The effect of Zespri Green Kiwifruit on digestive and gut health functions

A multi-country, randomised, cross-over clinical intervention study

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Project Team

• Principal Investigators
  – Professor Richard Gearry (NZ)
  – Professor Giovanni Barbara (Italy)
  – Professor Shin Fukudo (Japan)

• Project Manager
  – Lynley Drummond (Drummond Food Science Advisory Ltd)

• Project Leader
  – Dr Juliet Ansell (Innovation Leader [Health and Nutrition], Zespri)
Project Team

• Research Team
  – Plant and Food Research Ltd (Christchurch and Palmerston North) Sarah Eady, Alison Wallace, Dr Chrissy Butts, Hannah Dinnan, Philippa Wadsworth

• Statistics
  – Dr Barbara Kuhn-Sherlock (BKS Consulting)
Relevant disclosures

• Richard Garry
  – Zespri advisory board member, funding for research
• Lynley Drummond
  – Zespri advisory board member, funding for research
• Giovanni Barbara, Shin Fukado
  – Zespri advisory board member, funding for research
• Juliet Ansell
  – Zespri employee
• Plant and Food Research Staff, Barbara Kuhn-Sherlock
  – Contractors to Zespri for research services
Background (Constipation)

• Constipation affects 15% of adults in western countries
  – May occur alone (functional constipation)
  – May occur with abdominal pain (Irritable Bowel Syndrome-Constipation predominant)

• Significant effect on physical and mental quality of life

• Significant impact on school and work

• Improvement of quality of life in adults with effective therapy
Background (Gastrointestinal discomfort)

- Gastrointestinal discomfort
  - less well studied and defined
  - may include pain, bloating, borbouromi
  - may be related to constipation in some individuals
  - significant impact on quality of life
  - significant impact on school and work
What do we know about kiwifruit and the gut?

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Participants</th>
<th>Study Design</th>
<th>N</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Rush et al</td>
<td>NZ</td>
<td>&gt;60 years Constipated</td>
<td>Randomised, crossover, no control</td>
<td>38</td>
<td>↑ stool frequency</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>↑ ease of passing BM</td>
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<td>↑ Bulkier, softer stool</td>
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<tr>
<td>Chang et al</td>
<td>Taiwan</td>
<td>Adult IBS - constipated</td>
<td>Randomised study with capsule control</td>
<td>41</td>
<td>↑ stool frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ colonic transit time</td>
</tr>
<tr>
<td>Chan et al</td>
<td>Hong Kong</td>
<td>Constipated adults</td>
<td>Prospective observational study (no control)</td>
<td>53</td>
<td>↑ stool frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ bowel habit satisfaction</td>
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<td></td>
<td></td>
<td></td>
<td>↓ laxative use</td>
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<tr>
<td>Hiele (unpublished)</td>
<td>Belgium</td>
<td>Adult IBS - constipated</td>
<td>Prospective observational study (no control)</td>
<td>38</td>
<td>↑ stool frequency</td>
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<td></td>
<td></td>
<td>↓ ease of passing BM</td>
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<td>↓ abdominal bloating</td>
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</tbody>
</table>

Why is it important to demonstrate kiwifruit efficacy for bowel frequency and comfort?

• For consumers
  – to confirm what many people suspect is true
  – to provide high quality trusted efficacy and safety information

• For Health care providers
  – expectation of high quality research
  – develops a deeper understanding of the effects of kiwifruit on gut health

• For Zespri
  – Important as a responsible corporate citizen
  – accurate, independent data concerning benefits of consuming kiwifruit
  – as part of a validated health claim, enables marketing direct to consumers
How can Zespri Health Science be communicated?

Medical Specialists, Dietitians, Nutritionalists

Evaluate evidence, form opinions, give advice

Science communications, symposia and publications

Nutritionalists

Consumers

Key Topics

Nutrient Richness

Validated health claims

Digestive health

VITC

Metabolic health

Good digestion

Immune defence

Sugar control

Nutrition claims
The effect of Zespri Green Kiwifruit on digestive and gut health functions

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Hypotheses

• That consumption of two Zespri green kiwifruit (*Actinidia deliciosa* var Hayward) daily improves bowel motion frequency in constipated individuals by >1.5 complete spontaneous bowel motions / week

• That consumption of two Zespri green kiwifruit (*Actinidia deliciosa* var Hayward) daily improves gastrointestinal discomfort in constipated people

• That two Zespri green kiwifruit (*Actinidia deliciosa* var Hayward) are well tolerated by constipated individuals and healthy controls
Study design

- Randomised single-blinded cross-over design
- Powered to show an increase of 1.5 CSBM per week 90% power, 5% significance
Inclusion / exclusion criteria

Inclusion
• 18-65 years of age
• BMI 18-35
• Functional constipation (20)
• IBS-C (20)
• Healthy (20)

Exclusion
• GI alarm symptoms
• Significant chronic medical conditions
• Fasting glucose >7.2mmol/L
• Drugs affecting GI motility
• Pregnant / breastfeeding women
• Known kiwifruit or latex allergy
• Not prepared to stop other laxatives
Schedule of Assessments

START OF STUDY

Lead-in
2 weeks

Intervention 1
4 weeks

Washout
4 weeks

Intervention 2
4 weeks

Follow-up
2 weeks

Week
0
2
6
10
14
16

GSRS

Daily Diary

IBS - QoL

Food Diary

Stool Sample

Blood Sample (Vitamin C)

SmartPills (Italy/NZ)

Radiopaque markers (Japan) (sub-cohort)

POMS

IBS- SSI

Rome III

BASELINE
Clinical assessments

• Primary outcome
  – Daily bowel habit diary (CSBM, BM, CBM, SBM)

• Secondary outcomes
  – Daily bowel habit diary (ease of defaecation / straining, stool form)
  – Weekly Gastrointestinal Symptom Rating Scale
    • 7-grade scale, 5 domains (reflux, abdominal pain, indigestion, bowel dysfunction)
  – IBS-Quality of Life Questionnaire
  – Colonic transit measured by SmartPill in a subgroup
  – Profile of mood score (POMS)
  – Food diaries (to ensure no changes to habitual diet)
  – Faecal microflora / vitamin C
### GSRS Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Symptom</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Increased passage of stools, Urgent need for defeacation</td>
<td>Loose stools</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Abdominal distension, Eructation</td>
<td>Bourbourigmus, Increased flatus</td>
</tr>
<tr>
<td>Constipation</td>
<td>Decreased passage of stools, Feeling of incomplete evacuation</td>
<td>Hard stools</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Abdominal pain, Nausea and vomiting</td>
<td>Sucking sensations</td>
</tr>
<tr>
<td>Reflux</td>
<td>Heartburn</td>
<td>Acid regurgitation</td>
</tr>
</tbody>
</table>
# Bristol Stool Chart

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>Type 2</td>
<td>Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
<td>Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>Type 4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces. Entirely Liquid</td>
</tr>
</tbody>
</table>
What is SmartPill?
An ingestible capsule utilizing sensor technology to evaluate GI motility, specifically delayed gastric emptying (gastroparesis) and chronic constipation

Replaces
- Scintigraphy
- Sitzmarks® (ROM)

Complements
- Endoscopy
- Antroduodenal Manometry
SmartPill® Tracing

- **Gastric Transit**
- **Small Bowel Transit**
- **Colonic Transit**

- **pH**
- **Temperature**
- **Pressure**

- **Temperature**: Confirms ingestion and passage from the body.
- **Pressure**: Provides motility indices from the antrum and duodenum.
- **pH**: Identifies physiological landmarks, calculating regional transit times.
Safety

• Rescue therapy with bisacodyl 5g suppositories available and reported

• Reactions to kiwifruit and psyllium sought throughout study

• All adverse events after consent recorded and potential causality attributed
Statistics

• Analyses completed by statistician blinded to the treatment allocation

• Analyses completed for four patient groups
  – Healthy controls (HC)
  – Functionally constipated (FC)
  – IBS-C
  – All constipated (FC and IBS-C combined)

• Raw data analysed for least-squares means / 95% confidence intervals

• Appropriately transformed data for generation of p values
Results
CONSORT Diagram showing disposition of participants

225 expressions of interest in study

80 individuals screened

8 individuals declined enrollment following screening

60 participants enrolled

20 healthy participants enrolled
n=20 completed

10 participants enrolled and completed SmartPill™

20 IBS constipated participants enrolled
n=19 completed

8 participants enrolled and completed SmartPill™

12 individuals failed screening (6 individuals had blood parameters out of range; 4 did not meet the diagnostic criteria for IBS constipation; 2 had medical co-morbidities)

20 functionally constipated participants enrolled
n=19 completed

10 participants enrolled and completed SmartPill™
# Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy (20)</th>
<th>Functional Constipation (19)</th>
<th>IBS-C (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>12 (60)</td>
<td>16 (84)</td>
<td>19 (100)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>44.5 (14)</td>
<td>45.5 (15)</td>
<td>47.3 (13)</td>
</tr>
<tr>
<td>Pakeha, n (%)</td>
<td>15 (75)</td>
<td>16 (84)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.9 (4.7)</td>
<td>25.8 (4.6)</td>
<td>24.5 (3.8)</td>
</tr>
<tr>
<td>IBS severity, mean (SD)</td>
<td>49 (39) c</td>
<td>115 (56) b</td>
<td>191 (64) a</td>
</tr>
</tbody>
</table>

Means with different superscripts are significantly different (p<0.001)
Primary Outcome – Increase in CSBM

* $p<0.05$, ** $p<0.01$
Secondary outcome – constipation (straining)

Scores: 0=No, 1=at least 1 BM, 2=all BM
*p<0.05, **p<0.01, ***p<0.001
Secondary outcome – stool form (Bristol)

* $p<0.05$, ** $p<0.01$, *** $p<0.001$, # $p<0.10$ (trend)
Secondary outcomes – constipation (Rome III)

* p<0.05, ** p<0.01, *** p<0.001
Secondary outcomes – gastrointestinal comfort (GSRS)

**p<0.05, **p<0.01, ***p<0.001
Secondary outcomes – quality of life

* *p<0.05, **p<0.01, ***p<0.001
Secondary outcomes – colonic transit time

*p<0.05, **p<0.005, ***p<0.0005
Data to follow ...

- Analysis of faecal microbiota
- Profile of Mood Score
- Food diaries
- Vitamin C measurements
Conclusions

IMPROVED BOWEL MOTION FREQUENCY

• Consumption of two Zespri green kiwifruit (Actinidia deliciosa var Hayward) daily improves bowel motion frequency in constipated individuals by 2 complete spontaneous bowel motions / week

• FDA recognises an increase of 1CSBM / week to be clinically significant
Conclusions

IMPROVED GASTROINTESTINAL COMFORT

• Consumption of two Zespri green kiwifruit (Actinidia deliciosa var Hayward) daily improves gastrointestinal discomfort in constipated people

• Reduced straining
• Reduced abdominal pain
• Reduced bloating/distension
• Reduced incomplete evacuation

• Improved quality of life
Conclusions

NO CONCERNING SAFETY SIGNALS

• That two Zespri green kiwifruit (*Actinidia deliciosa* var Hayward) are well tolerated by constipated individuals and healthy controls

• No diarrhoea in healthy controls / symptomatic participants

• No other treatment-related adverse events
Limitations

• Participants were not blinded to the intervention - many subjective outcomes
  – very difficult to blind participants to ingestion of a whole food
  – a positive control was used to demonstrate similar efficacy in the same cohort

• Relatively small numbers
  – however a consistent effect observed

• Little mechanistic data available
Future Directions

• Awaiting results of Italian and Japanese studies

• May form part of an EFSA application for a validated health claim

• Possibility of echo studies in other Zespri markets to support validated health claims in these regions
Acknowledgements