constipation, but rather to represent a subset of the general healthy population, which might experience one or more symptoms of functional constipation with no need for medication. Therefore, we did not use diagnostic criteria to characterize these subjects or meet all the Rome III criteria [43-45], in line with the EFSA health claim regulation which predisposes that studies are made in a healthy population which is not diseased [46]. For recruitment purposes, we focused on one of these symptoms as the inclusion criterium (i.e., a low frequency of defecation: defecation 3- 5 days during the week assessed by a 7-day bowel diary, meaning that the defecation event would occur roughly every second day). Other inclusion criteria included: provision of signed and dated informed consent prior to any study procedures, ages between 18 and 70 years (both inclusive), body mass index (BMI) ≥ 19 and ≤ 29 kg/m^2 at the screening visit, maximum total score on fibre intake questionnaire max 17 points for women and 20 points for men (where each point represents approximately 1 g fibre intake) [47], and use of adequate contraception in females of childbearing potential. Exclusion criteria included: regular use of laxatives, use of medication which alters study subjects' gastrointestinal function (e.g. including but not exclusive neuroleptic medication, medication for Parkinson disease, opioids), history of digestive disease (e.g. celiac disease, Crohn's disease, ulcerative colitis, gastrointestinal malignancy, fistula of intestine, ischemic colitis, bile acid malabsorption, repeated diverticulitis), type I and II diabetes, previous major gastrointestinal surgery (e.g. intestinal resection, total gastrectomy, subtotal gastrectomy) or surgical treatment of obesity (within 6 months before the screening visit), present cancer (except basal cell skin cancer or squamous cell skin cancer, carcinoma *in situ*), untreated thyroid disease, history of stroke or myocardial infarction within six months prior to the screening visit, subjects who were actively dieting for weight loss, or had eating disorders (anorexia, bulimia), lack of compliance to the study procedures, females who were pregnant or breast-feeding or planning pregnancy, known or suspected abuse of alcohol (more than 14 units of alcohol per week, one unit = 4 cl spirit, 12 cl wine or 33 cl medium strong beer/cider), allergy/hypersensitivity/intolerance to study products, vegetarians or regularly consuming fibre supplements/fibre supplemented foods, and any clinically significant disease or condition which, in the Investigator's opinion, could interfere with the results of the study. Participants had the opportunity to withdraw from the study at any time.

Power calculations were based on a comparison of stool bulk (g/day) measured at the end of each treatment period (active and placebo) based on the clinical study site typical variation (unpublished data) and Cummings et al., 2004 [48]. A sample size of 50 completed subjects was calculated in order to be able to detect a difference of 20 g in mean daily stool bulk between the treatment periods with a probability of 80 % at α level of 0.05. With a sample size of 26 subjects per group (ITT population), using an estimated standard deviation of 50 g (unpublished data) for the stool bulk, we would be able to detect a difference

of 38.5 g in mean daily stool bulk between the treatment groups with a probability of 80 % at α-level of 0.05. In total, 115 subjects were screened and signed the informed consent at visit 1, and 73 subjects were randomized to ensure that at least 50 subjects would have completed the study. Indeed, 51 subjects completed the study according to the protocol. The flow diagram of the study participants is presented in Figure 1. Altogether, 10 subjects dropped out of the study and 10 subjects were withdrawn from the study. In total, 51 subjects successfully completed the study.

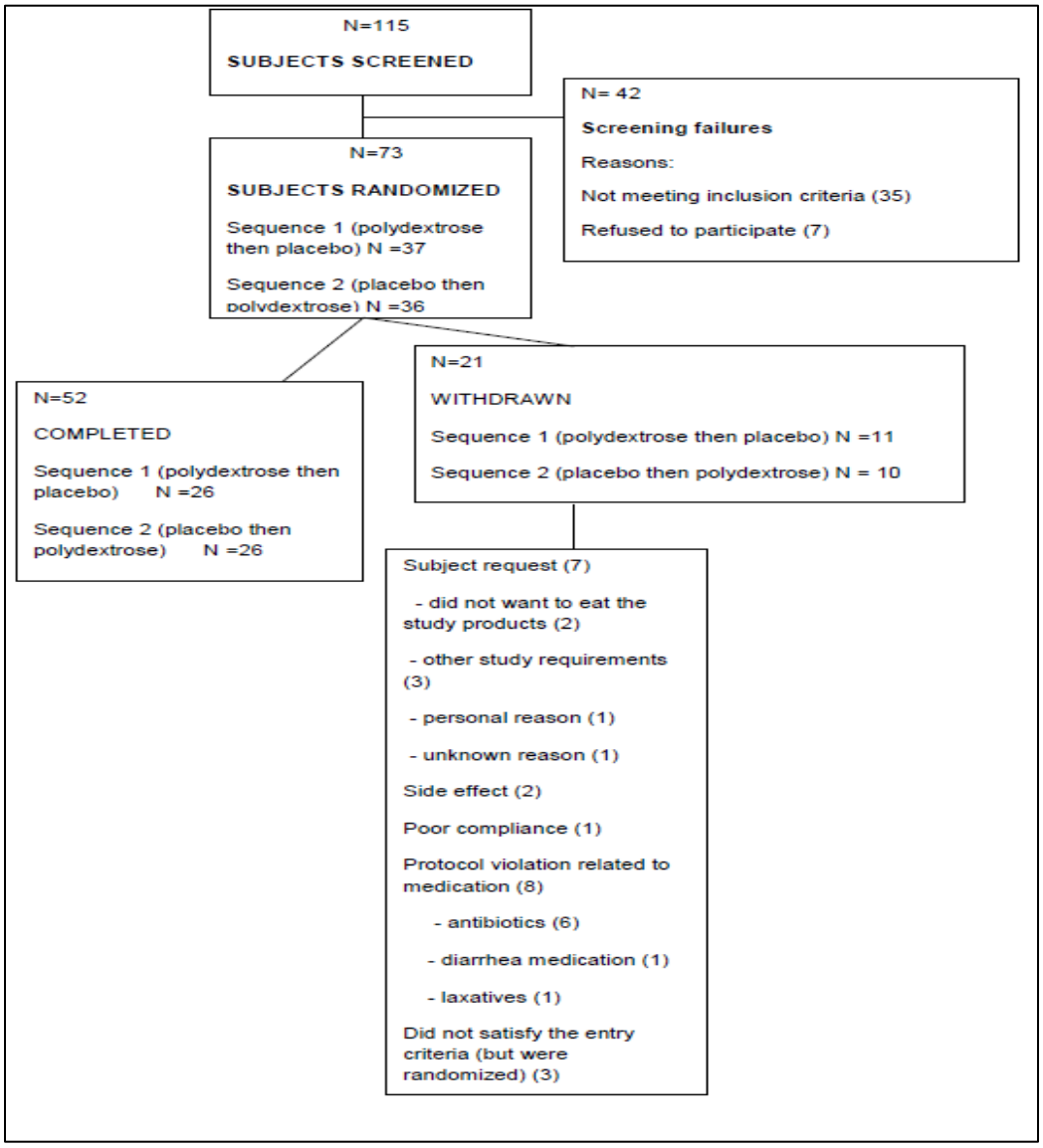


Figure 1. Flow diagram of study participants.

Study products: Drink mixtures were packaged into non-transparent dose sachets, dissolved in 200 ml of water by subjects, and consumed with a meal, two portions a day. Biscuits (three pieces) were packaged in a single-serving transparent wrapping and were provided to the subjects, with the advice of consuming all three of them (one portion) a day, with or without the meal. The daily dose of PDX ingredient (Tate & Lyle, STA-LITE®) was 18 g (12 g from the drink mixtures and 6 g from the biscuits) providing 16.2 g dietary fibre/d (as analyzed by AOAC method 2009.01). STA-LITE® Polydextrose is a highly branched dextrose polymer with a broad molecular

weight range (162 to 20,000) and is a non-sweet, low-calorie, soluble fibre ingredient providing a minimum of 90% polydextrose. In the placebo products, maltodextrin replaced PDX and differed in the amount of fibre per gram (1.7 g, as analyzed by AOAC method 2009.01) (Supplementary Table 1 - S1). The subjects were advised to keep at least three hours between consumption of the study products.

Study design: The study was analyzed as a randomized, double-blind, placebo-controlled, parallel study. The study was divided into two periods, namely a 2-week run-in period and one 4-week intervention period. All people involved in the study, including study staff and study participants, were blinded to treatment selections. Study products were blinded as well, by using a numeric code to identify product groups. At visit 3, after evaluating all the inclusion and exclusion criteria (visits 1 and 2), the participants were randomly allocated using a randomization list, generated based on the random number tables by Oy Foodfiles Ltd, into one of the two groups. One group (PDX) consumed polydextrose enriched drink mixtures and biscuits during the 4-week intervention period, while the other group (CON) consumed placebo products. Both study sites had their own blocked randomization list with a block size of 4 and allocation rate of 1:1. At the beginning of the run-in period, participants were advised to maintain their lifestyle (i.e., physical activity, alcohol, tobacco, and dietary supplement consumption) and dietary habits (including consumption of fibre sources) throughout the study, with the exception that, during the intervention periods, the subjects were advised to replace an iso-caloric part of their usual diet (mainly white bread, pastries, drinks, sugar, sweets, chocolate, ice-cream and or yoghurt) with the study products, since these provided an additional energy intake of 1380 kJ (330 kcal) per day. Consumption of PDX-containing foods other than study products was forbidden during all study periods. Examples of foods containing PDX were provided to subjects. Any concomitant medication and/or dietary supplements that affect the gastrointestinal tract were prohibited during the study. Concomitant medication and food supplements were recorded at visit 1, and any changes in medication and supplements were recorded at each visit. The study subjects were instructed to record the consumption of the study products each day in their diary during the intervention periods. Treatment compliance was set to >80% product consumption.

Fecal wet and dry weight: Feces were collected at home by subjects, during four consecutive days (96 h) of the intervention period, before the transit time measurement. The fecal collection started on the 21st intervention day at the earliest, or on the 24th intervention day at the latest. The subjects received verbal and written instructions on how to perform the fecal collection. The participants were advised to defecate directly into a provided plastic bag, tie a knot in the bag, put the bag with feces into a second resealable plastic bag, and place it immediately into a home freezer. If participants were not able to put the feces into a home freezer, they were advised to store the feces in a cold environment and bring the sample to the study unit within 6 hours. At the study unit, all the feces were placed in a freezer and stored at – 20 °C. Fecal wet weight was measured at each study unit using an electronic scale (Precisa balances, series XB, Precisa Gravimetrics AG, Dietikon, Switcherland at the Kuopio site and Vetek, FEJ-2000, Vetek AB, Vaddo, Sweden at the Uppsala site). The frozen feces were weighed on the day the study subject delivered the last fecal samples of the collection or on the following day. The fecal wet weight was weighed separately for each subject and for each collection day (g/day). The weight was measured twice and the mean of two measurements from the clinic was used in the

statistical analyses. The frozen feces were then sent for the fecal dry weight analyses to Novalab Oy (Karkkila, Finland). The frozen feces were reweighed (the whole collection, g/4 days) at Novalab Oy before frozen homogenization. Before the fecal dry weight analysis, the feces were pooled and homogenized with rapidly moving cutting edges. Then the stool mass was melted at room temperature and from the pooled and homogenized fecal mass, two samples (1.6 –37.0 g) were taken and dried at 60 ° C for 12 hours or until stable weight. The dry weight was measured from both samples and the mean of these two replicates was used in the data analyses. The number of pellets in the radiograph film was calculated by the same qualified radiologist. After entering the data into the database, 100 % of entered data was verified against the case report forms or source data by a separate person.

Bristol Stool Form (BSF) score and defecation frequency: The study subjects recorded defecation frequency (i.e., number of stools during a 7-day period) and the form of each stool during seven consecutive days in the run-in and intervention periods using the BSF scale in the subject diary [49,50]. The BSF scale includes the following seven stool forms: 1 = separate hard lumps, like nuts (difficult defecation), 2 = sausage shaped but lumpy, 3 = like a sausage or snake but with cracks on its surface, 4 = like a sausage or snake, smooth and soft, 5 = soft blobs with clear cut edge, 6 = fluffy pieces with ragged edges, a mushy stool, 7 = watery, no solid pieces. The subjects were provided the scale with pictures of stool forms as part of their diaries.

Total colonic transit time: Total colonic transit time (cTT) was assessed with the radio-opaque marker technique [51] at the end of the intervention period. The participants ingested 20 radio-opaque, barium sulfate impregnated polyethylene pellets located inside gelatin capsules (10 pellets per capsule) with water at 24-hour intervals for three consecutive days, and one simple abdominal radiograph (one projection) was taken at the supine position 24 hour after the ingestion of the last pellets. The pellets were ingested during the last day of fecal collection (4th day of fecal collection window) at the earliest, to avoid the presence of pellets in the collected feces for analysis. The subjects recorded the exact time of ingestion of the pellets. The number of markers found on abdominal film was counted by the same qualified radiologist. The dose of radiation exposure was 0.4 mSv per abdominal single projection radiograph. The total dose of radiation exposure during the study was 0.8 mSv per subject. The dose was estimated by the Radiation Protection Committee of Uppsala University Hospital. The abdominal radiographs were taken at the private clinics Medicinsk Röntgen (Uppsala, Sweden) and Terveystalo (Kuopio, Finland). Women of childbearing potential performed the urine pregnancy test on the morning prior to the radiograph. The radiograph was taken only if the pregnancy test result was negative. The total colonic transit time was calculated in two separate manners. First, it was calculated assuming that the participant ingested a capsule containing 20 pellets for three days, the pellets were ingested at 24-hour intervals and the radiograph was taken 24 h after the last pellets ingestion using the following formula: $cTT = (\Delta T/N) \times n = (24/20) \times n$, where ΔT is the time interval between consecutive ingestion of pellets in hours, N is the number of pellets ingested each day and n is the number of pellets seen on the x-ray [51].

Second, it was calculated using the actual number of pellets ingested and the actual time between the pellet ingestion times and the actual time between the last pellet ingestion (reported by participant) and the radiograph (reported by the clinic conducting the radiograph). The following formula was used:

cTT = (ΔT1 / N1) x n1 + (ΔT2 / N2) x n2 + (ΔT3 / N3) x n3, where: ΔT1 = time (h) between pellets ingestion on day 1 and 2, ΔT2 = time (h) between pellets ingestion on day 2 and 3, ΔT3 = time (h) between pellets ingestion on day 3 and x-ray, N1 = number of pellets ingested on day 1, N2 = number of pellets ingested on day 2, N3 = number of pellets ingested on day 3, n1 = number of day 1 pellets on the x-ray, n2 = number of day 2 pellets on the x-ray, n3 = number of day 3 pellets on the x-ray.

Ease of stool passage: Participants assessed the ease of stool passage at the end of the intervention period using a five-point scale (1 = very easy, 2 = easy, 3 = neither easy nor difficult, 4 = difficult, 5 = very difficult) [9].

Gastrointestinal tolerance score: The study subjects ranked on a four-point scale (\=none, 2=mild, 3=moderate, 4=severe) the following subjective tolerance variables daily: burping, cramping, distension/bloating, flatulence, nausea, reflux (heartburn) and vomiting [9]. The gastrointestinal tolerance variables were ranked once at the end of the intervention period and the scores recalled the tolerance during the previous one week (7 day-period).

Body measurements: Body measurements were body weight, height, and BMI. Non-fasting body weight was measured at the beginning of the run-in period (at visit 1) using a digital scale (Seca 707, Vogel & Halke GmbH & Co, Hamburg, Germany at the Kuopio site and CL-2400, Carl Lidén, Gothenburg, Sweden). Body weight was measured while the subject was wearing light indoor clothing, without shoes. Weight was recorded to the nearest 0.1 kg. Two repeated weight measurements were performed and the mean of the two measurements was used in statistical analyses. The third measurement was performed if the two measurements differed by 0.5 kg or more. In that case, the mean of two measurements within 0.5 kg was used in statistical analyses. Body height without shoes was recorded at the beginning of run-in period (at visit 1). The height was measured while the subject was in the so-called Frankfurt position: auditory canal was horizontally on the same level with the top of the lower eyelid. The height was recorded to the nearest crossed half of centimeter. BMI was calculated as follows: body weight (kg) / body height $(m)^2$.

Dietary and fibre intake: Background dietary intake was assessed by a 24-hour food recall at baseline (at visit 1) at the end of the treatment period. The 24-hour food recalls were completed by interviewing the participants. The subjects were asked to report everything that they had consumed and drank on the previous day starting at midnight. The recall session was not interrupted. After reporting, the participant was invited to add any items not initially recalled. The subjects were asked for the following detailed information: 1) the time when foods and drinks were consumed, 2) a full description of the foods and drinks, including brand names when available, 3) any foods likely to be eaten in combination e.g. milk in coffee, 4) recipes and other combinations of foods e.g. sandwiches, 5) the quantity consumed, based on household measures and/or photographs of different portion sizes of foods and weights, and 6) any leftovers or second helpings. When the details were added, the interviewer reviewed all the foods eaten and drunk chronologically, prompted for any additional eating or drinking occasions or foods/drinks possibly consumed, and clarified any ambiguities regarding type of food eaten or portion size. The interviewer recorded all the information on the record sheet. In determining the amounts of foods and drinks, the portion size picture booklet [52-54] or portions guide [55] was used. Energy and nutrient intake were assessed with Micro-Nutrica (version 2.5) dietary analysis software (The Social Insurance Institution, Turku, Finland) (at Kuopio site) and Dietist XP (Kost och Näringsdata AB, Bromma, Sweden)

(at Uppsala site), without including the study products in the results. In addition to the 24-hour food recall, the dietary fibre intake was also assessed with the dietary fibre intake questionnaire [47] at the screening visit (visit 1), and at the end of the treatment period. The Finnish version of the fibre intake questionnaire was used at the Kuopio site and the Swedish translation of the questionnaire was used at the Uppsala site. At the screening visit the dietary fibre intake questionnaire was completed by interviewing the participant. At other visits the dietary fibre intake questionnaire was completed based on the subjects reporting during a 24-hour food recall interview. The dietary fibre intake questionnaire measured the fibre intake during the previous day without including the fibre intake from the study products.

Statistics: Statistical analyses were performed according to the Statistical analysis plan (SAP). The data was analyzed with Excel, StatXact and SPSS software. The General linear model for the repeated measures was used in the parallel analysis of the primary outcome. Since a significant ($p < 0.05$) carry-over effect was observed after the initial treatment, the results of the study, originally planned as a cross-over design, are analyzed here as a parallel study and p-values are presented for the treatment period, calculated according to the SAP. Differences between the study groups were analyzed using the student's t-test and the Wilcoxon rank sum test. The Wilcoxon rank sum test compares the sums of ranks and therefore it is distribution free and less likely than the t-test is significant because of outliers. This test is presented in the summary tables below as the primary outcome assessment of significance. All p-values presented are two-sided. The Pearson chi-square test was used to test that the sex and race were comparable in the groups. The exact 2-sided p-values are presented for the Pearson chi-square test. The Intention-to-treat (ITT) analysis set included all randomized subjects fulfilling the entry criteria for those who completed the study. The Per Protocol (PP) analysis set included all randomized individuals who finished the study adhering to the inclusion/exclusion criteria or break further aspects of the protocol that could potentially compromise the study efficacy (i.e., compliance with sample collection, consumption of products >80%, following pellet consumption procedure and completion of symptom questionnaires). All analyses were performed using both the ITT and PP populations. A p-value < 0.05 was considered to be statistically significant.

RESULTS

Subjects: All subjects who fully completed the study were included in the ITT population (n = 52). One subject was excluded from the PP data set because there was a 5-day break in the study product consumption before the fecal collection (non-compliant with protocol). Baseline characteristics for the ITT and PP sample populations can be seen in Table 1. Only PP data will be shown in the results; the PP data sets were defined separately for each efficacy variable, considering occasions when subject data was not complete. More specifically, for the primary outcome the PP was n = 51 (n = 26 in the PDX group, n = 25 in the CON group), for the secondary outcomes transit time, BSF, ease of stool passage, stool frequency, tolerance, fibre intake, and dietary intake, the PP dataset was n = 48 (25 PDX, 23 CON), 50 (26 PDX, 24 CON), 50, 50, 50, 51, and 51, respectively. No statistically significant differences ($p > 0.05$) in the baseline characteristics (i.e., gender and ethnic origin distrib-utions, age, body weight and number of defecation days a week) between the treatment groups were identified (Supplementary Table 2 – S2). Study product compliance was good in both study groups: in the PDX group 98.9 (1.8) %, (range 93 – 100 %) of the intended PDX products were consumed and in the CON group 98.0 (4.0) %, (range 85 -100 %) of the intended placebo products were consumed.

Table 1. Baseline characteristics of the participants in the ITT and PP populations.

	ITT population (n = 52)	PP population (n = 51)
Gender, males/females (%)	13 (25%) / 39 (75%)	12 (24%) / 39 (76%)
Ethnic origin, Caucasians/Asians (%)	50 (96%) / 2 (4%)	49 (96%) / 2 (4%)
Age, mean years (SD)	47.9 (14.8)	48.3 (14.6)
Body weight, mean kg (SD)	69.6 (12)	69.7 (12)
Height, mean cm (SD)	166.8 (9.2)	166.5 (9.1)
BMI, mean kg/m^2 (SD)	24.9 (2.9)	25 (2.8)
Defecations, days per week (SD)	3.8 (0.7)	3.8 (0.7)

Fecal wet and dry weight: Summary results for total fecal wet and dry weight outcomes are reported in Table 2. 4-day total fecal wet and dry weight was higher in the PDX, compared to the CON group (406.7 ± 210.1 and 286 ± 167 g; 110.4 ± 47.1 and 84.7 ± 46.4 g respectively, $p < 0.05$). Average daily fecal wet and dry weight was also higher in the PDX, compared to the CON group (101.7 ± 52.5 and 71.5 ± 41.8; 27.6 ± 11.8 and 21.2 ± 11.6 respectively, $p < 0.05$). The 4-day fecal wet weight was 120.7 g greater, and the dry weight was 25.7 g greater in the PDX group compared to the CON. Therefore, the 18g/d consumption of PDX led to a 1.68 g greater fecal wet weight and 0.36 g greater fecal dry weight per day per g of PDX consumed ($p < 0.05$).

Table 2. Effect of PDX treatment on total fecal wet and dry weight.

Outcome1	PDX		CON		p-value*
	Mean	SD	Mean	SD	
Fecal wet weight (g/4 days)	406.7	210.1	286.0	167.0	0.0467
Fecal dry weight (g/4 days)	110.4	47.1	84.7	46.4	0.0446
Fecal wet weight (g/day)	101.7	52.5	71.5	41.8	0.0467
Fecal dry weight (g/day)	27.6	11.8	21.2	11.6	0.0446

[1] Weighed frozen before homogenization. * Significance of the difference between the study groups was analyzed with the Wilcoxon rank sum test.

BSF score and defecation frequency: Summary results for the BSF scores and defecation frequency are illustrated in Table 3. The mean BSF score for both PDX and CON groups at baseline was towards the lower end of the scale (i.e., 3.4 ± 1.2 and 2.9 ± 3.6, respectively, indicating a form "like a sausage or snake but with cracks on its surface"), supporting how the enrolled population was healthy but with some evidence of mild constipation. The mean BSF score for the 7-day period at the run-in and intervention period did not significantly differ between the treatment groups (Table 3, $p > 0.05$). Similarly, the defecation frequency did not differ between the groups at the end of the intervention period (Table 3, $p > 0.05$).

Table 3. Effect of PDX treatment on the secondary outcomes stool consistency, defecation frequency, total colonic transit time, and ease of stool passage.

Outcome	PDX		CON		p-value*
	Mean	SD	Mean	SD	
Stool consistency[1]					
BSF scale, at run-in	3.4	1.2	2.9	3.6	0.1
BSF scale, after intervention	3.7	0.8	1.4	1.2	0.75
BSF scale, change	0.3	1	0.7	1.6	0.85
Defecation frequency[1]					
Stools per week, at run-in	3.9	0.9	4.3	1.1	0.12
Stools per week, after intervention	4.9	1.9	5	2	0.1
Stools per week, change	1	1.7	0.7	1	0.69
Total colonic transit time (cTT)[2]					
cTT, assumption (h)	36.1	16.8	39.8	14.4	0.45
cTT, actual (h)	35.3	16.7	39.3	14.1	0.36
Ease of stool passage[1]					
Ease of stool passage score	2.8	0.6	2.6	1.1	0.70

[1] n = 50 (one subject had stomach flu during data collection and was, therefore, excluded from the analysis). Scores were rated as follows: 1 = separate hard lumps, like nuts (difficult defecation), 2 = Sausage shaped but lumpy, 3 = Like a sausage or snake but with cracks on its surface, 4 = Like a sausage or snake, smooth and soft, 5 = Soft blobs with clear cut edge, 6 = Fluffy pieces with ragged edges, a mushy stool, 7 = Watery, no solid pieces.

[2] n = 48 (three subjects terminated the consumption earlier and were, therefore, excluded from the analysis). The assumption is based on that the 20 markers have been ingested at 24-hour intervals for three consecutive days, while the actual was calculated with the actual intervals between the marker ingestions and actual number of markers ingested.

* Significance of the difference between the study groups was analyzed with the Wilcoxon rank sum test.

Total colonic transit time: As shown in Table 3, the actual colonic transit time was ~4 hours shorter among the subjects who consumed PDX, compared to the subjects who consumed placebo products. Such difference, however, did not reach statistical significance as our study was underpowered to detect a statistical difference for this secondary outcome measurement ($p > 0.05$, Table 3).

Ease of stool passage: Summary results for ease of stool passage are shown in Table 3. Briefly, there was no significant difference in the subjective feeling of the ease of stool passage scores between the study groups ($p > 0.05$, Table 3). Both groups rated the ease of stool passage typically as neither easy nor difficult.

Fibre and dietary intake: After four weeks of treatment, the background dietary fibre intake, as assessed by the questionnaire, was higher compared to the screening visit (12.8 vs. 16.5 g in the PDX group and 12.2 vs. 14.4 g in the CON group, respectively), albeit not statistically significant between the study groups ($p > 0.05$, Supplementary Table 3 – S3). The background dietary fibre intake, assessed using the 24-hour food recall, seemed to decrease slightly after the four-week treatment period, compared to baseline in both study

groups (-0.9 g per day in the PDX group, and – 2 g per day in the CON group, respectively) but such difference between the study groups was not statistically significant (p> 0.05, Supplementary Table 3 – S3). The background dietary fibre intake results did not include the fibre intake from the study products. However, the inclusion of the study products with three servings per day contributing to 16 g of fibre per day, doubled most of the subjects' fibre consumption in the PDX group (Supplementary Table 3 – S3). The dietary intake results from the background diet, without including the study products, are presented in Supplementary Table 3 – S3. Briefly, the proportion of energy intake from protein was higher in the PDX group compared to the CON group ($p < 0.05$, Supplementary Table 3 – S3). On the contrary, the proportion of energy intake from saturated fatty acids was lower in the PDX group compared to the CON group ($p < 0.05$, Supplementary Table 4 – S4).

Gastrointestinal tolerance score and adverse effects: The mean score for abdominal bloating/distension were mild on average, with a mean score of 2.2 and 1.9 in the PDX and CON group, respectively ($p > 0.05$). Flatulence scores were also mild on average and differed significantly between the two groups with mean scores of 2.7 and 2.1 in the PDX and CON group, respectively ($p < 0.05$, Table 4). There were no other significant differences in the gastrointestinal tolerance scores between the groups and all the scores were low, indicating that the subjects didn't have any major gastrointestinal problems except constipation, which was in the inclusion criterion. All the encountered adverse events were non-serious (e.g., headache, tooth ache, common cold, joint or back pains, cough, fever, and mild gastrointestinal symptoms) and there were no serious adverse events.

Table 4. Gastrointestinal tolerance scores.

Outcome1	PDX		CON		p-value*
	Mean	SD	Mean	SD	
Burping	1.5	0.8	1.4	0.7	0.9
Abdominal cramping	1.5	0.8	1.8	0.8	0.15
Abdominal distension/ bloating	2.2	0.9	1.9	0.8	0.24
Flatulence	2.7	0.7	2.1	0.6	0.008
Nausea	1.2	0.7	1.3	0.6	0.69
Reflux	1.3	0.5	1.3	0.6	0.95
Vomiting	1	0.2	1	0	1

[1] n = 50 (one subject had stomach flu during data collection and was, therefore, excluded from the analysis).

[*] Significance of the difference between the study groups was analyzed with the Wilcoxon rank sum test.

DISCUSSION

Previous studies have reported the effects of PDX in doses of 8-30 g on increasing fecal bulk and consistency, softening stools, and helping to ease passage [9,28-30,36]. The effect of PDX on defecation frequency and colonic transit time has, however, not been fully understood. In addition, most of the available literature focused either on heavily constipated subjects or healthy individuals [9,28-32,33-36]. Although we did not use diagnostic criteria, nor meet all the Rome III criteria, to classify the level of constipation in these subjects, our aim was to study a healthy population, which is not

diseased, but still showing one or more symptoms of mild constipation.

In the present trial, consumption of 18 g PDX-enriched ingredients (cookies, drink mixture) per day for 4 weeks by 26 subjects significantly increased fecal bulk by approximately 120 g / 4 day (wet weight, +42%), in comparison to the CON group. More specifically, for every gram of PDX ingredient (over 4 days) consumed, we observed an increase of 6.7 g fecal wet weight. This is particularly relevant, as stool weight has been inversely associated with certain diseases of the colon. For example, an increase in fecal weight after fibre consumption may reduce the risk of colon cancer, such that an increase in daily stool weights from 100 g to 200 g/day might decrease the risk of colon cancer by approximately one third with, at greater stool weights, cancer risks becoming very low [56]. The number of subjects per study group was similar to the total number of subjects used in previous cross-over studies, and such effect was comparable to the one observed in previous studies in both heavily constipated and healthy subjects [9,28,30]. Similarly, the variation of stool weights in both study groups was similar to the one found in healthy subjects in previous PDX studies [9,28].

Unlike some previous findings in healthy subjects, we did not demonstrate a significant effect on defecation frequency of PDX supplementation [28,32]. However, our findings are consistent with other studies demonstrating that increased fecal bulk does not necessarily lead to increased defecation frequency [9,33].

In the present study, the inclusion of PDX led to a difference in colonic transit time of close to 4 hours. The observed change in transit time, individual variations, and rather small sample size for this secondary outcome may not have been sufficient to reach statistical significance and increase daily defecation frequency in the studied subjects. However, it is worth noting how, in general, any increase in transit time could be considered to be beneficial and of clinical relevance. Decreased transit time and fecal bulking may have other beneficial consequences, such as diluting the cytotoxic or carcinogenic materials in fecal mass, and thus reducing exposure to colonic epithelium. The results of this study are similar to previous studies with PDX where transit time was not affected in healthy subjects [28,33], although a single study reported a decreased orofecal transit after consumption of 8 g of PDX [30]. A dose-response was also showed with PDX consumptions of 4,8 and 12 g/day with increased fecal weight, and a drop in fecal pH, which in turn can suppress the production of enteric toxins (i.e., indole, p-cresol) [32].

Part of the subjects' dietary habits (e.g., by removal of white bread, pastries, drinks, sugar, sweets, chocolate, ice-cream and/or yoghurt) was necessary to be modified to keep their diets iso-caloric, considering the inclusion of PDX-test products. This could have potentially influenced dietary tolerance and bowel symptoms. However, all PDX test products were well tolerated in general with GI symptoms such as burping, abdominal cramping, abdominal distension/bloating, nausea, reflux, and vomiting showing no significant difference between the two treatments. The only GI symptom showing a slight increase was flatulence, observed in the PDX group compared to CON. Recent studies indicate that increases in flatulence are common for fibre, especially those that are (partially) fermented in the colon. Symptoms were rated mild to moderate in most cases, and no severe adverse events were reported during either of the treatments. These findings agree with previous trials that showed how doses as high as 90 g/day, or 50 g as bolus, are well tolerated and prove to be a feasible way to increase fibre intake [9,28,57]. The participants of our study showed in fact very low dietary fibre intakes at the screening visit, in line with the observation that average

fibre intakes are well-below the recommended amounts globally [4]. Even though traditional sources of fibre (such as whole grains, fruits, and vegetables) are first indicated to increase fibre intake, fibre fortification has also shown to help adhering to fibre intake recommendations, while providing additional public health benefits, without an additional energy intake that could potentially derive from the above-mentioned sources [11, 58, 59]. Indeed, recent studies have shown how PDX fortification could deliver health benefits in addition to increase the nutritional quality and sensory properties of different types of packaged goods (e.g., yoghurt, biscuits, jams, bread), as well as functional foods intended, as "natural or processed foods containing biologically active compounds that, when consumed in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit by utilizing specific biomarkers to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [60-65].

CONCLUSION

Overall, the present study demonstrates that daily consumption of 18 g PDX significantly increases fecal bulking in healthy subjects with one or more symptoms of mild constipation. The PDX intervention also caused a 4-hour decrease in transit time, but for this secondary outcome the study groups were not powered enough to detect significant differences. For the first time, therefore, we showed how PDX could also aid mildly constipated individuals, in addition to healthy or highly constipated adults. These results, together with the low caloric value of PDX, highlight how this ingredient could be a good candidate to be used to reformulate foods such as yoghurt, biscuits, jams, and bread by replacing caloric carbohydrates with reduced caloric and sugar content, enriching food items easily consumed to enhance fibre intake and support bowel function. This is in addition to the previous physiological health benefits attributed to PDX such as aiding glucose management, increasing satiety, reducing voluntary energy intake at a subsequent meal, and supporting the growth of beneficial gut bacteria. Lastly, modeling studies have indeed shown how utilizing fibres to reduce sugar and calories can be effective tools to boost daily fibre intake and decrease sugars at the same time.

Competing Interests: Tate & Lyle contributed to the study design, data interpretation, to write the manuscript and to the decision to publish the results. Davide Risso, Ieva Laurie, and Kavita Karnik are employees of Tate & Lyle, while Essi Sarkkinen declares no conflict of interest.

Author's Contributions: Conceptualization, E.S.; methodology, E.S.; formal analysis, E.S., D.R.; investigation, D.R., I.L., E.S.; resources, K.K.; data curation, E.S., I.L.; writing—original draft preparation, D.R.; writing—review and editing, I.L., E.S. K.K.; visualization, D.R., E.S; supervision, K.K., E.S.; project administration, D.R., I.L.; funding acquisition, K.K. All authors have read and agreed to the published version of the manuscript.

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