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Review

Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials

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ABSTRACT

Gastrointestinal microbiota, consisting of microbial communities in the gastrointestinal tract, play an important role in digestive, metabolic, and immune functioning. Preclinical studies on rodents have linked behavioral and neurochemical changes in the central nervous system with deficits or alterations in these bacterial communities. Moreover, probiotic supplementation in rodents has been shown to markedly change behavior, with correlated changes in central neurochemistry. While such studies have documented behavioral and mood-related supplementation effects, the significance of these effects in humans, especially in relation to anxiety and depression symptoms, are relatively unknown. Thus, the purpose of this paper was to systematically evaluate current literature on the impact of probiotic supplementation on anxiety and depression symptoms in humans. To this end, multiple databases, including Medline, PsycINFO, PubMed, Scopus, and Web of Science were searched for randomized controlled trials published between January 1990 and January 2016. Search results led to a total of 10 randomized controlled trials (4 in clinically diagnosed and 6 in non-clinical samples) that provided limited support for the use of some probiotics in reducing human anxiety and depression. Despite methodological limitations of the included trials and the complex nature of gut-brain interactions, results suggest the detection of apparent psychological benefits from probiotic supplementation. Nevertheless a better understanding of developmental, modulatory, and metagenomic influences on the GI microbiota, specifically as they relate to mood and mental health, represent strong priorities for future research in this area.

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CFS, Chronic Fatigue Syndrome; CNS, Central nervous system; CY, conventional yogurt; DASS, Depression Anxiety Stress Scale; GBA, gut-brain axis; GF, germ-free; GHQ, General Health Questionnaire; GI, gastrointestinal; HAMA, Hamilton Anxiety Rating Scale; IBS, Inflammatory Bowel Syndrome; LEIDS-r, Leiden Index of Depression Sensitivity; PC, probiotic capsule; POMS, Profile of Mood States; PY, probiotic yogurt; RCT, Randomized Controlled Trial; STAI, State Trait Anxiety Inventory.

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1. Introduction

Microbial organisms in the human gastrointestinal tract, known as the gastrointestinal (GI) microbiota, play an important role in human health and well-being [1-3]. Composed largely of communities of bacteria, the GI microbiota exert a dynamic regulatory influence on the development and maintenance of digestive, metabolic, and immune functioning within hosts [1-5]. Moreover, early life deficits in certain bacterial communities or their later alterations (ie, dysbiosis) appear to influence human pathophysiology and development, particularly in inflammatory bowel disorders and colorectal cancer [4,6]. The apparently extensive nature of microbial influences on host physiology has motivated some to view the GI microbiota as virtually an additional organ, with functions that merit more intensive examination [1]. The Human Microbiome Project is now making a consolidated effort to better characterize the diversity and relevance of these internally residing microorganisms [7].

Preclinical animal models, largely involving rodents and swine, have played an important role in shaping current understanding of the local and systemic immune-metabolic effects of the GI microbiota. Among these, are several recent rodent-based investigations that suggest roles for the GI microbiota in regulating key aspects of central nervous system (CNS) physiology, mood, and behavior [8-17]. Specifically, these include demonstrations of altered neurochemical-behavioral profiles in germ-free (GF) mice. These GF studies point to: (a) regional differences in central gene expression, neurochemical concentrations, and turnover rates [8-13], (b) exaggerated hypothalamic-pituitary-adrenal axis stress responses [8,10,11,13], (c) reductions in anxious behaviors linked to changes in the GI microbiota, [9-11], and (d) greater social cognitive deficits [14], additionally related to the GI microbiota. These and other related investigations have shown that bacterial colonization early in life in GF mice can result in neurochemical modifications that influence stress and anxiety [8,9,11,12]. Similar beneficial neurochemical and behavioral effects have also been reported in mice with normal GI microbiota after supplementation with probiotic bacteria, primarily the *Bifidobacteria* (eg, *Bifidobacterium longum 1714, Bifidobacterium breve 1205*) [15,16] and *Lactobacillus* strains (eg, *Lactobacillus rhamnosus JB-1*) [17]. In parallel, swine-based models also highlight the critical role of the GI microbiota and bacterial supplementation in enhancing immune development and functioning [18-26]. These data include evidence of altered immune development and function in differentially raised (conventional vs isolator-raised) newborn [18,19] and GF piglets [20,21]. Moreover, probiotic supplementation in swine has been shown to positively impact GI microbiota, leading to: (a) increased production of short (eg, Butyrate) and branched chain fatty acids [22], (b) reduced concentrations of *Clostridium* and increased concentrations of *Lactobacillus* [22,23], (c) improved immune functioning [22,24], (d) greater antioxidant activity [25], and (e) reduced expression of proteins linked to the stress response [26] following supplementations with *Lactobacillus fermentum I5007* [22,25,26], *Lactobacillus delbrueckii subsp. bulgaricus 2038* [23], and *Lactobacillus acidophilus* [24].

Taken together, these observations highlight the importance of interrelationships between GI microbiota, CNS, and immune functioning in rodents and swine [8,9,11,12,26]. However, questions remain about the effectiveness of probiotic supplementation in improving human mental health, specifically in relation to anxiety and depressive symptomatology. Given that probiotic supplementation in humans has previously been linked to improved gastrointestinal, immune, and cardiovascular health [27-29], the primary objective of this review is to systematically evaluate findings from published randomized controlled trials (RCTs), evaluating the effects of probiotic supplementation on depressive and anxiety symptoms in healthy and clinically diagnosed patients. Specifically, we evaluated the hypothesis that probiotic supplementation in humans would result in reduced depressive and anxiety symptoms, an important question with translational implications for psychiatric research.

2. Approach: search strategy and inclusion criteria

A systematic literature search was carried out using MEDLINE, PsycINFO, PubMed, Scopus, and Web of Science databases for the period of January 1990 to January 2016. Search terms included probiotic* OR bacteria OR bifidobacterium OR lactobacillus AND depression* OR anxiety* OR mental health (see Appendix A for the exemplar MEDLINE search strategy). These searches were further supplemented by reviewing bibliographies of the trials selected for inclusion to identify additional studies. Studies included were English language, peer-reviewed, RCTs assessing the effect(s) of probiotic supplementation on anxiety and depressive symptoms (as either primary or secondary outcomes) in healthy or clinical adult (mean age ≥18 years) samples. For the purpose of this review, as consistent with international definitions, probiotics were defined as *live* microorganisms whose consumption in adequate amounts produce specific health benefits [30]. Two reviewers (MP & MM) evaluated search results for potentially relevant trials, and obtained full-text versions of the studies selected for inclusion as outlined in Fig. 1. The current review follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for conducting systematic reviews and meta-analyses [31].

2.1. *Data extraction and ratings of bias*

Relevant information from selected studies including sample characteristics (eg, target population, age range, gender composition), intervention characteristics (eg, probiotic source, strain, dose), and specific outcomes (eg, depressive and anxiety symptoms) were independently extracted by 2 reviewers (MP and MM) according to a pre-specified format. Finally, the potential sources of bias across selected trials were evaluated using the Cochrane Collaboration's tool for assessing bias [32]. Possible discrepancies in these processes were resolved by consensus or by consultation with a third reviewer (PR), amidst efforts to contact primary study authors for clarifications.