

Probiotics in Psychosocial Stress and Anxiety. A Systematic Review

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ABSTRACT

Background & Aims: Recent mounting evidence suggest that probiotics supplementation can have a positive effect on mood and psychological symptoms such as stress and anxiety disorders. The majority of studies, however, rely on animal models, while clinical data are still inconsistent. In this systematic review, we examined if and to which extent probiotics can influence psychological stress and anxiety disorders.

Methods: The search of online databases Medline, PubMed, Scopus, Web of Science and clinical trials.gov provided relevant studies up to November 2019. We included double blind, randomized and placebo controlled or prospective studies, as well as studies measuring preclinical psychological symptoms of perceived stress and anxiety, before and after supplementation with a probiotic.

Results: Twelve studies met the inclusion criteria (3 on stress, 4 on anxiety, and 5 both on stress and anxiety), accounting for 1,521 participants. The improvement of stress, anxiety, and stress-anxiety was reported in 1/3, 3/4, and 2/5 studies, respectively.

Conclusions: Available studies suggest that probiotics may improve psychological symptoms associated particularly with anxiety. Further research needs to investigate whether probiotics also improve psychological stress disturbances.

Key words: microbiota – probiotics – IBS – anxiety – stress.

Abbreviations: *B.*: *Bifidobacterium*; CFS: Chronic fatigue syndrome; CFU: Colony-Forming Units; DASS: Depression Anxiety and Stress Scale; GHQ: General Health Questionnaire; HAD: Hospital Anxiety and Depression Scale; HAMA: Hamilton Anxiety Rating Scale; IBS: irritable bowel syndrome; *L.*: *Lactobacillus*; *Lc*: *Lactococcus*; SCFAs: short chain fatty acids; SI: symptom intensity; *St.*: *Streptococcus*; STAI: State Trait Anxiety Inventory; VAS: Visual Analogical Scale.

INTRODUCTION

Psychological stress and anxiety are the most common causes of mental health disorders, mainly in developed countries [1]. Stress is a feeling of strain and pressure and according to the duration, psychological stress can be either acute or chronic [2]. On the other hand, pervasive worry, fear, and alterations of behaviour characterize anxiety disorders, interfering with normal routine and the quality of life [3]. With the progress of studies in brain and mental disorders, the role of the interplay

between gut microbiota, metabolic pathways with respect to mental disturbance, has emerged [4]. Gut microbes and related metabolites communicate with the brain through the *vagus* nerve and therefore can have an impact on the central neurochemistry [5]. Alteration in the composition of gut microbiota might be involved in stress-related response [6], and chronic fatigue in irritable bowel syndrome (IBS) [7]. Thus, probiotics can represent game changers also in mental disorders treatment [8].

Probiotics are microorganisms that positively supplement the gut providing beneficial effects [9]. Gastrointestinal symptoms such as constipation, diarrhoea, and abdominal pain are frequent in many mental diseases. This aspect points to the importance of maintaining a balanced connection between gut and brain [10]. The effects through which probiotics may influence the brain are various. Firstly, it is remarkable that specific probiotics modulate intestinal permeability, mitigate stress-induced glucocorticoids and/

or inflammatory cytokine responses in association with a reduction of depression and anxiety-related behaviour [11, 12]. Secondly, probiotics influence microbial-derived metabolites, including short chain fatty acids (SCFAs). In particular, dietary carbohydrates (e.g., resistant starches and soluble dietary fibers) act as substrates for intestinal fermentation, and result in SCFAs (e.g., acetate, propionate, and butyrate). Both the species and quantity of colonic microbiota govern the rate and amount of SCFAs production. In addition, the type of carbohydrate and gut transit time influence the characteristics of SCFAs. In general, butyrate provides the major energy source for colonocytes, the liver mainly takes up propionate, while acetate enters the peripheral circulation and is metabolized by peripheral tissues. Thus, SCFAs have a large number of physiologic effects, including cell signalling pathways, anti-inflammatory properties, and a positive modulation of gene expression [13].

In principle, probiotics can have several beneficial effects on mental disorders and related gastrointestinal symptoms, but their action is still under debate [14]. A number of experimental approaches in animal models investigated the modulatory effect of probiotics on gut-brain interactions. Protocols looked at the effects of microbial manipulations by antibiotics and faecal transplantation in mice under stress-conditions [15]. In germ-free mice, studies found a correlation between intestinal dysbiosis and anxiety related behaviour, with increased exploration of aversive zones and improved serotonergic function [16].

Despite the growing interest of research in this field, the literature is lacking regarding the role of probiotics in psychological stress and anxiety in humans. Here, we designed a systematic review to evaluate the data concerning the effectiveness of probiotics in human mood disorders. The paper focuses on the outcome of the treatment with the most trialled probiotics.

METHODS

Searching strategy

The systematic search concerned the following databases: Medline, PubMed, Scopus, Web of Science and clinical trials.gov. Search terms included “bacteria”, “cultured,” and “probiotics”, along with “anxiety”, “stress”. Therefore, all relevant articles written in English, from January 1991 to November 2019 were included. The reference lists of identified articles were carefully searched for additional information.

Study selection

The selection included double blind, prospective, randomized and placebo-controlled studies. No constraint existed on dosage, strain, or form/pharmacological conditioning of probiotics. No exclusion criteria regarding gender existed. Exclusion criteria included: animal studies; research studies dealing only with major depression; children (mean age ≤ 16 years), or older adults (mean age $65 \geq$ years); pregnant women; probiotics not living at time of administration (e.g. heat killed); triple blind, single arm and open label trials; absence of a scale for the measurement of anxiety and stress; studies reporting no or inconsistent results.

The PRISMA process allowed the study selection (preferred reporting items for systematic reviews and meta-analyses).

Dimensions of psychological symptoms

We analysed the main scales for stress and anxiety (eventually accompanied by depression) in the selected studies.

Psychological stress was defined as a perceived feeling of irritability and tension, which interfered with normal daily routine and sleep quality [14, 17-23]. Authors used different scales to quantify psychological stress. Tools included the general scale for pain or discomfort, i.e., the 10-cm Visual Analogue Scale (VAS with 0=“no stress” and 10=“extreme stress”) [17, 22]. Another study used an indirect method for psychological stress measurement (i.e., State Trait Anxiety Inventory= STAI) [19].

Studies evaluated psychological stress and anxiety by Depression Anxiety and Stress Scale (DASS) [14, 21]. Other authors used combined scales, i.e., General Health Questionnaire (GHQ) (indirect measure of psychological stress) associated with STAI (for anxiety) [18]. Anxiety and stress were also assessed by the Hospital Anxiety and Depression Scale (HAD) associated with STAI [20] or the Hamilton Anxiety Rating Scale (HAMA) associated with DASS [23]. Anxiety alone was assessed by HAD [24, 25, 26] or HAMA [23].

Outcome

The primary outcome was the psychological effects of probiotics in anxiety or psychological stress using at least one scale for the evaluation of symptoms. The secondary outcome was the determination of the most studied probiotic mixtures.

Data extraction and risk of bias

Only studies with results were included in the analysis. The following data were extracted from each study: authors and year, sample size and characteristics, study design, duration, strains and cell density (expressed in CFU, Colony-Forming Units), modality of assumptions of probiotics, measurements and outcome/findings. The title and abstract for each search result were screened by two independent reviewers (PV) and (AC). They independently applied the inclusion/exclusion criteria to the study. In cases of a non-consensus, an independent party DLD, PP took the decision.

RESULTS

The flow-chart of the systematic literature search and selection process is depicted in Fig 1. We initially found 1,555 records. After screening, the final group consisted of 12 records accounting for 1,521 participants. All studies passed the quality assessment at $> 50\%$ (data not shown). The characteristics of the included studies appear in Table I. The years of publication ranged from 2004 to 2018. Three papers, out of the 12 selected studies [18, 19, 23] were based on prospective randomized, placebo-controlled studies with parallel groups, meanwhile the others were randomized, double blind placebo-controlled studies. In the study of Marcos et al. (2004) [19], no information existed regarding gender.

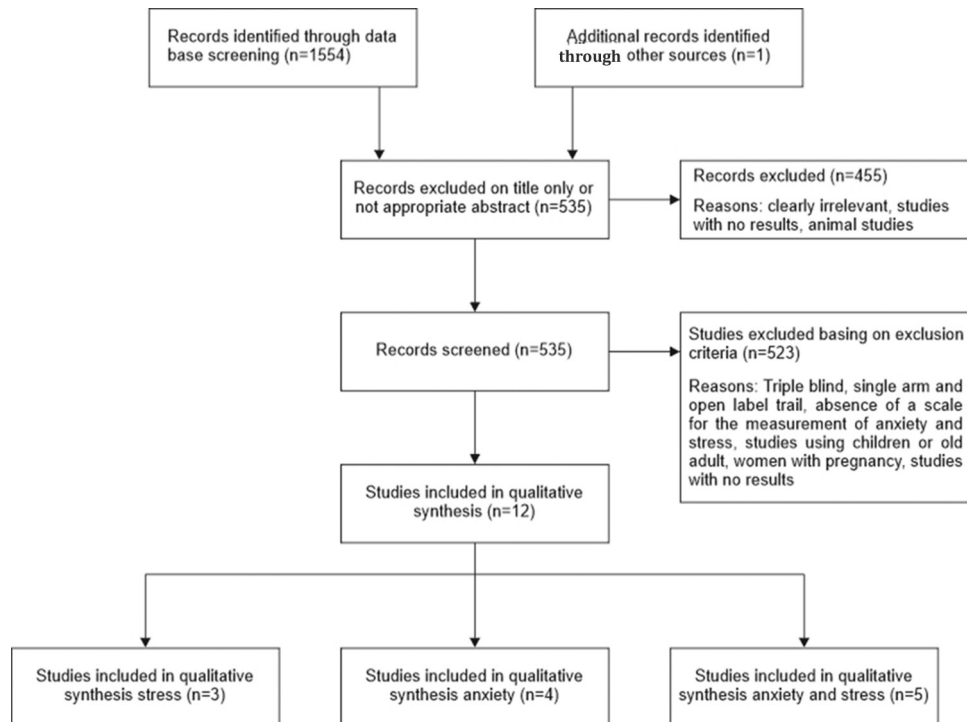


Fig. 1. Flow chart of the systematic literature search and selection process using preferred reporting items for systematic reviews and meta-analyses (PRISMA) process.

All selected studies assessed commensal bacterial species. All formulations contained *Lactobacilli* and/or *bifidobacteria* but also *Streptococcus* [19, 23] and *Lactococcus* [24]. No other bacterial species were trialled in the included studies. Four studies [24-27] used one probiotic strain and the other seven studies described a mixture of strains.

Lactobacillus (L.) casei was trialled in 5 out of the 12 selected studies, but no improvement of psychological stress was reported [20, 27], while an improvement of anxiety was reported [21, 25]. The studies of Kato-Kataoka et al. [20], and Takada et al. [18] used *L. casei* (strain 9029) with a cell density of 1.0×10^9 CFU/ml in milk (100 ml milk daily, thus 1.0×10^{11}). Meanwhile, in the study of Rao et al. [25], the same strain was given as sachets at higher cell-density (2.40×10^{10} CFU/g daily sachet). A different strain of *L. casei* (DN-114001) at different cell-density (1×10^8 CFU/ml daily) was also trialled in the mixture of strains in the study of Marcos et al. (2004) [19] and in the work of Mohammadi et al. [21] at cell-density of 1×10^7 CFU/g (100 g/daily, thus 1×10^9). *Bifidobacterium (B.) longum* was also tested in 5 out the 12 selected studies. Improvement of symptoms was reported in all studies except in the work of Diop et al. [22] valuating psychological stress and in the one of Romjin et al. [14] valuating both stress and anxiety. In particular *B. longum* was contained in the probiotic formulations at cell-density of 3×10^9 CFU/g in the studies of Diop et al. [22], Lamgkamp-Henken et al. [17], and Colica et al. [27]. Mohammadi et al. (2015) [21] trialled *B. longum* at cell-density of 1×10^7 CFU/g, meanwhile in the work of Romjin et al. [14], *B. longum* NCC3001 was tested as a single strain probiotic at cell-density of 1×10^{10} CFU/g. No studies, except the one of Simren et al. [28], among those included in our systematic review, reported information on the composition of diet during the study period (e.g. percentage of proteins) or reported a supplementation of daily diet with fibres.

Psychological stress

Three studies were included in our analysis accounting for 785 subjects [17, 19, 22]. All subjects were healthy. Two studies used the VAS scale to monitor the stress [17, 22]. The follow-up of the studies with stress ranged from 6 to 11 weeks. In the work of Marcos et al. [19], *L. casei* was contained in the trial in the multiple strains formulation, but no improvement of stress was reported. The only study reporting an improvement of psychological stress was the one of Langkamp-Henken et al. [17] (*B. bifidum* R0071, *B. longum* ssp. *infantis* R0033 and *L. helveticus* R0052) meanwhile in that of Diop et al. [22] (*L. acidophilus* Rosell-52 and *B. longum* Rosell-175), the improvement existed for stress-related abdominal pain ($p=0.04$) but not for psychological disturbance.

Anxiety

Four studies reported on the effect of probiotics in anxiety, with a total sample of 335 subjects [24-28]. IBS was reported in 218 out of the 335 subjects (65.07%). The length of the follow-ups ranged from 3 weeks to 2 months. All studies reported an improvement of anxiety, except the one by Pinto-Sanchez et al. [24], which reported an improvement of the total HAD score, with an amelioration of the depression score but not that of anxiety (Table I). In the study of Colica et al. [27], the improvement of anxiety occurred within 3 weeks. This study was the only one, among those considering anxiety, that trialled multiple strain probiotics.

Psychological stress and anxiety

Five out of the 12 identified studies examined both psychological stress and anxiety, with 400 subjects included in the analysis with a follow-up ranging from 6 to 12 weeks [14, 18, 20, 21, 23]. Only one study considered patients with moderate mood alteration (moderate score in DASS questionnaires) [14]. Takada

Table I. Characteristics of the selected studies

Authors and year	Sample size and characteristics	Study design	Duration	Strains and cell-density (Colony-Forming Units, CFU)	Modality of administration	Psychological symptom / Scale	Outcome/key findings
Marcos et al., 2004 [19]	155 Healthy students aged 18–23 years old	Prospective, randomized, placebo controlled and parallel study	6 weeks	1x10 ⁷ CFU/ml of <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>St. salivarius</i> subsp. <i>thermophilus</i> (1x 10 ⁸ /ml), <i>L. casei</i> DN114001 (1x10 ⁸ /ml)	Milk	Stress / STAI	Unchanged
Diop et al., 2008 [22]	37 Healthy volunteers 18–60 years old	Randomized double blind placebo-controlled study	3 weeks	3x10 ⁹ CFU/g of <i>L. acidophilus</i> Rosell-52 and <i>B. longum</i> Rosell-175 (all same cell-density)	Sachets	Stress / SI (VAS)	Unchanged
Langkamp-Henken et al., 2015 [17]	583 Healthy undergraduate students average age 20 years	Randomized double blind placebo-controlled study	6 weeks	3x10 ⁹ CFU/g of: <i>B. bifidum</i> R0071, <i>B. longum</i> ssp. <i>infantis</i> R0033 and <i>L. helveticus</i> R0052 (all same cell-density)	Capsule	Stress / SI (VAS)	Improved
Rao et al., 2009 [25]	39 Patients with CFS aged 18–65 years old	Randomized double blind placebo-controlled study	8 weeks	2.4 x 10 ¹⁰ CFU/g of <i>L. casei</i> Shirota 9029	Sachet	Anxiety / HAD	Improved
Simren et al., 2010 [28]	74 Adults with IBS; average age 44	Randomized, double-blind, controlled study	8 weeks	5x10 ⁷ CFU/ml of: <i>L. paracasei</i> subsp. <i>paracasei</i> F19, <i>L. acidophilus</i> La5, and <i>B. lactis</i> Bb12 (all same cell-density)	Milk	Anxiety / HAD	Improved
Colica et al., 2017 [27]	45 Healthy volunteers aged 20–75 years old	Prospective, randomized, placebo controlled and parallel study	3 weeks	3 x 10 ⁹ CFU/g of: <i>L. helveticus</i> R0052, and <i>B. longum</i> R0175 CNCM strain I-3470 (all same cell-density)	Sachets	Anxiety / HAMA	Improved
Kato-Kataoka et al., 2016 [20]	47 Healthy 4th-grade medical students average age 23	Randomized, double-blind, placebo-controlled, parallel-group trial	8 weeks	1.0x10 ⁹ CFU/ml <i>L. casei</i> Shirota 9029	Milk	Anxiety / STAI Stress / HAD	Unchanged anxiety Improved stress
Mohammadi et al., 2016 [21]	70 Healthy petrochemical workers aged 20–60 years old	Randomized double blind placebo-controlled study	6 weeks	1 x 10 ⁷ CFU/ml of: <i>B. lactis</i> BB12, <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>L. bulgaricus</i> , <i>B. breve</i> , <i>B. longum</i> (all same cell-density) <i>St. thermophiles</i> (2.9 x 10 ¹⁰)	Yogurt	Anxiety and Stress / DASS	Both improved
Pinto Sanchez et al., 2017 [24]	144 IBS patients average age 43 years	Double-blind, randomized placebo-controlled, single-center pilot study.	6 weeks	1.5x10 ¹⁰ CFU/g of: <i>St. thermophilus</i> , <i>L. bulgaricus</i> ; <i>Lc. lactis</i> , <i>L. acidophilus</i> , <i>St. thermophiles</i> , <i>L. plantarum</i> ; <i>B. lactis</i> , <i>L. reuteri</i> (all same cell-density)	Sachets	Anxiety / HAD	Unchanged anxiety Improved depression score
Romijn et al., 2017 [14]	79 Patients with moderate self-reported mood alteration average age 36 years	Randomized double blind placebo-controlled study	8 weeks	1 x 10 ¹⁰ CFU/g of <i>B. longum</i> NCC3001	Sachet	Anxiety and Stress / DASS	Unchanged
Takada et al., 2017 [18]	94 Healthy students average age 23 years	A double-blind, placebo-controlled, randomized parallel-group trial	11 weeks	1.0 x10 ⁹ CFU/ml of <i>L. casei</i> Shirota 9029	Milk	Anxiety / STAI Stress / GHQ	Unchanged anxiety Improved stress-induced sleep disturbance

Table I (continued)

Lew et al., 2018 [23]	110 Healthy stressed adults, 18-60 years old	Double blind, randomized, placebo controlled study	12 weeks	1.0 x 10 ¹⁰ CFU/g of <i>L. plantarum</i> P8 2g/day	Sachet	Anxiety and Stress / DASS Anxiety / HAMA	Improved anxiety and stress
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Abbreviations: CFU: Colony-Forming Units; *L.*: *Lactobacillus*; *B.*: *Bifidobacterium*; *St.*: *Streptococcus*; *Lc.*: *Lactococcus*; STAI: State Trait Anxiety Inventory; SI: symptom intensity; VAS: (Visual Analogical Scale); CFS: Chronic fatigue syndrome; HAD: Hospital Anxiety and Depression Scale; GHQ: General Health Questionnaire; DASS Depression Anxiety and Stress Scale; HAMA: Hamilton Anxiety Rating Scale.

et al. [18] and Kato-Kataoka et al. [20] used *L. casei* in healthy medical students with mean age of 23 years. Treatment lasted 8 weeks [18] and 11 weeks [20] with a good safety profile, and no adverse events. In the study of Kato-Kataoka et al. [20] STAI score did not improve but sleep disturbance improved significantly. In addition, the proportion of stressed students decreased.

DISCUSSION

In this systematic review, we investigated the effects of probiotics on psychological stress and anxiety disorders. According to our inclusion criteria, our analysis is based on 1,521 participants. *Lactobacilli* and/or *bifidobacteria* were trialled in all the included studies, suggesting that strains of *lactobacilli* and *bifidobacteria* may provide psychological healthy benefits [29] and could be useful in treating physiological disturbances [30]. Anxiety is often associated with major depression, but we decided to exclude major depression forms from this systematic review. In fact, even if probiotic administration has beneficial effects on the Beck Depression Inventory scores on depressive disorders [31], antidepressants represent the gold standard for the treatment of this disease [32]. According to our results, *L. casei* and *B. longum* were one of the most studied strains. However, due to the contradictory results, especially those on psychological stress, we cannot draw definitive conclusions about the effectiveness of these two strains. This finding is in accordance with the work of Wallace and Milev [33] who systematically reviewed 10 randomized controlled trials on the effect of probiotic on anxiety, depression and stress. Liu et al. [34], after screening 12 clinical trials on the same topic, concluded that data in the literature are still inconsistent.

We indeed found that data are rather heterogeneous. Firstly, the pooled patients differed in terms of clinical and psychological conditions. For example, we included both the work of Romjin and Rucklidge et al. [14] with patients with psychiatric symptoms, and healthy individuals [23]. Even the inclusion and exclusion criteria differed between these studies. Moreover, supplement administration varied between the included studies in terms of the duration of the treatment, probiotic type and cell-density. However, according to our results, we could assume that the effect of probiotic *lactobacilli* and *bifidobacteria* strains in psychological stress seems to be more limited or absent if compared to that on anxiety. Even if evidence exists regarding the contribution of probiotics in improving stress [35], the literature is still very poor in this respect [36]. Moreover, a controlled diet was lacking in any of the selected studies, and all patients followed their normal routine-diet. Thus, since the composition of diet strongly impacts gut microbiota, relative metabolome and mental health

[37], this aspect should also be assessed in further studies in this field.

None of the studies with the exception of Kato-Katoka et al. [20], examined the microbiota at baseline or after treatment. Thus, there is the possibility of dysbiosis in patients considered otherwise healthy. In this case, the improvement of psychological outcome might be secondary to the restoration of gut microbial balance. In particular, the existence of dysbiosis is largely demonstrated in IBS [38, 39, 40], as well as the relationship between mood disorder and IBS onset [41]. Interestingly, both Pinto-Sanchez et al. [24] and Simren et al. [28] included IBS patients, and both studies reported an improved HAD score. Data suggest that probiotics could improve gastrointestinal disturbance and quality of life in IBS patients [42, 43], as well as in patients with Chronic Fatigue Syndrome [44].

CONCLUSIONS

This review indicates that treatment with probiotic *lactobacilli* and *bifidobacteria* strains may particularly improve psychological symptoms associated with anxiety. Despite extensive preclinical data, further studies need to determine the ultimate efficacy probiotics in alleviating psychological stress-related disorders. Moreover, more double-blind randomized controlled trials, and prospective studies need to address additional key points. These include the efficacy of other probiotic formulations in improving psychological outcome, the role of the diet, and the involvement of a possible dysbiosis in the onset of these disorders.

Conflicts of interest: None to declare.

Authors' contributions: D.L.D.: study concept and design; A.C, P.V. literature search and data acquisition; D.L.D., M.D.A., P.P.: data analysis. All the authors were involved in the writing of the manuscript and approved the final version.

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