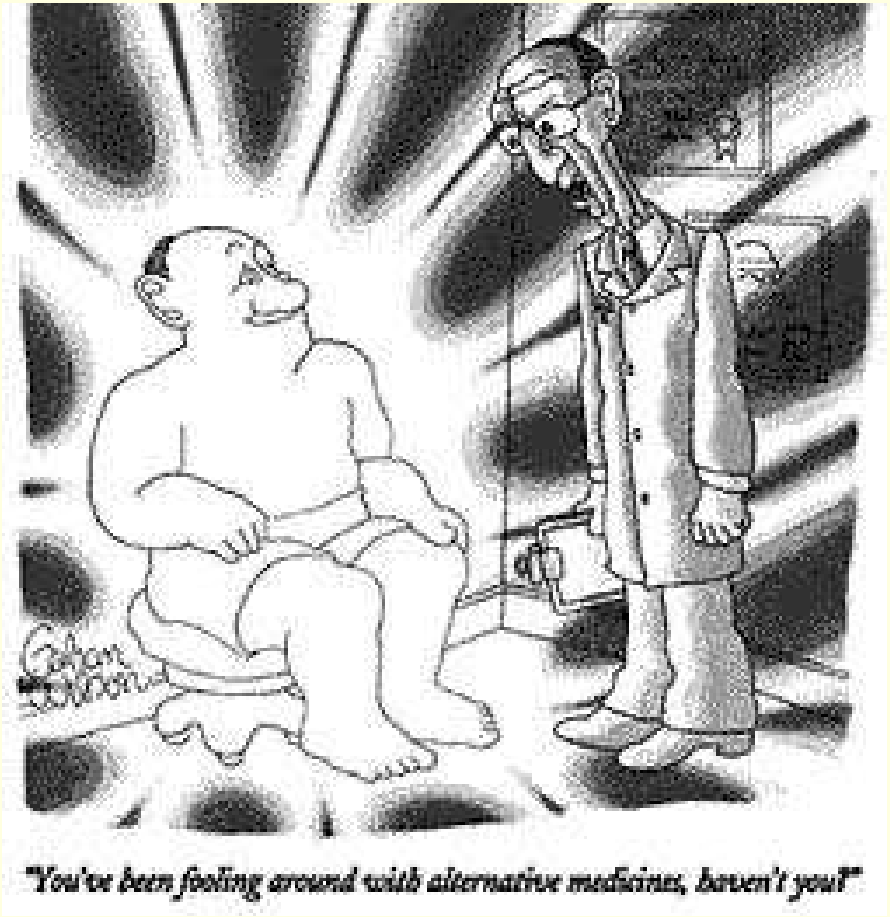
Pre- and Probiotics: From Basics to chronobiological needs



"You've been fooling around with alternative medicine, haven't you?"

Outline

- What are probiotics and how do they work
- Current proposed uses and a look at some of the evidence
- Chronobiological issues concerning their use

Cell quantity of our body

- **For context – Total Cells**
  - **You ~ 10,000 billion.**
  - **Them ~ 100,000 billion.**

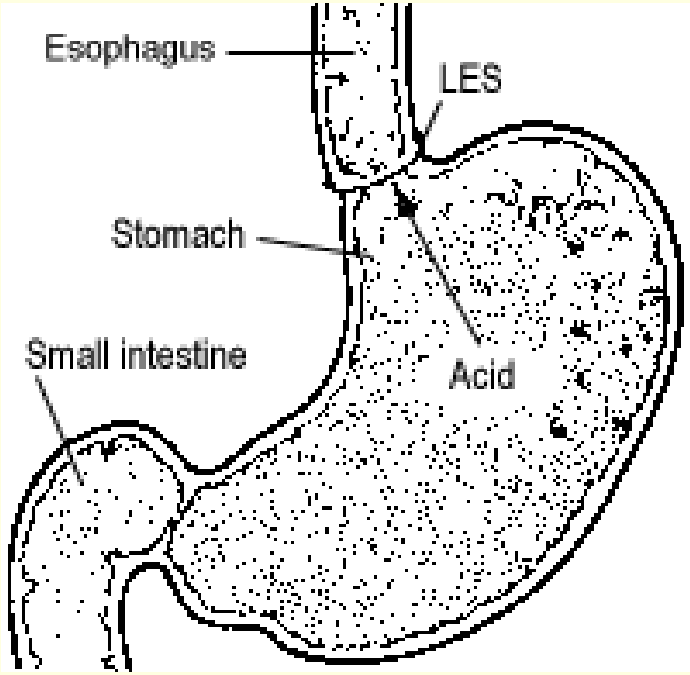
Probiotics: definitions

- World Health Organization:
  - “live microorganisms which when administered in adequate amounts confer a health benefit on the host”

- A bacterial strain that:
  - Survives the stomach acid and bile
  - Adheres to intestinal lining
  - Grows and establishes temporary residence in the intestines
  - Imparts health benefits

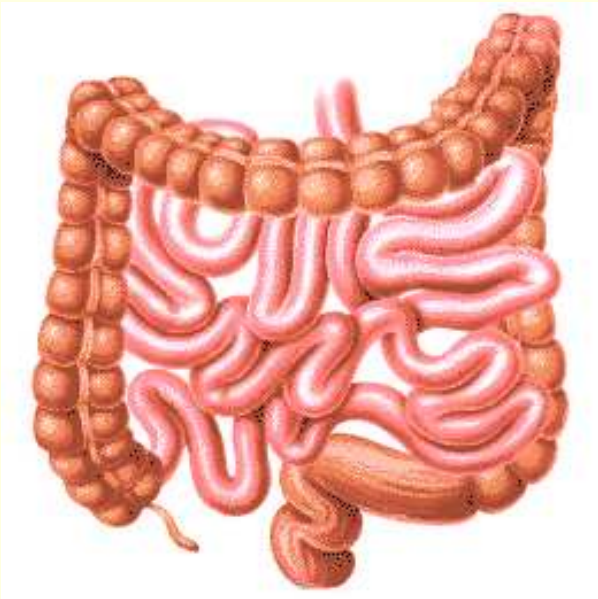
R Fuller. Probiotics: The Scientific Basis. London: Chapman and Halls. 1992

Predominant Flora: Stomach



<u>Stomach</u> (0-10^3 cfu/ml):
Gram+ aerobes,
Lactobacillus &
Streptococcus

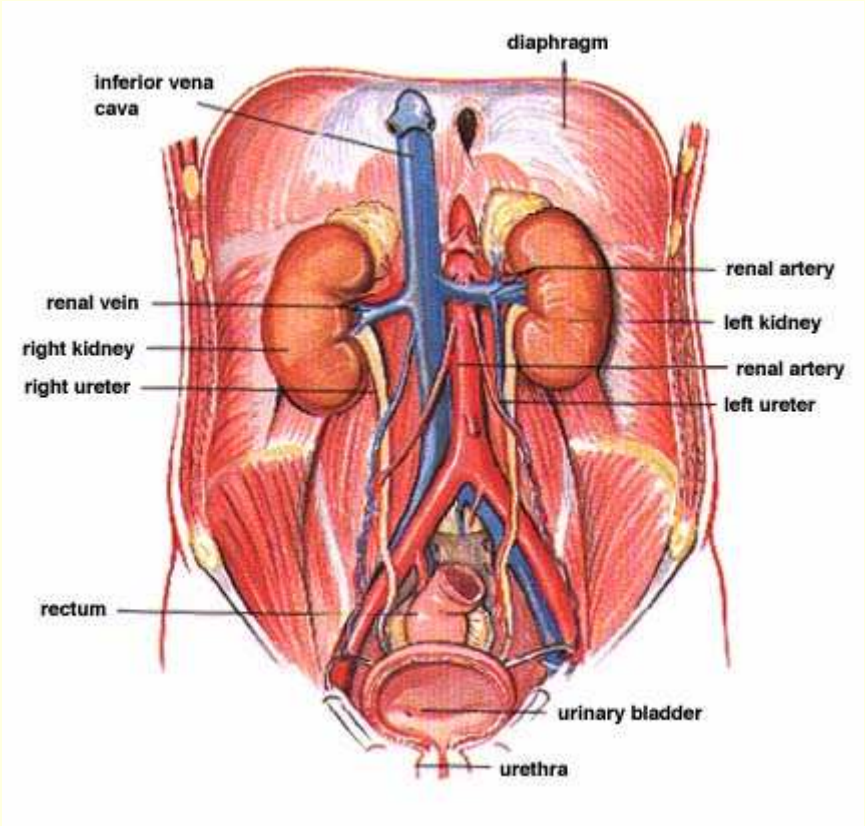
Predominant Flora: Intestines



Small intestine:
Proximal ileum (10^3-10^4 cfu/ml)
aerobic Gram+
Distal ileum (10^{11}-10^{12} cfu/ml)
Gram- anaerobes

Colon (10^{11}-10^{12} cfu/ml):
Bacteroides, Eubacteria,
Peptostreptococci, E. coli,
Bifidobacterium, Fusobacteria

Predominant Flora: Urinary Tract

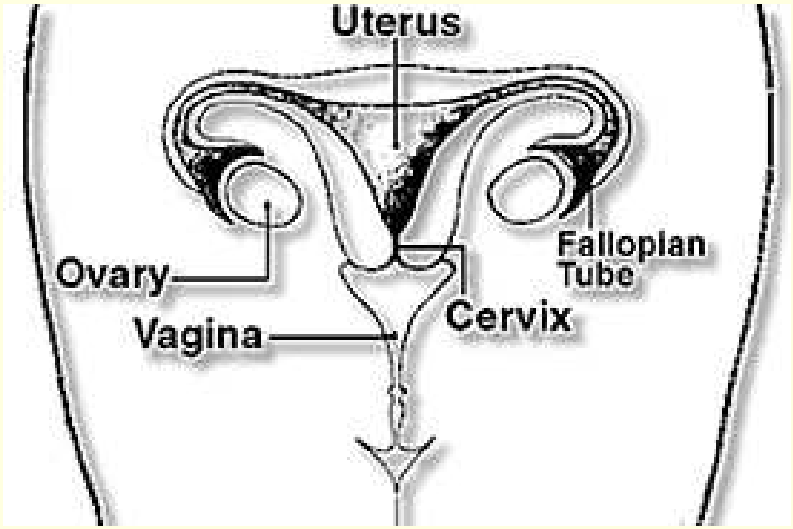


Kidneys: sterile

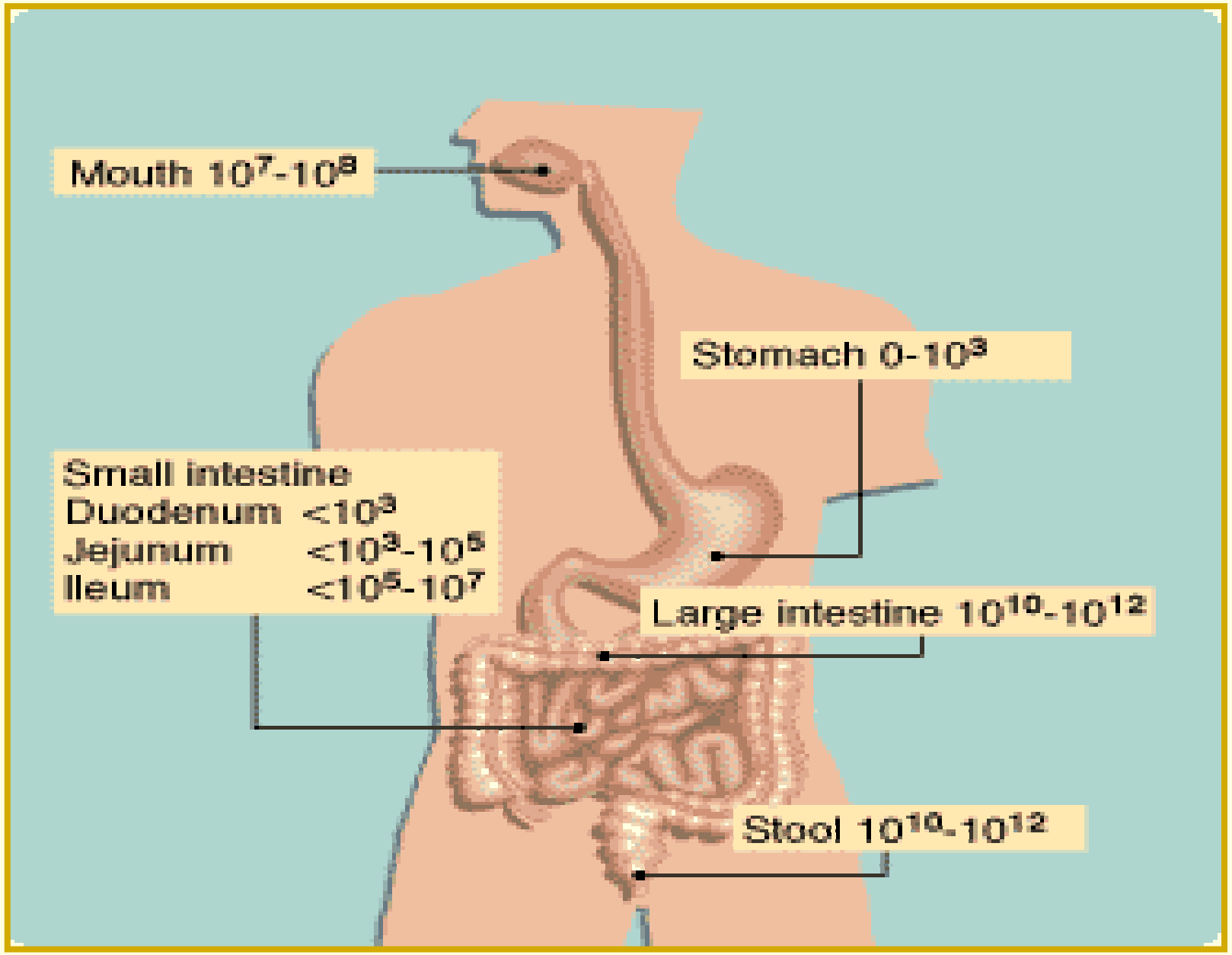
Bladder: sterile

Urethra: 10^1-10^2 E. coli

Predominant Flora: Vagina



Vagina: diverse aerobes & anaerobes including Lactobacillus jensenii, Lactobacillus acidophilus, Lactobacillus casei.


Mouth 10^7-10^8
Stomach 0-10^3
Small intestine
Duodenum <10^3
Jejunum <10^3-10^5
Ileum <10^5-10^7
Large intestine 10^{10}-10^{12}
Stool 10^{10}-10^{12}

(Fuller, 1992)

Probiotics

- *Lactobacillus* sp.
  - *salivaris*
  - *plantarum*
  - *ramnosus*
  - *acidophilus*
- *Streptococcus* sp.
- *Bifidobacterium* sp.
  - *infantis*
  - *lactis*
  - *longum*
  - *breve*
  - *bifidum*
- *Sacharomyces boulardii* (non-human)

Probiotics

- Colonization at birth
- Similar to maternal species
- Specific organisms vary by age in first year
- Become established by 1 year
- In children and adults, “Successful” treatment with probiotics leads to temporary colonization only

Probiotics: proposed mechanisms

- Adherence and subsequent stimulation of gut immune system
  - Up-regulation of mucin gene
  - Enhance secretory IgA
  - Maintain normal macrophage function
- Metabolism of essential nutrients
- Production of antimicrobial factors
- Provide favorable environment for growth of other beneficial bacteria
- Production of short-chain fatty acids with anti-inflammatory properties

Probiotics: Proposed uses

- Infectious diarrhea
- Antibiotic-associated diarrhea
- IBD, IBS, and pouchitis
- Necrotizing Enterocolitis
- Bacterial vaginosis
- Recurrent UTI’s
- Atopic diseases
- Immune system enhancement
- *H pylori* infections
- Dental caries
- Radiation induced diarrhea
- Cardiovascular risk reduction
- Constipation
- Rheumatoid arthritis

Probiotics: Proposed uses

Ratings: A: strong B: good C: fair

Rating the Evidence	Floch et al (2006)	Natural Standard (2006)
Infectious diarrhea	A	B
Antibiotic-associated diarrhea	A	C
Diarrhea prevention	B	B
Irritable bowle syndrome	C	B
Atopic dermatitis/Allergy	B	B/C

Floch, et al. Recommendations for Probiotic Use. J Clin Gastro. 40(3). 2006
www.naturalstandard.com

Probiotics: Proposed uses

Ratings: A: strong B: good C: fair

Rating the Evidence	Floch et al (2006)	Natural Standard (2006)
Ulcerative colitis	C	B
Crohn's disease	C	C
H pylori infection	C	A
Necrotic-Entero-Colitis	B	C
Bacterial vaginosis	C	C
Uterin tract infection	B	C

Floch, et al. Recommendations for Probiotic Use. J Clin Gastro. 40(3). 2006
www.naturalstandard.com

Probiotics: the evidence

- Antibiotic-associated diarrhea:
  - D'Souza et al (*BMJ* 2002)
    - Systematic review of 9 placebo-controlled studies (2 in children)
    - Various probiotics (4 uses *S Bouladarii*)
    - **60% reduction** in antibiotic associated diarrhea compared with placebo (OR 0.37, 95% CI 0.26-0.53)
  - Vanderhoof et al (*J Pediatr* 1999)
    - 202 children, 6 mo - 10 yr, otitis/pharyngitis, amox/amox-clav
    - Oral antibiotics in an outpatient setting for 10 days
    - *Lactobacillus GG*, 10 (<12kg) or 20 (>12kg) billion cfu's for 10 d
    - Rated stool consistency and frequency
    - **26% of controls and 8% of *L GG*** had diarrhea
    - Of those with diarrhea, **5.9 days in placebo, 4.7 days in *L GG***

Probiotics: the evidence

- Infectious diarrhea:
  - Van Niel et al (*Peds* 2002)
    - Systematic review of 9 studies (all outside US, 1-36 months)
    - Various probiotics (4 used *L GG*)
    - Mean reduction in diarrhea of 0.7 days (95% CI: 0.3-1.2)
    - **1.6 fewer stools in *L GG* groups** (95% CI: 0.7-2.6)
    - Dose response curve with higher *L GG* dose
  - Two other meta-analyses also showed benefits, particularly with *L GG*
    - Allen et al. *Cochrane Database Syst Rev*, 2004
    - Szajewska et al. *J Pediatr Gastroenterol Nutr*, 2001

Probiotics: the evidence

- Prevention of infections in day care:
  - Weizman et al (*Peds* 2005)
    - Double-blind, placebo-controlled RCT
    - 14 day care centers in Israel, 4-10 months of age
    - Formula with *BifidoB*, *LactoB*, or no probiotics (no breastfeeding)
    - Mean intake: 1 billion orgs
    - Intervention and follow-up totaled 12 weeks
    - Both probiotic groups had:
      - **Fewer febrile episodes**
      - **Fewer diarrhea episodes**
      - **Shorter diarrhea episodes**
    - No difference in rate or duration of respirator illnesses
    - ***LactoB* group did significantly better than *BifidoB* group**

Probiotics: the evidence

- Atopic disease:
  - Kalliomaki et al (*Lancet* 2001)
    - *L GG*, 10 bill cfu's, given to mother's with a family hx of a first degree relative with an atopic condition (asthma, eczema, allergic rhinitis).
    - Mothers for 2-4 weeks before delivery, then infants or lactating mothers for the first 6 months.
    - Outcome: atopic disease at 2 yrs.
    - **Frequency of eczema reduced from 46% to 23%** (RR 0.51, CI: 0.32-0.84)
  - Kalliomaki et al (*Lancet* 2003)
    - 4 yr follow up study (54 of 68 controls, 53 of 64 intervention)
    - **Relative risk reduction for atopic eczema of 0.57** (95% CI: 0.33-0.97)

Pre- Probiotics: prescribing

- How must they delivered?
- Which organism have to be use?
- What kind of prebiotics can be used?
- What dose and at what time?

Probiotics delivered after oral administration

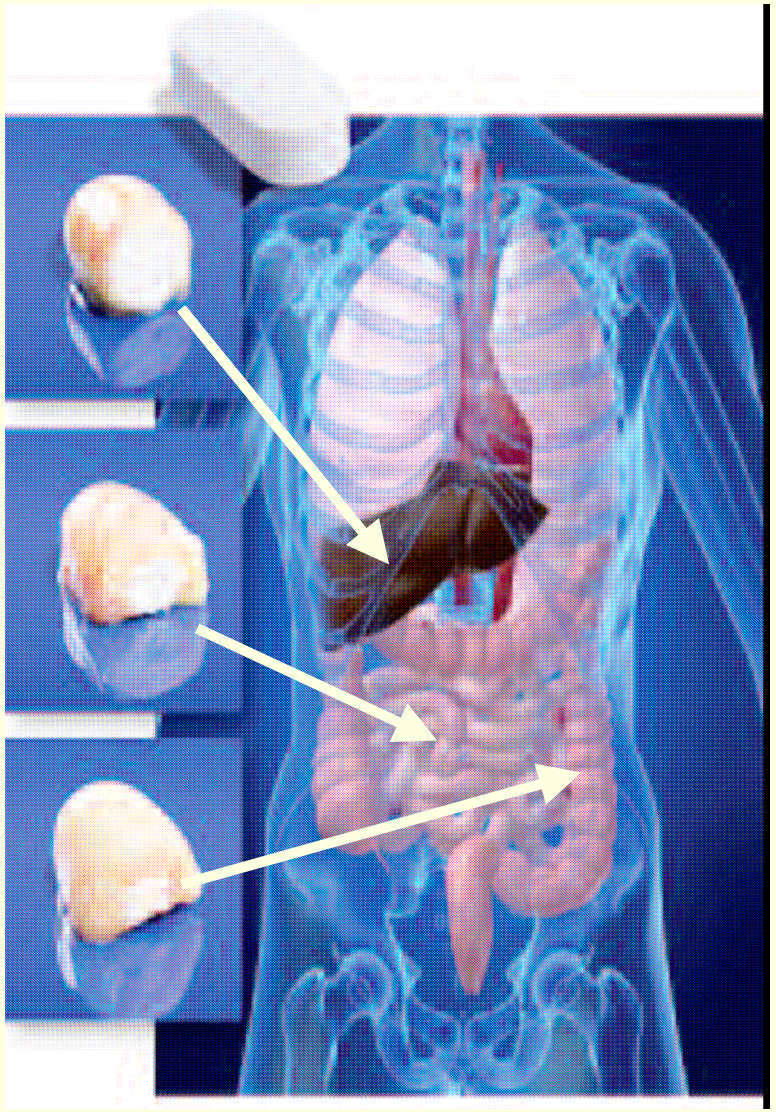
2×10^7 colon forming units (CFU)

Lactobacillus acidophilus
Lacto-bacillus plantarum
Lactobacillus salivarius
Lactobacillus rhamnosus
Bifidobacterium bifidum

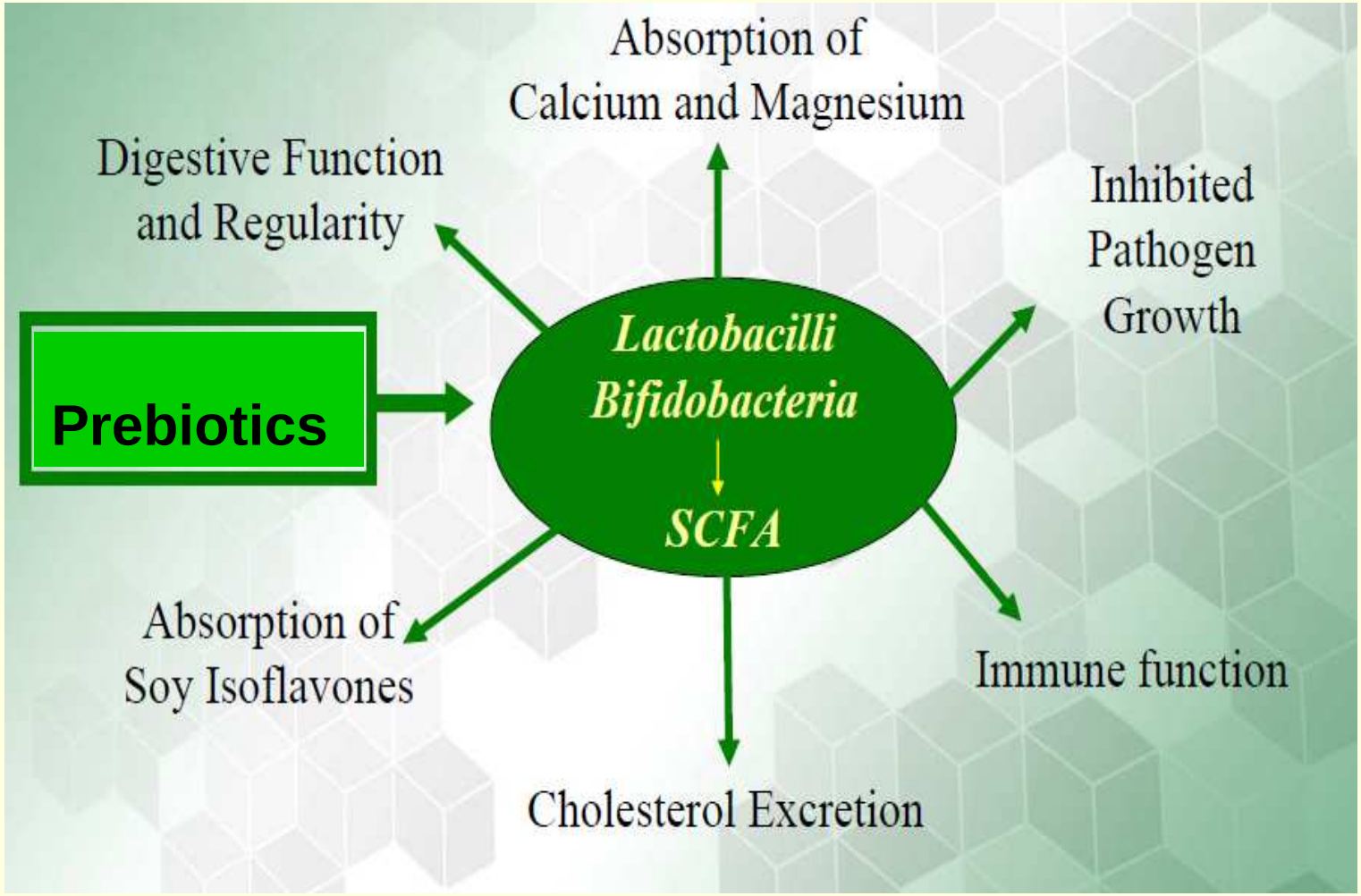
30 min
(10%)

120 min
(30%)

300 min
(60%)



Pre- Probiotics: interaction

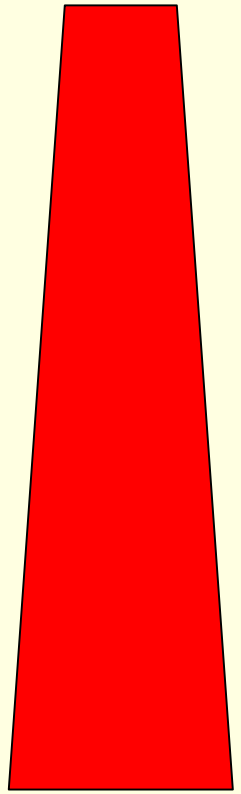


Differentiating prebiotics = Fructans

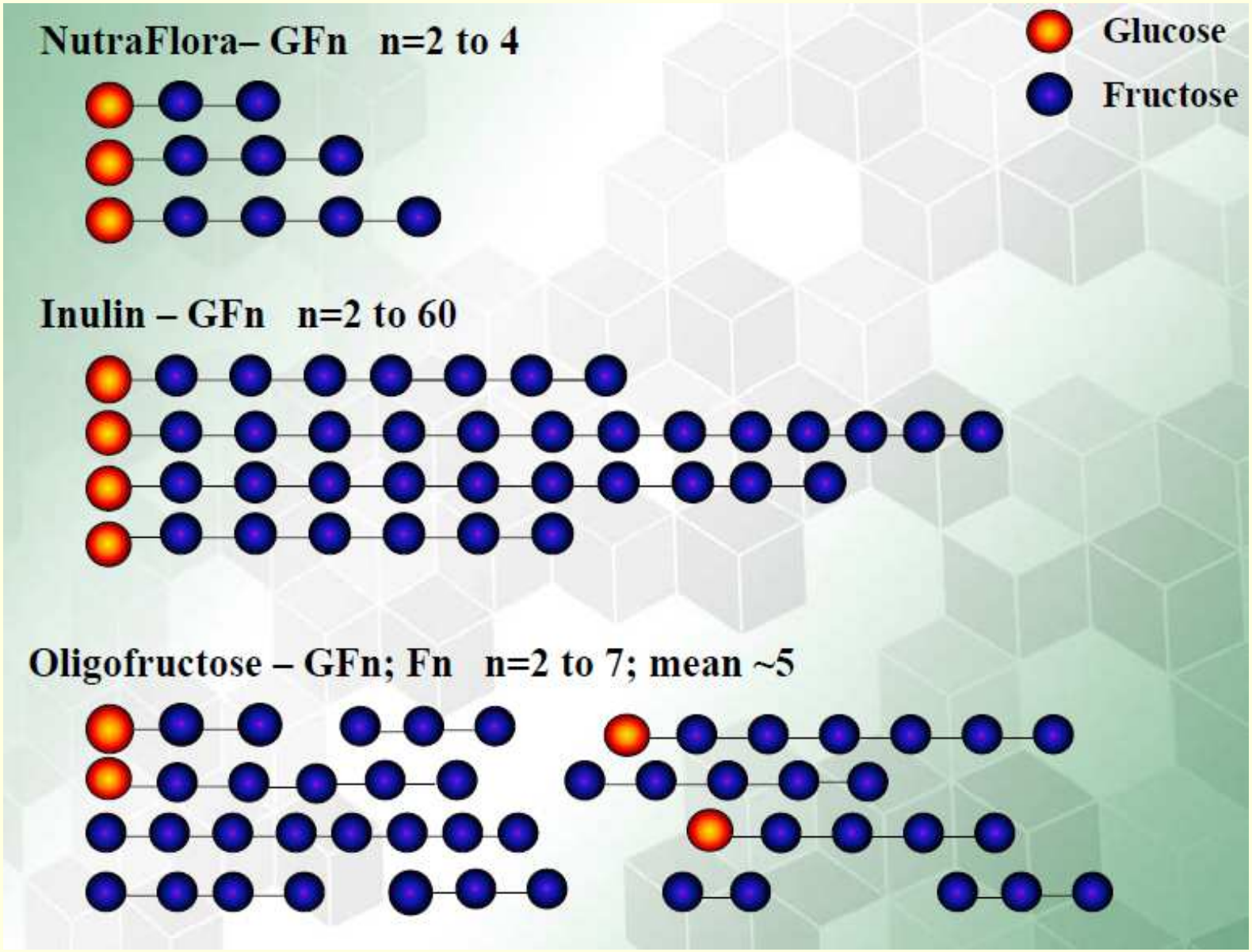
Inulin
- Polysaccharide extracted from chicory root

Oligofructose
- Enzymatic hydrolysis of inulin

scFOS
- Made from sugar by an enzymatic reaction

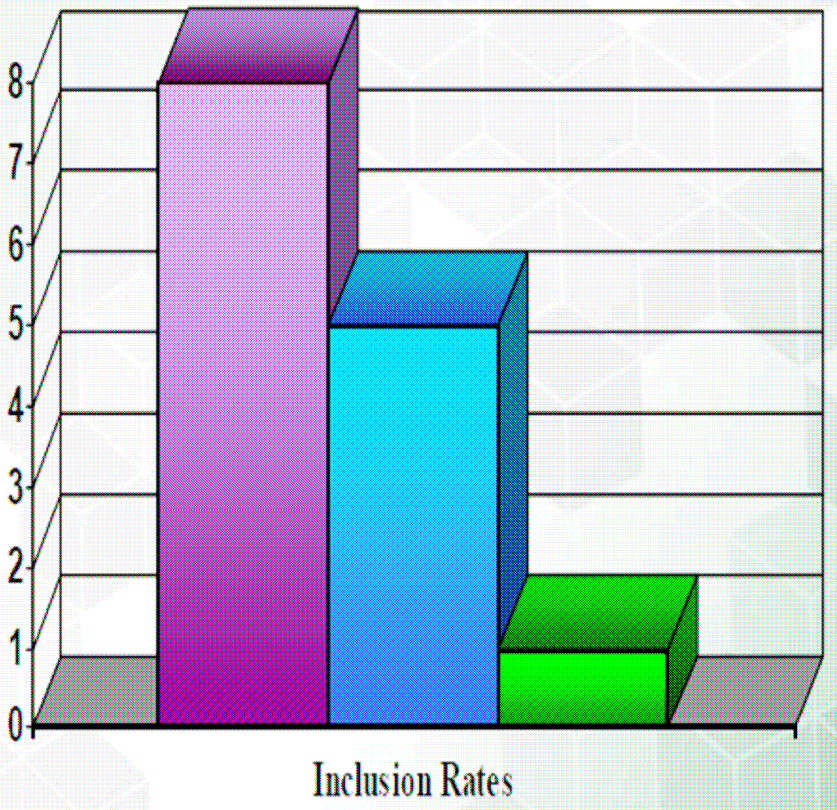


Prebiotics: chemical structure



Prebiotics: Efficacy

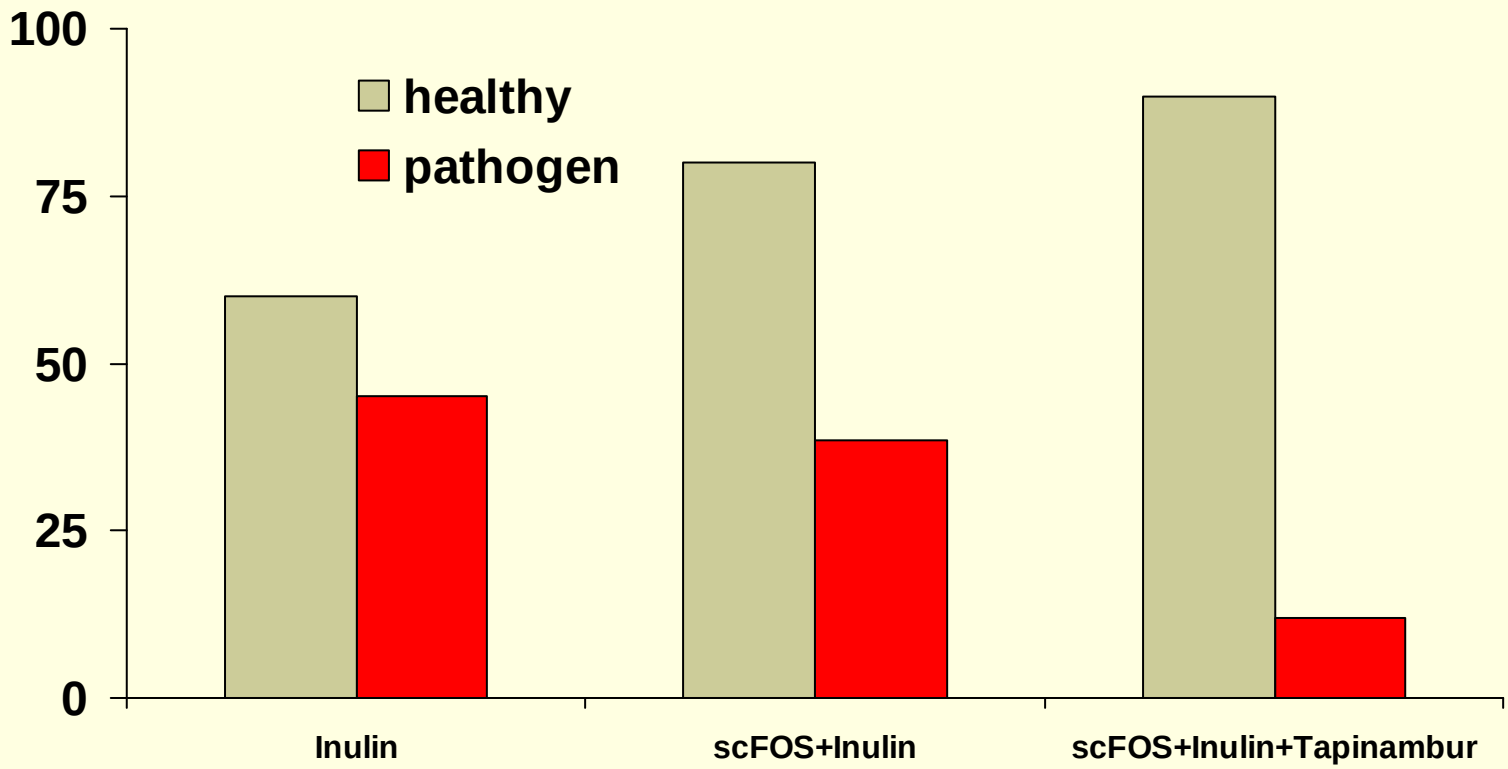
Grams per day required for *Bifidobacteria* growth



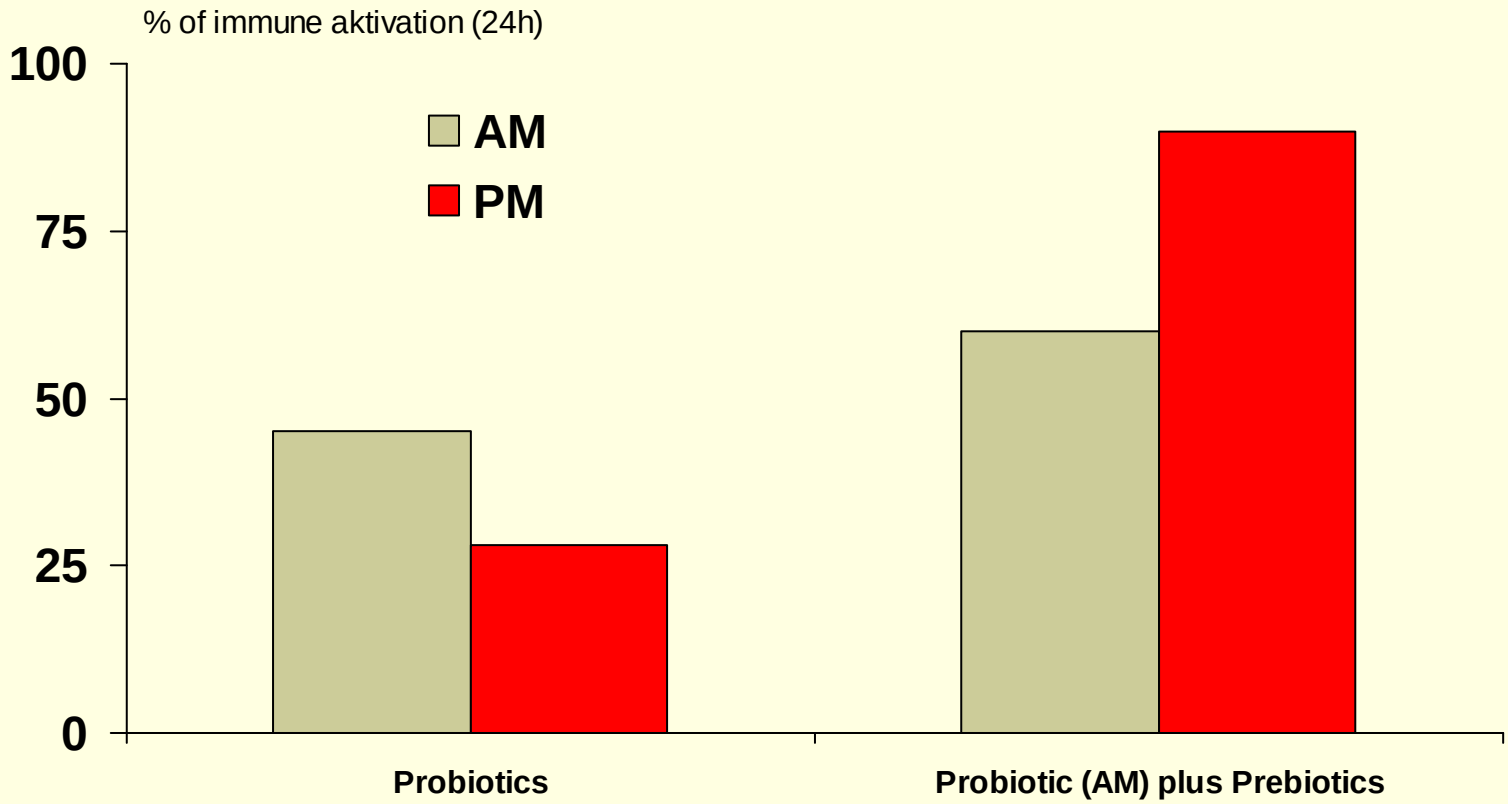
Hidaka 1986, Mitsuoka 1986, Okada 1984

Tapinambur (*Helianthus tuberosus*)

Prebiotics: Efficacy



Pro- and Prebiotics: Timing



Williams et al. in press 2011

Pre- Probiotics: Proposed formulation

AM tablet (morning) daily dose

Probiotic complex 26 billions* CFU** containing:

lactobacillus acidophilus 30 %,

lactobacillus plantarum 30 %,

lactobacillus salivarius 15 %,

lactobacillus rhamnosus 20 %,

bifidobacterium bifidum 5 %

260 mg scFOS®

PM capsule (evening) daily dose

900 mg scFOS®

200 mg Inulin

150 mg Topinambour extract

25 mg Coral Calcium®