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REVIEW

Probiotics in health and disease: fooling Mother Nature?

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Abstract

Probiotics are ubiquitous, consumption by the general public is common, and the dogma remains that they are beneficial for general and gut health. However, evolving evidence suggests a potentially "harmful" impact of many commercially available probiotics. There is also significant variability in formulations that leads to a lack of a universally acceptable definition of probiotics. In this perspective, we review the flaws with definition, relevant observational and randomized studies that showed both positive and negative impacts on health and disease, unbiased interpretation of key trials, emerging evidence from microbiome and immuno-oncological studies, and impact on systemic immunity. We propose that caution be exercised prior to endorsements of their illness-directed consumption and rampant general usage. As a deeper understanding of the human microbiome accrues and our ability to manipulate this complex ecosystem improves, the probiotic of tomorrow might be the precision tool that deals with diseases on a broad front. Gut microbiome, akin to fingerprints, is indigenous to an individual and 'one size fits all' prescription strategy should be discouraged until a more universally acceptable 'favorable taxa' or a 'personalized probiotic,' to complement an individual's native microbiota, gets fashioned.

Keywords Commercial probiotics · Gut microbiome · Dysbiosis

Introduction

Probiotics are ubiquitous, consumption by the general public is common, and the dogma remains that they are beneficial for general and gut health. Hundreds of studies have endorsed the use of probiotics in a whole host of illnesses. Probiotics currently constitute one of the most commonly consumed nutritional supplements worldwide [1].

A descriptive study across 145 hospitals in the U.S. found that 96% of those hospitals were using probiotics, and *Clostridioides difficile* infection (CDI) and concurrent antimicrobial use were the commonest indications [2]. Probiotic use remains prevalent in the general population, with or without a gastrointestinal illness, despite recently growing conflicting evidence.

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Clinical efficacy in general health

Probiotics are generally assumed to be beneficial, which are commonly used both as a guideline-indicated adjunctive therapy for defined illnesses and as an over-the-counter supplement for general well-being. Besides gut health and infections, several studies have shown a positive impact on cardiovascular risk. For example, several randomized trials showed an increase in HDL, and a reduction in triglycerides and LDL, body mass index, fasting sugar, and insulin sensitivity [3–5].

Tyagi et al. showed in mouse models that butyrate produced as a result of *Lactobacillus rhamnosus* GG supplementation resulted in bone anabolism [6]. Savino et al. showed that a single-strain probiotic (*Lactobacillus reuteri*) improved infantile colic in a randomized-controlled trial (RCT) consisting of 46 infants [7]. Similarly, several other studies demonstrated the benefit of probiotics in general health and well-being.

Trials endorsing clinical efficacy in illnesses

Probiotics have been studied and recommended in medical guidelines, mainly in the setting of infection-related outcomes: antibiotic-associated diarrhea (AAD), and CDI. These are also commercially marketed for colonization and/or infection with other multidrug-resistant infections or 'post-antibiotic reconstitution.' While RCTs and meta-analyses have shown efficacy of probiotics in certain infections, the bulk of evidence endorsing their use has been observational. For example, a meta-analysis incorporating 82 RCTs including 11,811 participants, majority with lactobacillus-based intervention, demonstrated a statistically significant association of probiotics with a reduction in AAD (RR 0.58; 95% CI 0.50–0.68; $P < 0.001$; NNT 13) [8]. A similar systematic review in the pediatric population, including 33 studies with 3938 participants under the age of 18 years, also showed that concurrent use of probiotics with antibiotics reduced AAD, compared to the control group (RR 0.46; 95% CI 0.35–0.61; NNT 10) [9]. McFarland et al. also showed in a meta-analysis that probiotics significantly reduced AAD and CDI in 25 and 6 RCTs, respectively [10]. Similarly, Hungin et al. showed in a systematic review that probiotics were beneficial in irritable bowel syndrome (IBS) and AAD in 19 and 10 RCTs, respectively [11]. Panigrahi et al. published a large, randomized, double-blind, placebo-controlled trial in which they showed that *Lactobacillus plantarum* plus fructo-oligosaccharide significantly reduced neonatal sepsis and death in 4556 rural Indian neonates [12]. World Allergy Organization consensus guidelines recommend probiotics for the prevention of allergy/eczema in high-risk infants and during pregnancy and breastfeeding [13]. Other studies have shown beneficial effects of probiotics against specific bacterial infections such as CDI and *H. pylori* [14, 15].

Randomized trials negating probiotics' efficacy

In parallel to the trials that showed efficacy of probiotics, there has been nearly equivalent number of trials that showed a lack of efficacy. For example, probiotics (*Bifidobacterium breve* BBG-001) failed to prevent necrotizing enterocolitis and sepsis in a large, multicenter, phase-III RCT (the PiPS trial), performed in preterm newborns in southeast England [16]. In another multicenter double-blind, placebo-controlled RCT (the PLACIDE trial), a multistrain preparation of lactobacilli and bifidobacteria was shown to be ineffective in the prevention of AAD or CDI in elderly inpatients [17]. Another RCT performed in the United Kingdom in 934 children and adults with pharyngitis showed that probiotics (lactobacilli and bifidobacteria) were ineffective in reducing the severity of symptoms [18]. This was a critical finding as upper respiratory tract infections and pharyngitis constitute one of the largest infectious disease burdens in the community setting globally and such a finding would limit rampant use of over-the-counter probiotics. In addition, two recent well-designed trials on probiotics' usage to treat gastroenteritis in infants and children indicated that two common commercially available probiotics in North America do not impact outcomes of acute gastroenteritis in children under 4 years of age [19, 20].

Trials suggesting probiotics' harm

In addition to the evidence showing positive or no benefits, there have been several studies that showed harmful effects of probiotics. For example, The PROPATRIA (Probiotics in Pancreatitis Trial) was a well-designed RCT that showed higher mortality in the probiotic arm (multistrain preparation) as compared to the placebo arm (16% vs 6%) in a study that aimed to reduce infectious complications in 298 patients with severe acute pancreatitis [21]. Hyperlactatemia due to increased bacterial fermentation of carbohydrates was postulated to be contributing to increased mortality in the probiotic arm. Suez et al. showed that probiotics significantly delayed gut microbiome reconstitution [22]. Didari et al. further concluded in a systematic review, incorporating all studies in humans and mouse models till 2013, that probiotics (most trials included *Bifidobacterium* and *Lactobacillus* species) may be associated with infections, sepsis, and gut ischemia [23]. They further noted that critically ill and immunocompromised hosts were at the highest risk.

Impact of differential gut colonization on probiotics' efficacy

Evolving evidence now hints towards a potential negative impact of commercial probiotics, contrary to the long-standing belief that if probiotics are not "beneficial," these are "harmless," at the very least. A study on 25 healthy volunteers introduced the concept of "resistors" and "persisters," negating the canonical notion of 'global goodness' associated with commercial probiotics. It was deemed to be contingent upon one's baseline gut taxa—the indigenous microbiota—if the probiotic would colonize the gut or gets rejected [24]. In a follow-up concurrent human and murine study, the investigators showed that probiotics delayed gut microbiome and transcriptome reconstitution for months, after antibiotic ingestion [22].

Quality of existing data around probiotics

A vast majority of probiotics' data stem from meta-analyses and underpowered RCTs and the information, both for and against commercial probiotics, should be interpreted considering the discrepancies between results of these two types of study methods. LeLorier et al. compared the results of 12 large RCTs that were published in 4 major medical journals with the results of 19 meta-analyses on the same topics. They concluded that the outcomes of the 12 RCTs were not predicted accurately 35% of the time by the meta-analyses published previously on the same topics [25]. Furthermore, there exists the possibility of publication bias giving an overly favorable view of probiotics in the literature (reviewed by Million et al.) [26].

Lack of universally acceptable definition (GRAS status vs a drug)

A major problem with the studies addressing benefit or harm associated with probiotic use suffer from the fact that "probiotics" is an ill-defined term, as preparations can contain vastly varying ingredients, making any scientifically rigorous judgment virtually impossible. Furthermore, most strains originated from the food industry: based on a role in food fermentation, easy cultivability, and wide availability and almost none are human-derived (apart from *Bifidobacterium infantum* in infant formula). Except for the latter, none have been 'rationally derived' from animal or human models, for preventing or treating a specific disease. Several recent studies have tried to decipher mechanistic underpinnings of probiotic interactions in a scientifically rigorous way with defined probiotic and target bacteria [27, 28].

Furthermore, most current probiotics are marketed as nutritional supplements, and have 'GRAS' status (GRAS: generally recognized as safe) under Food and Drug Administration (FDA) and cannot be marketed with a drug claim. None have been studied in a way similar to a drug that is brought to market: a quality-controlled product of verified potency, given at a specified dose, at a specific point in time of a disease or condition progression, for a specified time, to achieve a specific outcome. Hence, probiotics may not be truly 'GRAS' and there are currently insufficient data for physicians to be recommending probiotics indiscriminately.

Interaction with innate gut microbiota and impact on systemic immunity

Since the intimate link between the local gut and systemic immunity became apparent [29], the gut microbiota is being studied in a whole host of illnesses. Advancements in high-throughput analytical technologies and metagenomic methods allowed a comprehensive exploration of the gut microbiota [30]. It is now known that the number of the gut microbes and their collective genome is considerably larger than human cells and genome and the power of this robust "super-organism," bearing a "second genome," has been increasingly harnessed to change the natural course of a myriad of illnesses [31]. The diversity and compositional differences of the gut microbiota have been shown to impact obesity, hypertension, cardiovascular disease, autoimmunity, neurological disorders, carcinogenesis, and response to vaccines [32–37].

The critical impact of the gut microbiome on systemic immune responses is also becoming increasingly known. The local gut immune apparatus interacts with the systemic immune system via a variety of microbial gene products, metabolites, and immunomodulators. Gut immunological homeostasis is maintained by colonic microbial fermentation products which patronize T-cell differentiation through dendritic cell activation within mesenteric lymph nodes. Differential metabolite production by variable strains impacts the subsequent immune effector T cells such as TH1:TH2 cell ratios and TH17:Tregs (regulatory T cells) balance [29, 38].

Emerging immuno-oncological evidence

There is no "standard" gut microbial composition as it varies not just across communities, but also among individuals within a community and within individuals over time and the lifespan (Table 1). Based on the genomic evidence, the Bacteroidetes and Firmicutes phyla are the dominant bacterial populations in the gut microbiota and their balance or "imbalance" dictates inflammation and immune surveillance. The impact of individual strains is currently being elucidated mainly from studies in inflammatory bowel disease (IBD) and immuno-oncology settings. Several studies published recently in patients receiving immunotherapy for both solid tumors and hematologic malignancies showed that higher microbial diversity and an abundance of specific strains—*Akkermansia muciniphila,* Ruminococcaceae family and *Faecalibacterium* genus—were associated with a superior cytokine profile and greater effector T cells in the systemic circulation.

Table 1 Major gut microbial taxa and their predominant influence on systemic immunity and response to immunotherapy Adopted from: [39]

Gut Taxa	Immune effect/treatment response	Study type	Cancer type
Predominately positive influence			
Firmicutes			
Faecalibacterium prausnitzii	Boosts effector T cells and dampens Tregs.	Humans	Melanoma
Faecalibacterium spp.	Increases efficacy of anti-CTLA-4 immunotherapy.	Humans	Metastatic melanoma
Eubacterium limosum			
Clostridiales spp.	Boost CD8+ T cells and enhance anti-PD-1 responses.	Cell line	Colorectal
Ruminococcaceae spp.			Adenocarcinoma
Phascolarctobacterium spp.			Cell line (MC38)
Fusobacteria			
Fusobacterium ulcerans	Boost CD8+ T cells and enhance anti-PD-1 responses.	Cell line	MC38
Fusobacterium varium			
Verrucomicrobia			
Akkermansia muciniphila	Increase in memory T cells and decrease in Tregs in the TME.	Humans	Epithelial tumors
	Increases mucus layer of the gut to prevent lipopolysaccharides absorption.	Humans	Epithelial tumors
Mixed influence			
Bacteroidetes			
Bacteroides fragilis	Increases efficacy of anti-CTLA-4 immunotherapy.	Human/Animal/Cell line	Epithelial tumors
	Promotion of Tregs through polysaccharide-A.	Humans	Healthy humans
	Higher IL-12 levels in transplant recipients.	Animal/Cell line	Cervical cancer
Bacteroides thetaiotaomicron	Increases efficacy of anti-CTLA-4 and anti-PD-1 immunotherapy	Humans	Melanoma
Bacteroides spp.	Inferior response of anti-CTLA-4 immunotherapy	Humans	Metastatic melanoma
Actinobacteria			
Bifidobacterium longum	Increases CD8 + T cells.	Animal/Cell line Humans	Melanoma Melanoma
Bifidobacterium bifidum	Induces naïve T-cell differentiation into Tregs and increases IL-10.	Humans/in vitro	Healthy humans
	Increases the integrity of epithelial barrier.		
Predominately negative influence			
Proteobacteria			
Enterobacteriaceae	Inferior response and survival.	Humans	Pediatric cancers

This contrasted with those patients who, for instance, had lower diversity and abundant *Bacteroidetes* in their gut, manifest a dampened cytokine response and a correspondingly large number of immunosuppressive Tregs in their systemic circulation (reviewed by Abid MB) [39].

More recently, Tanoue et al. characterized the critical role of the gut microbiota in dictating inflammation and immune surveillance not only in the gut but also systemically [40]. The study delineated microbial strains that showed potential in enhancing responses to immunotherapy in mouse models. The positive effect was shown to be mediated through IFNγ-producing CD8+ T cells. Although studies have shown mixed results in identifying influential strains so far, Tanoue et al. provided vital information that could be harnessed towards fashioning a rationally designed probiotic, with proven efficacy, for future trials and clinical usage.

As the evidence around the microbial diversity or loss of its diversity and compositional differences evolve, the suggestion for the potential detrimental impact of commercial probiotics also grows in parallel. A recent cancer immunotherapy study showed that commercial probiotics lead to lower microbial diversity, the hallmark of substandard gut, and general health [41]. This is likely due to ingestion of an off-the-shelf, single-strain probiotic, whose immunological impact is not known, that dilutes the entire diversity of the communal microbiome of an individual. While this finding still needs to be validated, commercial probiotics lead to inferior survival and response to cancer treatment, specifically, and compromised gut health, in general.

Financial landscape of commercial probiotics

Despite the paucity of strong clinical evidence, the probiotics loom large in the healthcare supplement sector, with an estimated global industry size of USD 40 Bn in 2017 with projected growth to nearly USD 66 Bn in 2024 [42]. In comparison, the global market for antihypertensive therapy is estimated at USD 23 Bn by 2023 [43]. Unlike therapeutic drugs that must demonstrate consistent clinical safety and efficacy, the positioning of probiotics as dietary supplements remains unclear. On one hand, the lighter regulatory touch has allowed a diverse market and multiple products to flourish in the commercial space, but the downside is evident from the lack of regulations to develop products with definite therapeutic efficacy [44]. This has led to rampant and often inappropriate usage in a whole host of disease states: from upper respiratory tract infections, to gestational diabetes, unsurprisingly with mixed results [45, 46].

Call for caution and future directions

In addition to the issues discussed above related to the commercial probiotics, additional essential aspects that should remind clinicians that the conventional "can't hurt, might help" justification may no longer be true and that indiscriminate probiotics' prescription may be harmful. Some of those additional factors include a dearth of reliable products due to batch-to-batch variability, an absence of designer probiotics with much greater microbiome footprint, and lack of comparison to fecal microbiota transplants, especially those delivered via "pedigreed" capsules. As more concrete evidence emerges, it is also prudent that relevant medical societies/bodies re-consider their recommendations on commercially available probiotics. Emerging evidence calls for re-visiting the Infectious Disease Society of America (IDSA) clinical practice guidelines, for instance, for the management of infectious diarrhea published in 2017 which tacitly endorsed the use of probiotics, though deferred to other guidelines for specific probiotic selection [47].

In the wake of this growing body of evidence of the potentially 'harmful' impact of commercial probiotics, physicians' and professional bodies' endorsements of their illness-directed consumption and rampant general usage would, perhaps, be best avoided. As a deeper understanding of the human microbiome accrues and our ability to manipulate this complex ecosystem improves, the probiotic of tomorrow might be the precision tool that deals with diseases on a broad front. Gut microbiome, akin to fingerprints, is indigenous to an individual and there is considerable inter-individual and temporal variability in microbiome composition. Hence, 'one size fits all' prescription strategy should be discouraged until a more universally acceptable 'favorable taxa' or a 'personalized probiotic,' to complement an individual's native microbiota, gets fashioned. Large, placebo-controlled, multicenter trials with concomitant accrual of microbiome data before and after intervention are needed before a more rationally designed bacterial consortium becomes available.

Expert recommendations

- Probiotics should not be 'generally recognized as safe.'
- Data are unclear for probiotics usage for general health and as a nutritional supplement.
- Probiotics use should be limited to established indications only, containing the specific strains, whereby RCTs have shown therapeutic efficacy: AAD, CDI, IBS, IBD, and reduction of risk for neonatal sepsis and necrotizing enterocolitis.
- Probiotics may potentially be harmful to critically ill and immunocompromised hosts, and are best avoided in immuno-oncology patients, particularly during treatment.
- The probiotic of the future will be a rationally derived formulation that has been developed as a drug.
- Amidst ever-growing microbiome research, probiotics ought to be defined at the strain level for clinical use and mechanistic studies.
- Rather than being defined as a singular entity, novel microbiota from recent microbiome evidence with potential health benefits should be harnessed for defined clinical use and further research.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interest.

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