Nutrition 45 (2018) 125–134

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Probiotics and gastrointestinal conditions: An overview of evidence from the Cochrane Collaboration

Elizabeth A. Parker Ph.D., R.D. [a,*], Tina Roy B.S. [b], Christopher R. D'Adamo Ph.D. [a], L. Susan Wieland Ph.D. [a]

[a] Department of Family & Community Medicine, Center for Integrative Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
[b] The Commonwealth Medical College, Scranton, PA, USA

ARTICLE INFO

Article history:
Received 21 March 2017
Accepted 20 June 2017

Keywords:
Probiotic
Microbiota
Gastrointestinal conditions
Diarrhea
Inflammatory bowel disease
Liver disease

ABSTRACT

Alterations in the composition of the gut microbiota are associated with a number of gastrointestinal (GI) conditions, including diarrhea, inflammatory bowel diseases (IBD), and liver diseases. Probiotics, live microorganisms that may confer a health benefit to the host when consumed, are commonly used as a therapy for treating these GI conditions by means of modifying the composition or activity of the microbiota. The purpose of this review was to summarize the evidence on probiotics and GI conditions available from Cochrane, a nonprofit organization that produces rigorous and high-quality systematic reviews of health interventions. Findings from this review will help provide more precise guidance for clinical use of probiotics and to identify gaps in probiotic research related to GI conditions.

Introduction

Probiotics are defined by the World Health Organization as "live microorganisms, which when consumed in adequate amounts confer health and benefit to the host" [1]. Although most commonly consumed worldwide in the form of yogurt or other fermented dairy products, probiotics are found and administered in many different forms, including a wide variety of dietary supplements and functional foods. Consumption of probiotics in their various forms is common and increasing rapidly. Within the United States, 3.9 million adults used probiotic or prebiotic supplements in 2015—a fourfold increase from 2007 [2]. Sales figures suggest that probiotics are one of the supplement categories most often purchased by consumers. Whereas overall growth in the nutritional supplement industry slowed to 5% in 2014, probiotics grew 14.2% with nearly $1.4 billion in sales [3]. In addition to widespread use among consumers, a recent study revealed that 96% of hospitals used probiotics as part of inpatient clinical care [4]. The increasing use of probiotics in both hospitals and among the public at large demonstrates the increasing public health importance of clinical research on probiotics.

Probiotics, altered gut microbiota, and disease

A rapidly growing evidence base suggesting a variety of health benefits supports the increasingly common use of probiotics. More than 25 diseases or health conditions have been associated with the microbiota in the gastrointestinal tract, ranging far beyond gastrointestinal (GI) health into the realms of autoimmune disease, emotional health, and other areas [5]. Although the relationship between the microbiota and human health is broad ranging and the literature continues to expand, the health conditions that have been most consistently associated with the composition and activity of the microbiota are GI in nature. Probiotics are believed to provide an important role in human health by providing a protective effect on the microbiota in the GI tract through both colonization and transient activity, depending on the species. Probiotics have shown therapeutic benefits in adults and children across a broad range of health conditions, including autoimmune diseases [6–9], emotional disorders [10,11], and even as part of a potential treatment

This study was supported in part by National Institutes of Health (NIH) grant no. R24 AT001293 from the National Center for Complementary and Integrative Health (NCCIH) and the University of Maryland School of Medicine Summer Program in Obesity, Diabetes, and Nutrition Research Training (NIH grant T35 DK095737). All authors were responsible for the manuscript preparation, revision, and publication decisions, and have read and approved the final manuscript. The authors have no conflicts of interests to declare.

* Corresponding author. Tel.: +1 410 706 6189; fax: +1 410 706 6210.
E-mail address: eparker@som.umaryland.edu (E. A. Parker).

http://dx.doi.org/10.1016/j.nut.2017.06.024
0899-9007/

strategy for obesity [12–14]. However, the effects of probiotics have been most studied in GI conditions such as acute infectious diarrhea, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS). Antibiotic therapy typically is prescribed for infectious diarrhea, which has been shown to reduce the diversity of intestinal microbiota. The two main IBD conditions, Crohn's disease and ulcerative colitis, also are associated with a reduced microbial diversity [5]. Although the exact mechanisms of action are unknown, the use of probiotics is thought to increase microbial diversity by improving the balance of organisms within the intestinal tract and reducing the risk for colonization by pathogenic bacteria [15,16]. The clinical evidence surrounding probiotics for GI conditions is the focus of this overview.

Although probiotics have been shown to be efficacious in many randomized controlled trials (RCTs) and systematic reviews for a variety of health conditions, more precise evidence is needed to translate the growing evidence base to appropriate clinical practice. For instance, probiotics often are recommended in clinical practice without the necessary specification of numerous important factors related to the probiotic and the health condition for which they are being recommended. Probiotics are most broadly categorized by their genus (e.g., *Lactobacillus*), followed by their species (e.g., *acidophilus*), and most specifically, their strain (e.g., NCFM). The clinical effects of probiotics depend on many factors, including the species and strain of the probiotic. Different strains of the same species can yield heterogeneous clinical results [17]. One striking example is the vastly different effects noted among different strains of *Escherichia coli* species. *E. coli* 0157:H7 is a food-borne pathogen that can cause hemorrhagic diarrhea, kidney failure, and death. Within the same species, *E. coli* Nissle 1917 is a probiotic supplement that has been shown to improve IBD, IBS, and other GI disorders [18–20]. Despite the heterogeneity of effect of different strains of the same species, strains are rarely specified on most probiotic foods and supplements. This type of heterogeneity in effect often results in discrepancies between clinical outcomes of probiotic interventions. Combinations of different probiotic species and strains within the same capsule also introduce additional uncertainty due to unknown and poorly studied interactions between probiotic species. Additionally, the effective dosage of probiotics varies by species and strain. Probiotic dosage is most often measured as colony-forming units (CFU), and recommendations and clinical effects vary depending on the species and strain used and the pathogen or disease targeted [21]. Thus, identifying species and strains and specifying dosages is critically important to understanding how probiotics may or may not be effective for specific conditions. Lastly, even if the species, strains, and dosages are specified and concordant with the scientific literature, there are currently no product purity or labeling standards for probiotics to ensure that what is listed on the probiotic supplement label is actually in the bottle. The best current process to ensure probiotic purity and bottle-to-bottle consistency is third-party laboratory certification, which is flawed due to heterogeneity in testing methods between the various laboratories.

In addition to these confounding factors related to the probiotic intervention, factors related to the design of the clinical trial evaluating the probiotic also influences clinical outcomes. The specific outcomes studied and how they were assessed, the duration of probiotic treatment, and the length of follow-up should be clearly defined to more precisely describe the effects of probiotic treatment. The clinical heterogeneity observed in many studies and in clinical practice is a function of the many factors that can influence probiotic efficacy. Thus, the purpose of this review was to summarize the current evidence of probiotic therapy for GI symptoms to help provide more precise guidance for clinical use and to identify future needs for probiotics research. Systematic reviews and meta-analyses of probiotic interventions for GI-related medical conditions performed for the Cochrane organization will be the focus of this overview.

Cochrane and systematic reviews of probiotics

Cochrane, which was founded in 1983 as the Cochrane Collaboration, is one of the first and most highly regarded organizations focused on the production and dissemination of systematic reviews of health care interventions. It is an international nonprofit organization that currently includes >37 000 contributors, mostly volunteers, from more than 130 countries [22]. Cochrane reviews aim to be unbiased; Cochrane does not accept commercial funding and has policies to guard against both commercial and noncommercial conflicts of interest in the production of reviews. Cochrane reviews are methodologically rigorous and follow structured and transparent methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [23]. Cochrane reviews frequently have been observed to have higher methodological quality, better reporting, and more precise conclusions than non-Cochrane reviews on the same topics [24–29]. All Cochrane reviews undergo two peer reviews; once during the protocol stage and again after completion of the review before publication. Both protocols and completed reviews are published in the online Cochrane Library, where there are currently more than 2000 protocols and nearly 7000 completed reviews. Cochrane reviews are meant to be updated when new evidence becomes available, and many reviews in the Cochrane Library are currently on their fourth or later update. Cochrane reviews may therefore be expected to provide a high-quality, unbiased, and up-to-date assessment of the evidence on health care interventions such as probiotics.

Methods

To identify all reviews in the Cochrane Library whose primary focus was probiotics and the digestive system, two independent authors (EAP, TR) searched the titles and abstracts using the search term *probiotic*.* Each of the authors each read the title and abstract of every retrieved Cochrane review article to verify the inclusion of probiotics and disorders or symptoms affecting the digestive system. Cochrane reviews that included any trials comparing oral administration of probiotics to placebo or usual care were included in the present review. For this review, probiotics were defined as probiotics administered in any form (drink, powder, capsule) as a single species or as a cocktail of multiple species. Cochrane reviews that were withdrawn from publication or Cochrane reviews that contained trials where probiotic treatment was administered through enteral feedings were excluded. Cochrane reviews that did not feature comparisons that isolated the effects of probiotics also were excluded. For example, one Cochrane review compared oral bovine lactoferrin alone versus oral bovine lactoferrin in combination with a probiotic (*L. rhamnosus* GG) versus placebo [30]. Therefore, this Cochrane review did not include any comparisons isolating the effect of probiotics (e.g., probiotics alone versus placebo).

For each Cochrane review, the two authors extracted data on the number of trials included and the total number of participants. Because there is high variability in microbial composition in the GI system across the life span and changes in the microbiota are associated with increasing age [31], we extracted data on the ages of participants included in the trials. We identified the prespecified outcomes of each Cochrane review as well as the Cochrane review authors' conclusions regarding the prespecified outcomes.

We assigned the conclusions from each Cochrane review into one of the following categories:

- Category A: The Cochrane review indicated good evidence of a benefit from probiotics;
- Category B: The Cochrane review indicated good evidence of no benefit from probiotics;
- Category C: The Cochrane review indicated that there was not sufficient available evidence to allow benefits from probiotics to be determined.