Digestibility and bulking effect of ispaghula husks in healthy humans

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Abstract
The digestibility of ispaghula, a mucilage from *Plantago ovata* composed mainly of arabinoxylans, and its faecal bulking effect were studied in seven healthy volunteers who ingested a low fibre controlled diet plus either placebo or 18 g/day of ispaghula for two 15 day periods. Whole gut transit time and gas excretion in breath and faeces were not different during the periods of ispaghula and placebo ingestion. Faecal wet and dry weights rose significantly, however, during ispaghula ingestion. Faecal short chain fatty acid concentrations and the molar proportions of propionic and acetic acids also increased. Most of the ispaghula had reached the caecum four hours after ingestion in an intact highly polymerised form. During ispaghula ingestion, the increase in the faecal output of neutral sugars was accounted for by the faecal excretion of arabinose and xylose in an intact highly polymerised form; the apparent digestibilities of these sugars were 24 (11) and 53% (6) respectively (mean (SEM)). In conclusion, ispaghula is more resistant to fermentation than previously reported in humans, and its bulking effect largely results from intact material.

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The possible mechanisms by which dietary fibres increase stool weight fall into two broad categories. Firstly, mechanisms that act by increasing stool volume. These include the physical presence of the undigestible fibre in the colon, this fibre's water holding capacity, the stimulation of microbial growth, and the production of gas. The resulting increase in stool volume may cause colonic propulsion. Secondly, mechanisms that act primarily by stimulating colonic motility, particularly by mechanical action of the fibre on the colon, and an increase in certain colonic end products of fibre fermentation.

*Plantago ovata* husks, often referred to as ispaghula husks, are highly branched arabinoxylans widely used as a faecal bulking agent. The mechanism of the bulking effect of ispaghula is still unclear. In rats and during in vitro incubation with mixed faecal bacteria harvested from humans, ispaghula is only partially fermented, whereas in the only human study reported so far, Pryne and Southgate showed that it could be extensively fermented.

In this study, we aimed at determining the mechanism of the bulking effect of ispaghula in humans by assessing the digestibility of ispaghula, faecal bacterial mass, and transit time. Special care was taken to assess the production of gas and changes in the proportions of short chain fatty acids. In addition, caecal contents were sampled to discover the form in which ispaghula reached the caecum.

Methods
Seven healthy volunteers (five men and two women, aged 21–35 years) gave informed written consent to the study protocol, which was approved by the local ethics committee. None of them had a history of gastrointestinal disease, the use of laxatives or recent treatment with antibiotics. Four subjects were identified as producers of methane because their breath methane concentrations were at least one µl higher than the room air concentration.

EXPERIMENTAL DESIGN
The study comprised two 15 day periods with an interval of 21 days between them. In a randomised, blind, and cross over fashion, the subjects were given 12.9 g ispaghula husk pellets twice daily – that is, 18 g ispaghula/day (Spagulax, Beecham, Nanterre, France) throughout one period, and placebo (sucrose pellets) throughout the other. Ispaghula was mainly composed of neutral sugars, 90% of which consisted of arabinose and xylose (Table I). The ispaghula and placebo pellets were packaged in tubes, which also contained five grams of the faecal recovery marker polyethylene glycol 4000 (PEG). The contents of the tubes were swallowed whole during breakfast and dinner.

During each period, the subjects consumed a basal diet that consisted of conventional low fibre foods and provided 6 g dietary fibre and 1–2 g resistant starch per day as determined from food tables. Great care was taken to ensure that the dietary constituents were the same throughout the two periods. The ingredients for breakfast were given to the subjects to be prepared and eaten at home; lunch and dinner were prepared and eaten in the laboratory. At the end of each period (days 13–15), subjects were admitted to the clinical centre and given standardised test meals.

| Table I Neutral sugar composition of ispaghula husks (g/100 g dry matter) |
|--------------------------|--------------------------|--------------------------|
| Glucose                  | 47±4                     | 3±7                      |
| Xylose                   | 47±4                     | 3±7                      |
| Mannose                  | 1±1                      | 3±7                      |
| Rhamnose                 | 2±1                      | 3±7                      |
| Galactose                | 17±6                     | 3±7                      |
| Neutral sugars were measured according to Hoebler et al. The rest of the 100 g dry matter was not specifically assessed.
During both periods, subjects were asked to record daily symptoms (bloating, borboryg- 
mus, cramp, and flatus), which they them-
selves graded on a scale from 0 to 3 (none to 
severe). After seven days of equilibration, all 
stools were collected from day 8 to day 13 and 
immediately frozen at -20°C. On days 8, 9, 
and 10, subjects ingested with breakfast 20 
radio-opaque pellets of different shapes to 
permit measurement of mean orofaecal transit 
time according to the method of Cummings 
and Wiggins.18 On day 13, a test meal was 
given at 8 am (composition in Table II) with 
either ispaghula or placebo. End expiratory 
breath samples were taken before the meal, 
and every 30 minutes thereafter to measure 
orocael transit time and total excretion of 
hydrogen in breath over 12 hours. During the 
same period, rectal gases were collected using 
a flexible canula 4 mm in diameter whose tip was 
inserted into the rectum 12 cm from the anal 
verge, and which was connected to a laminated 
gas bag (ABS, Saint-Dié, France). Gas bags 
were closed with a stopcock, and changed 
every four hours. The effectiveness of this gas 
collection method has been previously vali-
dated in a water bath, and in six other subjects 
by instilling the non-absorbable gas sulphur-
hexafluoride into the rectum and checking its 
recovery.19 After test meal ingestion, no food 
was permitted until the end of exhaled breath 
and rectal gas collection, and subjects had to 
refrain from smoking, and stay in a recumbent 
position. In two subjects, leaks of gas were 
felt, and the experiment was repeated on the 
following day.

On day 14 of each period, four of the 
subjects were intubated with a polyvinyl tube 
led by an inflatable mercury bag as previously 
described.20 Progression of the tube was 
stopped when the sampling port had reached 
the caecum, as confirmed fluoroscopically. 
On day 15, the same test meal as on day 13 
given to these subjects at 8 am, and 0.5 ml of 
caecal contents was sampled within five 
minutes at two, four, six, and eight hours after 
the meal, while the subjects continued to fast. 
After each sampling, the tube lumen was 
flushed with nitrogen and the sample was 
immediately frozen at -20°C.

ANALYTICAL METHODS AND CALCULATION

For each stool, the pH was measured using 
a pH meter (Radiometer, Copenhagen, 
Denmark), PEG by turbidimetry,21 nitrogen 
by the Kjeldahl method, and ammonia, 
according to Assous et al.22 An aliquot from 
each stool was lyophilised to measure the dry 
weight and faecal bacterial mass according to 
the fractionation procedure of Stephen and 
Cummings.23 Briefly, the fractionation was 
achieved by repeated mixing in a stomacher of 
0.5 g dried stools combined with formylsaline 
(0.9% vol/vol NaCl and 1% vol/vol formalin) 
and sodium lauryl sulphate (0.1%) followed by 
filtering through nylon meshes. This procedure 
gives a fraction of coarse particles mainly of 
plant cell wall material, a fraction of fine 
particles, which also are from the plant cell 
wall, and the suspension of bacteria in large 
volume of washings. The bacterial fraction was 
centrifuged at 30 000 g for 30 minutes, and, 
and, after discarding the supernatant, the pellets 
were dried to constant weight. For the other 
measurements, the five faecal collections 
obtained from each subject throughout each 
period were pooled. Short chain fatty acids 
were determined by gas chromatography.24 
The solubility of carbohydrate molecules 
was determined as described by Delort-Laval 
and Mercier.25 Briefly, carbohydrates were 
extracted by ethanolic 80° (extraction of oligo-
sides), ethanol 40° (extraction of carbohydrate 
and a degree of polymerisation <65), and water. Neutral sugars were subse-
quently measured in the three extracts and in 
the residue after freeze drying, according to 
Hoepler et al.26 
The caecal contents of the four subjects 
sampled were pooled for each sampling time 
throughout the placebo and ispaghula periods, 
and analysed for carbohydrate molecule 
solubility and neutral sugars as described 
above. As the duration of sampling was 
limited to five minutes to reduce in vitro fer-
mentation in the tube and to avoid interfer-
ence with the normal physiology, we could not 
collect the caecal contents before the meal. 
The volume of the sample taken eight 
hours after ingestion of the test meal contain-
ing ispaghula was not sufficient to permit 
solubility analysis.

Concentrations of breath hydrogen were 
measured using an electrochemical cell 
(Exhaled Hydrogen Monitor, GMI Medical 
Ltd, Renfrew, Scotland). The total excess 
volume of hydrogen excreted in breath after 
the test meal was determined by integrating the 
area under the hydrogen concentration curve 
over basal values. For each subject, the total 
volume was determined from the reference 
nomogram and data were expressed in ml per 
total test period (12 hours). Orocael transit 
time was defined as the time elapsing between 
the beginning of the meal and the sustained 
increase in breath hydrogen (>5 μL/L). 
Methane concentrations in breath were 
measured by gas-liquid chromatography (IGC 
121 DFL-Intersmat, Country, France). Rectal 

gas volume was measured manually after its 
evacuation from the bag into a greaseless gas 
syringe, and gas composition was analysed using a mass spectrometer (QMG 511, 
Balzers, Balzers, Liechtenstein).

STATISTICAL ANALYSIS

Results are expressed as mean (SEM). 
Comparisons between the two periods were 
made using Wilcoxon’s matched pair signed 
rank test.

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**TABLE II** Test meal composition

<table>
<thead>
<tr>
<th>Item</th>
<th>Quantity</th>
<th>Composition</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggs*</td>
<td>2</td>
<td>250 ml Coffee</td>
<td></td>
</tr>
<tr>
<td>Cheese (Grayère)</td>
<td>30 g</td>
<td>Hydrolysed milk</td>
<td>10 g</td>
</tr>
<tr>
<td>White bread</td>
<td>100 g</td>
<td>Sucrose</td>
<td>10 g</td>
</tr>
<tr>
<td>Butter</td>
<td>30 g</td>
<td>Ispaghula or placebo</td>
<td>9 g</td>
</tr>
<tr>
<td>Strawberry jam</td>
<td>30 g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Boiled for 10 minutes.
Results

SYMPTOMS AND TOLERANCE
Ispaghula was well tolerated; the cumulative score of each symptom was very low, and was not different for the two periods. Cumulative scores (maximal value 36) of bloating, borborygms, cramps, and flatus were 4.4 (3-3), 1.9 (1-9), 2.0 (1-0), 9.3 (5-2) during the placebo period. They were 4.0 (2-6), 3.9 (2-2), 5.3 (3-0), 6.1 (2-8) during the ispaghula consumption.

BREATH AND RECTAL GASES
The excess volumes of hydrogen excreted in breath were 23.8 (5-9) and 38.6 (9-2) ml/12 hours after ispaghula and placebo meals respectively (p=0.02). In the four hydrogen producers, breath hydrogen excretion was not different for the two periods either in the fasting state, or after the test meal. The gases excreted by the rectum during these periods were not significantly different as regards total volume and composition, except for hydrogen, whose excretion was lower during the ispaghula period (Fig 1).

TRANSIT TIMES
Breath hydrogen excretion increased after both test meals in each subject permitting determination of orocaecal transit time. Mean oro-faecal transit time and orocaecal transit time were not significantly affected by ispaghula consumption. Mean oro-faecal transit times were 53 h (8) and 42 h (6) for placebo and ispaghula respectively (p=0.33), and orocaecal transit times were 325 min (38) and 330 min (41) (p=0.94).

FAECAL COMPOSITION
The percentages of ingested PEG recovered in stools were 100 (7) and 92 (6) for the placebo and ispaghula periods respectively. The number of stools, faecal wet and dry weights, and faecal water were significantly greater during the ispaghula period (Table III). Faecal bacterial mass, and faecal excretion of nitrogen, ammonia, and non-ammonia nitrogen were not different for the two periods (Table III).

Table IV gives the concentrations of neutral sugars (expressed per g dry and wet weight) in the pooled faecal contents during both the ispaghula and placebo periods. The total concentrations of neutral sugars were significantly higher during the ispaghula than the placebo ingestion period because of the higher faecal concentrations of arabinose and xylose. Faecal outputs of neutral sugars also increased significantly during ispaghula ingestion, and again, this was accounted for by the increased outputs of arabinose and xylose (Table V). The digestibilities of arabinose and xylose, calculated after correction for the excretion of these sugars measured during the placebo period, were respectively 24% (11) (range 12-36) and 53% (6) (range 46-60). Most of the arabinose and xylose excreted in stools was present in the insoluble fraction – that is, in the highly polymerised fraction – compared with the ingested ispaghula (Fig 2).

Table III: Number of stools, faecal weight, and composition during the periods of placebo and ispaghula ingestion

Table IV: Faecal concentrations of neutral sugars during the periods of placebo and ispaghula ingestion

Table V: Faecal outputs of neutral sugars during the placebo and ispaghula ingestion periods
COMPOSITION OF CAECAL CONTENT

The percentages of water in pooled caecal contents at any sampling performed were similar after ingestion of the meal with ispaghula and placebo (Table VII). Glucose was the main neutral sugar found in the caecum at all the times sampled after ingestion of the test meal with placebo. Caecal concentrations of neutral sugars, expressed per g dry and wet weight, were higher after ingestion of the test meal with ispaghula. Within the first four hours this was accounted for by the high concentration of glucose, and as from six hours by the high concentrations of arabinose and xylose, which became the predominant sugars (Table VII). Figure 3 shows the distribution of glucose, arabinose, and xylose in the fractions with different solubilities. Forty six per cent of the arabinose reaching the caecum two hours after the meal and 39% of the xylose were extracted in the 80° ethanol soluble fraction – that is, in the form of oligosides. As from four hours after the meal, however, these sugars were mainly present as insoluble highly polymerised molecules (Fig 3).

Discussion

This study confirms that ispaghula is a potent stool bulker in humans,8 9 and shows that it is fermented to a limited extent throughout the human colon.

The digestibility of arabinose and xylose was calculated after correction for basal excretion, assuming that ispaghula did not increase faecal excretion of the arabinose and xylose from the basal diet. Theoretically, some of the saccharides excreted may have been bacterial polysaccharides or endogenous materials, or both, the excretion of which could have been increased by fibre intake leading therefore to an underestimation of the ispaghula digestibility. Faecal bacterial mass and non-ammonia nitrogen did not rise significantly during ispaghula consumption, however, and arabinose and xylose are very rarely present in bacterial saccharides.27 Intestinal glyco- proteins do not contain arabinose or xylose,28 but do contain fucose, which was not detected here in stools.

The apparent digestibility of xylose was greater than that of arabinose. This suggests that the ispaghula backbone containing xylose might be more easily accessible to fermentative enzymes than the highly branched chains containing arabinose.29 Overall, the apparent digestibility of total neutral sugars contained in ispaghula was 54%. This is in agreement with the digestibility found in vitro and in rats,30 and in two of four volunteers studied by Pryme and Southgate31 during the consumption of 25 g ispaghula in the form of Isogel. In this last study, however, in which the mechanism of faecal bulking was not assessed and neutral sugars were not specifically measured in faeces, the apparent digestibility of ispaghula was higher in the two other volunteers (as much as 100%). Differences in the adaptation period (one week instead of two) do not seem to play an important part in digestibility of

Figure 2: Solubility (mean %) of arabinose and xylose excreted in the stools of seven healthy volunteers. Arabinose and xylooligosaccharides in the ingested ispaghula were totally insoluble; most of the arabinoyxylans recovered in faeces remained insoluble – that is, in the highly polymerised form.

Figure 3: Outputs of butyrate and valerate were also higher but not their faecal concentrations. Faecal pH was slightly but significantly lower during ispaghula ingestion at 6-5 (0-1) v 6-7 (0-1) (p=0.03).
Solubility (%) of arabinose, xylose, and glucose in the pooled caecal contents of four subjects sampled two, four, and six hours after ingestion of the test meal with ispaghula. A large part of the molecules recovered two hours after the meal were soluble in ethanol 80%—that is, in the form of oligosides; arabinoxylans recovered four hours after the meal were insoluble (highly polymerised form).

Figure 3: Solubility (%) of arabinose, xylose, and glucose in the pooled caecal contents of four subjects sampled two, four, and six hours after ingestion of the test meal with ispaghula.

Ispaghula as we found no significant modifications of digestibility in four other volunteers who ingested ispaghula for 31 days (data not shown). Individual differences in colonic flora might be responsible for individual variations in ispaghula digestibility; in our study, however, these variations were small. The nature of the ispaghula used might also influence its digestibility, as shown with other varieties of the same fibre. An interesting feature of our ispaghula preparation was its insolubility in both water and ethanol.

The partial fermentation of ispaghula led to increased faecal concentrations and excretion of short chain fatty acids but did not significantly affect the faecal bacterial mass. Ispaghula was well tolerated in our study as in others, and did not increase either rectal expulsion of gas or the excretion of methane and hydrogen in breath. For unknown reasons, rectal hydrogen was even slightly lower after ingestion of the meal with ispaghula. The rise in the faecal concentration of short chain fatty acids was mainly accounted for by the increased concentrations of propionic acid (+230%) and acetic acid (+130%). An increase in the concentration of propionic acid was previously reported during the incubation of ispaghula with human faeces, and in the colonic and faecal contents of rats consuming ispaghula. Propionic acid may reduce contractile activity in rat isolated colon mounted in vitro. In our study, ispaghula did not affect transit time. This has also been reported by other workers in healthy volunteers; in constipated patients, however, ispaghula has been shown to reduce transit time.

The incomplete fermentation of ispaghula in humans is probably caused by its slow metabolism by colonic bacteria, as shown in rats. It has been suggested that the distal fermentation of fibres in the rectosigmoid could have a beneficial effect on colonic carcinogenesis due to the beneficial actions of butyrate in our volunteers, however, the increase in faecal concentration of butyrate during ispaghula consumption did not reach statistical significance.

The rise in faecal dry weight (about 13 g/day) was mainly accounted for by the increased excretion of neutral sugars (8 g/day), especially arabinose and xylose. As in the ingested ispaghula, arabinose and xylose in stools were mainly present in the insoluble highly polymerised fraction, and only a small proportion consisted of osmotically active oligosides—that is, in the 80% ethanol soluble fraction. Compared with the placebo period, a slight non-significant increase in bacterial mass occurred during ispaghula ingestion. The large increase in faecal water may be consistent with previous in vitro determinations of the water holding capacity of ispaghula. In rats consuming ispaghula, Nyman and Asp reported also an increase in faecal water holding capacity, which they determined by a centrifugation method. Such an increase was not found, however, by Edwards et al, who used a dialysis method, and the water holding capacity determined by dialysis on a residue fermented in vitro was only 4 g H₂O/g ispaghula. These last findings could suggest that a proportion of the additional water in faeces is not bound to undegraded fibre or bacteria. Short chain fatty acids resulting from the distal fermentation and to a lesser extent undigested oligosides could maintain water in the lumen, and reduce the amount of free water absorbed.

Small fractions of arabinose and xylose reached the caecum two hours after ispaghula ingestion and were chiefly recovered as oligosides—that is, in the fractions extracted by 80% ethanol; these fractions probably resulted from the slight gastric and intestinal degradation of ispaghula previously described in humans by Anderson et al. As shown by the rise of caecal arabinose and xylose measured six hours after ispaghula ingestion (Table VII) most of the ispaghula only reached the caecum after four hours, and most of the caecal arabinose and xylose were present in the form of highly polymerised molecules as in the ingested ispaghula (Fig 3). This result was in keeping with the orocecal transit time assessed by the hydrogen breath test. Interpretation of these results need to assume that caecal fluid sampled was homogeneous, as only concentrations can be measured. Asspiration of the viscous caecal contents through a narrow tube proved to be more difficult than in our previous study using a lactulose meal.

Glucose was the main sugar in caecal contents during the placebo period, and was chiefly present in the insoluble fraction at all sampling times (data not shown). Glucose concentrations were higher two and four hours after ingestion of the meal with ispaghula than after placebo, and glucose was present in the oligoside fraction extracted by 80% ethanol. The origin of this increased delivery of glucose when ispaghula was consumed is not clear. It might result from overnight residues in the
terminal ileum, which moved on in response to the test meal or to the trapping of dietary oligosaccharides containing glucose by the small fraction of ispaghula reaching the caecum at four hours in highly polymerised form. The amount of glucose delivered to the colon during the first four hours after the meal with ispaghula was small, however, and did not lead to increased excretion of hydrogen in breath. In addition, caecal glucose concentrations, expressed per g wet weight, were small, and a real increase in caecal contents was only assumed to occur four hours after meal ingestion with the delivery of ispaghula in its highly polymerised form.

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