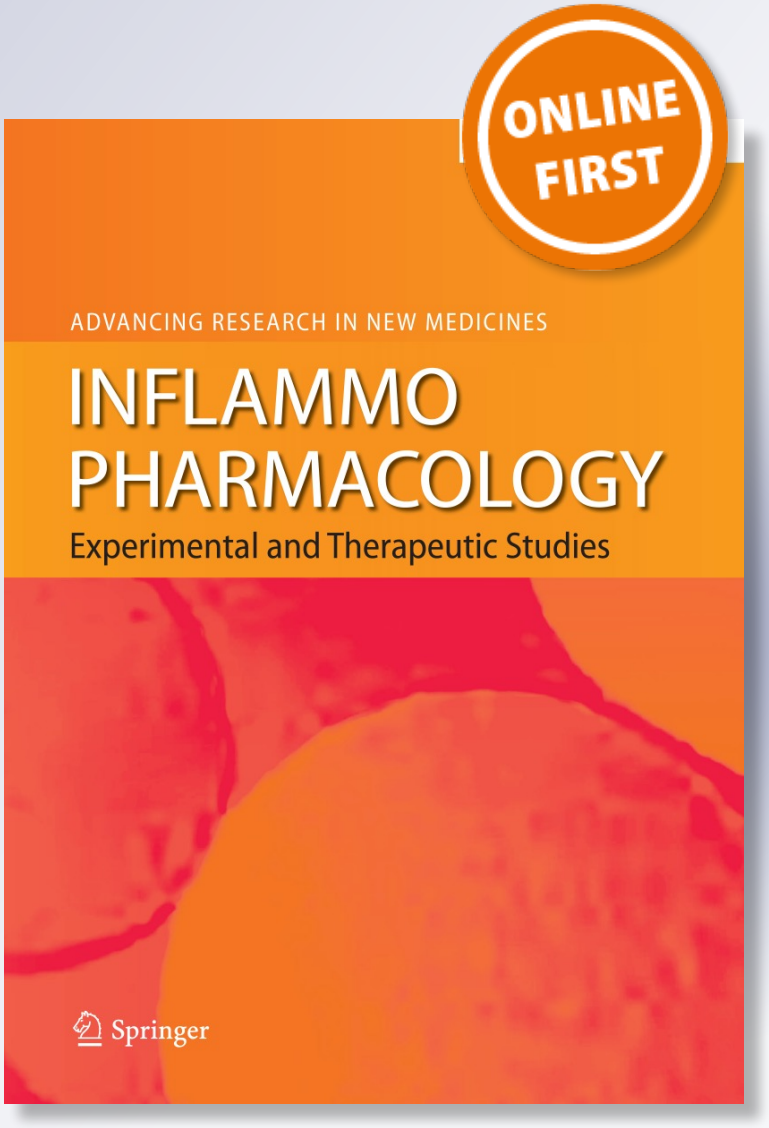
Probiotics, prebiotics and the gastrointestinal tract in health and disease

Luis Vitetta, David Briskey, Hollie Alford, Sean Hall & Samantha Coulson

Inflammopharmacology
Experimental and Therapeutic Studies

ISSN 0925-4692

Inflammopharmacol
DOI 10.1007/s10787-014-0201-4



Springer

Inflammopharmacol
DOI 10.1007/s10787-014-0201-4

Inflammopharmacology

REVIEW

Probiotics, prebiotics and the gastrointestinal tract in health and disease

Luis Vitetta · David Briskey · Hollie Alford · Sean Hall · Samantha Coulson

Received: 5 February 2014 / Accepted: 19 February 2014

Abstract The microbiome located in the human gastrointestinal tract (GIT) comprises the largest community (diverse and dense) of bacteria, and in conjunction with a conducive internal milieu, promotes the development of regulated pro- and anti-inflammatory signals within the GIT that promotes immunological and metabolic tolerance. In addition, host-microbial interactions govern GIT inflammation and provide cues for upholding metabolic regulation in both the host and microbes. Failure to regulate inflammatory responses can increase the risk of developing inflammatory conditions in the GIT. Here, we review clinical studies regarding the efficacy of probiotics/prebiotics and the role they may have in restoring host metabolic homeostasis by rescuing the inflammatory response. The clinical studies reviewed included functional constipation, antibiotic-associated diarrhoea, *Clostridium difficile* diarrhoea, infectious diarrhoea/gastroenteritis, irritable bowel syndrome, inflammatory bowel diseases and necrotizing enterocolitis. We have demonstrated that there was an overall reduction in risk when probiotics were administered over placebo in the majority of GIT inflammatory conditions. The effect size of a cumulative reduction in relative risk for the GIT conditions/diseases investigated was 0.65 (0.61–0.70) ($z = 13.3$); $p < 0.0001$ that is an average reduction in risk of 35 % in favour of probiotics. We also progress a hypothesis that the GIT comprises numerous micro-axes (e.g. mucus secretion, Th1/Th2 balance) that are in operational homeostasis; hence probiotics and prebiotics may have a significant pharmacobiotic regulatory role in maintaining host GIT homeostasis in disease states partially through reactive oxygen species signalling.

Keywords Microbiome · Clinical trials · Reactive oxygen species · Probiotics · *Lactobacillus* · *Bifidobacteria* · Prebiotics · Gastrointestinal tract · Inflammation · Internal environment · Nutrition

Introduction

Inflammatory reactions are defence mechanisms triggered by injury to tissues that can be prompted by either internal or external insults (Koch and Nusrat 2012). The functional interactions between the anatomical sub-structures of the gastrointestinal tract (GIT) (e.g. epithelial cell lining, mucosal tissues), the microbiota that inhabits this site and the milieu that ensues, lead to functional connections with complex metabolic outcomes.

It is reported that the products of bacterial metabolism in the GIT act as signalling molecules that impact the host's metabolic responses (Tremaroli and Bäckhed 2012). Although contentious, the idea that humans in utero are germ-free may no longer be accurate, (Jiménez et al. 2008) instead bacteria or bacterial antigen exposure at this developmental stage may occur indicating that signalling of mucosal development may actually commence in utero rather than in the neonatal stage. Furthermore, diet and medications (i.e. antibiotics) that a neonate is exposed to, in combination with the GIT microbiome in early life, may hold the key to aberrant molecular signals that predispose

L. Vitetta (✉) · H. Alford · S. Hall
Medlab, 66 McCauley St, Alexandria, Sydney 2015, Australia
e-mail: l.vitetta@uq.edu.au; luis_vitetta@medlab.co

L. Vitetta · D. Briskey · S. Coulson
School of Medicine, The University of Queensland, Brisbane, Australia

Published online: 16 March 2014

to chronic inflammatory disease development in adulthood (Neuman and Nanau 2012).

Recent analytical studies report that it is possible to classify humans into just three broad bacterial enterotypes (irrespective of whether chronic intestinal diseases are present or absent), hence these being dominated by three different genera, namely the *Bacteroides* and *Prevotella* (both belonging to the phylum *Bacteroidetes*) and *Ruminococcus* (Arumugam et al. 2011). Furthermore, it has been reported that this overall enterotype profile was conserved independently of gender, body mass index and geographical region/nationality, while notwithstanding the significant differences that exist in the long-term dietary habits between people from Western countries and those from Asian countries. In another study that investigated what linkages may exist between long-term dietary patterns with GIT microbial enterotypes, it was reported that higher fat and lower fiber intakes were associated with specific enterotypes (Wu et al. 2011). That is that the enterotypes seemed to be determined by the type of long-term diet exposure. Hence, the *Bacteroides* enterotype was positively related with animal protein and saturated fats, whereas the *Prevotella* enterotype was associated with a mostly plant-based dietary profile that consisted of high carbohydrates and low meat and dairy consumption. Further, a recent investigation demonstrated that short-term macronutrient changes in the diet, being either composed of entirely animal or plant products, substantially alter the microbial profile and microbial gene expression in humans (David et al. 2013). The authors reported that the animal-based diet increased the abundance of bile-tolerant microbes (*Alistipes, Bilophila* and *Bacteroides*) and decreased the levels of *Firmicutes* that metabolize dietary plant polysaccharides (*Roseburia, Eubacterium rectale* and *Ruminococcus bromii*). The reverse was true for the plant-based diet. Whereas the animal-based diet increased the abundance and activity of *Bilophila wadsworthia* and altered faecal bile acid profiles that are associated with IBD.

The increased consumption of fat-to-fiber ratio that occurs in Western diets has been reported to be among the major triggering factors of metabolic impairments and gut dysbiosis that can lead to obesity and type II diabetes mellitus (T2DM) (Roberfroid 2007). A recent study in mice showed that the gut microbiota could be regarded as a stamp of the metabolic phenotypes that inhabit the GIT and that this was independent of differences in host genetic make-up and dietary profile (Serino et al. 2012). This then proposes the notion that there may be a co-operative microbial–host induction of metabolic adaptation. Consequently, modifying the gut microbiota by administering appropriate dietary changes together with probiotic species and prebiotic fibers may represent a promising strategy to control or prevent inflammatory metabolic diseases of the GIT.

Methodology

A systematic search of the literature was conducted using PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE and CINAHL.

Search terms

Articles were identified using the search terms, "Diet" OR "Overweight" OR "Obesity" AND "Probiotics" OR "Prebiotics" OR "Commensal Bacteria" AND "Gastrointestinal Tract" and "Inflammation" AND "Crohn's Disease" AND 'Ulcerative colitis" AND "Irritable Bowel Syndrome" AND" Constipation" AND "Diarrhoea" AND "Gastrointestinal Infections" AND "Necrotizing Enterocolitis." The inclusion criteria for this review were: (1) an RCT and/or cross-over clinical trial that used either a placebo comparator or other as a control published on or after the year 2000, (2) human participants diagnosed with or without GIT inflammatory conditions, (3) other epidemiological observational and mechanistic studies, (4) the clinical study was published in English; and (5) the clinical study presented data in the form of a relative risk (RR) (95 % CI) reduction (test: probiotic with or without prebiotics versus a placebo or appropriate comparator) or that

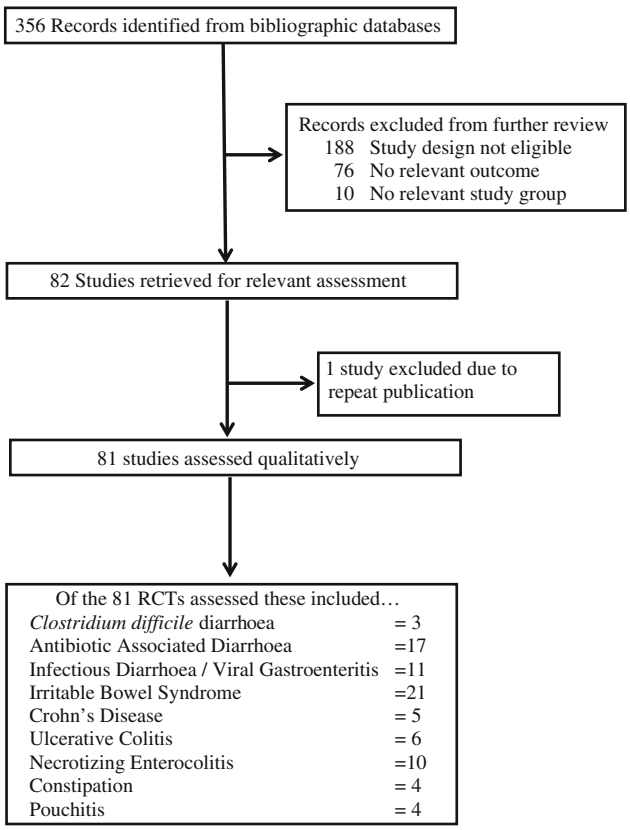


Fig. 1 Flow diagram of literature search for systematic review

Table 1 RCTs that administered probiotics with/without prebiotics reporting a benefit or otherwise for inflammatory conditions/diseases of the gastrointestinal tract as an effect size (risk ratio reduction and 95 % CI)

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Functional constipation			
Koebnick et al. 2003	*L. casei (Shirota)* Dose: 6.5 × 10^9 CFU/65 mL/day/ 5 weeks	0.27 (0.1–0.72)	Significant improvement in chronic constipation
Yang et al. 2008	*B. lactis* DN-173010 Dose: 1.25 × 10^{10} CFU/100 g of fermented milk/day/2 weeks	0.32 (0.23–0.43)	Significant improvement in stool frequency by probiotic (71 %) over control (8.3 %) in 2-week study period
Banaszkiewicz and Szajewska 2005	*L. rhamnosus* GG Dose: 1 mL/kg/day of 70 % lactulose plus 10^9 CFU/day/24 weeks	1.1 (0.58–1.9)*	No significant difference between treatments
Bu et al. 2007	Lcr35 8 × 108 CFU/day (250 mg/two capsules/b.i.d./4 weeks)	0.25 (0.1–0.61)	Significant improvement with probiotic over placebo
Tabbers et al. 2011[17]	*B. lactis* DN-173 010 Dose: 4.25 × 10^9 CFU/125 g/pot/b.i.d./ 3 weeks	0.86 (0.70–1.10)*	Non-significant ↑stool frequency over control
Mazlyn et al. 2013[14]	*L. casei strain Shirota* Dose: 3 × 10^{10} CFU/80 mL/day/4 weeks	0.71 (0.55–0.92)	↓severity in constipation/significant only after 4 weeks (authors noted that a longer intervention was required to properly assess this study outcome)
Antibiotic-associated diarrhoea			
Surawicz et al. 2000	*S. boulardii* Dose: 1 g/day (administered as 2x250 mg capsules b.i.d./4 weeks	0.33 (0.11–1.06)*	*S. boulardii* + high-dose vancomycin non-significant ↑67 % efficacy prevention of CDD recurrences over high-dose vancomycin alone
Szajewska et al. 2001	*L. rhamnosus* GG Dose: 6 × 10^9 CFU/day/until discharged	0.2 (0.1–0.66)	Significant↓nosocomial diarrhoea
Thomas et al. 2001	*L. rhamnosus* GG Dose: 20 × 10^9 CFU/day/2 weeks	0.98 (0.68–1.4)*	No statistically significant difference between probiotic and placebo in reducing antibiotic-associated diarrhoea
Armuzzi et al. 2001	*L. rhamnosus* GG Dose: 6 × 10^9 CFU/b.i.d./2 weeks	0.01 (0.03–0.43)	↓bloating ↓diarrhoea ↓taste disturbances
Cremonini et al. 2002	*L. casei* subsp. *rhamnosus* (GG) 6 × 10^9/ sachet *Saccharomyces boulardii* 5 × 10^9/sachet *L. acidophilus* and *B. lactis* 5 × 10^9/ sachet Dose: administered b.i.d./2 weeks	0.17 (0.02–1.27)*	↓diarrhoea—all probiotic combinations not significantly better than placebo
Jirapinyo et al. 2002	*L. acidophilus and B. infantis* Dose: 10^8 CFU/b.i.d./2 weeks	0.47 (0.18–1.21)*	Non-significant ↓diarrhoea
La Rosa et al. 2003	*L. sporogens* + prebiotic of Fructo-oligosaccharides Dose : 10^7 CFU/t.i.d./2 weeks	0.47 (0.29–0.77	Non-significant↓number of days and duration of events with antibiotic-induced diarrhoea

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Beniwal et al. 2003	Vanilla-flavored yogurt containing 10^6 CFU/g of *L. acidophilus*, *L. bulgaricus*, and *S. thermophilus* combined Dose: 227 g/b.i.d./8 days	0.52 (0.28–0.97)	Significantly reduced the incidence and duration of antibiotic-associated diarrhoea
Seki et al. 2003	*Clostridium butyricum* Dose: 10^7 CFU/g viable spores administered at 1–4 g/day/1 weeks	0.12 (0.05–0.28)	Effective treatment and prophylaxis for antibiotic-associated diarrhoea
Nista et al. 2004	*Bacillus clausii* Dose: 2×10^9 spores/t.d.s./2 weeks	0.88 (0.50–1.56)*	A non-significant↓prevalence of diarrhoea
Pereg et al. 2005	*L casei* DN-114 001 Dose: 100 mL of yogurt with 10^8 CFU/mL/day/8 weeks (6 days/week)	0.76 (0.49–1.17)*	A non-significant trend for reduction of the incidence of diarrhoea was reported
Corrêa et al. 2005	*B. lactis S. thermophilus* Dose: 10^7 and 10^6 CFU, respectively, of each/day/2 weeks	0.52 (0.21–1.23)*	Non-significant ↑stool frequency and ↓stool consistency
Kotowska et al. 2005	*S. boulardii* Dose: 250 mg/b.i.d./duration of antibiotic treatment	0.19 (0.07–0.55)	Significant↓prevalence of diarrhoea
Wenus et al. 2008	*L. rhamnosus* GG *L. acidophilus La-5* *B. lactis* Bb-12 Dose: 10^8 CFU/mL of LGG/Bb-12 and 10^7 CFU/mL La-5 administered as 250 mL/day/2 weeks	0.21 (0.05–0.93)	Significant ↓risk of antibiotic-associated diarrhoea
Frohmader et al. 2010[19]	*S. thermophilus* *B. breve* *B. longum,* *B. infantis* *L. acidophilus,* *L. plantarum,* *L. paracasei,* *L. delbrueckii* subsp. *Bulgaricus* Dose: 45×10^{10} multi–strain CFU/day/2 weeks	0.50 (0.27–0.93)	Significant↓frequency of liquid stool
Song et al. 2010	*L. rhamnosus* R0011 *L. acidophilus* R0052 Dose: 2×10^9 CFU/capsule/b.i.d./2 weeks	0.54 (0.17–1.74)*	Non-significant ↓antibiotic-associated diarrhoea
Cimperman et al. 2011[20]	*L.reuteri* ATCC 55730 Dose: 1×10^8 CFU/day/4 weeks	0.15 (0.02–1.11)*	Non-significant↓frequency of diarrhoea

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Clostridium Difficile diarrhoea			
Wullt et al. 2003	*L. plantarum* 299v Dose: metronidazole (400 mg t.i.d.) orally for 10 days in combination with either a fruit drink containing oats fermented with *L. plantarum* 299v (5×10^{10} CFU/d) or placebo (fruit drink with chemically acidified oats) once a day for 38 days.	0.55 (0.22–1.35)*	Although efficacy was not significant probiotic group had less symptom recurrence.
Plummer et al. 2004	*L. acidophilus* *B. bifidum* Dose: one capsule 2×10^{10} CFU/capsule/day/3 weeks	0.33 (0.07–1.59)*	Non-significant↓diarrhoea events for test over control (NS)
Lawrence et al. 2005	*L. rhamnosus* GG Dose: LGG 2.8×10^{11} CFU/capsule (40 mg lyophilized LGG and 320 mg inulin) or one placebo capsule (360 mg inulin)/t.i.d. adjunctively with anti-*C. difficile* antibiotics	1.53(0.54–4.35)*	No significant difference between treatments
Infectious/traveller's diarrhoea/gastroenteritis			
Guandalini et al. 2000	*L. rhamnosus* GG Dose: rehydration solution containing 10^{10} CFU/250 mL/until diarrhoea resolved	0.57 (0.34–0.81) 0.35 (0.12–0.59)	Significantly shorter duration of diarrhoea in retrovirus positive children Significantly reduced duration of diarrhoea
Szajewska et al. 2001	*L. rhamnosus* GG Dose: 2.46 g powder at 6×10^9 CFU/sachet b.i.d./for duration of hospital stay	0.13 (0.02–0.79)	Significant improvement of probiotic over control.
Chouraqui et al. 2004	*B. lactis* Bb 12 Dose: 10^6 CFU/g powder resulting in 1.5×10^8 CFU/L/day/on average approx. 20–21 weeks	0.94 (0.53–1.66)*	No significant difference between groups
Salazar-Lindo et al. 2004	*L. casei* strain GG Dose: 10^9 CFU/mL in a milk formula of 150 mL/kg/day—maximum administered 1,000 mL	1.01 (0.46–2.21)*	No improvement in management of diarrhoea
Weizman et al. 2005	*B. lactis* Bb-12 or *L. reuteri* SD 2112 Dose: all at 1×10^7 CFU/g powder/day/12 weeks	0.39 (0.19–0.79) 0.05 (0.01–0.34)	Both strains effective in ↓diarrhoea
Margreiter et al. 2006	*L. gasseri* and *B. longum* versus *Enterococcus faecium* Dose: 25 mg of 2×10^7–2×10^8 CFU/capsule/t.i.d. versus 75×10^6 CFU/capsule/t.i.d.	1.9 (0.74–4.96)**	This study reported equivalent therapeutic efficacy for the 2 treatment regimens.
Grossi et al. 2010	*L. paracasei* B 21060 + prebiotic Dose: 7 g sachet dissolved in water/juice of symbiotic preparation administered at 10^{11} CFU/day/10 days	0.43 (0.12–1.62)	No difference in acute diarrhoea incidence at the end of the study However, significant difference in duration of diarrhoea

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Nagata et al. 2011[41]	*L. casei Shirota* Dose: 4×10^{10} CFU/80 mL bottle/day/12 weeks	1.25 (0.88–1.79)*	No difference in number of cases with viral gastroenteritis between groups ↓mean duration days of fever after onset significantly decreased by test over placebo
Virk et al. 2013	Synbiotic containing: 4.5×10^9 CFU *Enterococcus faecium,* a probiotic yeast of 5×10^8 CFU *S cerevisiae* strain CNCM I 4444 and a prebiotic fructo–oligosaccharide Dose: 2 capsules/day.	1.13 (0.87–1.5)*	No significant difference of test synbiotic over placebo
Pouchitis			
Gionchetti et al. 2000[22]	*S. Thermophiles* *B. breve* *B. longum,* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii subsp. Bulgaricus* Dose: 5×10^{11} multi-strain CFU/g/6 g/day/36 weeks	0.85 (0.71–1.02)	↓frequency of flare-ups of chronic pouchitis effective in maintaining remission
Gionchetti et al. 2003[23]	*S. Thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii subsp. Bulgaricus* Dose: 9×10^{11} multi-strain CFU/day/52 weeks	0.25 (0.06–1.03)	↓frequency of flare-ups of chronic pouchitis effective in maintaining remission
Mimura et al. 2004[24]	*S. Thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii subsp. Bulgaricus* Dose: 30×10^{11} CFU/g × 3/day/52 weeks	0.16 (0.06–0.46)	↓frequency of flare–ups of chronic pouchitis—effective in maintaining remission at 1 year
Crohn's disease			
Guslandi et al. 2000	*S. boulardii* Dose: mesalamine 1 g t.i.d. or mesalamine 1 g b.i.d. plus a preparation of *S. boulardii* 1 g/day/24 weeks	0.17 (0.02–1.8)*	Relapse in the probiotic treatment group was 6.25 % as compared to the control 37.5 %. The low participant numbers precluded significance

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Prantera et al. 2002	*L. rhamnosus* GG Dose: 2.46 g satchet of 6×10^9/b.i.d./52 weeks	1.50 (0.90–2.4)*	No significant difference from placebo in disease remission or disease improvement
Schultz et al. 2004	*L. rhamnosus* GG Dose: 2×10^9 CFU/day/24 weeks	1.2 (0.1–14.7)*	No significant difference in remission between test and placebo groups. Groups with low numbers
Marteau et al. 2006	*L. johnsonii*, LA1, Nestle′ Dose: 2×10^9 CFU/day/24 weeks	0.77 (0.53–1.11)*	No difference in recurrence between test and placebo groups
Van Gossum et al. 2007	*L. johnsonii*, LA1, Nestle′ Dose: 10^{10} CFU/day/12 weeks	1.10 (0.27–4.4)*	Post elective ileo-caecal resection recurrence
Ulcerative Colitis			
Ishikawa et al. 2003	*B. breve* *B. bifidum* *L. acidophilus* Dose: *fermented milk* 100 mL of 10^9CFU/day/52 weeks	0.30 (0.11–0.81)	Probiotic supplementation maintained remission
Kato et al. 2004	*B. breve* strain Yakult *B. bifidum* strain Yakult *L. acidophilus* Dose: 10^9 CFU/100 mL bottle/day/12 weeks	0.43 (0.15–1.2)*	While there was a greater response to the probiotic treatment the result was not significant highlighting the low participant numbers.
Kruis et al. 2004	*E. coli* of strain Nissle 1917 (serotype O6:K5:H1) Dose: $2.5–25 \times 10^9$ CFU/day/52 weeks	1.06 (0.86–1.19)*	Probiotic equal efficacy to pharmaceutical in maintaining remission
Sood et al. 2009	*S. Thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii* subsp. *Bulgaricus* Dose: 3.6×10^{12} multi-strain CFU/b.i.d./12 wks	0.68 (0.55–0.84)	Significant↓UC disease activity index and remission in the active treatment over placebo at 6 and 12 weeks
Matthes et al. 2010	*Escherichia coli* strain Nissle 1917 Dose: regimes tested were 20 mL of 4×10^9 versus 20 mL of 2×10^9 versus 10 mL of 10^9 CFU versus placebo/day/8 weeks	0.87 (0.54–1.4)*	Re: in the intention to treat analysis…time to remission was shorter in the 40 mL administered group. The result was not significant highlighting the low participant numbers

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Tursi et al. 2010	*S. thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii* subsp. *Bulgaricus* Dose: 3.6×10^{12} multi-strain CFU/b.i.d./8 weeks	0.66 (0.45–0.97)	↓UC disease activity index
Irritable bowel syndrome			
Nobaek et al. 2000	*L. plantarum* (DSM9843) Dose: 400 mL of 5×10^7 CFU/mL/day/4 weeks	0.59 (0.38–0.92)	A non-significant↓abdominal pain and flatulence
Niedzielin et al. 2001[29]	*L. plantarum* 299 V Dose: 400 mL of 5×10^7 CFU/mL/day/4 weeks	0.10 (0.01–0.40)	Significant↓abdominal pain and overall IBS symptomatology normalisation of stools frequency test versus placebo
Kim et al. 2003	*S. thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii* subsp. *Bulgaricus* Dose: 45×10^{11} multi-strain CFU/b.i.d./8 weeks	1.1 (0.6–1.95)*	A non-significant↓bloating stool-related symptoms in diarrhoea-associated IBS
Kim et al. 2005	*S. thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii* subsp. *Bulgaricus* Dose: 45×10^{11} multi-strain CFU/b.i.d./8 weeks	0.77 (0.42–1.4)*	A non-significant improvement in overall symptomatology of IBS
Kajander et al. 2005	*L. rhamnosus* GG (ATCC 53103, LGG) *L. rhamnosus* Lc705 (DSM 7061), *P. freudenreichii* ssp. *Shermanii* JS (DSM 7067) *B. animalis* ssp. *Lactis* Bb12 (DSM15954) Dose: ONE cap all at 8–9 $\times 10^9$ multi-strain CFU/day/24 weeks	0.42 (0.23–0.77)	Significant change in total IBS symptom score including ↓abdominal pain + ↓bloating/distension + ↓flatulence + ↓borborygmi

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Whorwell et al. 2006[33]	*B. infantis* 35624 Note 3 dose regimens were investigated and reported Dose 1: 1×10^6 CFU/day/4 weeks Dose 2: 1×10^8 CFU/day/4 weeks Dose 3: 1×10^{10} CFU/day/4 weeks Overall RR reduction:	0.96 (0.72–1.30)* 0.88 (0.69–1.11)* 1.16 (0.90–1.50)* 0.90 (0.76–1.10)*	Combined variable of scores for abdominal pain/discomfort, bloating, and bowel habit satisfaction Non-significant improvements ↓abdominal pain ↓bloating ↓bowel dysfunction
Guyonnet et al. 2007	*B. animalis* DN-173 010 Dose: 1.25×10^{10} CFU/day/6 weeks	0.88 (0.66–1.75)*	Non-significant improvement in constipation—predominant IBS and health-related quality of life
Gawronska et al. 2007	*L. rhamnosus* GG Dose: 3×10^9 CFU/day/4 weeks	0.70 (0.50–0.99)	Significant improvements in pain frequency and severity
Drouault-Holowacz et al. 2008[35]	*L. rhamnosus* GG Dose: 1×10^{10} CFU/day/4 weeks	0.98 (0.69–1.37)*	↓abdominal pain borderline significance ($p < 0.048$) trend toward lower abdominal pain score ($p > 0.05$)
Enck et al. 2008[37]	*E. coli* (DSM 17252) *E. faecalis* (DSM 16440) Dose: 3–9 $\times 10^7$ CFU/day/8 weeks	0.51 (0.39–0.66)	Significant↓abdominal pain ↓global symptom score
Andriulli et al. 2008	Symbiotic formulation each 7 g sachet contains *L. paracasei* B21060 [5×10^9 CFU xylo-oligosaccharides (700 mg) glutamine (500 mg) arabinogalactone (1,243 mg) Dose: 7 g in 100 mL of water/b.i.d./12 weeks	0.93 (0.68–1.3)* 0.46 (0.24–0.89)	Overall IBS symptomatology not significantly different between groups Significant ↓ in diarrhoea between groups in favour of the test
Hong et al. 2009	*B. bifidum* BGN4 *B. lactis* AD011 *L. acidophilus* AD031; *L. casei* IBS041 Dose: 20×10^9 CFU/sachet/b.i.d./8 weeks	0.89 (0.54–1.46)*	No significant change between groups in overall IBS symptomatology
Simrén et al. 2010	*L. paracasei,* ssp *L. paracasei* F19, *L. acidophilus* La5, *B. lactis B1.* Dose: 400 mL of fermented milk of 5×10^7 CFU/day/8 weeks	0.85 (0.62–1.7)*	No significant treatment effect between active and control.
Cui and Hu 2012	No clear information given re species or dose. Test: 2 Bifid triple viable capsules administered t.i.d./4 weeks Placebo: 200 mg of placebo administered t.i.d./4 weeks	0.51 (0.30–0.85)	Significant difference trend of overall management of IBS symptomatology of test probiotic over placebo

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Ki Cha et al. 2012[39]	*S. thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. delbrueckii* subsp. *Bulgaricus* Dose: 1×10^{10} multi-strain CFU/day/8 weeks	0.59 (0.4–0.89)	↓abdominal pain ↓bloating
Kruis et al. 2012	*E. coli* Nissle 1917 Dose: 2.5–25 $\times$ 10^9 CFU/day/12 weeks	0.81 (0.57–1.17)*	No difference between groups response to treatment was significant in the probiotic group versus placebo in a subgroup prior to IBS development
Ducrotté et al. 2012	*L. plantarum* 299v (DSM 9843) Dose: 1×10^{10} CFU/capsule/day/4 weeks	0.24 (0.17–0.35)	Significant effective symptom relief, particularly of abdominal pain and bloating
Dapoigny et al. 2012	*L. casei rhamnosus Lcr35* Dose: 6×10^8 CFU/day/4 weeks	1.20 (0.8–1.80) 0.64 (0.44–0.93)	Overall IBS symptomatology improved in placebo over test with significant ↓in diarrhoea sub analysis in test over placebo
Roberts et al. 2013	*B. lactis* (strain I-2494 DN-173 010) *S. thermophiles* (CNCM strain I-1630) *L. bulgaricus* (CNCM strain I-1632 and I-1519) Dose: 1.25×10^{10} CFU *B. lactis* and 1.2×10^9 CFU/cup of *S. thermophiles* and *L. bulgaricus*/day/4 weeks and 8 weeks	0.92 (0.6–1.54)* 5.4 (2.1–13.8)	4 weeks no difference between groups 8 weeks placebo more significantly effective ($p = 0.001$)
Capello et al. 2013	Symbiotic preparation contains thermophile bacteria: 5×10^9 *L. plantarum* 2×10^9 *L. casei* subp. *Rhamnosus* 2×10^9 *L. gasseri* 1×10^9 *B. infantis* 1×10^9 *B. longum* 1×10^9 *L. acidophilus* 1×10^9 *L. salivarus* 1×10^9 *L. sporogenes* 5×10^9 *S. thermophiles* Prebiotic inulin 2.2 g 1.3 g of tapioca-resistant starch Dose: 5 g sachet/b.i.d./4 weeks	0.71 (0.46–1.16)* 0.80 (0.52–1.24)* 0.84 (0.6–1.19)*	Symbiotic preparation demonstrated a non-significant beneficial effect in ↓ flatulence and bloating severity in IBS. Overall RR reduction not significant

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Yoon et al. 2014	*B. longum* *B. bifidum* *B. lactis* *L. acidophilus* *L. rhamnosus* *S. thermophiles* Dose: all at 5 × 10 CFU/capsule (500 mg)/b.i.d./4 weeks	0.51 (0.27–0.98)	Significant difference between test probiotic multi-strain and placebo groups re overall improvement in IBS symptomrtology
Necrotizing Enterocolitis			
Dani et al. 2002	*L. rhamnosus* GG Dose: 6 × 10^9 CFU/day/1 week	0.49 (0.15–1.61)*	No effective reduction in incidence
Costalos et al. 2003	*Saccharomyces boulardii* Dose: 50 mg/kg every 12 h	0.59 (0.19–1.78)*	No improvement
Bin-Nun et al. 2005	*B. infantis* *S. thermophilus* *B. bifidus* Dose: 10^9 CFU/day/until discharged	0.1 (0.01–0.77)	Significant reduction in incidence and severity and with no deaths from necrotizing enterocolitis
Lin et al. 2005	*L. acidophilus* *B. infantis* 125 mg/kg/dose/b.i.d. with breast milk until discharged	0.21 (0.05–0.94)	Significant reduction in incidence and severity
Mohan et al. 2006	*B. lactis* Bb12 Dose: 1.6 × 10^9 CFU/day 1–3 and 4.8 × 10^9 CFU/4–21 days	1.62 (0.16–16.4)*	No improvement in reduction of antibiotic resistant organisms
Manzoni et al. 2006	*L. casei* subspecies *rhamnosus* Dose 6 × 10^9 CFU/day/6 weeks maximum	1.0 (0.71–1.40)	Significant reduction in gut fungal (*candida*) colonization
Lin et al. 2008	*L. acidophilus* NCDO 1748 *B. bifidum* NCDO 1453 Dose: added to breast milk or mixed feeding all at 1 × 10^9 CFU/125 mg/kg/b.i.d./6 weeks	0.35 (0.4–3.23)	Significant reduction in incidence and severity and death
Rougé et al. 2009	*L. rhamnosus* GG *B. longum* BB536 Dose:10^8 CFU/day/until discharged	2.18 (0.2–23.2)*	No improvement in gastrointestinal tolerance to enteral feeding
Samanta et al. 2009	*B. infantis* *B. bifidum* *B. longum* *L. acidophilus* Dose: each at 2.5 × 10^{10} CFU (125 g/kg) with expressed breast milk/b.i.d./till discharged	0.35 (0.13–0.92)	Enteral administration significantly reduced morbidity due to necrotizing enterocolitis

Table 1 continued

Conditions/diseases references	Strain(s), Dose regimen *L.* = *Lactobacillus* *B.* = *Bifidobacterium* *S.* = *Streptococcus* *E.* = *Escherichia*	Effect size RR (95 % CI)*	Outcome
Fernández-Carrocera et al. 2013	*L. acidophilus* 1.0 × 10^9 CFU/g *L. rhamnosus* 4.4 × 10^8 CFU/g *L. casei* 1.0 × 10^9 CFU/g *L. plantarum* 1.76 × 10^8 CFU/g *B. infantis* 2.76 × 10^7 CFU/g *S. thermophilus* 6.6 × 10^5 CFU/g Dose: 1 g pack/day/until discharged	0.50 (0.20–1.26)	Post-hoc analysis showed significant risk reduction for necrotizing enterocolitis or death

* $p > 0.05$ b.i.d. = twice per day, t.i.d. = three times per day

** This study not included in the final overall analysis due to equivalent efficacy between the two treatments

the data allowed for the calculation of a RR (95 % CI). A flow diagram of the literature search for articles included in this systematic review is presented in Fig. 1.

Probiotics, prebiotics and inflammatory git conditions

Numerous clinical studies suggest probiotics can improve health outcomes in various end-organs (Vitetta and Sali 2008; Vitetta et al. 2012). Hence, probiotics have been profiled accordingly, and that is that upon administration can improve the health of the host beyond their intrinsic and basic nutritional content (Fuller 1989). Hence it was noted that probiotic bacteria employed in clinical trials investigated in this review have included organisms from different genera (i.e. *Bifidobacteria, Lactobacilli*); different species from a specified genera (i.e. *Lactobacillus acidophilus*; *Lactobacillus bulgaricus, Lactobacillus rhamnosus*); as well as those organisms from different strains within a species (i.e. *Lactobacillus acidophilus La–1*, *Lactobacillus acidophilus NCFM*) whilst administered as single- or multi-strain preparations as well as symbiotics (preparations of probiotics and prebiotic mixtures). This hierarchical profiling serving to highlight that different strains from the same species vary and hence may have the capacity to elaborate different physiological functions within the GIT as demonstrated by the different effects on different inflammatory GIT conditions/diseases.

Bifidobacteria and *Lactobacilli* have been the predominant genera studied and have demonstrated significant clinical efficacy in a number of health GIT conditions (Table 1). High level evidence-based studies have reported significant efficacy with specific probiotic strains in GIT inflammatory conditions such as constipation (in adults and children), diarrhoea (in adults and children), Crohn's disease (CD), ulcerative colitis (UC), irritable bowel syndrome (IBS) viral gastroenteritis, pouchitis and necrotizing enterocolitis.

The demonstrated efficacy in this critical review has been presented as an effect size of relative risk reduction with the administration of a probiotic versus a comparator. The effect sizes as a relative risk reduction (95 % CI) for probiotics over a placebo/comparator for the GIT conditions reviewed (Fig. 2) were significant for antibiotic-associated diarrhoea [0.72 (0.62–0.84); $p < 0.0001$]; infectious diarrhoea/gastroenteritis [0.68 (0.55–0.84); $p < 0.0001$]; IBS [0.71 (0.65–0.77); $p < 0.0001$]; ulcerative colitis [0.63 (0.53–0.76); $p < 0.0001$]; necrotizing enterocolitis [0.4 (0.27–0.59); $p < 0.0001$]; constipation [0.59 (0.5–0.68); $p < 0001$] and pouchitis [0.19 (0.11–0.32); $p < 0.0001$]. Whereas, and although the trend was in favour of probiotics the effect size relative risk reduction was not significant for *clostridium difficile* diarrhoea [0.70 (0.32–1.55); $p = 0.38$; and for Crohn's disease [0.86 (0.63–1.16); $p = 0.30$. This latter result, possibly a reflection of the few studies included in this review. Others have reported significant risk reductions in these GIT conditions (Ritchie and Romanuk 2012). The overall effect size relative risk reduction for the administration of probiotics versus a placebo/comparator was statistically significant for probiotics 0.65 (0.61–0.70) ($z = 13.3$); $p < 0.0001$, reflecting a clinical risk reduction of 35 %.

Manipulating metabolic changes in the GIT—a mechanistic overview

The commensal microbiome contribution

Microbiota that colonizes the human GIT exhibits a high phylogenetic diversity, reflecting their vast metabolic

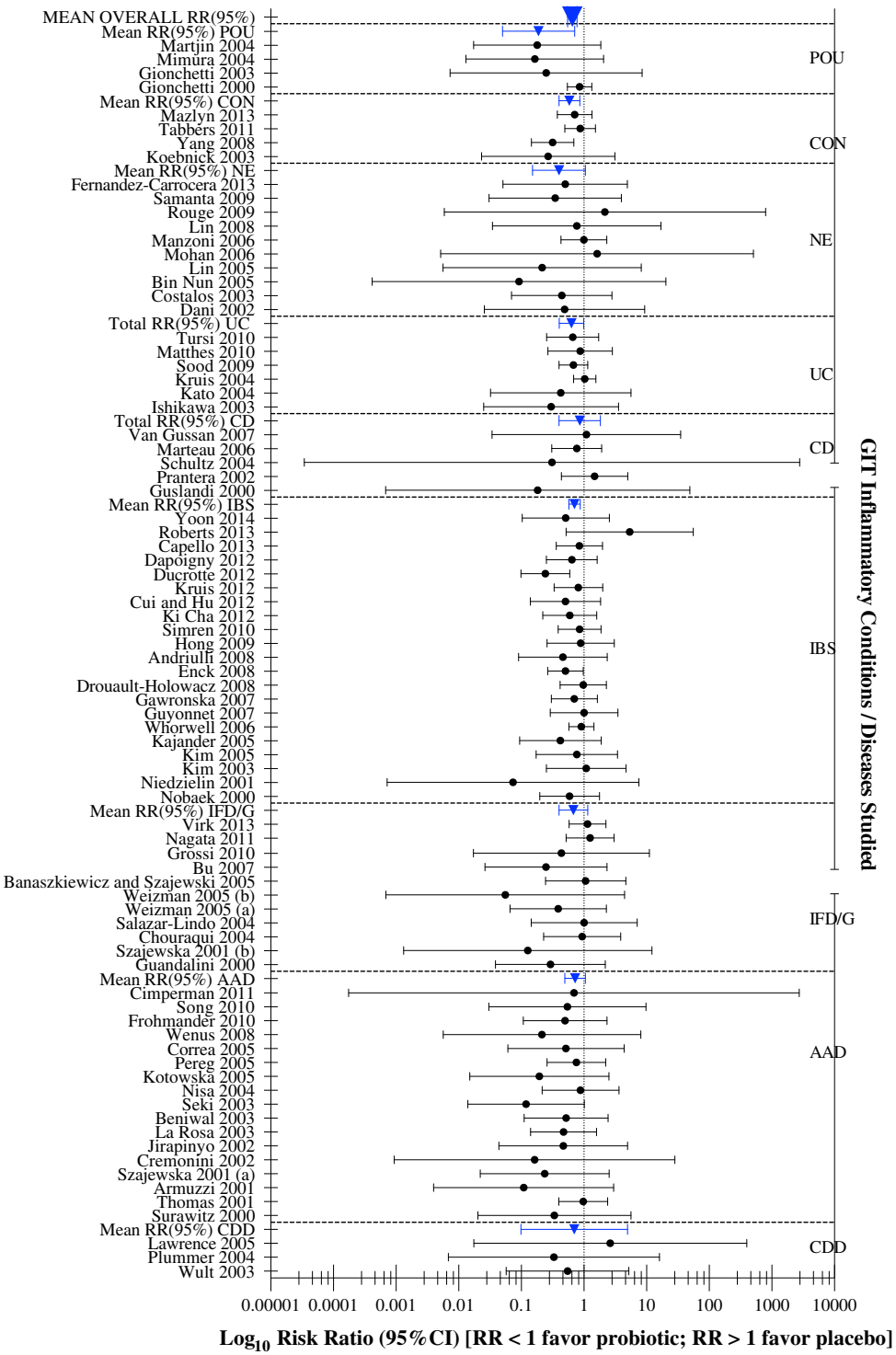


Fig. 2 Effect size [risk ratio (95 % CI)] for the effect of probiotics over placebo/comparator in the prevention and treatment of gastrointestinal tract inflammatory diseases/conditions

potential. The environmental/microbiological picture is one that continues throughout life to functionally co-operate with the host which first initiated from the interactions first disseminated from the time of birth and possibly even in utero. Germ-free mice studies have shown that triggering natural development and maturation of the immune system are only partially encoded in the host's genes, demonstrating that fundamental cues are required from the symbiotic microbial cohort for homeostatic development (Hooper 2004). How bacteria colonize the GIT provides initial clues as to the signals required by the GIT to develop a regulated immune–metabolic–inflammatory competent

profile. Up-regulated immune responses in an individual are necessary to protect the GIT from pathogenic cells. The immune system achieves this by initiating a pro-inflammatory response. The microbiota, act partly in an immune-surveillance role by detecting pathogenic bacteria and stimulating the immune system, subsequently initiating an appropriate eradicative inflammatory response (Eckmann 2006). Once the pathogenic cells have been cleared, the requisite is for an anti-inflammatory signal response that restores the balance between pro-and anti-inflammatory reactions. Accordingly, the healthy gut may be seen as one that is in a constant state of regulated inflammation. The role that commensal bacteria play in promoting an anti-inflammatory response is not well understood but is reported to be in part accomplished by the interaction of the bacteria with the intestinal epithelial cells that not only provide a physical barrier but also facilitate the interactions between GIT bacteria and host immune cells to achieve mucosal immunological equilibrium (Goto and Ivanov 2013). Failure to re-regulate inflammatory responses can increase the risk of developing inflammatory conditions of the host's gut architecture such as IBD or IBS. Accumulating evidence indicates that the balance of commensal bacteria within the GIT may be associated with the development of some GIT disorders (Swidsinski et al. 2002). Patients with IBD or IBS are reported to present with increased pro-inflammatory or potentially pathogenic bacterial species with the *Bacteroides*, (Swidsinski et al. 2002) *Escherichia coli* (Mylonaki et al. 2005; Martin et al. 2004) and *Enterococci* genera together with decreased *Bifidobacteria* and *Lactobacilli* species (Van de Merwe et al. 1988). The etiology of IBD is not fully understood, but is considered to be T cell-driven inflammation resulting from a persistent preponderance of pro- over anti-inflammatory cytokine production (Hvas et al. 2007).

Nutrition/supplementation contribution

GIT commensal bacteria metabolize food components that typically serve as energy sources. Additional factors such as sanitary conditions, birth delivery mode or antibiotic use drive the fluctuations of the microbial community during the first year or two of life (Adlerberth 2008). Furthermore, select studies clearly show that the specific consumption of foods that contain bioactive compounds may enhance health or increase the risk of disease. Such as is the case with human milk oligosaccharides that constitute the third most abundant class of molecules in breast milk optimizing the GIT microbial composition (Li et al. 2009). Other studies show that at least part of the protective effect of cruciferous vegetables is due to their relatively high content of fiber and phytochemicals such as glucosinolates (Marcobal and Sonnenburg 2012). Dietary fiber can be fermented by gut bacteria, to yield short chain fatty acids and other metabolites that may go on to suppress adverse inflammatory conditions. Additional studies that report the specific consumption of dietary compounds such as phytoestrogens show that metabolites elaborated by the GIT microbiome can then provide specific health benefits such as enhanced bone health (Chiang and Pan 2013).

Recent findings suggest that a high-fat diet interacts with GIT bacteria to promote early inflammatory changes in the gut that contribute to the development of obesity and insulin resistance (Ding and Lund 2011). The innate immune system recognizes and responds to the structural components of gram-negative bacteria (e.g. lipopolysaccharide), resulting in inflammation. Toll-like receptors (TLRs) are pattern recognition receptors that have a central role in innate immunity (O'Neill et al. 2013). Lipopolysaccharide (LPS) is a component of the outer membrane of Gram-negative bacteria. LPS binding to the host receptor, TLR4, triggers an inflammatory reaction characterised by the release of large number of inflammatory mediators that allow the host to respond to the invading pathogen (Montero Vega and de Andrés Martín 2008). The mechanism that drives this response is partly through the activation of transcriptional factors such as NF-κB via the balanced action of constitutively expressed nitric oxide/inducible nitric oxide synthase to maintain homeostasis.

Mice fed diets high in saturated fats (72 % energy as fat) for 4 weeks reported an endotoxemia characterised by significant increases in plasma endotoxin levels i.e. LPS (Burcelin et al. 2008). This then shown to be a risk for inducing innate immune responses through the activation of TLR4 leading to inflammation by secreting pro-inflammatory cytokines and chemokines. Moreover, dietary fats and carbohydrates appear to be involved in inflammation through TLR4 activation. Free saturated fatty acids aggravate the expression and activity of TLR4 that is induced by high glucose in human monocytes along with increased signalling molecules such as superoxide generation that increase NF-κB activity leading to increased pro-inflammatory signals such as IL-6. But are these signals fundamentally adverse? It is further postulated that as a consequence, chronic activation of the immune system is associated with the development of obesity, insulin-resistance and T2DM through LPS, free fatty acid and products from dying cells that can bind TLR4 at the surface of innate immune cells and activate inflammatory pathways implicated in the pathogenesis of chronic diseases (Nakamura and Omaye 2012).

Tien et al. (2006) have reported that the anti-inflammatory activity demonstrated by probiotics within the GIT, in particular *Lactobacillus casei*, is modulated by their targeting the stability of I-κβα, the specific NF-κB inhibitor, resulting in the mitigation of this major pro-inflammatory pathway. Therefore, they have hypothesized

that certain commensal microbiota has the ability to actively influence the homeostatic control of intestinal inflammation, inhibiting NF-κB activation, even in the presence of pro-inflammatory pathogenic and commensal microorganisms. This data would tend to suggest that increased calorie consumption increases certain bacterial species that promote pro-inflammatory GIT profiles by influencing NF-κB activation that then increases the risk of metabolic diseases. Alternatively, a diet that promotes a healthy GIT milieu such as vegetarian, Palaeolithic or Mediterranean diets encourages optimum ratios of bacterial species by re-regulating pre- and pro-inflammatory signals that reduce the risk of metabolic disease development (Kim et al. 2013; Scoditti et al. 2012). The overall requisite is the regulated control of these intracellular molecular responses. It seems plausible to posit that reactive oxygen species (ROS) may be the upstream early signal that provides an overall message to regulate the response that controls GIT inflammation.

Probiotics as signal transducers in the GIT

Over the last few decades, the role of oxidative stress has been proposed to play a major role in the development of diseases such as inflammatory bowel disease (Abdullah et al. 2013). This inference further nurtures support for the administration of antioxidant therapies. We assert that this is incorrect and further that there are no reported clinical trials that support this conclusion.

ROS are known to play a major role in maintaining normal physiological function (Linnane et al. 2007). The investigations on protein albumin thiol oxidations and serum protein carbonyl formations overemphasize the molecular damage that is attributed to ROS activity. These assertions have been previously considered and have challenged the commonly held view that proteins are randomly oxidized in an uncontrolled process by superoxide anion, hydrogen peroxide, nitric oxide and peroxynitrite, thereby contributing directly to the development of inflammatory conditions. This concept is untenable, misrepresenting stringently regulated cellular redox metabolic processes. Elsewhere we have discussed the oxidation of protein amino acid residues (Linnane et al. 2007) and scientifically contended that oxidatively modified proteins do not simply arise as the result of random oxidative damage (e.g. hydroxylation of various amino acid residues, sulphoxidation of methionines and nitrosylation of sulphydryl groups).

Probiotic bacteria have been reported to promote a range of GIT physiological functions that include a regulated control over immune responses, epithelial barrier function and cellular proliferation (Bermudez-Brito et al. 2012). The mechanism proposed for the GIT control of pathogens involves (a) direct anti-microbial activity through the production of bacteriocins or other inhibitors of pathogenic bacteria gene expression, (b) competitive exclusion of pathogenic bacteria by competing for binding sites or stimulation of epithelial barrier function, (c) stimulation of immune responses via increases of sIgA and anti-inflammatory cytokine factors and the rescue and regulation of pro-inflammatory cytokines, and (d) inhibition of virulence gene(s) or protein expression in gastrointestinal pathogenic bacteria (Amalaradjou and Bhunia 2012). The active mechanism that induces this complex control of pathogenic activity implicates ROS.

Recent important advances in cellular signalling have demonstrated that some genera of human commensal GIT bacteria can induce a rapid increase of ROS that then elicit a strong physiological response through the activation of epithelial NADPH oxidase-1 (Nox1) (Neish 2013; Lin et al. 2009). In addition, reports site in vitro experiments with epithelial cells that, when co-cultured with specific probiotic bacteria, show an increased and rapid oxidation reaction of soluble redox sinks, namely glutathione and thioredoxin (Neish 2013; Lin et al. 2009). This very much indicates the presence of a regulated process. This effect was demonstrated as an increase in the oxido-reductase reaction of transcriptional factor activations such as NF-κB, NrF2 and the antioxidant response element, reflecting a cellular response to increased ROS production that is regulated (Neish 2013; Lin et al. 2009). This effect must be decisive to elicit a restrained anti-infective response with a minimal chance of pro-inflammatory damage to the tissue. These reactions define potent regulatory effects on host physiological functions that include immune function and intracellular signalling.

The reported mechanisms of action for probiotics are similarly aligned acting to enhance the epithelial barrier, increase bacterial adhesion to the intestinal mucosa with an attendant inhibition of pathogen adhesion to the competitive exclusion of pathogenic microorganisms (Neish 2013; Lin et al. 2009; Lee 2008). Furthermore, probiotic strains have also been reported to generate a range of anti-microbial substances and to positively affect and modulate immune system function. Lee (2008) has reported that the enteric commensal bacteria, by rapidly generating ROS, negotiate an acceptance by the GIT epithelia. Different strains of commensal bacteria can elicit markedly different levels of ROS from contacted cells. *Lactobacilli* are especially potent inducers of ROS generation in cultured cells and in vivo, though all bacteria tested have some ability to alter the intracellular oxido-reductase environment. Yan et al. (2007) has reported that there are soluble factors that are produced by strains of *lactobacilli* that are capable of mediating beneficial effects in in vivo inflammatory models. This result expands our understanding that

there are ROS-stimulating bacteria that possess effective specific membrane components and/or secreted factors that activate cellular ROS production to maintain homeostasis.

It has been reported that redox signalling by microbial ROS formation is in response to microbial signals via formyl peptide receptors and the gut epithelial Nox1 (Lin et al. 2009). As we have previously documented (Linnane et al. 2007) ROS generated by Nox enzymes have been shown to function as essential second messengers in multiple signal transduction metabolic pathways through the rapid and transient oxidative inactivation of a distinct class of sensor proteins bearing oxidant-sensitive thiol groups. These redox sensitive proteins include tyrosine phosphatases that attend as regulators of the MAP kinase pathways (Linnane et al. 2007; Lin et al. 2009). These reports focus our understanding on the importance of second messenger functionality for the maintenance of homeostasis and bring into serious question the elimination of ROS by antioxidant supplements for the amelioration of GIT inflammatory diseases such as IBD. The established importance of recent investigations regarding probiotic/microbial-elicited ROS clarifies that stimulated cellular proliferation and motility is strictly controlled and is a regulated signalling process for proper innate immunity and gut barrier function (Lin et al. 2009; Collier-Hyams et al. 2006; Neish et al. 2000). The observations that the vertebrate epithelia of the intestinal tract, supports a tolerable low-level inflammatory response toward the GIT microflora, can be viewed as an adaptive activity that maintains homeostasis.

Discussion

It has become clear from numerous studies derived from different experimental model systems that enteric bacteria are a critical component in the maintenance of health as well as in the initiation and dys-regulation of gastrointestinal inflammation that may lead to dysbiosis and ultimately GIT disease (Howarth and Wang 2013). Also an enhanced understanding of the molecular mechanisms underlying bacterial signalling and tolerance in the small and large bowel may provide clues to the localized microbiotic-controlled axis that operates within the GIT to maintain homeostasis, such as in the secretion of mucus. Mucus production has been reported to be stimulated by high-fiber diets, confirming that under in vivo physiological conditions, an adaptive GIT-derived feedback micro-axis mechanism is in place for sensing and responding to normally induced mechanical stress with an increase in lubrication of the GIT lumen (Enss et al. 1994; Schmidt-Wittig et al. 1996). A more recent study (Miyake et al. 2006) has demonstrated that lubrication in the GIT can be rapidly and precisely fine-tuned to widely fluctuating dietary-dependent levels of mechanical stress. This further supports our contention that feedback GIT micro-axes that are associated with mucus secretion, Th1/Th2 modulation or the secretion of proteins (e.g. secretin) that regulate GIT homeostasis which are fundamentally influenced by the GIT microbiome. The value of ROS signalling, rather than leading to macromolecular damage, has been relatively undervalued. We suggest that proper commensal bacterial signalling is of utmost importance in maintaining GIT homeostasis.

Furthermore, this critical review has highlighted the significant pharmacobiotic importance of certain probiotic genera/strains that can exert a significant health benefit by rescuing a dysbiotic GIT microbiota profile. The microbial community composition is governed by the host's age, diet and internal environment and bacterial phylogeny influencing immunological tolerance and inflammatory responses within individuals (Vitetta et al. 2013). Prudent dietary practices with perhaps regular probiotic/prebiotic supplementation that achieve and preserve the internal milieu may be the rationale for health maintenance and GIT inflammatory disease prevention. Clearly, the number of human intervention studies assessing the effect of probiotics in inflammatory diseases of the GIT supports this contention.

Although overall, the connection between the gut microbiota, energy homeostasis, inflammation and its role in the pathogenesis of GIT inflammatory conditions are increasingly recognized, further studies are required to confirm probiotic, prebiotic and symbiotic relevance, biological acceptability, mode of action and the long-term effects of these supplements. The challenge is for clinical trials with robust designs and sharp end-points.

Acknowledgments Luis Vitetta has received National Institute of Complementary Medicine and National Health and Medical Research Council of Australia competitive funding and Industry support for research into probiotics.

Conflict of interest The authors have no further conflicts of interest relevant to the content of this review.

References

Abdullah M, Syam AF, Simadibrata M, Gunawan J, Makmun D, Rani AA (2013) New insights on the pathomechanisms of inflammatory bowel disease. J Dig Dis 14(9):455–462

Adlerberth I (2008) Factors influencing the establishment of the intestinal microbiota in infancy. Nestle Nutr Workshop Ser Pediatr Progr 62:13–29

Amalaradjou MA, Bhunia AK (2012) Modern approaches in probiotics research to control foodborne pathogens. Adv Food Nutr Res 67:185–239

Andriulli A, Neri M, Loguercio C, Terreni N, Merla A, Cardarella MP, Federico A et al (2008) Clinical trial on the efficacy of a new symbiotic formulation, Flortec, in patients with irritable

bowel syndrome: a multicenter, randomized study. J Clin Gastroenterol 42(Suppl 3 Pt 2):S218–S223

Armuzzi A, Cremonini F, Ojetti V, Bartolozzi F, Canducci F, Candelli M, Santarelli L, Cammarota G, De Lorenzo A, Pola P, Gasbarrini G, Gasbarrini A (2001) Effect of Lactobacillus GG supplementation on antibiotic-associated gastrointestinal side effects during *Helicobacter pylori* eradication therapy: a pilot study. Digestion 63(1):1–7

Arumugam M, Raes J, Pelletier E et al (2011) Enterotypes of the human gut microbiome. Nature 473(7346):174–180

Banaszkiewicz A, Szajewska H (2005) Ineffectiveness of Lactobacillus GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. J Pediatr 146(3):364–369

Beniwal RS, Arena VC, Thomas L, Narla S, Imperiale TF, Chaudhry RA, Ahmad UA (2003) A randomized trial of yogurt for prevention of antibiotic-associated diarrhea. Dig Dis Sci 48(10):2077–2082

Bermudez-Brito M, Plaza-Diaz J, Munoz-Quezada S, Gomez-Llorente C, Gil A (2012) Probiotic mechanisms of action. Ann Nutr Metab 6:160–174

Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M, Hammerman C (2005) Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr 147(2):192–196

Bu LN, Chang MH, Ni YH, Chen HL, Cheng CC (2007) Lactobacillus casei rhamnosus cr35 in children with chronic constipation. Pediatr Int 49(4):485–490

Burcelin R, Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R (2008) Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes 57(6):1470–1481

Cappello C, Tremolaterra F, Pascariello A, Ciacci C, Iovino P (2013) A randomised clinical trial (RCT) of a symbiotic mixture in patients with irritable bowel syndrome (IBS): effects on symptoms, colonic transit and quality of life. Int J Colorectal Dis 28(3):349–358

Chiang SS, Pan TM (2013) Beneficial effects of phytoestrogens and their metabolites produced their by intestinal microflora on bone health. Appl Microbiol Biotechnol 97(4):1489–1500

Chouraqui JP, Van Egroo LD, Fichot MC (2004) Acidified milk formula supplemented with bifidobacterium lactis: impact on infant diarrhea in residential care settings. J Pediatr Gastroenterol Nutr 38(3):288–292

Cimperman L, Bayless G, Best K et al (2011) A randomized, double-blind, placebo-controlled pilot study of *Lactobacillus reuteri* ATCC 55730 for the prevention of antibiotic-associated diarrhea in hospitalized adults. J Clin Gastroenterol 45(9):785–789

Collier-Hyams LS, Sloane V, Batten BC, Neish AS (2006) Cutting edge: bacterial modulation of epithelial signaling via changes in neddylation of cullin-1. J Immunol 175:4194–4198

Corrêa NB, Péret Filho LA, Penna FJ, Lima FM, Nicoli JR (2005) A randomized formula controlled trial of *Bifidobacterium lactis* and *Streptococcus thermophilus* for prevention of antibiotic-associated diarrhea in infants. J Clin Gastroenterol 39(5):385–389

Costalos C, Skouteri V, Gounaris A, Sevastiadou S, Triandafilidou A, Ekonomidou C et al (2003) Enteral feeding of premature infants with Saccharomyces boulardii. Early Hum Dev 74(2):89–96

Cremonini F, Di Caro S, Covino M, Armuzzi A, Gabrielli M, Santarelli L, Nista EC, Cammarota G, Gasbarrini G, Gasbarrini A (2002) Effect of different probiotic preparations on anti-helicobacter pylori therapy-related side effects: a parallel group, triple blind, placebo-controlled study. Am J Gastroenterol 97(11):2744–2749

Cui S, Hu Y (2012) Multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. Int J Clin Exp Med 5(3):238–244

Dani C, Biadaioli R, Bertini G, Martelli E, Rubaltelli FF (2002) Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. Biol Neonate 82(2):103–108

Dapoigny M, Piche T, Ducrotte P, Lunaud B, Cardot JM, Bernalier-Donadille A (2012) Efficacy and safety profile of LCR35 complete freeze-dried culture in irritable bowel syndrome: a randomized, double-blind study. World J Gastroenterol 18(17):2067–2075

David L, Maurice C, Carmody R et al (2013) Diet rapidly and reproducibly alters the human gut microbiome. Nature. (Epub ahead of print)

Ding S, Lund PK (2011) Role of intestinal inflammation as an early event in obesity and insulin resistance. Curr Opin Clin Nutr 14:328–333

Drouault-Holowacz S, Bieuvelet S, Burckel A et al (2008) A double blind randomized controlled trial of a probiotic combination in 100 patients with irritable bowel syndrome. Gastroenterol Clin Biol 32(2):147–152

Ducrotté P, Sawant P, Jayanthi V (2012) Clinical trial: *Lactobacillus plantarum* 299v (DSM 9843) improves symptoms of irritable bowel syndrome. World J Gastroenterol 18(30):4012–4018

Eckmann L (2006) Sensor molecules in intestinal innate immunity against bacterial infections. Curr Opin Gastroenterol 22(2):95–101

Enck P, Zimmermann K, Menke G et al (2008) A mixture of *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) for treatment of the irritable bowel syndrome—a randomized controlled trial with primary care physicians. Neurogastroenterol Motil 20(10):1103–1109

Enss ML, Schmidt-Wittig U, Honer K et al (1994) Mechanical challenge causes alterations of rat colonic mucosa and released mucins. Alterations of mucosa and mucins. J Exp Anim Sci 36:128–140

Fernández-Carrocera LA, Solis-Herrera A, Cabanillas-Ayón M, Gallardo-Sarmiento RB, García-Pérez CS, Montaño-Rodríguez R, Echániz-Aviles MO (2013) Double-blind, randomised clinical assay to evaluate the efficacy of probiotics in preterm newborns weighing less than 1500 g in the prevention of necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 98(1):F5–F9

Frohmader TJ, Chaboyer WP, Robertson IK, Gowardman J (2010) Decrease in frequency of liquid stool in enterally fed critically ill patients given the multispecies probiotic VSL#3: a pilot trial. Am J Crit Care 19(3):e1–e11

Fuller R (1989) Probiotics in man and animals. J Appl Bacteriol 66(5):365–378

Gawrońska A, Dziechciarz P, Horvath A, Szajewska H (2007) A randomized double-blind placebo-controlled trial of Lactobacillus GG for abdominal pain disorders in children. Aliment Pharmacol Ther 25(2):177–184

Gionchetti P, Rizzello F, Venturi A et al (2000) Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double blind, placebo controlled trial. Gastroenterology 119:305–309

Gionchetti P, Rizzello F, Helwig U et al (2003) Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo controlled trial. Gastroenterology 124:1202–1209

Goto Y, Ivanov I (2013) Intestinal epithelial cells as mediators of the commensal-host immune cross talk. Immunol Cell Biol 91:204–214

Grossi E, Buresta R, Abbiati R, Cerutti R (2010) Pro-DIA study group. Clinical trial on the efficacy of a new symbiotic formulation, Flortec, in patients with acute diarrhea: a

multicenter, randomized study in primary care. J Clin Gastroenterol 44(Suppl 1):S35–S41

Guandalini S, Pensabene L, Zikri MA, Dias JA, Casali LG, Hoekstra H et al (2000) Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr 30(1):54–60

Guandalini S, Magazzu G, Chiaro A et al (2010) VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr 51(1):24–30

Guslandi M, Mezzi G, Sorghi M, Testoni PA (2000) Saccharomyces boulardii in maintenance treatment of Crohn's disease. Dig Dis Sci 45(7):1462–1464

Guyonnet D, Chassany O, Ducrotte P, Picard C, Mouret M, Mercier CH, Matuchansky C (2007) Effect of a fermented milk containing Bifidobacterium animalis DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. Aliment Pharmacol Ther 26(3):475–486

Hong KS, Kang HW, Im JP, Ji GE, Kim SG, Jung HC, Song IS, Kim JS (2009) Effect of probiotics on symptoms in Korean adults with irritable bowel syndrome. Gut Liver 3(2):101–107

Hooper LV (2004) Bacterial contributions to mammalian gut development. Trends Microbiol 12:129–134

Howarth GS, Wang H (2013) Role of endogenous microbiota, probiotics and their biological products in human health. Nutrients 5(1):58–81

Hvas CL, Kelsen J, Agnholt J et al (2007) Crohn's disease intestinal CD4 +T cells have impaired interleukin-10 production which is not restored by probiotic bacteria. Scand J Gastroenterol 42(5):592–601

Ishikawa H, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T (2003) Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. J Am Coll Nutr 22(1):56–63

Jiménez E, Marín ML, Martín R et al (2008) Is meconium from healthy newborns actually sterile? Res Microbiol 159(3):187–193

Jirapinyo P, Densupsoontorn N, Thamonsiri N, Wongarn R (2002) Prevention of antibiotic-associated diarrhea in infants by probiotics. J Med Assoc Thai 85(S2):S739–S742

Kajander K, Hatakka K, Poussa T, Färkkilä M, Korpela R (2005) A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. Aliment Pharmacol Ther 22(5):387–394

Kato K, Mizuno S, Umesaki Y, Ishii Y, Sugitani M, Imaoka A, Otsuka M et al (2004) Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. Aliment Pharmacol Ther 20(10):1133–1141

Ki Cha B, Mun Jung S, Hwan Choi C et al (2012) The effect of a multispecies probiotic mixture on the symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Clin Gastroenterol 46(3):220–227

Kim HJ, Camilleri M, McKinzie S et al (2003) A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 17(7):895–904

Kim HJ, Vazquez Roque MI, Camilleri M et al (2005) A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterol Motil 17(5):687–696

Kim MS, Hwang SS, Park EJ et al (2013) Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation. Environ Microbiol Rep 5(5):765–775

Koch S, Nusrat A (2012) The life and death of epithelia during inflammation: lessons learned from the gut. Annu Rev Pathol 7:35–60

Koebnick C, Wagner I, Leitzmann P, Stern U, Zunft HJ (2003) Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. Can J Gastroenterol 17(11):655–659

Kotowska M, Albrecht P, Szajewska H (2005) *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. Aliment Pharmacol Ther 21(5):583–590

Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J et al (2004) Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut 53(11): 1617–1623

Kruis W, Chrubasik S, Boehm S, Stange C, Schulze J (2012) A double-blind placebo-controlled trial to study therapeutic effects of probiotic Escherichia coli Nissle 1917 in subgroups of patients with irritable bowel syndrome. Int J Colorectal Dis 27(4): 467–474

La Rosa M, Bottaro G, Gulino N, Gambuzza F, Di Forti F, Inì G, Tornambè E (2003) Prevention of antibiotic-associated diarrhea with Lactobacillus sporogens and fructo-oligosaccharides in children. A multicentric double-blind vs placebo study. Minerva Pediatr 55(5):447–452

Lawrence SJ, Korzenik JR, Mundy LM (2005) Probiotics for recurrent Clostridium difficile disease. J Med Microbiol 54(Pt 9):905–906

Lee WJ (2008) Bacterial-modulated signaling pathways in gut homeostasis. Sci Signal 1:pe24

Li F, Hullar MA, Schwarz Y et al (2009) Human gut bacterial communities are altered by addition of cruciferous vegetables to a controlled fruit- and vegetable-free diet. J Nutr 139(9): 1685–1691

Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, Oh W (2005) Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics 115(1):1–4

Lin HC, Hsu CH, Chen HL, Chung MY, Hsu JF, Lien RI et al (2008) Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics 122(4):693–700

Lin PW, Myers LE, Ray L, Song SC, Nasr TR, Berardinelli AJ et al (2009) Lactobacillus rhamnosus blocks inflammatory signaling in vivo via reactive oxygen species generation. Free Radic Biol Med 47:1205–1211

Linnane AW, Kios M, Vitetta L (2007) Healthy aging: regulation of the metabolome by cellular redox modulation and prooxidant signaling systems: The essential roles of superoxide anion and hydrogen peroxide. Biogerontology 8:445–467

Manzoni P, Mostert M, Leonessa ML, Priolo C, Farina D, Monetti C et al (2006) Oral supplementation with Lactobacillus casei subspecies rhamnosus prevents enteric colonization by Candida species in preterm neonates: a randomized study. Clin Infect Dis 42(12):1735–1742

Marcobal A, Sonnenburg JL (2012) Human milk oligosaccharide consumption by intestinal microbiota. Clin Microbiol Infect 18(Suppl. 4):12–15

Margreiter M, Ludl K, Phleps W, Kaehler ST (2006) Therapeutic value of a Lactobacillus gasseri and Bifidobacterium longum fixed bacterium combination in acute diarrhea: a randomized, double-blind, controlled clinical trial. Int J Clin Pharmacol Ther 44(5):207–215

Marteau P, Lémann M, Seksik P, Laharie D, Colombel JF, Bouhnik Y, Cadiot G et al (2006) Ineffectiveness of Lactobacillus

johnsonii LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. Gut 55(6):842–847

Martin HM, Campbell BJ, Hart CA et al (2004) Enhanced Escherichia coli adherence and invasion in Crohn's disease and colon cancer. Gastroenterology 127:80–93

Matthes H, Krummenerl T, Giensch M, Wolff C, Schulze J (2010) Clinical trial: probiotic treatment of acute distal ulcerative colitis with rectally administered Escherichia coli Nissle 1917 (EcN). BMC Complement Altern Med 15(10):13

Mazlyn MM, Nagarajah LH, Fatimah A, Norimah AK, Goh KL (2013) Effects of a probiotic fermented milk on functional constipation: a randomized, double-blind, placebo-controlled study. J Gastroenterol Hepatol 28(7):1141–1147

Mimura T, Rizzello F, Helwig U et al (2004) Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut 53:108–114

Miyake K, Tanaka T, McNeil PL (2006) Disruption induced mucus secretion: repair and protection. PLoS Biol 4(9):e276

Mohan R, Koebnick C, Schildt J, Schmidt S, Mueller M, Possner M et al (2006) Effects of Bifidobacterium lactis Bb12 supplementation on intestinal microbiota of preterm infants: a double-blind, placebo-controlled, randomized study. J Clin Microbiol 44(11):4025–4031

Montero Vega MT, de Andrés Martín A (2008) Toll-like receptors: a family of innate sensors of danger that alert and drive immunity. Allergol Immunopathol (Madr) 36(6):347–357

Mylonaki M, Rayment NB, Rampton DS et al (2005) Molecular characterization of rectal mucosa-associated bacterial flora in inflammatory bowel disease. Inflamm Bowel Dis 11(5):481–487

Nagata S, Asahara T, Ohta T et al (2011) Effect of the continuous intake of probiotic-fermented milk containing Lactobacillus casei strain Shirota on fever in a mass outbreak of norovirus gastroenteritis and the faecal microflora in a health service facility for the aged. Br J Nutr 106(4):549–556

Nakamura Y, Omaye S (2012) Metabolic diseases and pro- and prebiotics: mechanistic insights. Nutr Metab 9:60

Neish AS (2013) Redox signaling mediated by the gut microbiota. Free Radic Res. doi:10.3109/10715762.2013.833331

Neish AS, Gewirtz AT, Zeng H, Young AN, Hobert ME, Karmali V et al (2000) Prokaryotic regulation of epithelial responses by inhibition of I kappa B-alpha ubiquitination. Science 289:1560–1563

Neuman MG, Nanau RM (2012) Inflammatory bowel disease: role of diet, microbiota, life style. Transl Res 160(1):29–44

Niedzielin K, Kordecki H, Birkenfeld B (2001) A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299 V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 13(10):1143–1147

Nista EC, Candelli M, Cremonini F, Cazzato IA, Zocco MA, Franceschi F, Cammarota G, Gasbarrini G, Gasbarrini A (2004) Bacillus clausii therapy to reduce side-effects of anti-Helicobacter pylori treatment: randomized, double-blind, placebo controlled trial. Aliment Pharmacol Ther 20(10):1181–1188

Nobaek S, Johansson ML, Molin G, Ahrné S, Jeppsson B (2000) Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 95(5):1231–1238

O'Neill LA, Golenbock D, Bowie AG (2013) The history of toll-like receptors—redefining innate immunity. Nat Rev Immunol 13(6):453–460

Pereg D, Kimhi O, Tirosh A, Orr N, Kayouf R, Lishner M (2005) The effect of fermented yogurt on the prevention of diarrhea in a healthy adult population. Am J Infect Control 33(2):122–125

Plummer S, Weaver MA, Harris JC, Dee P, Hunter J (2004) Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of C. difficile diarrhoea. Int Microbiol 7(1):59–62

Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C (2002) Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut 51(3):405–409

Ritchie ML, Romanuk TN (2012) A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One 7(4):e34938

Roberfroid MB (2007) Inulin-type fructans: functional food ingredients. J Nutr 137(11 Suppl):2493Se502S

Roberts LM, McCahon D, Holder R, Wilson S, Hobbs FD (2013) A randomised controlled trial of a probiotic 'functional food' in the management of irritable bowel syndrome. BMC Gastroenterol 7(13):45

Rougé C, Piloquet H, Butel MJ, Berger B, Rochat F, Ferraris L (2009) Oral supplementation with probiotics in very-low-birth-weight preterm infants: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr 89(6):1828–1835

Salazar-Lindo E, Miranda-Langschwager P, Campos-Sanchez M, Chea-Woo E, Sack RB (2004) Lactobacillus casei strain GG in the treatment of infants with acute watery diarrhea: a randomized, double-blind, placebo controlled clinical trial [ISRCTN67363048]. BMC Pediatr 4:18

Samanta M, Sarkar M, Ghosh P, Ghosh JK, Sinha MK, Chatterjee S (2009) Prophylactic probiotics for prevention of necrotizing enterocolitis in very low birth weight newborns. J Trop Pediatr 55(2):128–131

Schmidt-Wittig U, Enss ML, Coenen M et al (1996) Response of rat colonic mucosa to a high fiber diet. Ann Nutr Metab 40:343–350

Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC (2004) Lactobacillus GG in inducing and maintaining remission of Crohn's disease. BMC Gastroenterol 4:5

Scoditti E, Calabriso N, Massaro M et al (2012) Mediterranean diet polyphenols reduce inflammatory angiogénesis through MMP-9 and COX-2 inhibition in human vascular endothelial cells: a potentially protective mechanism in atherosclerotic vascular disease and cancer. Arch Biochem Biophys 527(2):81–89

Seki H, Shiohara M, Matsumura T, Miyagawa N, Tanaka M, Komiyama A, Kurata S (2003) Prevention of antibiotic-associated diarrhea in children by Clostridium butyricum MIYAIRI. Pediatr Int 45(1):86–90

Serino M, Luche E, Gres S et al (2012) Metabolic adaptation to a high fat diet is associated with a change in the gut microbiota. Gut 61(4):543–553

Simrén M, Ohman L, Olsson J, Svensson U, Ohlson K, Posserud I, Strid H (2010) Clinical trial: the effects of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome—a randomized, double-blind, controlled study. Aliment Pharmacol Ther 31(2):218–227

Song HJ, Kim JY, Jung SA, Kim SE, Park HS, Jeong Y, Hong SP et al (2010) Effect of probiotic Lactobacillus (Lacidofil® cap) for the prevention of antibiotic-associated diarrhea: a prospective, randomized, double-blind, multicenter study. J Korean Med Sci 25(12):1784–1791

Sood A, Midha V, Makharia GK, Ahuja V, Singal D, Goswami P, Tandon RK (2009) The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. Clin Gastroenterol Hepatol 7(11):1202–1209

Surawicz CM, McFarland LV, Greenberg RN, Rubin M, Fekety R, Mulligan ME, Garcia RJ, Brandmarker S, Bowen K, Borjal D, Elmer GW (2000) The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. Clin Infect Dis 31(4):1012–1017

Swidsinski A, Ladhoff A, Pernthaler A et al (2002) Mucosal flora in inflammatory bowel disease. Gastroenterology 122(1):44–54

Szajewska H, Kotowska M, Mrukowicz JZ, Armańska M, Mikołajczyk W (2001) Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J Pediatr 138(3):361–365

Tabbers MM, Chmielewska A, Roseboom MG, Crastes N, Perrin C, Reitsma JB, Norbruis O, Szajewska H, Benninga MA (2011) Fermented milk containing Bifidobacterium lactis DN-173 010 in childhood constipation: a randomized, double-blind, controlled trial. Pediatrics 127(6):e1392–e1399

Thomas MR, Litin SC, Osmon DR, Corr AP, Weaver AL, Lohse CM (2001) Lack of effect of Lactobacillus GG on antibiotic-associated diarrhea: a randomized, placebo-controlled trial. Mayo Clin Proc 76(9):883–889

Tien MS, Girardin SE, Regnault B et al (2006) Anti-inflammatory effect of Lactobacillus casei on Shigella-infected human intestinal epithelial cells. Immunol 176:1228–1237

Tremaroli V, Bäckhed F (2012) Functional interactions between the gut microbiota and host metabolism. Nature 489(7415):242–249

Tursi A, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, Forti G et al (2010) Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 105(10): 2218–2227

Van de Merwe JP, Schroder AM, Wensinck F et al (1988) The obligate anaerobic faecal flora of patients with Crohn's disease and their first-degree relatives. Scand J Gastroenterol 23 (9):1125–1131

Van Gossum A, Dewit O, Louis E, de Hertogh G, Baert F, Fontaine F et al (2007) Multicenter randomized-controlled clinical trial of probiotics (Lactobacillus johnsonii, LA1) on early endoscopic recurrence of Crohn's disease after lleo-caecal resection. Inflamm Bowel Dis 13(2):135–142

Virk A, Mandrekar J, Berbari EF, Boyce TG, Fischer PR et al (2013) A randomized, double blind, placebo-controlled trial of an oral synbiotic (AKSB) for prevention of travelers' diarrhea. J Travel Med 20(2):88–94

Vitetta L, Sali A (2008) Probiotics, prebiotics and gastrointestinal health. Med Today 9:65–70

Vitetta L, Briskey D, Hayes E et al (2012) A review of the pharmacobiotic regulation of gastrointestinal inflammation by probiotics, commensal bacteria and prebiotics. Inflammopharmacology 20(5):251–266

Vitetta L, Linnane AW, Gobe GC (2013) From the gastrointestinal tract (GIT) to the kidneys: live bacterial cultures (probiotics) mediating reductions of uremic toxin levels via free radical signaling. Toxins (Basel) 5(11):2042–2057

Weizman Z, Asli G, Alsheikh A (2005) Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics 115(1):5–9

Wenus C, Goll R, Loken EB, Biong AS, Halvorsen DS, Florholmen J (2008) Prevention of antibiotic-associated diarrhoea by a fermented probiotic milk drink. Eur J Clin Nutr 62(2):299–301

Whorwell PJ, Altringer L, Morel J et al (2006) Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 101(7): 1581–1590

Wu GD, Chen J, Hoffmann C et al (2011) Linking long-term dietary patterns with gut microbial enterotypes. Science 334(6052): 105–108

Wullt M, Hagslätt ML, Odenholt I (2003) Lactobacillus plantarum 299v for the treatment of recurrent Clostridium difficile-associated diarrhoea: a double-blind, placebo-controlled trial. Scand J Infect Dis 35(6–7):365–367

Yan F, Cao H, Cover TL, Whitehead R, Washington MK, Polk DB (2007) Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. Gastroenterology 132:562–575

Yang YX, He M, Hu G, Wei J, Pages P, Yang XH, Bourdu-Naturel S (2008) Effect of a fermented milk containing Bifidobacterium lactis DN-173010 on Chinese constipated women. World J Gastroenterol 14(40):6237–6243

Yoon JS, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW et al (2014) Effect of multispecies probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Gastroenterol Hepatol 29(1):52–59