Probiotic Research and Clinical Benefits

Research highlights

- ✓ Probiotics are live microorganisms that provide health benefits to the host when ingested in adequate amounts
- ✓ Mechanisms underlying the effects of probiotics include supporting barrier function, competitive adherence to the mucosa and epithelium, antimicrobial activity, production of beneficial compounds, and modulation of the immune system to convey an advantage to the host
- ✓ Strain-specific probiotics have demonstrated significant potential as therapeutic options for the prevention and treatment of several indications, such as:
  - Reducing pain after colonoscopy
  - Reducing traveler's diarrhea
  - Decreasing pain during IBS
  - Decreasing duration of the common cold
- ✓ Appropriate strain and dose selection for specific clinical applications is critical for eliciting positive outcomes

Introduction

The body of probiotic research, as well as probiotic use, is growing. Data from the 2012 National Health Interview Survey (NHIS) show probiotics to be the third most commonly used dietary supplement other than vitamins and minerals, and the use of probiotics quadrupled between 2007 and 2012.[1] As public awareness of probiotics continues to expand, it is important for healthcare practitioners to increase their understanding of probiotic research and literacy surrounding probiotic definitions and use.[2] In 2013, the International Scientific Association for Probiotics and Prebiotics (ISAPP) updated the definition of probiotics to **"live microorganisms that, when administered in adequate amounts, confer a health benefit on the host."**[3] This definition is consistent with the World Health Organization (WHO) and Food and Agriculture Organization (FAO) definition[4] and helped to minimize confusion and bring clarity to researchers, consumers, industries, regulatory agencies, and healthcare professionals. For example, although fermented foods and commensal microorganisms in the gut may be sources for probiotic strains, until these strains have been clinically studied and adequately characterized for content, stability, and health effects at the sufficient amount, they cannot be called "probiotics."

Identification and safety

The ISAPP guidelines for defining probiotics provide a benchmark for the differentiation of probiotics based upon levels of scientific evidence for their efficacy.[3] The establishment of standards and guidelines represents a necessary first step in helping ensure that probiotic use is safe and effective—important for clinicians and patients alike.[5] For example, a report of the Joint FAO/WHO working group on probiotics in food set forth guidelines that probiotic strains be characterized at a minimum with a series of tests, including resistance to antibiotics, production of metabolites, production of toxins, hemolytic activity, side effects in human studies, and postmarket adverse events, with an additional recommendation to evaluate whether immunocompromised animals would be infected by the probiotic strain.[4] Further, the European Union assembled a panel to assess and substantiate methodologies to ensure the highest possible standards of products marketed as probiotics. These guidelines extended the FAO and WHO recommendations to include the stability of the strain through the gastrointestinal (GI) tract, resistance to technological processing, shelf life stability, and labeling direction.[6]

Probiotic consumption is considered safe, and complications are rare for most populations.[7] Epidemiologic evidence suggests no overall increase in population risk or adverse events in healthy individuals based on usage data.[8,9] However, some reports indicate probiotics should be avoided in certain at-risk populations.[10] Safety concerns include the following:

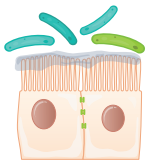
- Common side effects are typically transient but include gas and bloating
- The critically ill and those who are severely immunocompromised should avoid probiotics

Clinically studied doses for efficacy

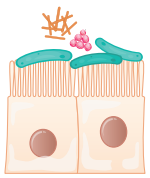
A meta-analysis of probiotic trials demonstrated that efficacy is specific both to the indication as well as to the specific strain.[11] Therefore, each strain and each dose requires clinical evidence for demonstration of efficacy. Furthermore, increasing the dose of the probiotic strain or combination of strains may or may not be more effective.[12] In the case of adult inpatients receiving antibiotic therapy, GI symptoms decreased more significantly with a higher dose (17 billion CFU v. 4.17 billion CFU) of a four-strain probiotic combination (*L. acidophilus* NCFM, *L. paracasei* Lpc-37, *B. lactis* Bi-07, and *B. lactis* BI-04), indicating a dose-dependent effect for antibiotic-associated diarrhea (AAD).[13] In addition, whole gut transit time (WGTT) and the frequency of functional GI symptoms were improved in a dose-dependent manner in patients administered 1.8 and 17 billion CFU of *B. lactis* HN019.[14] Conversely, in patients with irritable bowel syndrome (IBS), a meta-analysis demonstrated that a single strain, low dose, and short treatment duration were more effective with respect to overall symptom response and quality of life.[15] Similarly, 5 and 50 billion CFU of *B. lactis* HN019 had similar effectiveness on enhancing cellular immunity in the elderly.[16] Thus, increasing the dose does not always result in more significant benefits.

Mechanisms of action

The mechanisms of action of probiotics are complex and likely differ by strain (which is identified by genus, species, subspecies [if applicable] and an alphanumeric strain identifier) as demonstrated often in *in vitro* studies (commonly used bacterial probiotics include *Lactobacillus* and *Bifidobacterium* genera, and *Saccharomyces boulardii* [SB], a probiotic yeast). Figure 1 illustrates proposed major mechanisms of action that probiotics may exert on the host, including the following:[17,18]

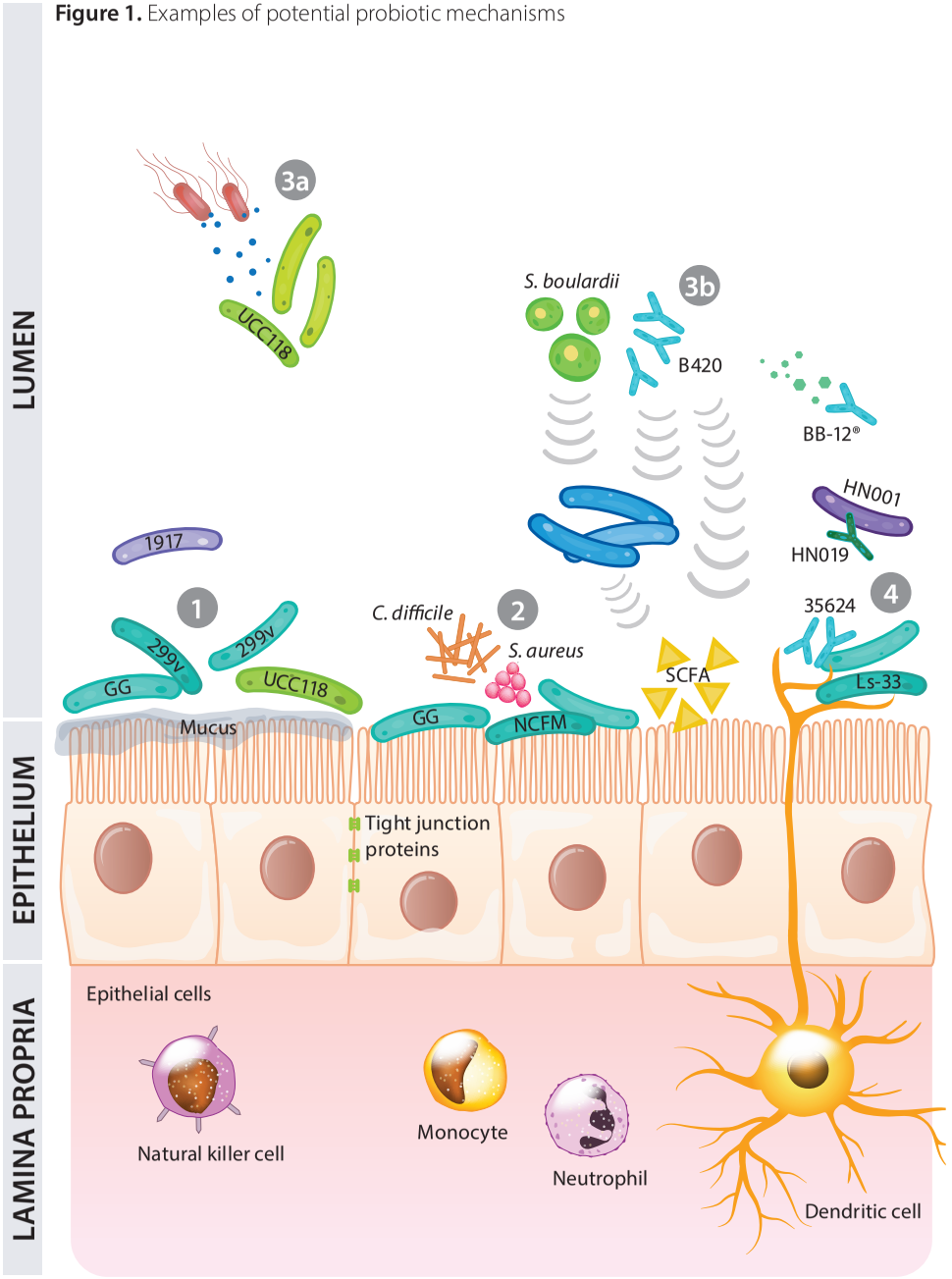
1. 

Support barrier function: Probiotics may prevent barrier breakdown (e.g. *E. coli* Nissle 1917, 8-species combination*),[18] decrease apoptosis of intestinal cells (e.g., *L. rhamnosus* GG),[18] increase mucin production (e.g., *L. plantarum* 299v),[19] or prevent disruption of tight junction proteins (e.g., *L. salivarius* UCC118),[20] thus blocking pathogen invasion through the intestinal wall and preventing the subsequent inflammation.[21]

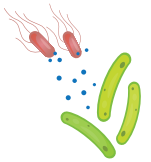
2. 

Cell adhesion: Probiotics often adhere to the intestinal epithelium and competitively bind to cell receptors that inhibit attachment and growth of pathogens (e.g., *L. rhamnosus* GG and *L. acidophilus* NCFM exhibited high adhesion and inhibited adhesion of several pathogens including *C. difficile* and *S. aureus*).[22]

Figure 1. Examples of potential probiotic mechanisms



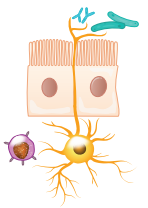
3. **Production of antimicrobial substances and beneficial metabolites:**

a. 

Producing bacteriocins that suppress pathogen growth (*L. salivarius* UCC118 was characterized to produce a bacteriocin that *in vitro* inhibited the growth of some bacteria[23] and *in vivo* prevented *Listeria* infection[24]).

b. 

Producing enzymes associated with metabolism of bile acids (e.g., *B. lactis* BB-12®)[25] and/or producing short-chain fatty acids (SCFA) (e.g., in human clinical trials, *B. lactis* B420[26] and *S. boulardii*[27]). SCFA provide energy to colon cells and also impact peripheral tissues via interactions with SCFA receptors, affecting glucose homeostasis, inflammation, tissue insulin sensitivity, and lipid metabolism.[28–30]

4. 

Immune system modulation: Probiotics may interact with immune cells such as dendritic cells[31,32] and may block proinflammatory molecule production (e.g., 8-species combination*)[33] and upregulate anti-inflammatory cytokines and growth factors (e.g. *B. infantis* 35624 and *L. salivarius* Ls-33 induced anti-inflammatory cytokine interleukin-10 [IL-10] *in vitro* through interaction with dendritic cells).[31] Clinical examples include *B. lactis* HN019 and *L. rhamnosus* HN001 (see clinical studies in Table 1).

Clinical benefits

When evaluating clinical studies, the condition and ages of the population treated, the dose used, the methods used to evaluate outcomes, and many other factors need to be examined to understand the strength and specific relevance of the evidence.[11] Clinical evidence pertaining to probiotics can be diverse, ranging from prevention of disease or side effects of standard disease therapies to the treatment of acute or chronic diseases or relief of disease symptoms.[11] It is important to recognize that some published meta-analyses and reviews do not specify strains or doses and may pool probiotics inappropriately at the genus level. Table 1 summarizes key clinical research for the efficacy of specific probiotics for several conditions.

Table 1. Summary of Key Clinical Research

Health-Related Indication	Strain	Dose	Result
Prevention			
Antibiotic-associated diarrhea (AAD)†	*S. boulardii*	4–20 billion CFU/d for adults[11,34] and 5–40 CFU/d for under 18 years[35]	Prevention of adult and pediatric AAD[11,35]
	Combination of *L. acidophilus* CL1285, *L. casei* LBC80R, *L. rhamnosus* CLR2	50 or 100 billion CFU/d[36–38]	Lower incidence of adult AAD in a dose-dependent manner[36–38]
	Combination of *L. acidophilus* NCFM®, *L. paracasei* Lpc-37, *B. lactis* Bi-07, *B. lactis* BI-04	4.17 billion CFU/d or 17 billion CFU/d	Decreased nocosomial AAD symptoms, duration and incidence in dose-dependent manner[13]
Clostridium difficile infection (CDI)	*L. plantarum* 299v	10 billion CFU/d	Decreased incidence of CDI and milder severity of recurrent infection[39,40]
Traveler's diarrhea‡	*S. boulardii*	2.5 and 5 billion CFU/d	Reduced incidence of diarrhea (prevention)[41–43]
Helicobacter pylori eradication, coadjuvant therapy	*S. boulardii* as adjuvant therapy	10, 20, 22.5 billion CFU/d[44]	Increased eradication rates and decreased overall therapy-related side effects (diarrhea)[44]
Acute gastroenteritis in children	*L. rhamnosus* GG	10 billion CFU/d	Reduced the duration of diarrhea[45–48]
Fever, coughing, rhinorrhea (runny nose) in children	50:50 combination of *L. acidophilus* NCFM,® *B. lactis* Bi-07	10 billion CFU/d	Reduced incidence and duration of fever, cough, and rhinorrhea (runny nose) in children aged 3–5 years[49]
Pediatric infections (colds)	*B. lactis* Bb-12®	10 billion CFU/d	Significant reduction in the occurrence of respiratory tract infections in infants (1–2 months)[50]
Pain after colonoscopy	50:50 combination of *L. acidophilus* NCFM and *B. lactis* Bi-07	25 billion CFU/d	Significant reduction in duration of pain post-colonoscopy[51]
Treatment			
Irritable bowel syndrome (IBS)‡	*B. infantis* 35624	100 million CFU/d[52] or 10 billion CFU/d[53]	Significant relief of IBS symptoms[52,53] and improved cytokine profiles[52] Note: 1 million and 10 billion CFU/d doses were not effective in study[52]
	L. plantarum 299v§	10 billion CFU/d	Decreased pain and bloating[54,55]
Mild to moderate ulcerative colitis‡	*E. coli Nissle* 1917	50 billion twice daily	Maintenance of clinical remission[56,57]
	8 species combination*	3,600 billion CFU/d[58,59], managed by stable medication in adults and 450–1,800 billion CFU/d (weight-based dose) in children[60]	Improved symptoms and remission of ulcerative colitis in adults and children[58–60]
Functional gut symptoms	*B. lactis* HN019	1.8 billion CFU/d or 17.2 billion CFU/d	Improved whole gut transit time; reduced abdominal pain, nausea, gurgling, and flatulence in a dose-dependent manner[14]
Immune cell activity	*L. rhamnosus* HN001	5 billion CFU/d[61] or 25 billion CFU/d[62]	Increased phagocytic activity in peripheral blood[61] and natural killer (NK) cell tumor killing activity[61,62]
	B. lactis HN019	5 or 50 billion CFU/d	Increased phagocytic activity of neutrophils and monocytes and NK cell activity; no significant difference between high and low dose; and increased proportions and activity of relevant immune defense cells[16]
Common cold	Combination of *L. plantarum* HEAL 9 (DSM 15312), *L. paracasei* 8700:2 (DSM 13434)	1 billion CFU/d	Decreased severity and duration of common cold[63]

AAD, antibiotic-associated diarrhea; CFU, colony forming units; *L., Lactobacillus; B., Bifidobacterium; S., Saccharomyces; C., Clostridium; E., Escherichia*

**B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii* subsp. *bulgaricus, Streptococcus thermophilus*

† In 2017, the World Gastroenterology Organisation Global Guidelines affirmed that at least 10 billion CFU *L. casei* DN-114 001 or at least 10 billion CFU of *L. acidophilus* CL1285 and *L. casei* LBC80R and CL1285 or 250 mg twice daily of *S. boulardii* had strong evidence for efficacy for AAD[64]

‡ The 2015 Latin-American Pediatric Gastroenterology guidelines recommended *S. boulardii* for traveler's diarrhea, the 8-species combination or *L. rhamnosus* GG for IBS, and the 8-species combination for ulcerative colitis[48]

§ In 2017, the World Gastroenterology Organisation Global Guidelines listed 10 billion CFU of *L. plantarum* 299v with strong evidence for reducing the severity of abdominal pain[64]

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