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Synbiotics for Improved Human Health: Recent Developments, Challenges, and Opportunities

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Synbiotics for Improved Human Health: Recent Developments, Challenges, and Opportunities

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Abstract

Research on combining pro- and prebiotics as synbiotics to enhance human and animal health has accelerated in the past 10 years, including many clinical trials that have assessed a diverse range of synbiotic formulations. In this review, we summarize these studies as well as the commercial applications of synbiotics that are available. In particular, we critically assess the claimed health benefits of synbiotic applications and the ecological and therapeutic factors to consider when designing synbiotics and discuss the implications of these concepts for future research in this field.

FUNCTIONAL IMPORTANCE OF THE COLONIC MICROBIOTA

The human gastrointestinal (GI) tract is colonized by approximately 10^{14} microbial cells, with the majority (10^{11}–10^{12} cells/g) residing in the colon and fewer than 10^{2}–10^{3} cells/g in the stomach and proximal ileum (Sartor 2008, Vyas & Ranganathan 2012). This microbiota serves several critical physiological functions. It protects the host from infection by invasive pathogenic microorganisms by competing with them for nutrients and niches (Belkaid & Hand 2014, Stecher & Hardt 2008, Yasmin et al. 2015) and producing antimicrobial substances, including bacteriocins and other antagonistic peptides and small molecules (Buffie & Pamer 2013, Jonkers 2016). In addition, the microbiota aids in the development of the adaptive and innate immune systems; produces essential vitamins, amino acids, and other metabolites; and facilitates utilization of nutrients, especially polymeric carbohydrates (Walsh et al. 2014). Finally, the microbiota contributes caloric energy to the host. Assuming a typical European diet, the gut microbiota can potentially yield as much as 140–180 kcal/day via fermentation of the 50–60 g of carbohydrates that escape host metabolism (McNeil 1984).

The extent and rate of carbohydrate digestion and utilization in humans depend primarily on anatomical location. Initially, carbohydrates are hydrolyzed in the mouth via amylases, and starch and glycogen are further hydrolyzed into simple sugars, which are absorbed in the small intestine. In the large intestine, indigestible substrates, including various dietary fibers and carbohydrates, are hydrolyzed and fermented by bacteria. The colon offers a favorable environment for anaerobic microbes, with high quantities of nutrients that escape host digestion, a thick mucus layer secreted by a high number of Goblet cells, reduced intestinal motility, and a favorable pH (Wlodarska et al. 2015). Because approximately 70% of the constituents of the gut microbiota reside in the large intestine, these organisms may have a profound effect on energy storage, host metabolism, and intestinal health (Vyas & Ranganathan 2012). The proximal part of the large intestine is responsible for most of the absorption of the short-chain fatty acids (SCFAs; mainly acetate, butyrate, and propionate) that are produced by the colonic bacteria from fiber fermentation at a rate of approximately 0.5–0.6 mole/day (Angelakis & Lagier 2016, McNeil 1984, Vyas & Ranganathan 2012), depending on the microbiota composition, nature of the fermentable carbohydrate, and dietary intake (Jonkers 2016).

SCFAs have several beneficial effects on host health (Puertollano et al. 2014, Tan et al. 2014), and as the preferred energy source for colonocytes (Suzuki et al. 2008), SCFAs promote epithelial integrity (Tan et al. 2014). Additionally, SCFAs affect the thickness of the mucus layer, support epithelial cell survival, and regulate expression of tight junction proteins (Jonkers 2016, Krishnan et al. 2015). Disruption of gut integrity has been attributed to serious intestinal diseases, including celiac disease, inflammatory bowel disease (IBD), and colorectal cancer (Den Besten et al. 2013, Puertollano et al. 2014, Tolhurst et al. 2012). The local and systemic immunomodulatory properties of SCFAs include the suppression of NF-κB activity (Park et al. 2007, Tedelind et al. 2007, Vinolo et al. 2011). In addition, SCFAs exhibit anti-inflammatory properties by modulating immune cell chemotaxis, reactive oxygen species, and cytokine release (Tan et al. 2014). SCFAs also regulate colonic mobility and blood flow and can influence colon pH, which has a direct impact on the uptake and absorption of nutrients and electrolytes (Tazoe et al. 2008).

Butyrate formation by the colonic microbiota is of particular interest, as this compound has been shown to have multiple biological effects. Butyrate has anti-inflammatory properties, inhibits interleukin (IL)-12, and upregulates IL-10 in monocytes (Hamer et al. 2008, Park et al. 2007). In addition, butyrate (among other SCFAs) has signaling capacities via G protein–coupled receptors (Brown et al. 2003, Kasubuchi et al. 2015, Krishnan et al. 2015, Tang et al. 2011, Tolhurst et al. 2012) and increases levels of anorectic hormones such as PYY and GLP-1 that contribute to energy metabolism and appetite control (Jonkers 2016). Butyrate also induces apoptosis of neutrophils

(Aoyama et al. 2010) and has anticancer activity in several human cell lines (Foglietta et al. 2014, Wang et al. 2013, Yamamura et al. 2014).

The impact of GI microbiota on the health of humans and animals is now one of the most-studied fields in biology and medicine. Although the medical importance of the GI microbiota has been recognized for more than a century, multi-omics technologies now provide tools necessary to gain a community-wide, high-throughput assessment of this complex microbial ecosystem. Discoveries made during the past 20 years have dramatically changed the way that clinicians and researchers associate the gut microbiota with both nutrition and medicine. In particular, it is now becoming possible to establish mechanisms by which the gut microbiota interacts with the host and thereby alters microbiota composition and activity of the GI microbiota. Although it remains difficult to establish cause-and-effect relationships in humans, research in animal models has clearly established that the GI microbiota, and alterations thereof, contribute to several pathologies. Thus, although the microbiota provides many beneficial effects for the host, the composition of an individual's microbiota may also predispose that individual to certain intestinal as well as systemic diseases, including obesity and diabetes.

The strong associations of the composition, function, and dysbiotic patterns of the GI microbiota with a wide range of pathologies provide a rationale for modulation of the microbiota to improve human health (Flint et al. 2012, Frank & Pace 2008, Lemon et al. 2012, Marchesi et al. 2015). Several strategies to achieve this goal have been explored, including modifying the diet and dietary components and the use of prebiotics and probiotics. Although the GI microbiota in healthy humans is generally resistant to these therapeutic interventions, they all have the potential to alter the microbiota to some extent.

MODULATION OF THE GUT MICROBIOTA WITH PRO-, PRE-, AND SYNBIOTICS

Among the first strategies proposed to modulate the gut microbiota was the administration of live microbes. Indeed, what we now call probiotics have been produced and consumed for more than 100 years (Kolida & Gibson 2011, Mechnikoff 1908), long before the term was formally defined. Probiotics are currently defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al. 2015, p. 506). There are hundreds of probiotic strains and products in the marketplace, and many clinicians recommend probiotics to patients for a variety of conditions, including antibiotic-associated diarrhea, acute gastroenteritis, general GI disorders [such as irritable bowel syndrome (IBS) and infant colic], and mild ulcerative colitis (UC), and to improve lactose digestion (Sanders 2015). Systematic reviews and meta-analyses have shown that probiotics may aid the treatment of antibiotic-associated diarrhea (D'Souza et al. 2002); prevention of necrotizing enterocolitis in preterm neonates (Deshpande et al. 2010); induction of remission and maintenance of IBD (Shen et al. 2014); prevention and control of hyperglycemia (Ruan et al. 2015); improvement in levels of total cholesterol, high-density lipoproteins (HDLs), and tumor necrosis factor (TNF)-α in patients with nonalcoholic fatty liver disease (NAFLD) (Gao et al. 2016); and reduction of glucose and insulin as well as a homeostatic model assessment of insulin resistance in diabetes patients (Sun & Buys 2016). Jonkers (2016) also reports the effectiveness of probiotics for preventing or reducing the severity of infectious and antibiotic-associated diarrhea and respiratory tract infections.

Despite this extensive scientific literature, no health claim for probiotics has been approved in Europe or the United States by the responsible regulatory agencies [European Food Safety Authority (EFSA) and US Food and Drug Administration (FDA)]. In contrast, Canada has accepted a limited number of non-strain-specific claims about the general nature of probiotic microorganisms (**http://www.inspection.gc.ca**), as has Japan (Farnworth 2008).

In contrast to the century-old history of probiotics, the prebiotic concept was formally introduced only in 1995. Defined originally as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health" (Gibson & Roberfroid 1995), the current criteria for the definition of prebiotics are now the subject of considerable debate (Bindels et al. 2015a, Hutkins et al. 2016, Katsnelson & Writer 2016, Valcheva & Dieleman 2016). Although the general requirements of a prebiotic have been retained in the most recently proposed definition (Gibson et al. 2017), some key elements of the definition, including specificity and selectivity, have been questioned (Bindels et al. 2015a). The Canadian Food Inspection Agency has now established its own definition for prebiotics, but neither the FDA nor the EFSA currently provides a definition.

The most widely studied prebiotics are the simple fructans and galactans, available commercially as inulins, fructooligosaccharides (FOSs), and galactooligosaccharides (GOSs). A variety of other oligosaccharides, including isomaltooligosaccharides, mannan oligosaccharides, pectins, resistant starches, xylooligosaccharides, arabinoxylans, and human and bovine milk oligosaccharides, have also been studied for their potential prebiotic properties (Krumbeck et al. 2016). Prebiotics are suggested to provide health benefits through several different mechanisms, including compositional or metabolic changes to the resident microorganisms, stimulation of growth and/or activity of putative health-promoting bacteria, and production of SCFAs (Verspreet et al. 2016). SCFAs reduce the local pH, induce the production of immunomodulatory cytokines, and stimulate mucin production (Preidis & Versalovic 2009).

Some prebiotics are reported to have fermentation-independent health effects; for example, human milk oligosaccharides may protect infants from infections by inhibiting adherence of pathogens to the epithelial cells that line the GI tract (Yu et al. 2016). Similar effects have been reported for GOSs (Quintero-Villegas et al. 2014). Recently, microbiota-independent effects of resistant starch on improved insulin sensitivity and other metabolic benefits have been reported (Bindels et al. 2017). Similarly, systematic meta-analyses have shown that prebiotic treatments can reduce fasting insulin levels (Beserra et al. 2015), aid in the treatment of diarrhea (Zaman & Sarbini 2015) and other infectious diseases (Lohner et al. 2014), and restore bowel function (Collado Yurrita et al. 2014). There are also reports that prebiotics may contribute to abdominal pain, diarrhea, and increased production of gas depending on the doses, nature of the prebiotic, and susceptibility of the host (Jonkers 2016).

SYNBIOTIC CONCEPTS AND DEFINITIONS

When Gibson & Roberfroid (1995) first articulated the prebiotic concept more than 20 years ago, they also envisioned that pre- and probiotics could be combined as synbiotics. Later, Kolida & Gibson (2011) described the two general ways synbiotics could enhance the effects of their component parts. Complementary synbiotics are those that contain pro- and prebiotics chosen independently of one another, with each responsible for a particular effect or health benefit. Accordingly, the best-case scenario for such a synbiotic is that each constituent, namely, the pro- and prebiotic, would have a beneficial effect and the effects would be additive. In this complementary approach, the prebiotic component is not necessarily preferentially fermented by the probiotic strain and could theoretically support other members of the GI microbiota. The probiotic strain would gain no ecological advantage by being combined with the prebiotic and indeed may not be capable of fermenting the substrate at all.

In contrast, synergistic synbiotics also consist of a probiotic strain and a prebiotic substrate, but the difference is that the prebiotic is specifically intended to support the growth of the cognate probiotic (Kolida & Gibson 2011). Accordingly, there is no requirement for other members of the

gut microbiota capable of fermenting the prebiotic to be present. It is well known in the clinical diet/microbiota literature that response phenotypes are highly individual, with a portion of test subjects failing to respond to treatment (Cook et al. 2016, Korpela et al. 2014, Salonen et al. 2014, Serrano-Villar et al. 2017). As described below, synergistic synbiotics have the important advantage of addressing nonresponder outcomes by providing both the strain and its growth substrate in situ.

RATIONALE FOR SYNERGISTIC SYNBIOTICS

When prebiotics are introduced with a probiotic strain that does not ferment the substrate in vitro or does so slowly in vivo, the outcome may be highly unpredictable and would likely depend on the composition of an individual's gut microbiota. As noted above, it is apparent from human clinical studies that a bifidogenic response or other changes in the microbiota following prebiotic supplementation occurs in some subjects but not in others. The nature of the responder/nonresponder phenotype (i.e., what makes a responder a responder) remains the subject of considerable interest. Davis et al. (2011) suggested that bacterial strains capable of fermenting GOSs or other prebiotics in the colon might be absent in the nonresponder population. Similarly, the inability of specific gut microbes to outcompete other members of the gut microbiota could also affect the responder status of subjects. Indeed, Davis et al. (2011) showed that even a high abundance of taxa that would be expected to ferment a given prebiotic substrate was not a reliable predictor of whether or not the prebiotic causes a shift in abundance of that taxa.

The variable response to prebiotics has been observed in other studies. Salonen et al. (2014) showed that obese male individuals on a resistant starch diet could be divided into responders and nonresponders based on the shifts in the composition of their gut microbiota, and in this case, a high microbial diversity correlated with a low dietary responsiveness. Similarly, Martínez et al. (2010) have reported a microbial responder and nonresponder phenotype in normal-weight human subjects who had consumed resistant starches. Kovatcheva-Datchary et al. (2015) divided their study cohort into responders versus nonresponders based on their metabolic response to a barley kernel–based bread. A subsequent analysis of the gut microbiota of both groups showed that the *Prevotella* to *Bacteroides* ratio was significantly higher in the responder group.

Predicting whether or not a given subject will be a responder and ultimately obtain a beneficial health effect from a prebiotic is difficult. Response to treatment depends not only on the functional and taxonomic composition of the gut microbiota but also on host abiotic factors. The latter include the nature of the digestive enzymes provided by the host, stomach and intestinal pH, and transit time, all of which can ultimately affect enrichment of bacterial members, even if a suitable growth substrate is provided (Martínez et al. 2010).

One of the advantages of synergistic synbiotics is that such formulations could address the responder/nonresponder phenomenon. To become established in the GI tract, a probiotic must not only secure nutrients and other growth factors but also outcompete the resident microbiota. By providing the probiotic organism with a niche opportunity in the form of a selectively fermentable prebiotic, the strain is given a competitive advantage. Thus, its competitive fitness can be significantly increased and its persistence enhanced (Kolida & Gibson 2011). This approach is consistent with invasion ecology theory, whereby an invading species is successful when it can exploit novel resources or outcompete commensals for those resources for successful colonization and establishment (Catford et al. 2009, Costello et al. 2012, Walter et al. 2018).

This theoretical scenario has recently been demonstrated in a human probiotic feeding trial (Maldonado-Gómez et al. 2016). In this study, metagenomic analyses revealed that an autochthonous strain of *Bifidobacterium longum* subsp. *longum* could colonize subjects only if genes

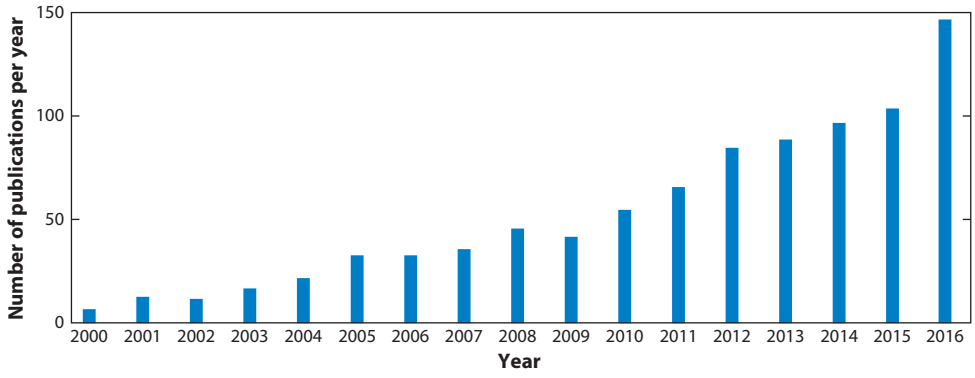

Figure 1

Number of publications on the topic of synbiotics over the past 15 years.

that encoded for enzymes involved in the degradation of specific complex carbohydrates were absent. This study showed that even for autochthonous bacteria that possess the ecological traits to be successful in the gut, resources are essential for successful colonization, which is in accordance with ecological theory (Mallon et al. 2015, Walter et al. 2018). For synbiotic applications, this would suggest that a supply of resources may relax competition (at least temporarily) and provide the new species with an advantage sufficient to overcome the colonization challenge (Mallon et al. 2015, Walter et al. 2018).

SYNBIOTICS IN PRACTICE

Although there are many publications on synbiotics (more than 140 were published in 2016 alone) (**Figure 1**), our literature search revealed little evidence for synergism between pro- and prebiotics used in human studies (**Table 1**). Most of these studies included lactobacilli and bifidobacteria as the probiotic component and inulin, various oligosaccharides, or dietary fibers as the prebiotic component (Shukla et al. 2011). Although several studies provided evidence for synergism in animals, only one study in human subjects provided such evidence (**Table 1**).

There are a variety of reasons why synergism between a pro- and a prebiotic is rarely observed in vivo. Most importantly, most synbiotics used in research to date have not been rationally designed and have instead been formulated on rather arbitrary criteria, such as shelf life, availability, cost, industrial performance, or other marketing considerations (Crittenden et al. 2006, Govender et al. 2014). Therefore, in many cases, probiotic strains were used that may not have utilized the respective prebiotic. Even when in vitro or in situ screenings of synbiotic combinations are applied, these techniques do not account for the ecological factors that will affect the probiotic strain in vivo nor how other autochthonous members of the gut microbiota may compete with the probiotic strain for the prebiotic substrate (Davis et al. 2011, Sonnenburg et al. 2010, Ventura et al. 2009). It can be challenging to identify a prebiotic that will specifically and selectively enhance the probiotic strain of interest. New strategies to develop synergistic synbiotic combinations now include in vivo selection of synbiotic combinations (Krumbeck et al. 2015) or multitaxon insertion sequencing (Wu et al. 2015). The latter uses a transposon library to identify genes encoding for fitness determinants based on the relative abundance of a gene's multitaxon insertion sequencing reads in the output community compared with the input library. This method allows identification of key fitness features of gut bacterial strains and gene-level characterization of responses to prebiotics and other dietary interventions.

Table 1 Synergistic synbiotics reported in the literature

Reference(s)	Probiotic component	Prebiotic component	Subjects	Increase in probiotic abundance	*P* value	Outcome
Tanaka et al. 1983	*Bifidobacterium breve* 4006	Transgalactosylated oligosaccharide	Healthy adults	Probiotic: 9–10.2 log/g feces Synbiotic: 10–10.5 log/g feces[a]	0.05	Not measured
Wang et al. 1999	*Bifidobacterium* Lafti^{TM} 8B	Amylomaize	BALB/c mice	Probiotic: 4.3% recovery rate Synbiotic: 27.92% recovery rate in feces	0.05	Not measured
Femia et al. 2002	*Lactobacillus rhamnosus* LGG® + *Bifidobacterium lactis* Bb12	Oligofructose-enriched inulin	Male F344 rats	LGG®: Probiotic: $4.8 \pm 3.4 \times 10^5$ Synbiotic: $21.1 \pm 18 \times 10^5$ CFU/g feces Bb12: Probiotic: $6.1 \pm 8.1 \times 10^5$ Synbiotic: $8.4 \pm 12 \times 10^5$ CFU/g feces	Not given	Antitumoric activity in azoxymethane-induced cancer
Ogawa et al. 2005, 2006	*Lactobacillus casei* subsp. *casei* JCM 1134^{TM}	Dextran	BALB/c mice	Probiotic: 1×10^4 CFU/mg feces Synbiotic: 1.4×10^6 CFU/mg feces[a]	0.01	Significantly elevated NK cell activity in spleen mononuclear cells
Krumbeck et al. 2015	*Bifidobacterium adolescentis* IVS-1	Galactooligosaccharide	Male Sprague–Dawley rats	Probiotic: 7.9 ± 0.1 log10 cells/g colon content Synbiotic: 9.47 ± 0.2 log10 cells/g colon content	0.0001	None

[a]Absolute microbial numbers are not given in the original publication and have been estimated by the author through careful evaluation of graphs in the original publication.

Abbreviation: NK, natural killer.

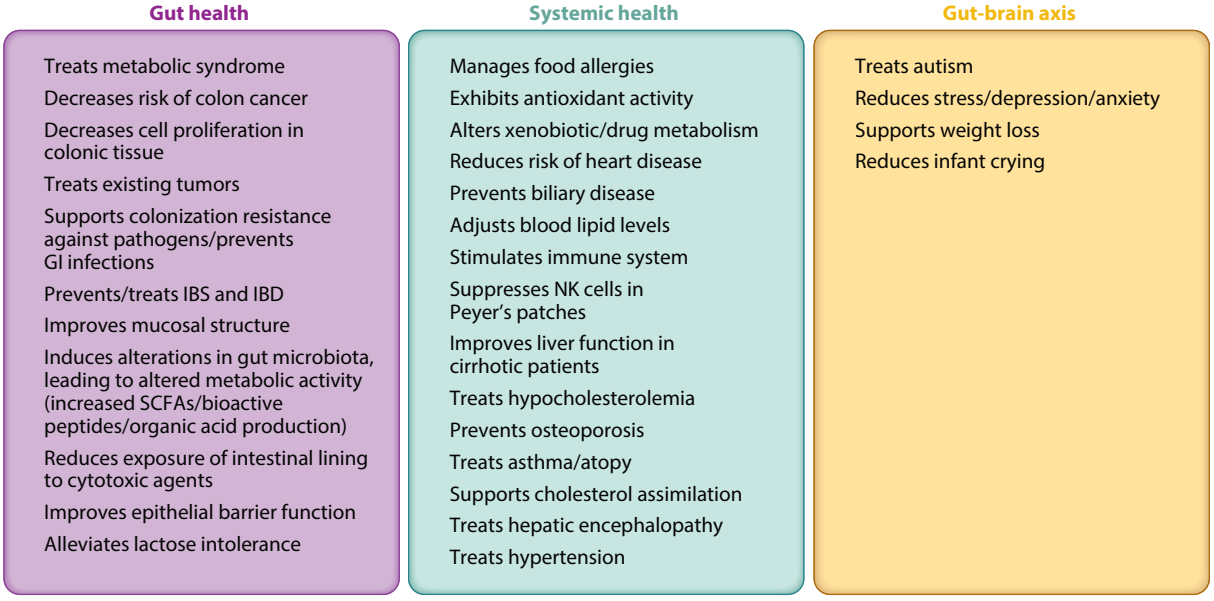

Figure 2

Health claims made for synbiotics in human populations. Abbreviations: GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NK, natural killer; SCFAs, short-chain fatty acids.

SYNBIOTICS AND THEIR OUTCOMES ON HUMAN HEALTH IN CLINICAL STUDIES

The reported literature on synbiotics includes a wide range of studies with varying subject groups. Research subjects have included humans of all ages as well as companion animals (mainly dogs and cats) and food production animals such as chickens, cows, pigs, cattle, rabbits, and fish (Abdel-Raheem et al. 2012, Awad et al. 2008, Bengmark 2012, Cerezuela et al. 2011, Hart et al. 2012, Hasunuma et al. 2011, Gagné et al. 2013, Mugambi et al. 2012, Sopková et al. 2017). Rodent animal models have also been widely used (Asahara et al. 2016, Bindels et al. 2015b, Krumbeck et al. 2015, Simeoli et al. 2015). In this review, we focus on human clinical studies and the health claims made for synbiotic combinations to improve human health. It is important to note that despite the many health claims made for synbiotic combinations in the literature and the commercial market (**Figure 2**), no claims have been approved by regulatory agencies in the United States or Europe. Nevertheless, several meta-analyses and systematic reviews suggest that synbiotic treatments may provide beneficial health effects (**Tables 2** and **3**).

There are several challenges involved in evaluating synbiotic clinical studies. As with other studies on pro- or prebiotics, doses, durations of treatment, targeted populations, and measured treatment effects are often different, and all can affect measured treatment outcomes. Even the funding source has been suggested to influence outcomes (Mugambi et al. 2013). There are, however, considerations unique to synbiotics. In particular, few synbiotic trials consider each synbiotic component independently; thus, it is not possible to establish whether improvement of a clinical end point in the synbiotic treatment group was indeed more beneficial than the pro- or prebiotic treatment alone (**Table 4**). Therefore, the synbiotic concept cannot be validated in such cases. Another experimental challenge is to show whether the test strain has become established

Table 2 Overview of published meta-analyses of synbiotic treatments[a]

Reference	Disease phenotype	Number of trials/subjects	*P* value	Type of synbiotic	Subjects	Outcome
Shukla et al. 2011	HE	1 trial ($n = 55$)	0.004	Probiotic: PP, LM, LPSP, LP2 Prebiotic: BG, I, P, RS	HE patients	Synbiotic use reduced the risk of no improvement of minimal HE
		1 trial ($n = 60$)		Probiotic: BL Prebiotic: FOS, vitamins B1, B2, B6, B12		
Ford et al. 2014	IBS, chronic idiopathic constipation	2 trials ($n = 198$)	0.09	Probiotic: BL, BB, LR, LA, LB, ST, LC Prebiotic: FOS	IBS patients	No reduced symptoms
		2 trials ($n = 160$)	0.003	Probiotic: BL2, LP, LR, LA Prebiotic: FOS		Beneficial for treatment of chronic idiopathic constipation
Kinross et al. 2013	Clinical outcome after elective surgery	8 trials ($n = 361$)	0.002	Probiotic: LC, LP2, LP, LM, LA, LB, BL2, ST, PP, BB, EF, CB, BM, LS, BB2, LL Prebiotic: OAF, OF, BG, I, P, RS, GOS	Patients undergoing elective surgery	Incidence of postoperative sepsis was reduced by synbiotics
		4 trials ($n = 135$)	0.03	Probiotic: PP, LM, LP2 Prebiotic: BG, I, P, RS		Synbiotics reduced the length of postoperative antibiotic use
		2 or 3 trials each ($n = 198$–260)	>0.05	Probiotic: LC, LP2, LP, LM, LA, LB, BL2, ST, PP, BB, EF, CB, BM, LS, BB2, LL Prebiotic: OAF, OF, BG, I, P, RS, GOS		No significant changes observed for prevention of pneumonia, wound infection, urinary tract infection, mortality, and length of hospital stay
Beserra et al. 2015	Glycemia, insulin concentrations, lipid parameters	2 trials ($n = 364$)	0.04	Probiotic: BL, LC, LR, ST, BB, LA, LB Prebiotic: FOS	Adults with overweight or obesity	Reduced plasma fasting insulin concentrations
		3 trials ($n = 260$)	<0.05	Probtiotic: LS2, BL, LA, BB Prebiotic: I, FOS		Reduced plasma triglyceride concentrations
		2, 3, or 4 trials each ($n = 49$–104)	Not given	Probiotics: LC, LR, ST, BB, LA, BL, LB, LS2 Prebiotic: I, FOS		No significant changes observed for total cholesterol, LDL-c, HDL-c, and fasting glucose

(*Continued*)

Table 2 (*Continued*)

Reference	Disease phenotype	Number of trials/subjects	*P* value	Type of synbiotic	Subjects	Outcome
Mugambi et al. 2012	Growth, stool frequency	2 trials ($n = 227$)	0.29	Probiotic: BL, LR, LP Prebiotic: GOS, scFOS	Infants	Synbiotics failed to improve growth rate but significantly improved stool frequency
		2 trials ($n = 122$)	0.006	Probiotic: BL Prebiotic: GOS, FOS		
Chang et al. 2016	AD	6 trials ($n = 369$)	0.03	Probiotic: LR, BL2, LA, BB, LC, ST, BI, LB, LS Prebiotic: FOS, lcFOS, GOS, scGOS, starch	Children	Synbiotics support the treatment of atopic dermatitis, particularly when mixed strains of bacteria are used
			0.048			Synbiotics support the treatment of atopic dermatitis in children >1 year
		2 trials ($n = 1,320$)	0.26	Probiotic: BL, BB, LR, PF Prebiotic: GOS, scFOS		Synbiotics do not support prevention of AD
Sawas et al. 2015	Prevention of infections after liver transplant	4 trials ($n = 246$)	<0.001	Probiotic: BB, BL2, LP2, PP, LPSP, LM, LA, LC, LR, LB2 Prebiotic: GOS, fiber	Adult patients receiving a liver transplant	Synbiotics reduced infection rate of urinary tract and intra-abdominal infections as well as length of hospital stay and duration of antibiotic use
Manzanares et al. 2016	Clinical outcomes (barrier function, pancreatitis, multiple organ failure), in burn patients	4 trials ($n = 302$)	0.36	Probiotic: PP, LM, LPSP, LP2, LA, BL2, LB, ST Prebiotic: OF	Critically ill adult patients (≥18 years)	Subanalysis on synbiotics showed no effect on infections
Wu et al. 2017	Clinical outcomes in surgical patients	11 trials ($n = 918$)	0.005	Probiotic: BB, LC, PP, LM, LP, LP2, LA, LB, BL2, ST, LPSP Prebiotic: RS, P, BG, GOS, I	Adults (≥18 years)	Subanalysis on synbiotics showed beneficial effects on site infections

(*Continued*)

Table 2 (*Continued*)

Reference	Disease phenotype	Number of trials/subjects	*P* value	Type of synbiotic	Subjects	Outcome
Chowdhury et al. 2014	Perioperative effect for elective abdominal surgery	18 trials ($n = 603$)	0.003	Abstract for oral presentation, thus none given	Patients undergoing abdominal surgery	Postoperative infectious complications reduced by synbiotics; no effect on mortality or noninfectious complications
Nikbakht et al. 2017	Improvement of high fasting blood glucose	4 trials ($n = 206$)	0.15	Probiotic: LC, LR, ST, BB, LA, BL, LB, LS2 Prebiotic: FOS, I	Adults (≥18 years)	Subanalysis on synbiotics showed no significant improvement
Kasatpibal et al. 2017	Reduction of postoperative complications	31 trials ($n = 2,952$)	Not given	Not specified	Adult patients undergoing surgery	Synbiotics reduced surgical site infections, sepsis, length of hospital stay, and duration of antibiotic treatment better than pro- or prebiotics alone; no effect on mortality
Yang et al. 2016	Prevention of infections after GI surgery	16 trials ($n = 1,370$)	Not given	Probiotic: LC, ST, BB, LA, BL2, LB, LP2, PP, LM, LP, LS2, BM, CB Prebiotic: FOS, GOS, OAF, OF, BG, I, P, RS	Patients undergoing GI surgery	Subgroup analysis of synbiotic trials showed no health benefits due to synbiotics

[a]Adapted and updated from Krumbeck et al. (2016). Abbreviations: AD, atopic dermatitis; GI, gastrointestinal; HE, hepatic encephalopathy; IBS, irritable bowel syndrome.
Probiotic types: BB, *Bifidobacterium breve*; BB2, *Bifidobacterium bifidum*; BI, *Bifidobacterium infantis*; BL, *Bifidobacterium longum*; BL2, *Bifidobacterium lactis*; BM, *Bacillus mesentericus*; CB, *Clostridium butyricum*; EF, *Enterococcus faecium*; LA, *Lactobacillus acidophilus*; LA2, *Lactobacillus affinolactis*; LB, *Lactobacillus bulgaricus*; LB2, *Lactobacillus brevis*; LC, *Lactobacillus casei*; LL, *Lactococcus lactis*; LM, *Leuconostoc mesenteroides*; LP, *Lactobacillus paracasei*; LP2, *Lactobacillus plantarum*; LPSP, *Lactobacillus paracasei* subsp. *paracasei*; LR, *Lactobacillus rhamnosus*; LS, *Lactobacillus salivarius*; LS2, *Lactobacillus sporogenes*; PF, *Propionibacterium freudenreichii*; PP, *Pediococcus pentosaceus*; ST, *Streptococcus thermophilus*.
Prebiotic types: BG, β-glucan; FOS, fructooligosaccharide; GOS, galactooligosaccharide; I, inulin; lc, long-chain; OAF, oat fiber; OF, oligofructose; P, pectin; RS, resistant starch; sc, short-chain.

Table 3 Overview of systematic reviews of synbiotic treatments

Reference(s)	Disease phenotype	Number of trials/subjects	*P* value	Type of synbiotic	Subject	Outcome
Ghouri et al. 2014, Saez-Lara et al. 2015	UC maintenance	1 trial ($n = 120$)	0.03	Probiotic: BL Prebiotic: Psyllium	Patients with UC	IBDQ score: improved quality of life
	UC induction and maintenance	1 trial ($n = 41$)	0.05	Probiotic: BB Prebiotic: GOS		Improvement of endoscopic grading compared to standard therapy group
	UC induction	1 trial ($n = 18$)[a,b]	0.06	Probiotic: BL Prebiotic: Synergy I (I + OF mix)		Sigmoidoscopy score not improved
			0.05			Inflammatory markers improved
	Management of CD	1 trial ($n = 35$)	0.02	Probiotic: BL Prebiotic: Synergy I (I + OF mix),	Patients with CD	Improved clinical response compared to placebo
		1 trial ($n = 24$)[a]	>0.05	Synbiotic 2000 Probiotic: LA2, PP, LP2, LPSP Prebiotic: BG, I, P, RS		No improvement in endoscopic, clinical, and laboratory parameters
Saez-Lara et al. 2015	UC	1 trial ($n = 10$)	Not given	Synbiotic therapy: Probiotic: BB, BL, LC Prebiotic: psyllium	Patients with active CD	Synbiotic is safe and effective
Fernandes et al. 2016	Inflammatory markers in adult patients with overweight or obesity	4 trials ($n = 234$)	Not given	Probiotic: LS2, LC, LR, ST, BL, LB Prebiotic: I, FOS	Overweight or obese patients	Some synbiotics and prebiotics may have immunomodulatory effects

[a]Also discussed in Hedin et al. (2007).
[b]Also discussed in Zigra et al. (2007).
Abbreviations: CD, Crohn's disease; IBDQ, inflammatory bowel disease questionnaire; UC, ulcerative colitis.
Probiotic types: BB, *Bifidobacterium breve*; BL, *Bifidobacterium longum*; LA2, *Lactobacillus affinolactis*; LB, *Lactobacillus bulgaricus*, LC, *Lactobacillus casei*, LP2, *Lactobacillus plantarum*; LPSP, *Lactobacillus paracasei* subsp. *paracasei*; LR, *Lactobacillus rhamnosus*, LS2, *Lactobacillus sporogenes*; PP, *Pediococcus pentosaceus*; ST, *Streptococcus thermophilus*.
Prebiotic types: BG, β-glucan; FOS, fructooligosaccharide; GOS, galactooligosaccharide; I, inulin; P, pectin; OF, oligofructose; RS, resistant starch.

in the GI tract. Most importantly, strain-specific approaches, which are essential to demonstrate that the test strain was indeed present, have not been reported.

As noted above, the effectiveness of synbiotic treatments on a range of disease phenotypes has been summarized by both meta-analyses and systematic reviews. In general, however, these reports are constrained by the small number of studies and disparate composition of the treatments. In the sections below, recent human trials that applied synbiotics to treat specific clinical disorders are reviewed individually. These include trials on metabolic syndrome, IBD, diarrhea, colon cancer,

Table 4 Overview of meta-analyses of synbiotic treatments that combine pro- and synbiotic trials into single analyses

Reference	Disease phenotype	Outcome
Pitsouni et al. 2009	Patients undergoing abdominal surgery	Pro/synbiotic treatment may reduce postoperative infections after abdominal surgery
Rossi et al. 2012	Patients with chronic kidney disease	Limited but supportive evidence for the effectiveness of pre- and probiotics in reducing uremic toxins. No conclusion about synbiotics
Zhang et al. 2010	Patients with acute pancreatitis	Pre-, pro-, or synbiotic treatment shows no statistically significant benefit. Safety and efficacy: Use pre-, pro-, or synbiotics with caution in critically ill patients and patients with severe acute pancreatitis
Watkinson et al. 2007	Patients admitted to adult intensive care units	There is currently a lack of evidence to support the use of pre-, pro-, or synbiotics
He et al. 2013	Patients undergoing colorectal resection for cancer	Pro/synbiotic administration has a positive effect on the incidence of diarrhea ($P = 0.001$), symptomatic intestinal obstructions ($P = 0.008$), operative total infections ($P = 0.0010$), and pneumonia infection ($P = 0.04$)
		Pro/synbiotics administration increases numbers of *Lactobacillus* ($P < 0.00001$) and decreases the counts of Enterobacteriaceae
Dang et al. 2013	Prevention of eczema	Pro/synbiotics may reduce incidence of infant eczema. Prebiotics alone have no effect
Lytvyn et al. 2015	Prevention of postoperative infections following abdominal surgery in adults	Pro/synbiotics reduce the risk of surgical site infections compared to placebo or standard of care and have potential benefits for urinary tract infections with no increased risk of adverse events. No occurrence of serious adverse events reported as related to study product
Petrof et al. 2012	Critically ill patients, including burn, multiple trauma, pancreatic, diarrhea, general intensive care unit	Clinical trials suggest that probiotics may reduce overall infection rates in critically ill patients
Chen et al. 2016	Prevention of postoperative infections following colorectal surgery in adults	Perioperative pro/synbiotics administration is associated with a significant reduction in total postoperative infectious complications ($P < 0.00001$), pneumonia ($P = 0.003$), wound infection ($P = 0.005$), and length of hospital stay ($P = 0.009$). No significant differences in the incidence of intra-abdominal abscess or urinary infection
Arumugam et al. 2016	Decrease of postoperative sepsis in gastrointestinal surgical patients	Pro/synbiotics significantly reduced risk of postoperative sepsis by 38% ($P < 0.0001$)

IBS, and kidney and liver diseases. Only randomized and placebo-controlled trials (RCTs) using clearly described products are discussed.

Metabolic Syndrome

Metabolic syndrome refers to metabolic aberrancies strongly associated with obesity that collectively contribute to the risk of coronary heart disease and type II diabetes (Cornier et al. 2008). Risk factors include central obesity, impaired glucose tolerance, dyslipidemia, and hypertension (Andersen & Fernandez 2013, Van Vliet-Ostaptchouk et al. 2014). Several synbiotic formulations have been used in clinical trials to assess improvement of metabolic syndrome. Eslamparast et al.

(2014) conducted a double-blind RCT analyzing the effect of FOSs (250 mg) and a probiotic cocktail (Protexin®) of seven different strains (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *B. longum*, and *Lactobacillus bulgaricus*) on 38 subjects suffering from metabolic syndrome. Subjects were instructed to consume the supplement or placebo (maltodextrin) twice daily for 28 weeks. They were also instructed to follow strict dietary recommendations, lower energy intake, and increase physical activity. At the end of the study, individuals in the synbiotic treatment group had improved levels of insulin resistance, fasting blood sugar, triacylglycerides, and serum HDLs compared to the placebo treatment group. No difference was observed in body mass index, low-density lipoprotein (LDL) levels, anthropometric parameters, and energy intake/expenditure. The authors concluded that synbiotic treatment can increase the efficacy of a dietary therapy in the management of metabolic syndrome and insulin resistance. However, an analysis of the gut microbiota was not included, and based on the study design, it was not possible to confirm that the synbiotic treatment was more effective than the pro- or prebiotic treatment alone.

A similar synbiotic cocktail was tested for its potential ability to support a weight-loss regime (Rabiei et al. 2015). Forty-six patients with metabolic syndrome consumed the synbiotic or placebo (maltodextrin) twice a day for 12 weeks. All patients experienced significant weight loss, and the synbiotic treatment reduced systolic blood pressure ($P < 0.05$). However, 90% of the subjects in the synbiotic group used medication to reduce blood pressure compared to 75% in the placebo group before and throughout the duration of the study. The fecal microbiota was not examined, and the nature of the study design precludes any conclusions about the efficacy of the pre- or probiotic strains.

The combination of FOSs (3 g) with *Lactobacillus plantarum*, *Lactobacillus delbrueckii*, *L. acidophilus*, *L. rhamnosus*, and *Bifidobacterium bifidum* (2×10^8 CFU total) was assessed in an open-label RCT. The treatment was provided twice daily for six months to subjects suffering from nonalcoholic steatohepatitis (Wong et al. 2013). Reductions in intrahepatic triglyceride ($P = 0.034$) and serum aspartate aminotransferase ($P = 0.008$) levels were observed in the synbiotic treatment group compared to the standard treatment group ($n = 10$, for each). Again, no assessment of microbiota was reported.

In healthy adults, the combination of FOSs (10 g) and *Lactobacillus salivarius* (2×10^9 CFU) significantly reduced total cholesterol, LDL cholesterol, and the concentrations of CRP, IL-6, and TNF-α compared to the placebo and probiotic-only groups. Further, serum inflammatory markers and triglycerides were decreased and HDL cholesterol was increased compared to a placebo after six weeks of treatment ($P < 0.05$) (Rajkumar et al. 2015). Selective plating was used to compare the number of *Lactobacillus* in fecal samples among all three groups. The pro- and synbiotic treatments significantly increased the number of *Lactobacillus* compared to the placebo, but there was no significant difference between the pro- and synbiotic treatments.

A double-blind, parallel-design RCT of 20 healthy subjects found that the synbiotic treatment of FOSs (10 g) and Ecologic® 825 (1.5×10^{10} CFU) led to significantly more stools, but no differences in intestinal barrier function (measured by urinary sugar recoveries and ratios; plasma levels of zonulin, cytokines, and chemokines; and GI symptom scores) were seen compared to the control group after two weeks of treatment (Wilms et al. 2016). Ecologic® 825 comprises *L. acidophilus*, *L. casei*, *Lactobacillus paracasei*, *L. plantarum*, *L. salivarius*, *Lactococcus lactis*, *B. bifidum*, and two strains of *Bifidobacterium lactis*.

Inflammatory Bowel Disease

UC and Crohn's disease (CD), the two types of IBD, are chronic inflammatory pathologies of the GI tract. Both conditions occur in individuals who are genetically susceptible and exposed

to unknown environmental risk factors (Haller et al. 2010). Although the etiology of IBD has been extensively studied, the disease pathogenesis is not fully known (Goyal et al. 2014). The characteristics of the inflammation are different in CD and UC, with CD occurring throughout the GI tract, typically involving the distal small intestine and colon with transmural inflammation and occasionally associated with granulomas. In contrast, UC inflammation is usually confined to the mucosa of the colon (Ardizzone & Bianchi Porro 2005, Molodecky et al. 2012). Both UC and CD are characterized by a relapsing and remitting course leading to a very significant reduction in quality of life during the disease (Mahida & Rolfe 2004).

Several synbiotic formulations have been used in clinical studies to treat IBD. A combination of 6 g of inulin/oligofructose (Synergy 1®) and 2×10^{11} CFU of *B. longum* was administered to UC patients (Furrie et al. 2005). The test strain had been isolated from a healthy human subject and assessed for its aerotolerance, acid tolerance, resistance to bile salt, and adherence to epithelial cells. Its ability to use the prebiotic substrate as an energy source was also established in vitro. The organism was further shown to alter the cytokine expression in an HT29 epithelial cell line and reduce proinflammatory cytokine levels in vitro. For the clinical study, 18 patients were divided into synbiotic and placebo groups, each receiving the respective treatments twice daily for 4 weeks. The synbiotic treatment led to reduced inflammation and regeneration of epithelial tissue compared to the placebo group, reduced mRNA levels of human β-defensins, and lowered levels of TNF-α and IL-1α. Although survival of the probiotic strain was not measured in a strain-specific manner, bifidobacteria-specific rRNA levels increased 42-fold in the synbiotic group compared to approximately fivefold in the placebo group. This study, however, did not investigate the effects of the probiotic independently.

Another clinical trial used a synbiotic comprising psyllium (8 g) and a *B. longum* strain (2×10^9 CFU) (Fujimori et al. 2009). Although psyllium is not ordinarily considered a prebiotic, it has prebiotic status in Japan (Tanaka et al. 2004). Subjects ($n = 120$) were UC outpatients. This trial included probiotic- and prebiotic-only treatment groups in the study design. Although most measured blood markers showed no differences among the three treatments, C-reactive protein was significantly decreased ($P = 0.04$) and total protein levels increased ($P = 0.03$) in blood samples from the synbiotic group. Hemoglobin and hematocrit increased only in the probiotic group ($P = 0.04$). Total IBD questionnaire scores showed significant improvement only in the synbiotic group. Based on these quality-of-life questionnaires, the investigators concluded that the synbiotic treatment led to a greater quality of life than the pre- or probiotic treatments alone. However, mechanisms responsible for this improvement and survival rates for the probiotic were not determined.

In another clinical study, the effect of a synbiotic containing GOSs (5 g) and *B. breve* (1×10^9 CFU) on subjects with mild to moderate UC was assessed (Ishikawa et al. 2011). Forty-one patients were treated with either a placebo or the synbiotic for one year. End points included endoscopic scores and myeloperoxidase levels in lavage solutions; both were significantly lower in the synbiotic-treated group. An analysis of the fecal microbiota by plate counting was also performed for subjects in the synbiotic group before and after the treatment. Of all assessed microbes, only Bacteroidaceae were significantly decreased after the synbiotic treatment. The abundance of *Bifidobacterium* remained the same, and *B. breve* was only detected (5.75 ± 1.65 $\log_{10}$ CFU/g feces) by culturing after the treatment. Therefore, it can be concluded that *B. breve* survived passage through the GI tract. Whether or not the applied prebiotic was supporting the probiotic could not be determined from this study. Interestingly, no bifidogenic effect was observed due to GOS treatment. This is contrary to results previously reported (Akiyama et al. 2015, Azcarate-Peril et al. 2017, Davis et al. 2010).

In a double-blind RCT, patients with CD who continued using their conventional CD medication showed improvements when given a combination of Synergy 1® (6 g) and 2×10^{11} CFU

B. longum (Steed et al. 2010). Compared to a placebo, the synbiotic reduced TNF-α gene expression ($P = 0.041$), disease activity indexes ($P = 0.02$), and histological scores ($P = 0.018$) after six months of treatment. The microbiota of tissue biopsies was analyzed in both a species- and a genus-specific manner. Interestingly, 8 of 13 patients in the synbiotic group had increased numbers of *B. longum* and bifidobacteria after three months compared to the baseline, and this increased to 11 patients after six months. The nature of this responder/nonresponder phenomenon was not addressed in the study.

Chermesh et al. (2007) investigated the potential of Synbiotic 2000® to prevent postoperative recurrence of CD. This formulation contained *Pediococcus pentoseceus*, *Lactococcus raffinolactis*, *L. paracasei* subsp. *paracasei*, and *L. plantarum* (each at 1×10^{10} CFU) and 2.5 g each of β-glucan, inulin, pectin, and resistant starch. The frequency of the treatment was not stated. The synbiotic had no effect on endoscopic or clinical relapse or the postoperative occurrence of CD compared to the placebo. However, it significantly improved weight gain and normalization of hemoglobin levels by the three-month follow-up. No analysis of the gut microbiota was done.

Diarrhea

Diarrheal diseases are often caused by infectious agents, resulting in loose or liquid bowel movements with increased frequency, water content, and volume. Worldwide, diarrhea is the leading cause of hospitalizations, morbidity, and mortality (Dinleyici et al. 2013). A multistrain mixture of *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* was combined with FOSs (626 mg) as a synbiotic and was tested in children with acute diarrhea (Dinleyici et al. 2013). Treatment with oral rehydration salts (ORSs) and intravenous therapy was also provided. Compared to a control group (receiving only ORSs and/or intravenous therapy), the synbiotic shortened the duration of diarrhea ($P < 0.0001$) and the hospital stay ($P = 0.002$). The gut microbiota of these children was not analyzed.

In a similar study, children with acute rotavirus diarrhea were treated with species of *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* (1×10^9 CFU total) and FOSs (990 mg) (Dewi et al. 2015). Standard fluid therapy and nutritional support were provided. Thirty-five children were enrolled in the synbiotic group and compared to a placebo group. The duration of diarrhea was significantly shorter in the synbiotic group ($P < 0.0001$), and for half of the patients receiving a synbiotic treatment, intestinal mucosal healing was reported 50 hours after administration. The gut microbiota was not analyzed. No further descriptions were given to explain why half of the group responded to the treatment.

An arabinogalactan (500 mg) and xylooligosaccharide (700 mg) mixture was used to formulate a synbiotic that also included *L. paracasei* B21060 (2.5×10^9 CFU). Subjects included 55 children with acute diarrhea, who received ORS treatment. The synbiotic group showed a higher resolution rate ($P = 0.005$) than the placebo group after the first 72 hours (Passariello et al. 2012). This study allowed for additional treatments (e.g., diosmectite, domperidone, or racecadotril) given by the parents after the first 72 hours, which may have influenced the total duration of diarrhea. No analysis of the fecal microbiota was performed.

A combination of *S. thermophilus*, *L. bulgaricus*, *Bifidobacterium animalis* subsp. *lactis*, and inulin (1 g) was assessed for its potential to prevent diarrhea, vomiting, and various infections in children (Ringel-Kulka et al. 2015). After 16 weeks of treatment, synbiotic-treated children had significantly fewer days of fever but significantly more days with watery stools ($P < 0.05$). In this RCT, no analysis of the microbiota or assessment of the effect of the individual components was performed.

GI symptoms, such as diarrhea, are frequently reported among HIV and AIDS patients. da Silveira et al. (2017) tested the efficacy of FOSs (6 g) and a mixture of *L. paracasei*, *L. rhamnosus*, *L. acidophilus*, and *B. lacti*s compared to a maltodextrin placebo. Patients ($n = 64$) consumed

treatments twice daily for 6 months together with a personalized eating plan. Both the synbiotic and placebo groups had a significant reduction of diarrhea and were not significantly different from one another. An analysis of the gut microbiota was not conducted, and no specific explanation was given as to why this synbiotic combination was selected.

Irritable Bowel Syndrome

IBS is an intestinal disorder characterized by abdominal pain, bloating, diarrhea, constipation, or alternating periods of these symptoms. The cause of this illness has not been established, but visceral hypersensitivity, genetics, the gut microbiota, constant low-grade inflammation, and environment are contributing factors (Ford et al. 2014). Approximately 11% of the world's population may be affected by IBS, with higher occurrences among women and younger individuals (Canavan et al. 2014, Endo et al. 2015). Physiological interventions, dietary manipulations, pharmacologic agents, and modulation of the gut microbiota are part of current treatments for IBS (Gibson et al. 2015).

A recent study examined the effect of *L. acidophilus* (1.8×10^7 CFU/g), *B. animalis* subsp. *lactis* Bb-12 (2.5×10^7 CFU/g), and Beneo dietary fibers (2%) on the quality of life and IBS symptoms of 76 constipation-predominant IBS patients (Šmid et al. 2016). The synbiotic was delivered twice daily in 180 g of fermented milk for 4 weeks. Several markers of IBS improved after four weeks, but there was no difference between the synbiotic and the placebo (fermented milk) groups.

An RCT assessed the effect of *L. acidophilus*, *B. animalis* subsp. *lactis*, *S. thermophilus*, and dietary fiber (90% inulin, 10% oligofructose) in fermented milk on the gut microbiota of 30 adults suffering from IBS (Matijašić et al. 2016). According to real-time polymerase chain reaction and relative afferent pupillary defect analyses of fecal samples, the presence of all three treatment bacteria was confirmed in the synbiotic group and decreased at the one-week follow-up. There was no significant difference detected in the abundance of the test bacteria within the synbiotic treatment group; strains were not detected in the control group. The effect of the synbiotic treatment on IBS symptoms was not assessed in this study. Finally, Cudmore et al. (2017) showed that a synbiotic containing psyllium fiber, inulin, *L. rhamnosus*, *B. bifidum*, *L. acidophilus*, *L. plantarum*, and *L. bulgaricus* significantly reduced the use of laxatives after a four-week treatment in adults with chronic constipation.

Colon Cancer

Colorectal cancer is the third-most common form of cancer. In addition to genetic factors, environmental factors such as radiation, chemical carcinogens, and diet contribute to tumorigenesis in the colon (Willett 2000). Current treatments are associated with a high risk of complications and low success rate. Investigators have suggested that by maintaining a healthy weight, diet, and physical activity, up to one-third of colon cancers may be prevented (Raman et al. 2013). Numerous pro-, pre-, and synbiotic studies using rodent models suggest that these treatments may have preventive and therapeutic properties.

Rafter et al. (2007) and Roller et al. (2007) assessed a combination of *L. rhamnosus* GG (LGG®), *B. lactis* Bb12, and Synergy 1® on colon cancer and polypectomized patients in two similar phase II anticancer studies. The synbiotic treatment was compared to a placebo in a 12-week trial. Fecal water obtained from the cancer patients did not improve barrier function in Caco-2 cells and increased production of interferon-γ. For polypectomized patients, several benefits were observed among the synbiotic group, including decreased DNA damage in colonic mucosa, reduced proliferation, and decreased secretion of IL-2. The investigators also assessed survival of each of the

probiotic strains in an independent study with healthy human subjects who consumed rifampicin-resistant mutants of each strain (Rafter et al. 2007). After consumption of the probiotics, both strains were isolated from feces by plating. For the study patients, a fecal analysis was performed not at the strain level but at the genus level. The number of *Lactobacillus* and *Bifidobacterium* consistently increased in the synbiotic group for both cancer and polypectomized patients over the 12-week trial, whereas *Clostridium* numbers decreased. As a probiotic-only treatment was not applied, a synergy between the probiotic strains and Synergy 1® could not be confirmed based on these data. Roller et al. (2007) did not analyze the fecal microbiota but referred to another study that reported that only 10% of the consumed amount of LGG® and Bb12 survived the GI tract in the same synbiotic treatment (Van Loo et al. 2005). Neither study analyzed the pro- and prebiotic components independently.

In a four-week crossover trial, the effect of the synbiotic combination of resistant starch (12.5 g) and *B. lactis* (5×10^9 CFU) on markers of early colorectal carcinogenesis was investigated in 20 healthy subjects (Worthley et al. 2009). Placebo, prebiotic-only, and probiotic-only arms were also included. Full analyses of the fecal microbiota were conducted using denaturing gradient gel electrophoresis and quantitative real-time polymerase chain reaction to assess levels of *B. lactis*. Results showed that the synbiotic treatment introduced significantly more changes to the gut microbiota than the placebo or the pro- or prebiotic treatments alone. However, levels of *B. lactis* in the probiotic and synbiotic treatment groups were not significantly different. No differences were detected for the SCFA profile, fecal ammonia or pH, serum inflammatory markers, or epithelial variables among the treatment groups.

Kidney and Liver Disease

Approximately 6–10% of adults suffer from varying degrees of chronic kidney disease (Jha et al. 2013), and the prevalence of NAFLD ranges between 6.3% and 33% (Charytoniuk et al. 2017). Both pro- and prebiotics have been suggested as possible therapies for these conditions (Koppe et al. 2015, Lambert et al. 2015, Vitetta & Gobe 2013). Recently, several synbiotic clinical trials for kidney and liver disease have been described. A synbiotic containing a nine-strain cocktail (bifidobacteria, lactobacilli, and streptococci) and a FOS/GOS mixture was given to chronic kidney disease patients (Rossi et al. 2016). Most of the measured biomarkers in this small study ($n = 31$) were unchanged by the treatment, although microbiota analyses revealed an increase in abundance of bifidobacteria and depletion of Ruminococcaceae. A combination of *B. longum* with FOSs was also used for treatment of liver disease (Malaguarnera et al. 2007, 2012). Although improvements in immune biomarkers and liver function were observed in both studies, the microbiota was not assessed and individual components were not included as controls.

The effect of a seven-strain mix containing species of *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* (2×10^8 CFU total) and FOSs (125 mg) was tested on 50 NAFLD patients (Mofidi et al. 2017). This RCT showed that the synbiotic group had a greater reduction of steatosis and fibrosis. Similarly, the same synbiotic cocktail improved the steatosis grade in an RCT involving 80 NAFLD patients but did not improve levels of alanine aminotransferase and aspartate transaminase compared to a placebo (Asgharian et al. 2016). The same cocktail plus vitamin E decreased the concentrations of liver transaminase and led to significant differences in total cholesterol and LDL cholesterol compared to the control groups (Ekhlasi et al. 2016).

Finally, there are several other published studies on synbiotics to treat the various diseases described above, but these are not included in this discussion due to their absence of suitable or appropriate controls (Andriulli et al. 2008, Basturk et al. 2016, Colecchia et al. 2006, Dughera et al. 2007, Fujimori et al. 2007, Rossi et al. 2015), very low patient numbers (Fernandes et al.

2016), or lack of evidence of effectiveness (Cruz-Mora et al. 2014, García-Menor et al. 2016, Virk et al. 2013).

COMMERCIAL SYNBIOTICS: OBSTACLES, CHALLENGES, AND FUTURE PROSPECTS

By 2018, the global market for probiotics is predicted to exceed $40 billion (Buriti et al. 2016), and the prebiotic market may soon reach $5 billion (Belorkar & Gupta 2016). Despite these market opportunities, however, several scientific and industrial barriers exist (Van den Nieuwboer et al. 2016). In particular, Van den Nieuwboer et al. (2016) suggested that the main barrier was the "difficulty in demonstrating clinical efficacy." This situation is complicated by the level of evidence required to support a health claim, which varies from country to country (Van Loveren et al. 2012). Currently, neither the EFSA nor the FDA has approved any health claim made for pro- or synbiotic combinations. Moreover, such products must be distinguished as either a pharmaceutical product or a food product (Govender et al. 2014). The FDA guidelines state that if any agent, including probiotics, is ingested for the purpose of curing, mitigating, treating, diagnosing, or preventing disease, it is classified as a drug and must undergo the same regulatory process as any new pharmaceutical. The European Union Nutrition and Health Claims regulations intend to (*a*) ensure that claims are "clear, accurate and based on scientific evidence" and (*b*) prohibit foods that bear "claims that could mislead consumers." Ultimately, high-quality human-intervention studies are necessary to support any health claims made for a product (Van Loveren et al. 2012).

Synbiotic products are commonly delivered to consumers in food form, including a range of cultured dairy and nondairy products. Although prebiotics can be used in most food applications, the environmental sensitivity of probiotics (and synbiotics) may limit their practical use in many nonrefrigerated foods (Saulnier 2008). However, new microencapsulation technologies that protect the bacteria against otherwise detrimental processing treatments could lead to a variety of new synbiotic products, including desserts, confections, juices, cheeses, or chocolate (Ahmadi et al. 2014, Angiolillo et al. 2014, Konar et al. 2016, Fratianni et al. 2014, Petreska-Ivanovska et al. 2014). Interestingly, many pre- and synbiotic products contain small amounts of the prebiotic component (on a per serving basis), which may be too low to induce a health effect. Low doses are used, in part, to avoid adverse GI complaints (De Vrese & Schrezenmeir 2008) but perhaps also for reasons of cost.

The development of clinically effective synbiotic combinations remains a challenging issue, and several requirements must be satisfied. As noted above, determining minimum effective doses of each component is usually expected. The inclusion of suitable controls for synbiotic trials is particularly challenging. Apart from standard placebo controls, probiotic-only and prebiotic-only controls may also be necessary to confirm additive or synergistic effects. The rationale for how the pro- and prebiotic were selected and combined should also be stated. Importantly, demonstrating causality requires specific detection, quantification, and enrichment of the test strain in the GI tract. Changes introduced to the gut microbiota should also be assessed to determine whether cross-feeding or other ecological events occurred, for example, niche competition, niche partitioning, or niche exclusion with the resident microbiota.

CONCLUDING REMARKS

Disturbances of the microbial composition in the GI tract have been associated with deterioration of host health and barrier, immune, and other functional activities. These developments may either be directly induced by the gut microbiota or via an altered metabolite synthesis (Jonkers

2016). Although the microbiota composition in the human GI tract is remarkably stable, it can be successfully modulated by certain synbiotic treatments. These treatments could offer considerable advantages to human health when selected on a rational basis that accounts for ecological and evolutionary considerations.

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