Are probiotic treatments useful on Fibromyalgia Syndrome or Chronic Fatigue Syndrome patients? A systematic review

Probiotics on Fibromyalgia and Chronic Fatigue Syndrome

Pablo ROMAN¹,², Francisco CARRILLO-TRABALÓN³, Nuria SÁNCHEZ-LABRACA¹, Fernando CAÑADAS⁴, Angeles F. ESTÉVEZ⁴, Diana CARDONA¹*.

¹ Department of Nursing Science, Physiotherapy and Medicine, Universidad de Almería, Almería, Spain. Ctra. Sacramento s/n, 04120 Almería, Spain.
² Department of Nursing, Universitat Jaume I, Castellón, Spain. Avenida de Vicent Sos Baynat, s/n, 12071 Castellón de la Plana, Spain.
³ Faculty of Health Sciences, Universidad de Almería, Almería, Spain. Ctra. Sacramento s/n, 04120 Almería, Spain.
⁴ Department of Psychology, Universidad de Almería, Almería, Spain. Ctra. Sacramento s/n, 04120 Almería, Spain.

Corresponding author

Dra. Diana Cardona, Departamento de Enfermería, Fisioterapia y Medicina. Universidad de Almería, Ctra. Sacramento s/n, 04120 La Cañada de San Urbano (Almería, Spain).

E-mail Address: dcardona@ual.es, Phone Number: (+34) 950 214 580
CONFLICT OF INTEREST STATEMENT AND FUNDING STATEMENT

The authors report no declarations of interest. PR was supported by a grant from University of Almeria Research Plan.

AUTORSHIP

Guarantor of the article: DC.

Author contributions: DC, PR and FCT initially conceptualized the study. PR and FCT developed the initial literature search strategy and performed eligibility screening, carried out the search and the data extraction and methodological quality assessment. DC was consulted when the consensus was not obtained between the two first authors. All the authors (PR, FCT, NS, FC, AFE and DC) discussed and extracted data of the included studies. PR assumed the main responsibility for the writing of the first draft of the manuscript. NS, FC, AFE and DC contributed critically in the corrections until getting the final version of the manuscript. All authors approved the final version of the manuscript.
Are probiotic treatments useful in Fibromyalgia Syndrome or Chronic Fatigue Syndrome patients? A systematic review

ABSTRACT

**Background.** Evidence suggests that the gut microbiota might play an important role in fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS).

**Aim.** Our goal is to systematically review the reported effect of probiotic treatments in patients diagnosed with FMS or CFS.

**Methods.** A systematic review was carried out using 14 databases (PubMed, Cochrane Library, Scopus, PsycINFO, and others) in February 2016 to search for randomized controlled trials (RCTs) and pilot studies of CFS or FMS patient, published in the last ten years (from 2006 to 2016). The Jadad scale was used to asseverate the quality of the clinical trials considered.

**Results.** Two studies (n=83) met the inclusion criteria, which were performed in CFS patients and both studies were considered as a “HIGH range of quality score”. The administration of *Lactobacillus casei* strain Shirota in CFS patients, over the course of 8 weeks, reduced anxiety scores. Likewise, this probiotic changed the faecal composition following 8 weeks of treatment. Additionally, the treatment with *Bifidobacterium infantis* 35624 in CFS patients, during the same period, reduced inflammatory biomarkers. The evidence about the usefulness of probiotics in CFS and FMS patients is remains limited.

**Conclusions.** The studied strains of probiotics have demonstrated a significant effect on modulating the anxiety and inflammatory processes in CFS patients. However, more
experimental research, focusing mainly on the symptoms of the pathologies studied, is needed.

**Keywords:** probiotics; fibromyalgia; chronic fatigue syndrome; gut-brain axis; microbiota; nutrition; systematic review
INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic, generalized and diffuse pain disorder accompanied by symptoms such as morning stiffness or rest, fatigue, depression and sleeping disorders, which etiology is still unknown (Wolfe et al., 1990, 2010). The European population has different prevalence rates of FMS, from 1.4% in France to 3.7% in Italy (Branco et al., 2010). Similar prevalence data have been found in other countries such as North America with an estimated prevalence rate ranging from 2.0% to 3.3% (reviewed in Jones et al., 2015). However, this rate of prevalence could be increased in relation to the diagnosis criteria used. For example, with the modified 2010 criteria (Wolfe et al., 2011), the prevalence rate increases to 5.4%, with a ratio of females to males of 2.3:1 (Jones et al., 2015).

FMS is often associated with other somatic syndromes such as chronic fatigue syndrome (CFS), a condition characterized by 6 months or more of persisting or relapsing fatigue caused by an over-production of pro-inflammatory cytokines; the CFS prevalence rate ranges from 3 to 20% (Penfold, St. Denis, & Mazhar, 2016). For example, while all patients with CFS present with high levels of fatigue, there is considerable overlap in patients with FMS, with a percentage of 86% reporting fatigue as well (Aaron, Burke, & Buchwald, 2000). In addition, Aaron and Buchwald (2001) and Buchwald and Garry (1994), found that between 35% to 70% of CFS patients met the criteria for FMS, reporting a considerable co-occurrence with CFS (Odds Ratio (OR)=23.2) (Kanaan, Lepine, & Wessely, 2007).

Although the most common symptom in FMS is pain and in CFS is fatigue, a high prevalence of gastrointestinal symptoms has been reported in both disorders (Aaron et al., 2000). In fact, 81% of FMS patients reported normal alternating with
irregular bowel pattern, and 63% had alternating diarrhoea and constipation (Triadafilopoulos, Simms, & Goldenberg, 1991). Similarly, 32.2% of CFS patients used various gastrointestinal drugs in comparison with control subjects (14.3%), indicating an OR of 2.67 (Jones, Nisenbaum, & Reeves, 2003).

Conversely, between 32% to 80% of patients with FMS met the criteria for irritable bowel syndrome (IBS), a common functional disorder of the gastrointestinal tract (Aaron & Buchwald, 2001; Riedl et al., 2008; Sperber et al., 1999; Whitehead, Palsson, & Jones, 2002), with considerable comorbidities (OR from 1.8 to 5.3) (Kanaan et al., 2007). Likewise, between 58 and 92% of patients with CFS met criteria for IBS (Aaron & Buchwald, 2001).

Cognitive and affective deficits, such as nervousness, memory loss, forgetfulness and confusion, have been documented in patients with CFS or FMS (Glass, 2008; Joyce, Blumenthal, & Wessely, 1996). Interestingly, it was demonstrated that the severity of these neurological and cognitive deficits is related to reduced levels of *Bifidobacterium* spp. and increased levels of *Enterococcus* spp, which have been detected in FMS as well as in CFS (Butt, Dunstan, McGregor, & Roberts, 2001). In addition, CFS patients show alterations in gut microbiota suggesting a probable link between intestinal colonization of gram-positive facultative anaerobic D-lactic acid bacteria and symptom expression, these bacteria have been reported to be associated with cognitive dysfunction and neurological impairment in patients with intestinal bacterial overgrowth (Sheedy et al., 2009). Pimentel and colleagues (2003) found an abnormal lactulose breath test in FMS patients (78%), which suggested bacterial overgrowth of the small intestine (SIBO), which represents one form of alteration of the normal gut microbiota characterized by a qualitative and quantitative change of the bacterial colonies that inhabit the small intestine. Under normal conditions, the upper
tract of the small intestine is mainly colonized by Gram-positive bacteria whose counts do not exceed $10^3$ organisms/mL. However, in the case of SIBO, the count of these colonies either increases to or exceeds $10^5 – 10^6$ organisms/mL (Slim, Calandre, & Rico-Villademoros, 2015). A later research study by Pimentel and colleagues (2004) demonstrated that 100% of FMS patients were diagnosed with SIBO compared to 84% of subjects with IBS and 20% of healthy subjects.

Other facts indicating that the gastrointestinal system is affected in FMS patients may include hypersensitivity to food components, celiac disease, non-celiac gluten sensitivity, lactose intolerance and FODMAPs (Fermentable oligo-, di-, mono-saccharides and polyol) (Slim et al., 2015). An increase in secretory immunoglobulin A (sIgA) has also been observed in FMS (Michalsen et al., 2005), which is related to fatigue, major depression and gastrointestinal symptoms (Maes, Kubera, & Leunis, 2008).

All of the aforementioned findings demonstrate the relevance of microbiota in FMS and CFS, pointing to the potential use of probiotics in these syndromes, as it has been recently suggested by several authors (Galland, 2014; Lakhan & Kirchgessner, 2010; Slim et al., 2015). Probiotics are live microorganism that, when administered in adequate amounts, confer a health benefit to the host (FAO/WHO, 2001). Several authors suggest that the effects of probiotics may be genus-specific or depend on the species or strain or the dose used (Umbrello & Esposito, 2016). IBS is one of the populations with more evidence from probiotic treatments (Didari, Mozaffari, Nikfar, & Abdollahi, 2015; Tiequn, Guanqun, & Shuo, 2015). In fact, pain and symptom severity scores in IBS patients have been reported to be reduced after the consumption of probiotics. Similarly, probiotics have been demonstrated as also useful in patients with SIBO (Khalighi et al., 2014). In recent years, the interest of the role of probiotics in
mood and emotional modulation has increased. Mood and emotional symptoms are also present in patients with FMS and CFS and may be affected by probiotics (Benton, Williams, & Brown, 2007; Messaoudi, Lalonde, et al., 2011; Messaoudi, Violle, et al., 2011; Steenbergen, Sellaro, van Hemert, Bosch, & Colzato, 2015). Probiotic effectiveness in improving depression and anxiety is produced through the connection between the gut and the brain or gut-brain axis (Carabotti, Scirocco, Maselli, & Severi, 2015; Cryan & O’Mahony, 2011; Cryan & Dinan, 2012; De Palma, Collins, Bercik, & Verdu, 2014; Diaz Heijtz et al., 2011; Maes et al., 2008; Sherwin, Rea, Dinan, & Cryan, 2016).

To summarize, the high comorbidity between FMS and CFS with gastrointestinal pathologies, such as IBS, as well as the high gastrointestinal symptomatology presented by these patients has been documented. In addition, several other symptoms presented in FMS and CFS patients, such as anxiety or depression, have been improved through treatment with probiotics in other populations. Altogether, these findings support our hypothesis that the probiotics could improve FMS and CFS symptoms. A better understanding of the probiotic effects in these pathologies is required to develop integrative approaches for patient care. Therefore, the aim of this study was to systematically review the reported effect of probiotic treatments in patients diagnosed with FMS or CFS.

**METHODS**

In February 2016, a systematic review of clinical trials and pilot studies was conducted. The process of reviews adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The Cochrane Handbook for Systematic Reviews (Higgins & Green, 2011) was also
consulted. The search was limited to studies published in the last ten years, from 2006 to 2016. The protocol for this review was not registered.

Research Question

The follow structured, Patient-Intervention-Outcomes question (PIO) (Stone, 2002) was used as follows: Are probiotics able to reduce or improve symptoms in FMS or CFS patients?

Data sources/Informations sources

The search was conducted in a total of 14 electronic bibliographic databases, due to the novelty and multidisciplinary approach of the topic. The search for clinical trials and pilot studies using probiotics for FMS or CFS was conducted using the following: Cochrane Library, ProQuest, Turning Research Into Practice (TRIP), Web of Science, PubMed, The Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, PsycINFO, ScienceDirect, AGRICOLA, DialnetPlus, LILACS, Scielo, National Institute for Health and Care Excellence (NICE), and the searches were complemented using the snowball strategy.

To identify the potential studies in electronic databases, structured by the PIO research question, the following keywords (MeSH or DeCS) were used: patients key words (“fibromyalgia” OR “fatigue syndrome, chronic”), AND intervention keywords (“probiotics” OR “lactobacillus” OR “bifidobacterium”), AND outcomes keywords (“pain” OR “depression” OR “anxiety” OR “fatigue” OR “muscle rigidity” OR “sleep wake disorders” OR “headache” OR “migraine without aura” OR “paresthesia”) in the title, key words or abstract. After a preliminary search, it was decided to exclude
outcome keywords in the definite searches because they limited too much of the available research.

**Study Eligibility Criteria**

The following inclusion criteria were used in this review: (1) randomized controlled trials (RCTs) or pilot studies in humans; (2) participants diagnosed with FMS or CFS; (3) publications from January 1, 2006 to February 1, 2016; (4) published in English or Spanish; and (5) adult participants aged 18 years or older.

**Study Selection and Methodologic Quality**

The two first authors carried out the databases search. Next, the studies were selected by the two same authors who, independently and in duplicate, reviewed all studies. If consensus could not be achieved, the third author was consulted and asked for a recommendation to include it or not. The selected data were discussed at a face-to-face meeting of all authors (reviewers); all authors also discussed the extracted data.

Full texts of potentially relevant articles were independently appraised by the same two authors using the Jadad Scale for Reporting Randomized Controlled Trials, a checklist with five simple items that help to evaluate the quality of RCTs in a simple way (Clark et al., 1999). In addition, this scale contains many of the important elements that have empirically been demonstrated to correlate with bias, and it has known reliability and external validity (Halpern & Douglas, 2005). The scoring is based on the quality of randomization, double blinding, and losses to follow-up and establishes a score of greater than 3 points as high quality and less than 3 points as low quality (Jadad et al., 1996).

**Data Extraction and Data Synthesis**
The major categories of the coded variables include the following: (1) reference, (2) number of enrolled patients, (3) probiotics used, (4) outcomes and (5) duration of the intervention.

Initially we planned to report the effectiveness of probiotics by using descriptive statistics. However, the few results and the heterogeneity of outcomes measures used across the studies made the meta-analysis impossible. Thus, we decided to report the effectiveness of probiotic treatments by using narrative summaries.

Complementary Search

Complementary searches were performed about other uses of specific probiotic strains used in FMS or CFS patients (Lactobacillus casei strain Shirota and Bifidobacterium infantis 35624). A brief (synthesis) of these results can be found in Table S1 and Table S2.

RESULTS

From a total of 537 eligible articles found in our initial search, we finally included 2 articles that met the inclusion criteria. The review and selection processes are detailed in Figure 1.

Figure 1. Flowchart of literature search carried out for this review.

Included studies

A total of 2 primary research papers (Groeger et al., 2013; Rao et al., 2009) were included in this review (detailed information is demonstrated in Table 1). We did not identify any clinical trials. These 2 articles could be considered pilot studies, although
only Rao et al. (2009) identified their study as a pilot study. Both studies were randomized and double-blinded. They included 4 groups (2 intervention and 2 control). Although the study of Groeger and colleagues (2013) included other pathologies and a healthy subject group, in our review, we focused only on the group with CFS patients. Neither of the included studies was focused on FMS patients. Eighty-three patients diagnosed with CFS, 8 men and 75 women randomly assigned, participated in both studies (the sample sizes ranged from 35 (Rao et al., 2009) to 48 (Groeger et al., 2013)). All of the included studies clearly described how the sample size was calculated. The age range of the participants was 18 to 65 years old. The studies were conducted in Ireland and Canada and were published in English.

Table 1. Included studies on Probiotics in CFS (n=2) or FMS (n=0).

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (EXP/CON)</th>
<th>Investigated probiotics (dose)</th>
<th>Outcomes</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao et al., 2009</td>
<td>48 (28/20)</td>
<td><em>Lactobacillus casei</em> strain Shirota (2.4*10^10 CFU per day)</td>
<td>Depression: BDI</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety: BAI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stool Samples</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inflammatory</td>
<td></td>
</tr>
<tr>
<td>Groeger et al., 2013</td>
<td>35 (19/16)</td>
<td><em>Bifidobacterium infantis</em> 35624 (1x10^10 CFU per day)</td>
<td>Plasma cytokine biomarker: CRP</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>levels: IL-6 and TNF-α.</td>
<td></td>
</tr>
</tbody>
</table>
EXP: Treatment group; CON: Placebo group; CFU: colony-forming units; BDI: Beck depression Inventory; BAI: Beck Anxiety Inventory; CRP: C-Reactive Protein; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor

**Methodologic Qualities of Studies: risk of bias and quality of evidence**

Table 2 presents the assessment of methodological quality and potential risk of bias in the included studies using the Jadad Scale. The study by Rao et al. (2009) obtained a score of 4 points, while the study by Groeger et al. (2013) obtained 3 points; thus, both studies were considered as a “HIGH range of quality score”.

**Table 2. Quality Appraisal based on Jadad Scale for RCTs (n = 2).**

<table>
<thead>
<tr>
<th>Appraisal Criteria</th>
<th>Rao et al., 2009</th>
<th>Groeger et al., 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was randomization mentioned?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2. Was method of randomization appropriate?</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>3. Was blinding mentioned?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>4. Was method of blinding appropriate?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>5. Was the fate of all patients in the trial known?</td>
<td>Y</td>
<td>U</td>
</tr>
</tbody>
</table>

**Scores** 4 3

N – no; NA – not applicable; U – unclear; Y – yes.
**Effects of intervention**

- **Specific intervention**

  The probiotics used in the included studies were the *Lactobacillus casei* strain Shirota (LeS) (Rao et al., 2009) and *Bifidobacterium infantis* 35624 (Groeger et al., 2013). The duration of the treatment for both studies was 8 weeks. More details about the use of these probiotics in other pathologies can be found in Table S1 and Table S2, as result of a complementary search.

- **Gut composition**

  In the study of Rao et al. (2009) the faecal composition of *Bifidobacteria* and *Lactobacillus* was assessed pre- and post- treatment. Compared to the placebo control group, the probiotic group demonstrated moderate increases in total faecal aerobes and anaerobes and significant increases in total faecal *Bifidobacteria* and *Lactobacillus*. Specifically, in the placebo group only 37.5% of subjects demonstrated an increase in *Bifidobacteria*, whereas 62.5% of participants demonstrated a decrease. In the probiotic group, 73.7% of the faecal samples increased in *Bifidobacteria*, and 26.3% decreased after the treatment.

  Concerning *Lactobacillus*, in the placebo group, 43.8% increased their levels, while 56.2% decreased. In the probiotic group, 73.7% increased, 21% decreased, and 5.3% had no change.

  Summarizing, the total faecal aerobes in comparison with the baseline decreased in the placebo group, while they increased in the probiotic group. With respect to total anaerobes, in the placebo group, they remained almost unchanged, while in the probiotic group, the total increased after the treatment.
• Anxiety and depression

According to the research of Rao et al. (2009), the anxiety of CFS patients was evaluated by the Beck Anxiety Inventory (BAI), and a significant decrease (p=0.011) was found in the anxiety scores in the probiotic group, compared with the placebo group. However, no significant difference (p=0.292) in depression, assessed by the Beck Depression Inventory (BDI), was observed among those taking probiotics.

• Inflammatory processes

Groeger and et al. (2013) reported that the oral administration of *Bifidobacterium infantis* 35624 modulated the cytokine milieu across non-gastrointestinal inflammatory disorders. Specifically, following the administration of the probiotic, they directed their analysis of plasma levels of C-reactive protein (CRP), a biomarker of inflammation, and the following peripheral pro-inflammatory cytokines: TNF-α and IL-6. Probiotic-fed CFS patients demonstrated reduced plasma levels of CRP (p=0.0285), TNF-α (p = 0.0214) and IL-6 (p = 0.054) compared to placebo-fed CFS patients. When comparing the probiotic-feeding effect to baseline (pre-treatment plasma levels), they also reported a significant post-treatment reduction in the plasma levels of CRP (p= 0.0393), TNF-α (p =0.0129) and IL-6 (p = 0.0021) in CFS patients. Contrastingly, in the placebo-fed CFS group, the plasma CRP and TNF-α levels increased slightly, while the plasma IL-6 levels remained unchanged after eight weeks of treatment.

Therefore, the individual’s biomarkers (CRP, TNF-α, and IL-6; represented by percentage changes from baseline) demonstrated that 71% of CFS patients in the probiotic group displayed decreased levels at week 8, whereas in the placebo group, only 11% of participants demonstrated a decrease in these levels at the same period.
Adverse effects and safety of probiotics

Rao et al. (2009) demonstrated that the LcS probiotic powder was well tolerated and that there were no significant adverse events reported in the probiotic group or in the placebo group. Groeger et al. (2013) did not assess whether the *Bifidobacterium infantis* 35624 was well tolerated; however, no significant adverse events were reported in the probiotic group.

**DISCUSSION**

This systematic review aimed to critically appraise and synthesize the existing empirical evidence on the effectiveness of probiotic administration for the treatment of FMS or CFS symptoms. To the best of our knowledge, this is the first systematic review of the effects of probiotics on these syndromes.

The available research concerning the potential usefulness of probiotic treatment for FMS or CFS is limited. Nevertheless, it seems, from the results of the two studies reviewed here (Groeger et al., 2013; Rao et al., 2009), that some probiotic strains might improve the symptoms of anxiety and inflammation in these populations.

However, it is worth noting that all the included studies were conducted in CFS patients and that neither of the studies were carried out in FMS patients. Additionally, neither of these studies were focused on fatigue, the core symptom of CFS. Interestingly, in a study excluded as an exploratory study, Sullivan, Nord and Evengård (2009) evaluated the effect of *Lactobacillus paracasei ssp. Paracasei* F19, *Lactobacillus acidophilus* NCFB 1748 and *Bifidobacterium lactis* Bb12 on fatigue and physical activity in 15 patients diagnosed with CFS. Their results demonstrated that
participants improved their neurocognitive functions by subjectively reporting that their short-term memory and capacity to concentrate (p=0.040) was affected from baseline to the end of the follow-up (day 72), but no significant differences in fatigue or in the remaining variables measured (health and physical activity) were observed. Another study carried out in patients with spondyloarthritis (Jenks et al., 2010), using a combination of probiotics (Streptococcus salivarius K12, Bifidobacterium lactis LAFTI B94, and Lactobacillus acidophilus LAFTI L10) for 12 weeks, patients demonstrated no significant benefit over placebo concerning fatigue. Finally, an improvement trend in fatigue (p<0.10) was observed when colorectal cancer patients who received a 12-week probiotic intervention containing Lactobacillus rhamnosus combined with Lactobacillus acidophilus were compared to a placebo group (Lee et al., 2014).

Although only CFS patients improved in their anxiety scores after receiving probiotics (Rao et al., 2009), there is much more evidence from other populations concerning both anxiety and depression. For example, Steenbergen et al. (2015) concluded that the intake of a multispecies probiotic for 4 weeks in healthy subjects could reduce negative thoughts associated with a sad mood, suggesting that the probiotic supplementation was a potential preventive strategy for depression. Another study carried out by Messaoudi, Lalonde, et al. (2011) in the general population demonstrated that Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 taken in combination for 30 days decreased the global scores on the Hospital Anxiety and Depression (HAD) scale. Similar results were also found in a population with low urinary free cortisol levels at baseline (Messaoudi, Violle, et al., 2011). Finally, Akkasheh and colleagues (2016) observed that an 8-week probiotic administration (containing Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium
bifidum) had beneficial effects on BDI scores (p=0.001) among patients with major depressive disorder compared with the placebo group.

Several studies have demonstrated beneficial effects from probiotics in IBS, a syndrome with a great comorbidity with CFS and FMS (Aaron & Buchwald, 2001; Kanaan et al., 2007). Lorenzo-Zúñiga et al. (2014) observed that a new combination of three different probiotic bacteria ((two Lactobacillus plantarum (CECT7484 and CECT7485) and one Pediococcus acidilactici (CECT7483)) was superior to a placebo in improving IBS-related quality of life in patients with IBS and diarrhoea. Similar results were found with prebiotics, demonstrating a significant effect (p<0.05) in anxiety scores but not in depression level, both assessed by the HAD (Silk, Davis, Vulevic, Tzortzis, & Gibson, 2009). Nevertheless, Dapoigny et al. (2012), using the same scale, did not observe any clinical difference between the probiotic group (Lactobacillus caseirhamnosus LCR35) and the placebo group. With respect to pain, probiotics (Lactobacillus rhamnosus GG) significantly reduced the frequency and severity of abdominal pain in children with IBS (Francavilla et al., 2010) and appeared to moderately increase the treatment success (Gawrońska, Dziechciarz, Horvath, & Szajewska, 2007). This reduction of pain after probiotic treatment was also observed in patients with rheumatoid arthritis. In fact, Mandel, Eichas and Holmes (2010) found that the probiotic group (Bacillus coagulans GBI-30, 6086) experienced a borderline statistically significant improvement in the patient pain assessment score (p=0.052) and a statistically significant improvement in the pain scale (p=0.046) in comparison with the placebo group. Additionally, and in accordance with the results obtained by Groeger et al. (2013), the probiotic group demonstrated reduced CRP levels compared with the placebo group. Finally, it is worth noting that Ringel-Kulka et al. (2014) provide a
possible mechanism of action by which probiotics (*L-NCFM*) modulate pain sensation in humans through opioid-mediated pathways.

In recent years, accumulating evidence has suggested that probiotics may have a positive effect on health through the brain-gut axis (Bercik & Collins, 2014; De Palma et al., 2014; Diaz Heijtz et al., 2011; Sherwin et al., 2016). Communication in this axis would take place via the following three different pathways: neural (mainly by the vagus nerve and the enteric nervous system), endocrine (cortisol) and immune (cytokines) (Carabotti et al., 2015; Cryan & Dinan, 2012; Cryan & O’Mahony, 2011; Petschow et al., 2013; Zhou & Foster, 2015). Several proposed mechanisms of action of probiotics include competition against the pathogenic bacteria that bind to the intestinal epithelial cells, enhancement of the intestinal epithelial barrier function, inhibition of pathogen growth by the secretion of antimicrobial peptides, and enhancement of the production of serum IgA as possible mechanisms (Hardy, Harris, Lyon, Beal, & Foey, 2013; Upadhyay & Moudgal, 2012). It has also been recently suggested that probiotics may affect the central nervous system via the BGA (i) by enhancing the production and delivery of neuroactive substances, such as gamma-amino butyric acid (GABA), serotonin, dopamine and acetylcholine; (ii) by the vagus nerve (Dinan, Stanton, & Cryan, 2013) and (iii) by decreasing pro-inflammatory cytokines, which are able to cross the blood-brain barrier and elicit mood and behavioural changes (Hardy et al., 2013). For instance, some probiotics have been demonstrated to induce an elevation in tryptophan levels in plasma (Desbonnet, Garrett, Clarke, Bienenstock, & Dinan, 2008), which is a precursor of serotonin. Serotonin has been implicated in emotional processes, cognition, motor function and pain, as well as in neuroendocrine functions, such as food intake, circadian rhythms and reproductive activity (Martinowich & Lu, 2008).
Despite the hypothesis of the usefulness of probiotics in FMS and CFS, this systematic review has shown that, till today, the number of clinical trials is too limited to conclude that probiotics are useful in these pathologies. This fact is due to the unknown etiology and widespread symptoms suffered by these patients. However, these results could be increased in the coming years with incoming clinical trials, controlled and double blind, such as the one that Roman and colleagues are performing from 2017.

This review is not free of limitations. There are some methodological limitations that we must highlight, the protocol of the review has not been registered. In addition, we imposed date restriction (from year 2006 to year 2016), however, this aspect might not influence in the results as this topic is very recent. Concerning the databases used, we included a large number that increased the number of repeated results. Likewise, we used “Lactobacillus” and “Bifidobacterium” as descriptors due to that those are the main probiotic strains, but not other strains such as “Streptococcus” or “Pediococcus” were included. Nevertheless, these and others probiotic strains are included in the descriptor “probiotic”, so that this circumstance may not interfere in the results.

CONCLUSIONS

Through this systematic review, we conclude that several probiotic strains (Lactobacillus casei strain Shirota and Bifidobacterium infantis 35624) demonstrate beneficial effects in CFS patients. However, none of the studies were carried out in FMS patients. These reported benefits include decreased anxiety levels and changes in the microbiota composition, as well as a reduction in several systematic inflammatory biomarkers. A large and exhaustive review of the literature was presented, suggesting the possible mechanism involved in these effects. However, due to the reduced number of studies included in this review, more research is required to clarify the possible
beneficial effects of probiotics for other symptoms of FMS and CFS such as fatigue or pain. Taking into account the results obtained with other populations, we also think that probiotics might improve emotional and cognitive processes in patients with FMS and CFS. Further studies should investigate this issue.

REFERENCES


Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., … Cazaubiel,


Petschow, B., Doré, J., Hibberd, P., Dinan, T., Reid, G., Blaser, M., … Sanders, M. E.


