Prebiotic Fibres: An Asian Perspective

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What are prebiotics?

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Prebiotic definition

“A dietary prebiotic is a selectively fermented ingredient that results in specific changes, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health”


IFIS Functional Foods Bulletin 2011; 7, 1–19
Reported prebiotic oligosaccharides

**Group A**
- Good microbiology with state of the art techniques
- Good human studies
- Health benefits shown

**Group B**
- Some good microbiology with state of the art techniques
- Some or poor human studies
- Few health benefits shown

**Group C**
- Little or poor microbiology often with questionable techniques
- No human studies
- No health benefits shown

- Inulin
- Fructo-oligosaccharides
- Galacto-oligosaccharides

- Xylo-oligosaccharides
- Isomalto-oligosaccharides
- Lactulose
- Lactosucrose

- Soybean oligosaccharides
- Gentio-oligosaccharides
Group A prebiotics

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Butyrate defence against pathogens

PropionateAcetate reduced pH

Ca++, Mg++ increased absorption

reduced renal toxin production

Bifidobacteria Firmicutes Methanogens

selective fermentation faecal bulking reduced gas production

improved bowel habit

maintenance of barrier function

M Cell

Zonulin Occludin GLP-2 ZO1

immunomodulation

Th2 Th1 IFN\(\gamma\) IL-10 TGF-\(\beta\) Tr

anti-inflammatory

impact on obesity?

high SCFA scavenging

reduced cancer risk?

reduced renal toxin production

Butyrate Acetate Propionate

defence against pathogens

reduced LPS translocation

Leptin GLP-1 PYY

increased satiety

immune stimulation

NK activity phagocytic activity

immunomodulation

selective fermentation

reduced gas production

prebiotics

reduced inflammation

maintenance of barrier function

improved bowel habit

reduced intestinal infection

impact on obesity?

impact on chronic kidney disease?
Group A prebiotics: Inulin and oligofructose

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### Inulin

<table>
<thead>
<tr>
<th>Plant</th>
<th>Edible part</th>
<th>Inulin (% fresh wt)</th>
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<tbody>
<tr>
<td>Chicory</td>
<td>Root</td>
<td>15-20</td>
</tr>
<tr>
<td>Jerusalem artichoke</td>
<td>Tuber</td>
<td>14-19</td>
</tr>
<tr>
<td>Globe artichoke</td>
<td>Heart</td>
<td>3-10</td>
</tr>
<tr>
<td>Onion</td>
<td>Bulb</td>
<td>2-6</td>
</tr>
<tr>
<td>Leek</td>
<td>Bulb</td>
<td>3-10</td>
</tr>
<tr>
<td>Garlic</td>
<td>Bulb</td>
<td>9-16</td>
</tr>
<tr>
<td>Camas</td>
<td>Bulb</td>
<td>12-22</td>
</tr>
<tr>
<td>Burdock</td>
<td>Root</td>
<td>3.5-4.0</td>
</tr>
<tr>
<td>Murnong</td>
<td>Root</td>
<td>8-13</td>
</tr>
<tr>
<td>Yacon</td>
<td>Root</td>
<td>3-19</td>
</tr>
<tr>
<td>Salsify</td>
<td>Root</td>
<td>4-11</td>
</tr>
<tr>
<td>Banana</td>
<td>Fruit</td>
<td>0.3-0.7</td>
</tr>
<tr>
<td>Rye</td>
<td>Cereal</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Barley</td>
<td>Cereal</td>
<td>0.5-1.5</td>
</tr>
</tbody>
</table>

Inulin-derived fructans

**Inulin**

\[
[Fru\beta_2 \rightarrow 1]_n Fru\beta_2 \leftrightarrow 1\alpha\text{Glc}
\]

\(n = 1 - 50\)

**Inulinase**

\[\downarrow\]

**Oligofructose**

\[
[Fru\beta_2 \rightarrow 1]_n Fru
\]

\[
[Fru\beta_2 \rightarrow 1]_n Fru\beta_2 \leftrightarrow 1\alpha\text{Glc}
\]

\(n = 1 - 5\)
Inulin in obese women

- 44 obese women (BMI >30) aged 18-65
- 16g inulin + oligofructose or maltodextrin per day for 3 months
- Microbiology by qPCR and HITChip
- Anthropometric measurements, inflammatory status and $^1$H NMR metabonomics

Dewulf et al. (2013) Gut 62: 1112-1121
HITChip analysis – phylum level

Baseline

Placebo

- Firmicutes: 61.2%
- Bacteroidetes: 34.7%
- Actinobacteria: 3.7%
- Others: 0.4%

3 Months

- Firmicutes: 58.3%
- Bacteroidetes: 36.9%
- Actinobacteria: 4.2%
- Others: 0.6%

Prebiotic

- Firmicutes: 57.5%
- Bacteroidetes: 29.9%
- Actinobacteria: 2.3%
- Others: 0.2%

HITChip analysis – species level

Placebo

Prebiotic

Relative contribution (%)

Baseline 3 months

Bifidogenic response

Inflammatory status

Plasma CRP (mg/dl)

Differential values

0.3
0.2
0.1
0.0
-0.1
-0.2

Placebo

Prebiotic

Serum LPS (EU/dl)

Differential values

0.0
-0.2
-0.4
-0.6

Placebo

Prebiotic

Dewulf et al. (2013) Gut 62: 1112-1121
Sucrose-derived fructans

Sucrose

Fru\(\beta_1\leftrightarrow 1\alpha\)Glc

β-Fructosidase

Glc

Fru\(\beta_1\leftrightarrow 1\alpha\)Glc

Short-chain FOS

\([\text{Fru}\beta_2\rightarrow 1]_n\text{Fru}\beta_2\leftrightarrow 1\alpha\)Glc

n = 1-3
Group A prebiotics: Galacto-oligosaccharides

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Galacto-oligosaccharides

Lactose
Gal\(\beta 1\rightarrow 4\)Glc

\(\beta\)-Galactosidase
Gal\(\beta 1\rightarrow 4\)Glc

GOS
Gal\(\beta 1\rightarrow 6\)Gal\(\beta 1\rightarrow 4\)Glc
Gal\(\beta 1\rightarrow 3\)Gal\(\beta 1\rightarrow 4\)Glc
Gal\(\beta 1\rightarrow 4\)Gal\(\beta 1\rightarrow 4\)Glc
Irritable bowel syndrome

Single blinded randomised placebo controlled study
66 D/C/A-IBS patients stratified on 4wk treatment

Significant improvements seen in:
• stool consistency
• flatulence
• bloating
• subjective global assessment
• composite score of symptoms
• anxiety

Metabolic syndrome

• 45 overweight adults with ≥3 metabolic syndrome risk factors
• 12 week cross over study feeding GOS or placebo

No significant changes in:
- *Atopobium* spp
- *Lactobacillus* spp
- *Clostridium coccoides/E. rectale*
- *E. cylindroides*
- *E. hallii*
- *Clostridium cluster IX*
- *Faecalibacterium prausnitzii*
- beta-proteobacteria

Metabolic syndrome

- Changes in C-reactive protein and faecal calprotectin

![Graph showing changes in CRP and Calprotectin levels over 12 weeks with statistical significance levels.]

Metabolic syndrome

• Changes in plasma triglycerides and cholesterol:HDL-cholesterol ratio

![Graph showing changes in plasma triglycerides and cholesterol:HDL-cholesterol ratio with significance markers.]

Group B prebiotics

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Butyrate, prebiotics, and propionate undergo selective fermentation in the gut. Faecal bulking improves bowel habit. Immune stimulation occurs through M Cells.

Reduced acetate, butyrate, and propionate contribute to reduced procarcinogenic enzyme activities, reduced pH, and reduced phenolic toxins. Reduced pH leads to reduced impact on chronic kidney disease and reduced cancer risk.

Calcium (Ca++) and magnesium (Mg++) are increased through reduced pH. This leads to increased absorption.
Group B prebiotics: Xylo-oligosaccharides

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Xylo-oligosaccharides

**Commercial sources**

- Corn cob xylan – dp 2-3
- Wheat arabinoxylan – dp 2-5
Xylo-oligosaccharides

- 20 healthy individuals in a randomized, controlled, crossover trial
- 10 g arabinoxylans (AXOS) per day for 3 weeks
- Faecal bacteriology and physiological parameters
Xylo-oligosaccharides

- Corn cob XOS (8g/day)
- *Bifidobacterium animalis* subsp. *lactis* Bi-07 (10⁹ cfu/day)
- Synbiotic combination
- 41 healthy adults (25-65 yr) for 21 d
- Faecal microbiology
- Immune function
Xylo-oligosaccharides

Group B prebiotics: Isomalto-oligosaccharides

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Isomaltose
Glc\(\alpha 1\rightarrow 6\)Glc

Isomaltotriose
Glc\(\alpha 1\rightarrow 6\)Glc\(\alpha 1\rightarrow 6\)Glc

Panose
Glc\(\alpha 1\rightarrow 6\)Glc\(\alpha 1\rightarrow 4\)Glc
Isomalto-oligosaccharides

- 13 constipated volunteers aged 82.5 ± 1.9 years
- Placebo (4 wk) - 10 g/d IMO (4 wk) - 10 g/d IMO (4 wk) - post (4 wk)
- Microbiology by FISH but using two qPCR primers as probes

**All significantly different from placebo p<0.05**

Isomaltol-oligosaccharides

Glucose  TC  LDL-C  HDL-C  TG

* significantly different from placebo p<0.05

Faecal mass (g/wk)

Defaecations per week

Wet
Dry

Group B prebiotics: Lactulose

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Lactulose

- Chemically synthesised
- Alkali-catalysed isomerisation of lactose

\[ \text{Lactulose} \quad \text{Gal}\beta 1\rightarrow 4\text{Fru}\beta \]
Lactulose

- 8 healthy adults
- 3g lactulose per day for two weeks
- Bacteriology by selective media

**Log10 per g faeces**

- **Total**
- **Bifidobacteria**
- **Bacteroides**
- **Eubacteria**
- **Peptococci**
- **Megasphaera**
- **Clostridia Lc+**
- **Clostridia Lc-**
- **Veillonella**
- **Lactobacilli**
- **Enterobacteria**
- **Streptococci**
- **Staphylococci**
- **Bacilli**

* *p<0.05
• ♣ p<0.01
♦ ♠ p<0.001

Before
4 days
7 days
14 days
Washout

**Lactulose**

- 12 healthy adults per group
- 20g lactulose per day for four weeks
- Glucose+lactose placebo
- Bacteriology by selective media

**Baseline**
- Placebo
- Lactulose

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**Graphs**

- **Log10 cells**
  - Bacteroides
  - Bifidobacteria
  - Clostridia
  - Coliforms
  - Eubacteria
  - Lactobacilli
  - Streptococci

- **Specific activity**
  - Azoreductase
  - 7α-Dehydroxylase
  - β-Glucuronidase
  - Nitroreductase
  - Urease

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**Chemicals**
- Acetate
- Propionate
- Butyrate
- Valerate
- Lactate
- Cresol
- Indole
- Phenol
- Skatol

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**References**

Lactulose

- 255 polypectomised adults
- 20g lactulose per day for 18 months or no treatment control
- Recurrence of adenoma determined
Lactulose

- 29 healthy adults fed 10g lactulose day\(^{-1}\) for 4 wks
- 19 healthy adults fed 10g OF + inulin day\(^{-1}\) for 4 wks
- Bacteriology by qPCR

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**Before**  | **After**  | **p**
---|---|---
Log\(_{10}\) bifidobacteria per g wet weight | p=0.017 | 9.2
 | 9 | 9
 | 8.8 | 8.9
 | 8.6 | 8.6
 | 8.4 | 8.4

**Before**  | **After**  | **p**
---|---|---
Urinary \(p\)-cresol (mg day\(^{-1}\)) | p=0.001 | 25
 | 20 | 20
 | 15 | 15
 | 10 | 10
 | 5 | 5

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Group B prebiotics: 
Lactosucrose

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Lactosucrose

\[ \text{Sucrose} \quad \text{Gal}\beta1\rightarrow4\text{Glc} \]

\[ \text{Lactose} \quad \text{Glc}\leftarrow\text{Fru}\beta1\leftrightarrow1\alpha\text{Glc} \]

\[ \beta\text{-Fructosidase} \]

\[ \text{Lactosucrose} \quad \text{Gal}\beta1\rightarrow4\text{Glc} \leftrightarrow 1\beta\text{Fru} \leftrightarrow 1\alpha\text{Glc} \]
Lactosucrose

- 17 healthy young women
- 12 g per day
- 96 weeks
- Mineral balance study

Group C prebiotics

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Soybean oligosaccharides

Raffinose
Galα1→6Glcα1↔2βFru

Stachyose
Galα1→6Galα1→6Glcα1↔2βFru

Verbascose
Galα1→6Galα1→6Galα1→6Glcα1↔2βFru

• Anaerobic faecal batch culture
• Microbiology by FISH

Gentio-oligosaccharides

Gentiobiose
Glcβ1→6Glcβ

Gentiotriose
Glcβ1→6Glcβ1→6Glcβ

- Anaerobic faecal batch culture
- Microbiology by FISH

Are bifidobacteria the mechanistic link?

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The gut microbiota

- Oligosaccharides
- Polysaccharides
- Mucins
- Proteins & peptides

Species:
- Bifidobacterium
- Lactobacillus
- Clostridium IV
  - F. prausnitzii
- Clostridium IX
- Clostridium XIVa
  - E. halli
  - R. hominis

Substances:
- CO₂
- Lactate
- Acetate
- Butyrate
- Propionate
- H₂
- Methane
- p-cresyl sulphate
- Indoxyl sulphate
- NH₄⁺ Amines

Processes:
- Acetogens
- H₂ Reducing Bacteria
- Sulfate Reducing Bacteria
- Methanogens
- H₂S
The gut microbiota

Oligosaccharides
- Bifidobacterium
- Lactobacillus

Polysaccharides
- Clostridium IV F. prausnitzii
- E. halli R. hominis

Bacteroides

Succinate

Clostridium IX

SO$_4^{2-}$

CO$_2$

Lactate

Acetogens

Acetate

Butyrate

Propionate

Mucins

Sulfate Reducing Bacteria

Methanogens

Methane

H$_2$

$\text{p-cresyl sulphae}$

Indoxyl sulphae

NH$_4^+$

Amines

clostridia peptostreptococci peptococci
To conclude…

• Regulatory authorities do not consider an increase in bifidobacteria a health benefit - need good human studies on Group B & C prebiotics
• Need to characterise changes in the microbiome and the metabolome as well as health outcomes
• Prebiotics do not act like drugs – they induce changes in a complex ecosystem
• There is potential for Group B and C prebiotics given more data
Thank you for your attention!

Any questions?