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

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Probiotics on Fibromyalgia and Chronic Fatigue Syndrome

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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 Garrity (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 hipersensivity 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/Information 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.

Insert Figure 1 around here

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).

Study	Participants (EXP/CON)	Investigated probiotics (dose)	Outcomes	Duration
Rao et al., 2009	48 (28/20)	*Lactobacillus casei* strain Shirota (2.4^{10} CFU per day)	- Depression: BDI - Anxiety: BAI - Stool Samples	8 weeks
Groeger et al., 2013	35 (19/16)	*Bifidobacterium infantis* 35624 ($1x10^{10}$ CFU per day)	- Inflammatory biomarker: CRP - Plasma cytokine levels: IL-6 and TNF-α.	8 weeks

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).

	Studies Retrieved for Quality Appraisal	
Appraisal Criteria	Rao et al., 2009	Groeger et al., 2013
1. Was randomization mentioned?	Y	Y
2. Was method of randomization appropriate?	U	U
3. Was blinding mentioned?	Y	Y
4. Was method of blinding appropriate?	Y	Y
5. Was the fate of all patients in the trial known?	Y	U
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 (LcS) (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

Aaron, L. A., & Buchwald, D. (2001). A review of the evidence for overlap among unexplained clinical conditions. *Annals of Internal Medicine*, *134*(9 Pt 2), 868–81. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11346323

Aaron, L. A., Burke, M. M., & Buchwald, D. (2000). Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Archives of Internal Medicine*, *160*(2), 221–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10647761

Akkasheh, G., Kashani-Poor, Z., Tajabadi-Ebrahimi, M., Jafari, P., Akbari, H., Taghizadeh, M., … Esmaillzadeh, A. (2016). Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition*, *32*(3), 315–320. https://doi.org/10.1016/j.nut.2015.09.003

Benton, D., Williams, C., & Brown, A. (2007). Impact of consuming a milk drink containing a probiotic on mood and cognition. *European Journal of Clinical Nutrition*, *61*(3), 355–61. https://doi.org/10.1038/sj.ejcn.1602546

Bercik, P., & Collins, S. M. (2014). The effects of inflammation, infection and antibiotics on the microbiota-gut-brain axis. *Advances in Experimental Medicine and Biology*, *817*, 279–89. https://doi.org/10.1007/978-1-4939-0897-4_13

Branco, J. C., Bannwarth, B., Failde, I., Abello Carbonell, J., Blotman, F., Spaeth, M., … Gran, J. T. (2010). Prevalence of fibromyalgia: a survey in five European countries. *Seminars in Arthritis and Rheumatism*, *39*(6), 448–53. https://doi.org/10.1016/j.semarthrit.2008.12.003

Buchwald, D., & Garrity, D. (1994). Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. *Archives of Internal Medicine*, *154*(18), 2049–53. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8092909

Butt, H., Dunstan, R., McGregor, N., & Roberts, T. (2001). Bacterial colonosis in patients with persistent fatigue. In *Proceedings of the AHMF international clinical and scientific conference*.

Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology : Quarterly Publication of the Hellenic Society of Gastroenterology*, *28*(2), 203–209. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25830558

Clark, H. D., Wells, G. A., Huët, C., McAlister, F. A., Salmi, L. R., Fergusson, D., & Laupacis, A. (1999). Assessing the quality of randomized trials: reliability of the Jadad scale. *Controlled Clinical Trials*, *20*(5), 448–52.

Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nature Reviews. Neuroscience*, *13*(10), 701–12. https://doi.org/10.1038/nrn3346

Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: the impact of the

gut microbiota on brain and behaviour. *Nature Reviews. Neuroscience*, *13*(10), 701–12. https://doi.org/10.1038/nrn3346

Cryan, J. F., & O'Mahony, S. M. (2011). The microbiome-gut-brain axis: from bowel to behavior. *Neurogastroenterology and Motility : The Official Journal of the European Gastrointestinal Motility Society*, *23*(3), 187–92. https://doi.org/10.1111/j.1365-2982.2010.01664.x

Dapoigny, M., Piche, T., Ducrotte, P., Lunaud, B., Cardot, J.-M., & Bernalier-Donadille, A. (2012). Efficacy and safety profile of LCR35 complete freeze-dried culture in irritable bowel syndrome: a randomized, double-blind study. *World Journal of Gastroenterology*, *18*(17), 2067–75. https://doi.org/10.3748/wjg.v18.i17.2067

De Palma, G., Collins, S. M., Bercik, P., & Verdu, E. F. (2014). The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both? *The Journal of Physiology*, *592*(14), 2989–97. https://doi.org/10.1113/jphysiol.2014.273995

Desbonnet, L., Garrett, L., Clarke, G., Bienenstock, J., & Dinan, T. G. (2008). The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. *Journal of Psychiatric Research*, *43*(2), 164–74. https://doi.org/10.1016/j.jpsychires.2008.03.009

Diaz Heijtz, R., Wang, S., Anuar, F., Qian, Y., Björkholm, B., Samuelsson, A., … Pettersson, S. (2011). Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 3047–52. https://doi.org/10.1073/pnas.1010529108

Didari, T., Mozaffari, S., Nikfar, S., & Abdollahi, M. (2015). Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. *World Journal of Gastroenterology*, *21*(10), 3072–84. https://doi.org/10.3748/wjg.v21.i10.3072

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: a novel class of psychotropic. *Biological Psychiatry*, *74*(10), 720–6. https://doi.org/10.1016/j.biopsych.2013.05.001

FAO/WHO. (2001). *Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Prebiotics in Food Including Powder Milk with Live Lactic Acid Bacteria*. *Food and Nutrition Paper* (Vol. 85). https://doi.org/10.1201/9781420009613.ch16

Francavilla, R., Miniello, V., Magista, A. M., De Canio, A., Bucci, N., Gagliardi, F., … Cavallo, L. (2010). A Randomized Controlled Trial of Lactobacillus GG in Children With Functional Abdominal Pain. *PEDIATRICS*, *126*(6), e1445–e1452. https://doi.org/10.1542/peds.2010-0467

Galland, L. (2014). The gut microbiome and the brain. *Journal of Medicinal Food*, *17*(12), 1261–72. https://doi.org/10.1089/jmf.2014.7000

Gawrońska, A., Dziechciarz, P., Horvath, A., & Szajewska, H. (2007). A randomized double-blind placebo-controlled trial of Lactobacillus GG for abdominal pain disorders in children. *Alimentary Pharmacology & Therapeutics*, *25*(2), 177–84. https://doi.org/10.1111/j.1365-2036.2006.03175.x

Glass, J. M. (2008). Fibromyalgia and cognition., *69 Suppl 2*, 20–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18537459

Groeger, D., O'Mahony, L., Murphy, E. F., Bourke, J. F., Dinan, T. G., Kiely, B., … Quigley, E. M. M. (2013). Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes*, *4*(4), 325–39. https://doi.org/10.4161/gmic.25487

Halpern, S. H., & Douglas, M. J. (2005). Appendix: Jadad Scale for Reporting Randomized Controlled Trials. In *Evidence-based Obstetric Anesthesia* (pp. 237–238). Oxford, UK: Blackwell Publishing Ltd. https://doi.org/10.1002/9780470988343.app1

Hardy, H., Harris, J., Lyon, E., Beal, J., & Foey, A. D. (2013). Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology. *Nutrients*, *5*(6), 1869–912. https://doi.org/10.3390/nu5061869

Higgins, J. P., & Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*.

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*, *17*(1), 1–12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8721797

Jenks, K., Stebbings, S., Burton, J., Schultz, M., Herbison, P., & Highton, J. (2010). Probiotic therapy for the treatment of spondyloarthritis: a randomized controlled trial. *The Journal of Rheumatology*, *37*(10), 2118–25. https://doi.org/10.3899/jrheum.100193

Jones, G., Atzeni, F., Beasley, M., Flüß, E., Sarzi-Puttini, P., & Macfarlane, G. J. (2015). The Prevalence of Fibromyalgia in the General Population: A Comparison

of the American College of Rheumatology 1990, 2010, and Modified 2010 Classification Criteria. *Arthritis & Rheumatology*, *67*(2), 568–575. https://doi.org/10.1002/art.38905

Jones, J. F., Nisenbaum, R., & Reeves, W. C. (2003). Medication use by persons with chronic fatigue syndrome: results of a randomized telephone survey in Wichita, Kansas. *Health and Quality of Life Outcomes*, *1*, 74. https://doi.org/10.1186/1477-7525-1-74

Joyce, E., Blumenthal, S., & Wessely, S. (1996). Memory, attention, and executive function in chronic fatigue syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry*, *60*(5), 495–503. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8778252

Kanaan, R. A. A., Lepine, J. P., & Wessely, S. C. (2007). The association or otherwise of the functional somatic syndromes. *Psychosomatic Medicine*, *69*(9), 855–9. https://doi.org/10.1097/PSY.0b013e31815b001a

Khalighi, A. R., Khalighi, M. R., Behdani, R., Jamali, J., Khosravi, A., Kouhestani, S., … Khalighi, N. (2014). Evaluating the efficacy of probiotic on treatment in patients with small intestinal bacterial overgrowth (SIBO)--a pilot study. *The Indian Journal of Medical Research*, *140*(5), 604–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25579140

Lakhan, S. E., & Kirchgessner, A. (2010). Gut inflammation in chronic fatigue syndrome. *Nutrition & Metabolism*, *7*(1), 79. https://doi.org/10.1186/1743-7075-7-79

Lee, J.-Y., Chu, S.-H., Jeon, J. Y., Lee, M.-K., Park, J.-H., Lee, D.-C., … Kim, N.-K.

(2014). Effects of 12 weeks of probiotic supplementation on quality of life in colorectal cancer survivors: a double-blind, randomized, placebo-controlled trial. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*, *46*(12), 1126–32. https://doi.org/10.1016/j.dld.2014.09.004

Lorenzo-Zúñiga, V., Llop, E., Suárez, C., Alvarez, B., Abreu, L., Espadaler, J., & Serra, J. (2014). I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *World Journal of Gastroenterology*, *20*(26), 8709–16. https://doi.org/10.3748/wjg.v20.i26.8709

Maes, M., Kubera, M., & Leunis, J.-C. (2008). The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuro Endocrinology Letters*, *29*(1), 117–24. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18283240

Mandel, D. R., Eichas, K., & Holmes, J. (2010). Bacillus coagulans: a viable adjunct therapy for relieving symptoms of rheumatoid arthritis according to a randomized, controlled trial. *BMC Complementary and Alternative Medicine*, *10*(1), 1. https://doi.org/10.1186/1472-6882-10-1

Martinowich, K., & Lu, B. (2008). Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *33*(1), 73–83. https://doi.org/10.1038/sj.npp.1301571

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

J.-M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *The British Journal of Nutrition*, *105*(5), 755–64. https://doi.org/10.1017/S0007114510004319

Messaoudi, M., Violle, N., Bisson, J.-F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. *Gut Microbes*, *2*(4), 256–61. https://doi.org/10.4161/gmic.2.4.16108

Michalsen, A., Riegert, M., Lüdtke, R., Bäcker, M., Langhorst, J., Schwickert, M., … Dobos, G. G. J. (2005). Mediterranean diet or extended fasting's influence on changing the intestinal microflora, immunoglobulin A secretion and clinical outcome in patients with rheumatoid arthritis and fibromyalgia: an observational study. *BMC Complementary and Alternative Medicine*, *5*(1), 22. https://doi.org/10.1186/1472-6882-5-22

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. D., Group, T. P., Oxman, A., … Hopewell, S. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Penfold, S., St. Denis, E., & Mazhar, M. N. (2016). The association between borderline personality disorder, fibromyalgia and chronic fatigue syndrome: systematic review. *British Journal of Psychiatry Open*, *2*(4), 275–279. https://doi.org/10.1192/bjpo.bp.115.002808

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

(2013). Probiotics, prebiotics, and the host microbiome: the science of translation. *Annals of the New York Academy of Sciences*, *1306*(1), 1–17. https://doi.org/10.1111/nyas.12303

Pimentel, M., Chow, E. J., & Lin, H. C. (2003). Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. *The American Journal of Gastroenterology*, *98*(2), 412–9. https://doi.org/10.1111/j.1572-0241.2003.07234.x

Pimentel, M., Wallace, D., Hallegua, D., Chow, E., Kong, Y., Park, S., & Lin, H. C. (2004). A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. *Annals of the Rheumatic Diseases*, *63*(4), 450–2. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15020342

Rao, A. V., Bested, A. C., Beaulne, T. M., Katzman, M. A., Iorio, C., Berardi, J. M., & Logan, A. C. (2009). A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathogens*, *1*(1), 6. https://doi.org/10.1186/1757-4749-1-6

Riedl, A., Schmidtmann, M., Stengel, A., Goebel, M., Wisser, A.-S., Klapp, B. F., & Mönnikes, H. (2008). Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *Journal of Psychosomatic Research*, *64*(6), 573–82. https://doi.org/10.1016/j.jpsychores.2008.02.021

Ringel-Kulka, T., Goldsmith, J. R., Carroll, I. M., Barros, S. P., Palsson, O., Jobin, C., & Ringel, Y. (2014). Lactobacillus acidophilus NCFM affects colonic mucosal opioid receptor expression in patients with functional abdominal pain - a randomised clinical study. *Alimentary Pharmacology & Therapeutics*, *40*(2), 200–

7. https://doi.org/10.1111/apt.12800

Roman, P., Estevez, A. F., Sánchez-Labraca, N., Cañadas, F., Miras, A., & Cardona, D. (2017). Probiotics for Fibromyalgia: Study design for a pilot double-blind, randomized controlled trial. *Nutrición Hospitalaria*, *34*(5), 1285–1290. https://doi.org/10.20960/nh.1300

Sheedy, J. R., Wettenhall, R. E. H., Scanlon, D., Gooley, P. R., Lewis, D. P., McGregor, N., … DE Meirleir, K. L. (2009). Increased d-lactic Acid intestinal bacteria in patients with chronic fatigue syndrome. *In Vivo (Athens, Greece)*, *23*(4), 621–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19567398

Sherwin, E., Rea, K., Dinan, T. G., & Cryan, J. F. (2016). A gut (microbiome) feeling about the brain. *Current Opinion in Gastroenterology*, *32*(2), 96–102. https://doi.org/10.1097/MOG.0000000000000244

Silk, D. B. A., Davis, A., Vulevic, J., Tzortzis, G., & Gibson, G. R. (2009). Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*, *29*(5), 508–18. https://doi.org/10.1111/j.1365-2036.2008.03911.x

Slim, M., Calandre, E. P., & Rico-Villademoros, F. (2015). An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms. *Rheumatology International*, *35*(3), 433–444. https://doi.org/10.1007/s00296-014-3109-9

Sperber, A. D., Atzmon, Y., Neumann, L., Weisberg, I., Shalit, Y., Abu-Shakrah, M., … Buskila, D. (1999). Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. *The American Journal of Gastroenterology*,

94(12), 3541–6. https://doi.org/10.1111/j.1572-0241.1999.01643.x

Steenbergen, L., Sellaro, R., van Hemert, S., Bosch, J. A., & Colzato, L. S. (2015). A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain, Behavior, and Immunity*, *48*, 258–64. https://doi.org/10.1016/j.bbi.2015.04.003

Stone, P. W. (2002). Popping the (PICO) question in research and evidence-based practice. *Applied Nursing Research : ANR*, *15*(3), 197–8.

Sullivan, A., Nord, C. E., & Evengård, B. (2009). Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. *Nutrition Journal*, *8*, 4. https://doi.org/10.1186/1475-2891-8-4

Tiequn, B., Guanqun, C., & Shuo, Z. (2015). Therapeutic effects of Lactobacillus in treating irritable bowel syndrome: a meta-analysis. *Internal Medicine (Tokyo, Japan)*, *54*(3), 243–9. https://doi.org/10.2169/internalmedicine.54.2710

Triadafilopoulos, G., Simms, R. W., & Goldenberg, D. L. (1991). Bowel dysfunction in fibromyalgia syndrome. *Digestive Diseases and Sciences*, *36*(1), 59–64. https://doi.org/10.1007/BF01300088

Umbrello, G., & Esposito, S. (2016). Microbiota and neurologic diseases: potential effects of probiotics. *Journal of Translational Medicine*, *14*(1), 298. https://doi.org/10.1186/s12967-016-1058-7

Upadhyay, N., & Moudgal, V. (2012). Probiotics: A review. *Journal of Clinical Outcomes Management*, *19*(2), 76–84. https://doi.org/10.1016/S2221-1691(11)60174-3

Whitehead, W. E., Palsson, O., & Jones, K. R. (2002). Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology*, *122*(4), 1140–56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11910364

Wolfe, F., Clauw, D. J., Fitzcharles, M.-A., Goldenberg, D. L., Häuser, W., Katz, R. S., … Winfield, J. B. (2011). Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *The Journal of Rheumatology*, *38*(6), 1113–22. https://doi.org/10.3899/jrheum.100594

Wolfe, F., Clauw, D. J., Fitzcharles, M.-A., Goldenberg, D. L., Katz, R. S., Mease, P., … Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care & Research*, *62*(5), 600–10. https://doi.org/10.1002/acr.20140

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., … Clark, P. (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism*, *33*(2), 160–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2306288

Zhou, L., & Foster, J. A. (2015). Psychobiotics and the gut-brain axis: in the pursuit of happiness. *Neuropsychiatric Disease and Treatment*, *11*, 715–23. https://doi.org/10.2147/NDT.S61997