The Latest on Pre- and Probiotics in Gut Health

UNIVERSITY *of* TASMANIA

Probiotic Advisor

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Disclosures and Conflicts of Interest:

- **I do <u>not</u> work for companies that manufacture or distribute probiotic or prebiotic products. Nor do I have financial interests in such companies.**

- I do work for Probiotic Advisor – a company that provides independent education and clinical tools in the areas of probiotics, prebiotics, the GIT microbiota, and GIT health.

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Probiotics

'Live microorganisms which when administered in adequate amounts confer a health benefit on the host'

(Hill et al, 2014)

Probiotics:

(Hill et al, 2014)

- Definition includes
  - preparations that contain viable, microbial agents that have been demonstrated to improve health
  - typically, these products will contain freeze-dried (lyophilized) or live bacteria or yeasts;
    - most commonly from the genera *Lactobacillus* and *Bifidobacterium*
  - powders, capsules, tablets, lozenges, oils, medicinal yoghurts, drinks

Food Sources of *Live and Active* Cultures:

(Hill et al, 2014)

- Includes
  - fermented foods, such as non-medicinal yoghurts, kombucha, sauerkraut, kim chi, kumis and kefir
    - these foods may contain a **diverse community** of microbes that are **not** well-defined in terms of strain composition or stability;
      - both of which can also differ from batch to batch
    - strains contained in these foods may also **lack specific therapeutic qualities**
      - e.g., they may not confer any health benefit on the host, beyond the enhanced nutritional profile of the fermented food
    - wild ferments **can't** be relied upon for therapeutic effects in the same way as products containing standardised , well-characterised and well-researched probiotic strains

Uses of Probiotics

- Traditional…
  - With/post antibiotics
  - Irritable bowel syndrome
  - Inflammatory Bowel Disease
  - Gut infections
  - Constipation
  - Dysbiosis
  - Lactose intolerance
  - Intestinal permeability
  - Vaginal thrush

Uses of Probiotics

- Novel…
  - Cervical dysplasia
  - Mastitis
  - Endometriosis
  - Prevention of gestational diabetes
  - Prevention of postpartum obesity
  - Prevention and treatment of atopic eczema
  - Non-Alcoholic Fatty Liver Disease
  - Anxiety
  - Depression
  - Low immunity/ recurrent infections
  - High cholesterol
  - Gastrooesophageal reflux
  - Prevention of urinary tract infections
  - Treatment of bacterial vaginosis
  - Small intestinal bacterial overgrowth (SIBO) prevention & treatment
  - Metabolic syndrome & type 2 diabetes
  - Obesity
  - Food allergies
  - Allergic rhinitis

Actions, Attributes and Characteristics are **Strain Specific**

(Hawrelak, 2021)

What is a "strain"?

- bacterial naming system:
  - ***Lactobacillus*** ***acidophilus*** **La5**
  - **Genus** **Species** **Strain**

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Potential of Probiotics in Diverticular Disease

- *Lactobacillus casei* Shirota (Yakult) (Nichols et al, 2020)
  - Small, open-label trial including 21 subjects with a previous history of acute diverticulitis
    - subjects consumed 1x Yakult drink daily for 12 months
    - diverticulitis incidence was assessed over the 12 month period and compared to the previous 12 months

	Diverticulitis free subjects	% free from diverticulitis	Attacks of diverticulitis	
			1 episode	2 episodes
The 12 months period before starting LcS*	8	38.1%	10	3
The 6 months period before starting LcS	11	52.4%	10	0
0-6 months of LcS	16	76.2%	4	1
6-12 months of LcS	19	90.5%	2	0
0-12 months of LcS*	14	66.7%	6	1

*Wilcoxon Matched Pairs test: p=0.021

Table 3a: *Changes in attack rate for diverticulitis 2013-14 on the basis of LcS intention to treat for probiotic naïve subjects (n = 21).*

Shows promise

Potential of Probiotics in Diverticular Disease

- VSL#3 (Original formula) (Tursi et al, 2007)
  - sold as Vivomixx in Australia
  - Randomised, open-label trial of 30 patients with acute diverticulitis who just achieved remission
  - Subjects randomised into 2 groups:
    - 1) balsalazide for 10d every month plus VSL#3 (450 billion CFU/d) for 15 days per month;
    - 2) VSL#3 for 15 days per month
  - Rates of remission over the 12 months:
    - 73.3% in the combination group
    - **60.0% in the probiotic group** (not significantly different between the groups)
  - GI symptoms of constipation, abdominal pain, and bloating were significantly better in the combined group at the end of the study (all P<0.05)

Not worth prescribing

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Potential of Probiotics in Diverticular Disease

- *Bifidobacterium infantis* 35624 (Align) (Stollman et al, 2013)
  - 12-month, RDBPC trial including 117 subjects with a recent episode of acute diverticulitis
  - After subjects achieved remission, they were randomised into 3 groups:
    - 1) mesalamine daily for 12 weeks;
    - 2) mesalamine + *B. infantis* 35624 (1.0 x 10^9 CFU/d) for 12 weeks;
    - 3) placebo

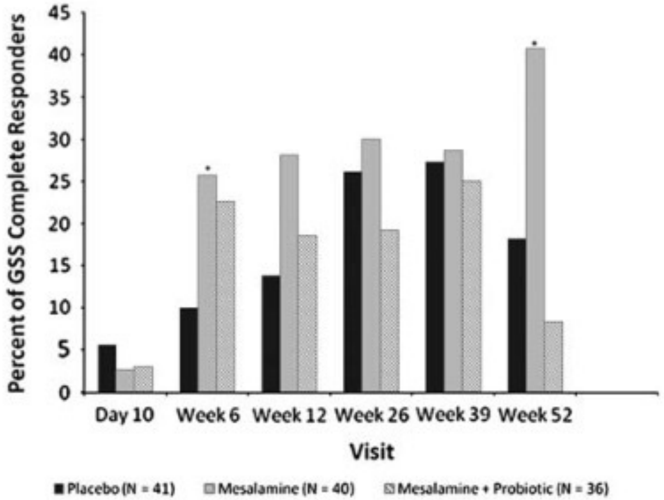


FIGURE 4. Global symptom score (GSS) complete responders. Responders scored 0 for all 10 symptoms. *Significant difference versus placebo.

Not worth prescribing

Probiotics in Constipation

- Meta-analysis of probiotics in adult functional constipation (Zhang, Jiang et al. 2020)
  - 15 RCTs were eligible and had poolable data
    - Pooling of the extracted data demonstrated that probiotic consumption:
      - significantly reduced the whole gut transit time by 13.75 h (95% CI −21.93 to −5.56 h) and
      - increased the stool frequency by 0.98 (95% CI 0.36 to 1.60) bowel movements per week

Probiotics in Constipation

- *L. reuteri* DSM 17938 in constipated adults (Ojetti, Ianiro et al. 2014)
  - RDBPC trial of 40 adults (mean 35.6 years) meeting the Rome III criteria for functional constipation
    - randomly assigned to 4-weeks treatment with either:
      - placebo;
      - *L. reuteri* DSM 17938 (1.0 x 10^8 CFU bid) 30 mins after eating
  - After 4 weeks:
    - there was a mean increase in bowel movements per week of 2.6 (95% CI 1.6-3.6) in the probiotic group versus 1.0 (95% CI 0.12-1.88) in the placebo group (P=0.046)
      - mean number of bowel movements per week was 5.3 in the probiotic group vs 3.9 in the placebo group.
    - no significant difference in the stool consistency between the two groups

Probiotics in Constipation

- *B. lactis* Bb12 in constipated adults (Eskesen, Jespersen et al. 2015)
  - RDBPC multi-centre trial in 1248 healthy adults (mean age 37.2 years) with low defecation frequency (2-4d/wk) and abdominal discomfort
  - After a 2-week run-in period, subjects were randomly assigned to 4-weeks treatment with:
    - placebo;
    - *B. lactis* Bb12 (1.0 x 10^9 CFU/d);
    - *B. lactis* Bb12 (1.0 x 10^{10} CFU/d)
  - No dose response observed
  - ITT - probiotic supplementation increased the probability of having a defecation frequency above baseline for at least 2 of the 4-week intervention with an overall (OR =1.31; 95 % CI 0.98 – 1.75; P=0.07)
  - PP – OR=1.43 (95%CI 1.04-1.96; P=0.03)
  - Post-hoc - defined responders as "*subjects with an increase in defecation frequency of ≥1 day/week for at least 50% of the time*"
    - OR=1.55 (95% CI 1.22-1.96; P=0.003)

Probiotics in Irritable Bowel Syndrome

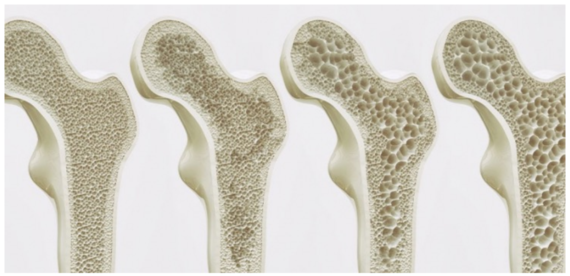
- Strain-specific systematic review and meta-analysis
  - 42 RCTs found that looked at specific probiotic strains and specific strain combinations in IBS (McFarland, Karakan et al. 2021)
    - 4 probiotic strains demonstrated significant improvements in abdominal pain relief:
      - *Bacillus coagulans* MTCC5260 (RR=4.9; 95% CI 3.3-7.3)
        - aka *B. coagulans* Unique IS-2
      - *Lactobacillus plantarum* 299v (RR=4.6; 95% CI 1.9-11.0)
      - *Saccharomyces cerevisiae var. boulardii* CNCM I-745 (RR= 1.5, 95% CI 1.1-2.1)
      - *S. cerevisiae* CNCM I-3856 (RR= 1.3, 95% CI 1.04-1.6)
    - 2 probiotic strains significantly reduced global IBS scores
      - *Bifidobacterium infantis* 35624 (SMD= -9.4; 95% C.I. -13.0 to -5.8)
      - *Bacillus coagulans* MTCC5260 (SMD= -2.5; 95% C.I. -2.8 to -2.2)

Probiotics in IBS-C

Trial Design	Probiotic Strain	Results
R,DB,PC	*Bifidobacterium animalis ssp lactis* DN-173 010 (2.5 x 10^{10} CFU/day)	In patients with constipation-predominant IBS, consumption of this strain resulted in a reduction in abdominal distension (P=0.02), an acceleration of gut transit time (P=0.049), a reduction in overall IBS symptom severity (P=0.032), as well as abdominal pain/discomfort (P=0.044), bloating (P=0.059), and flatulence scores (P=0.092) (Agrawal et al, 2009)
R,DB,PC	*Bifidobacterium animalis ssp lactis* DN-173 010 (2.5 x 10^{10} CFU/day)	IBS subjects who received fermented milk with *B. animalis* DN-173010 for 6 weeks, had significantly improved HRQoL discomfort scores (P<0.005) and decreased bloating (P=0.03) at week 3, relative to controls. In a subgroup of constipated IBS subjects (<3 bowel movements per week) stool frequency increased (P<0.001) relative to controls throughout the 6-week period. (Guyonnet et al, 2007)

Probiotics in Osteoporosis??

- *Lactobacillus reuteri* ATCCPTA 6475 (Osfortis) (Nilsson, Sundh et al. 2018)
  - 12-month, RDBPC trial including 90 women (aged 75-80 years old), with low bone mineral density (BMD)
  - Randomised to receive either:
    - 1) placebo;
    - 2) *L. reuteri* 6475 (1.0×10^{10} CFU/d);
  - Tibia total BMD, after study completion was -0.83% (95% CI -1.47 to -0.19%) in the probiotic group vs -1.85% (95% CI -2.64 to -1.07%) in the placebo group



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Probiotics for Improving Cognition??

- *Lactobacillus rhamnosus* GG (Sanborn, Azcarate-Peril et al. 2020)
  - RDBPC trial of 3 months duration in 200 community dwelling adults (aged 52-75 yo; mean age 64.3 years)
    - cognitive functioning assessed at baseline and after 3 months treatment with either:
      - *L. rhamnosus* GG (1.0 x 10^{10} CFU/d)
      - placebo
  - After 3 months:
    - PP analysis - participants with cognitive impairment in the probiotic group showed significantly greater improvement in total cognition score than participants with cognitive impairment in the placebo group and participants without cognitive impairment in the probiotic and placebo groups
    - ITT analysis - impaired persons in the probiotic group showed greater improvement in cognitive performance than impaired persons in the placebo group, intact persons in the probiotic group, and intact persons in the placebo group

Prebiotics

'a substrate that is ***selectively*** *utilised by host microorganisms conferring a health benefit'*

(Gibson et al., 2017)

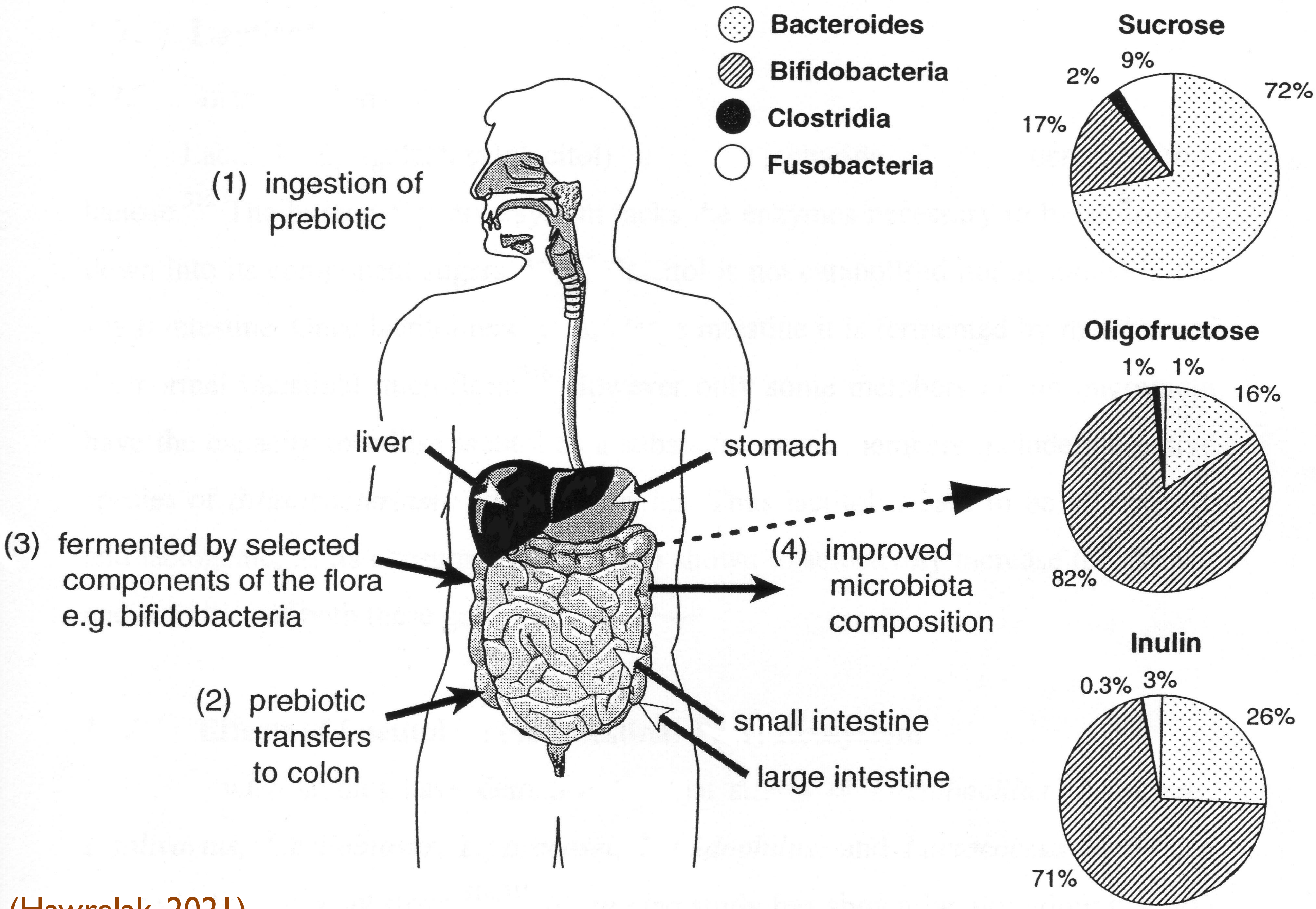
Prebiotics:

(Hawrelak, 2021)

For food ingredients to be classified as prebiotics, they must:

1. Neither be hydrolysed nor absorbed in the stomach or small intestine;
2. Act as a selective substrate for one or a limited number of potentially beneficial commensal bacteria in the large intestine;
3. Change the colonic microbiota ecosystem towards a healthier composition; and
4. Induce luminal or systemic changes that improve the health of the host

How do Prebiotics Work?



(Hawrelak, 2021)

Prebiotics and Potential Prebiotics

Prebiotic Compound	Food Sources	Targeted Microbes
Fructooligosaccharides (Inulin-Type Fructans)	Garlic, onion, Jerusalem artichokes, chicory root	Bifidobacteria, Faecalibacterium, & Akkermansia
Galactooligosaccharides	Cow's milk (traces)	Bifidobacteria & Faecalibacterium
Lactulose	UHT milk (traces)	Lactobacilli, Bifidobacteria, & Faecalibacterium, Akkermansia
Acacia gum	Gum Arabic (*Acacia senegal*)	Lactobacilli & Bifidobacteria
Glucomannan	Konjac root (*Amorphophallus konjac*)	Lactobacilli
Human milk oligosaccharides	Human breastmilk	Bifidobacteria
Lactitol	None	Lactobacilli & Bifidobacteria
Partially-hydrolysed Guar Gum	None	Bifidobacteria & multiple butyrate-producing species
Raffinose	Legumes, beetroot	Bifidobacteria
Xylooligosaccharides	Oats, rice husks, corn cobs	Bifidobacteria; Bacteroides

Inulin-FOS for Frailty??

- Oligofructose-enriched inulin (inulin-FOS) (Theou et al, 2019)
  - RDBPC trial assessing frailty levels in 50 older subjects living in nursing homes (mean age 73.8 years)
    - post-hoc analysis of the data
  - Randomised to receive 13 weeks treatment with either:
    - 1) placebo;
    - 2) prebiotic combination
      - 7.5g/day of what was essentially a 1:1 ratio of the 2 related prebiotics

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Inulin-FOS for Frailty

- Oligofructose-enriched inulin (inulin-FOS) (Theou et al, 2019)

Table 1. Frailty criteria and geriatric evaluation at baseline and post-treatment with Darmocare Pre® or placebo. * $p < 0.05$; ** $p < 0.01$.

Variable	Baseline		Significance	Post-Treatment		Significance
	Placebo Group (n = 22)	Dermocare Pre® (n = 28)	p Value	Placebo Group (n = 22)	Dermocare Pre® (n = 28)	p Value
Exhaustion (score 0–3: 0 "never"; 1 "A few times" (1–2 days per week); 2 "Often" (3–4 days per week); or 3 "Most of the time" (almost each day))	1.1 ± 1.7	1.4 ± 1.7	0.74	1.7 ± 1.2	0.8 ± 1.4 **	0.002
Slow walk (s) (time needed to walk 4.6 m)	8.6 ± 9.0	8.4 ± 6.0	0.91	8.7 ± 4.2	7.9 ± 4.5	0.48
Grip strength (right hand, kg)	11.5 ± 5.7	10.6 ± 8.2	0.61	10.2 ± 4.1	12.4 ± 3.2 *	0.04
Grip strength (left hand, kg)	10.2 ± 5.8	10.1 ± 7.6	0.92	9.1 ± 3.7	9.8 ± 3.5	0.50
Self health-perception (score 0–10, being 0 the worst and 10 the best)	7.1 ± 2.3	7.1 ± 2.1	0.96	6.8 ± 2.4	6.8 ± 2.0	0.96
Body mass index	26.1 ± 4.1	25.8 ± 4.2	0.97	26.0 ± 3.8	25.9 ± 4.1	0.96
Athens insomnia scale	3.4 ± 3.0	4.1 ± 4.7	0.77	4.5 ± 5.3	4.0 ± 4.3	0.68
Barthel index	76.2 ± 13.0	74.6 ± 17.7	0.69	78.3 ± 13.9	77.1 ± 29.9	0.87
Mini–Mental state examination	26.1 ± 2.2	26.5 ± 3.1	0.89	25.9 ± 2.1	26.4 ± 2.2	0.85

Prebiotics for Wrinkles??

- Lactulose and GOS combination (Jung, Kwon et al. 2017)
  - RDBPC trial assessing wrinkle-related parameters in 30 healthy women (mean age 52.1 years; range 40-60 years)
    - all had fine wrinkles at the outer corner of their eyes
  - Randomised to receive 8 weeks treatment with either:
    - 1) placebo;
    - 2) prebiotic combination (4.5g/day)
  - After the 8 weeks:
    - prebiotic group showed reduced mean wrinkle length and depth vs the placebo group (which showed slight increases in both these parameters)
      - differences in the changes of mean wrinkle length and depth between two groups were significant (both P<0.001)
    - Wrinkle Severity Rating Scale scores in the prebiotic group were decreased whereas scores were increased in the placebo group
      - placebo group: +0.14 vs prebiotic group: –0.86 (P<0.001)
    - crow's feet wrinkles were significantly improved in the prebiotic group compared with baseline (P<0.01)

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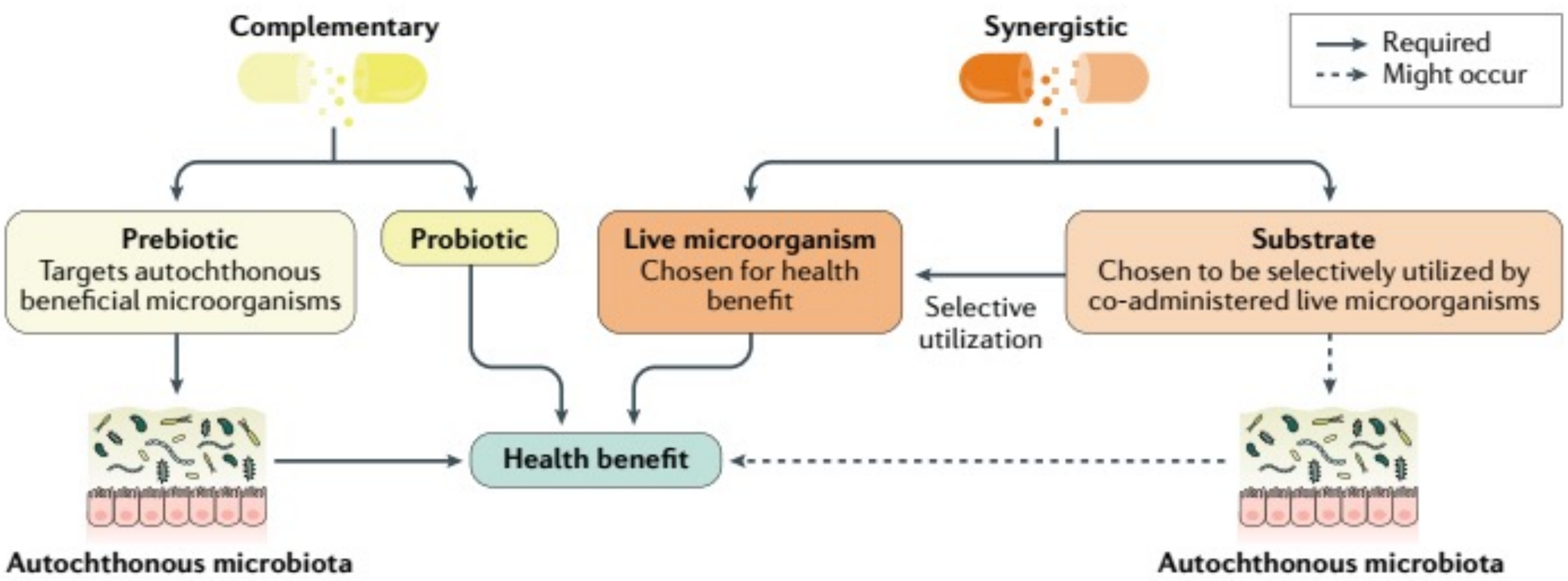
Synbiotics

- Synbiotics are: *a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host* (Swanson, Gibson et al. 2020)



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Synbiotics

- When considering the therapeutic potential of a product claimed to be a synbiotic, a number of factors should be assessed:
  - does the product use well-characterised and researched probiotic strains?
  - does the "prebiotic" substance meet the requirements to be truly considered a prebiotic?;
  - has the "prebiotic" been demonstrated to enhance the growth of the exact probiotic strain(s) contained in the product?
  - are both agents included in therapeutic doses?

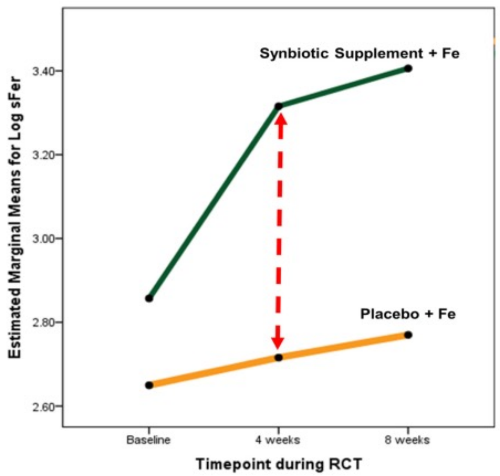
- Ideally, a synbiotic product should meet all four of these criteria.
  - many currently on the market do not

Synbiotics

- Individual probiotic strains have variable capacities to utilise different prebiotic substrates.
  - *Bifidobacterium lactis* Bb12 can utilise GOS, lactulose and FOS, but is unable to use lactitol (Vernazza et al, 2006)
  - *Lactobacillus rhamnosus* GG is unable to use lactulose, lactitol or FOS (Kontula et al, 1999)(Kaplan et al, 2000)
  - both *L. acidophilus* NCFM and *L. acidophilus* DDS-1 can utilise FOS (Kaplan et al, 2000)

Synbiotics for Iron Absorption

- Partially hydrolysed guar gum (PHGG) and *Bifidobacterium lactis* BL-04 (Sandroni, House et al. 2021)
  - RDBPC trial aimed at improving iron status in 20 female athletes (mean age years) with low iron status
    - all were either anaemic, iron deficient or iron depleted
  - Randomised to receive 8-weeks supplemental iron (28mg elemental iron as Ferrous sulphate) plus either:
    - placebo
    - PHGG (5g/d) and *B. lactis* BL-04 (8.0 x 10^9 CFU/d))



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Synbiotics for Type I Diabetes Mellitus

- *Bacillus coagulans* GBI-30, 6086 + FOS (Zare Javid, Aminzadeh et al. 2020)
  - RDBPC trial in 50 type 1 diabetics (mean age 10.4 years)
  - Randomised to receive 8-weeks supplementation with either:
    - placebo powder
    - *Bacillus coagulans* (used to be known as *Lactobacillus sporogenes*) GBI-30 (1.0×10^9 CFU/d) plus FOS (~400mg)

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Synbiotics for Type 1 DM

- *Bacillus coagulans* GBI-30, 6086 + FOS (Zare Javid, et al. 2020)

Table 3 Glycemic Status and Lipid Profile at Baseline and Post-Intervention

Variables	Intervention Group (n=22)	Control Group (n=22)	P-value*	P-value**	P-value***
FBG (mg/dl)					
Baseline	199.72±81.10	162.31±68.11	0.10		
End	163.68±75.88	171.63±73.89	0.72		
P-value	0.05	0.34			
Difference	−36.04±81.87	9.31±45.34		0.03	0.02
Insulin (μg/mL)					
Baseline	6.37±6.32	5.97±5.02	0.81		
End	10.90±8.20	7.57±7.12	0.15		
P-value	<0.001	0.18			
Difference	4.52±4.53	1.59±5.46		0.06	0.06
HbA1c (%)					
Baseline	8.90±1.95	9.60±2.23	0.27		
End	8.61±1.85	9.08±2.59	0.96		
P-value	0.01	0.08			
Difference	−0.28±0.52	−0.52±1.36		0.44	0.03
LDL-c (mg/dl)					
Baseline	79.81±13.55	74.45±17.06	0.25		
End	81.86±15.01	79.31±17.90	0.61		
P-value	0.14	0.06			
Difference	2.04±6.34	4.86±11.47		0.31	0.31

Table 4 The Mean ± SD of Hs-CRP and TAC at Baseline and Post-Intervention

Variables	Intervention Group (n=22)	Control Group (n=22)	P-value*	P-value**
Hs-CRP (ng/mL)				
Baseline	3054.64±3009.89	2267.73±2087.29	0.31	
End	1807.10±2258.92	2293.01±1899	0.44	
P-value	0.004	0.89		
Difference	−1247.54±1793.66	25.28±858.14		0.005
TAC (mmol/lit)				
Baseline	94.16±14.29	100.07±11.49	0.33	
End	101.12±14.35	92.37±4.27	0.002	
P-value	0.001	0.08		
Difference	6.96±8.61	−7.70±11.58		0.005

What are Postbiotics?

- Numerous definitions online:
  - *Postbiotics are byproducts of the fermentation process carried out by probiotics in the intestine*
  - *Non-viable metabolites produced by probiotics that exert biological effects on the host*
  - *Also called "short chain fatty acids"*
  - *Postbiotics are bioactive compounds made when the healthy bacteria in your gut… feed on various types of prebiotic food in your colon, such as fiber*
- The term is inconsistently used and lacks a clear definition

What are Postbiotics?

- Recently defined by the International Scientific Association of Probiotics and Prebiotics (ISAPP) as: (Salminen, Collado et al. 2021)
  - *a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host*

Box 2 | Criteria for a preparation to qualify as a postbiotic

- Molecular characterization of the progenitor microorganisms (for example, fully annotated genome sequence) to enable accurate identification and screen for potential genes of safety concern
- Detailed description of the inactivation procedure and the matrix
- Confirmation that inactivation has occurred
- Evidence of a health benefit in the host from a controlled, high-quality trial
- Detailed description of the composition of the postbiotic preparation
- Assessment of safety of the postbiotic preparation in the target host for the intended use

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