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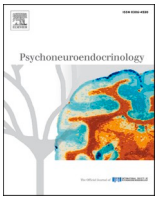

The gut microbiota-brain axis, psychobiotics and its influence on brain and behaviour: A systematic review

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ABSTRACT

The gut microbiota is the set of microorganisms present in the gut, and it is connected to the central nervous system via the gut-brain axis. Despite there is not a definitive description of the eubiotic microbiota architecture, numerous studies have demonstrated its involvement in human behaviour and its relationship with several pathologies. This is a systematic review about the association between dysbiosis on the gut microbiota and the presence of neurological or neuropsychiatric diseases such as cognitive impairment, Alzheimer's disease, Parkinson's disease, ADHD, and depression. Furthermore, this study analyzes the potential benefits of psychobiotics supplementation for these pathologies. Searches were conducted in the electronic databases PubMed and PsycINFO. 17 articles were included in this review, the majority were published after 2019. The results showed that gut dysbiosis predicts the development of these pathologies and influences their pathogenesis. In addition, it was found that different psychobiotics, mainly dietary fibers and probiotics of the *Lactobacillus* family, improved different cognitive functions such as cognitive performance and induce a reduced cortisol response. Improvement in different cognitive functions is possible when understanding gut microbiota-brain axis, enteric nervous system, neural-immune system, neuroendocrine system, and central nervous system's relationship.

1. Introduction

Gut microbiota is the set of microorganisms present in the intestinal tract. Many different functions in our body can be attributed to the gut microbiota, most importantly, the maturation and development of the Central Nervous System (CNS), as well as the development and modulation of the immune response (Castillo-Álvarez and Marzo-Sola, 2019). It is a fundamental part of the gut-brain network, and it communicates with the brain through the microbiota-gut-brain axis (Liang et al., 2018).

The gut microbiota has been linked to human metabolism, intestinal homeostasis, immune development (Lynch and Pedersen, 2016), and brain processes and behavior (Mayer et al., 2015; Morais et al., 2021). A stable and diverse gut microbiota, optimal for maintaining health, produces metabolites that fuel physiological and metabolic processes. This population of microorganisms performs complex functions including metabolizing food and drugs, maintaining the gut barrier integrity, immunomodulation, and protecting against pathogens, thus helping to maintain a stable gut ecosystem (Ahern and Maloy, 2020; Iebba et al., 2016). Alterations in the composition of gut microbiota, or dysbiosis, is associated with a wide variety of diseases like inflammatory bowel disease (Fasano, 2020), coeliac disease (Odenwald and Turner, 2017), metabolic syndrome (Fan and Pedersen, 2021; Pascale et al., 2018), diabetes mellitus (Sorini et al., 2019), colon cancer (Fidelle et al., 2020), as well as autism, anxiety, depression, and neurodegenerative diseases (Rutsch et al., 2020; Zhu et al., 2020).

In this regard, much attention has been devoted to the possible alterations of microbiota, associated to the inflammation and the appearance of cognitive and neurological disorders. However, the mechanisms linking intestinal bacteria and neurocognitive diseases are still unclear. The gut-brain axis studies have provided essential references to understand human cognition and its relationship to neuroendocrinology or gastrointestinal diseases (Maiuolo et al., 2021). This axis is a network that includes the gastrointestinal tract, the enteric nervous system, and the brain. Although the precise mechanisms involved in the interaction between the gut microbiota and brain remain to be fully determined, there are a number of potential pathways through which the gut microbiota can influence brain function (Borre et al., 2014). In this sense, microbiota–gut–brain communication can occur through

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multiple systems comprising the gut–brain axis (including the autonomic nervous system and enteric nervous system), neuroendocrine systems and the immune system. Microorganisms can influence CNS processes bidirectionally via the vagus nerve (Bonaz et al., 2017) and through modulation of the immune system (Erny et al., 2015), the hypothalamic-pituitary-adrenal (HPA) axis (Keller et al., 2017), and tryptophan metabolism, along with their ability to synthetize a number of neurotransmitters (O'Mahony et al., 2015; Sherwin et al., 2018) and produce metabolites, such as short-chain fatty acids (SCFAs) including acetate, butyrate, lactate, and propionate. These SCFAs are speculated to have a key role in microbiota–gut–brain crosstalk (Dalile et al., 2019; Mirzaeie et al., 2021; Sarkar et al., 2016; Silva et al., 2020). In addition to the long known role of the colon in energy supply and trophic factors (Pascale et al., 2018), as well as the regulation of T regulatory (Treg) cell colonies (Arpaia et al., 2013; Smith et al., 2013), growing evidence supports the idea that SCFAs also exert crucial physiological effects on the brain. SCFAs passes the gut-blood and blood-brain barriers, reaching the CNS and accumulating within cells. These metabolites could induce intracellular acidification (Bonnet et al., 2000) and can potentially affect to the signaling of calcium, the release of neurotransmitters, mitochondrial function, immune activation, and gene expression, modifying neuronal communication and behavior.

Although a more compelling causal relationship between altered gut microbial composition and brain dysfunction is still needed, it has been shown that disruption in any of these routes of communication between microbiota and brain may precipitate an inflammatory response of the organism. Inflammation is an adaptive physiological process that the immune system executes in response to pathogens and injury in addition to protecting the body against infection. Among the biological changes associated with inflammation is the activity of cytokines, proteins that modulate inflammation (Turner et al., 2014). Pathogenic microorganisms release metabolites and molecules derived from the microbiota that trigger cytokines in the host and cause inflammation in the CNS, greatly contributing to the origin and development of brain disorders (Zhu et al., 2020).

In this context, the alteration on the composition and function of gut microbiota can cause a state of dysbiosis or imbalance that will have negative long-term effects on the organism (López-Otín and Kroemer, 2021; Galland, 2014; Oriach et al., 2016). For instance, altered cognitive and emotional processes could appear when there is dysbiosis. Cognitive and emotional processes are regulated, in addition to the CNS, by other factors such as the immune system and the resident bacteria in the gastrointestinal tract. Evidence about the gut microbiota and its influence on brain and behaviour have been reported on animals models and human studies about mood disorders, Alzheimer's disease (AD), Parkinson's disease (PD) and Attention Deficit Hyperactivity Disorder (ADHD).

Depression and anxiety disorders are the most common psychological disorders amongst the adult population. Dysregulation of HPA axis signaling is implicated in mood disorders, typically associated with higher levels of cortisol and inflammatory mediators that lead to a sustained pro-inflammatory state (Keller et al., 2017). Brain neural structures, such amygdala play a crucial role in the generation, experience, and processing of emotional information (Phelps and LeDoux, 2005). The bacterial effects on the anatomy and physiology of the amygdala could be the explanation for many of the emotional and stress-related factors that have been attributed to the microbiome (Sarkar et al., 2018). In relation to neurotransmitters, serotonin has been implicated in the etiology of numerous disorders, such as depression and anxiety. Different investigations show how some treatments with prebiotics and probiotics could adjust the composition of the gut microbiota and increase the peripheral levels of the serotonin precursor, tryptophan, in the brain of animal models with depression and chronic stress (Desbonnet et al., 2009, O'Mahony et al., 2015). Precisely, the lack of gastrointestinal microbes in rats causes a decrease in the expression of neurotrophic factor derived from the brain in the cortex and hippocampus, in addition to a reaction of the HPA axis to stress (Sudo et al., 2004). Given the role of gastrointestinal bacteria in the bidirectional communication between the gut and the brain and the importance of diet in modifying the composition of the microbiota, it is being taking into consideration the possibility of the ingestion of psychobiotics as an additional therapy for the treatment of these disorders.

The evidence of relationship between AD (or prodromal stage of AD, as mild cognitive impairment -MCI-) and the gut microbiota has been also analysed. In fact, it is considered that the interaction between both genetic and environmental factors intervene in the pathogenesis of AD (Hu et al., 2016), one of these factors being the gut microbiota. Studies with animal models (Wang et al., 2019; Wu et al., 2017) have shown that gut dysbiosis is involved in the initiation, development, and progression of AD, including chronic neuroinflammation and oxidative stress, among others.

Cognitive and motor impairment in PD and its correlation to the alteration of the gut-brain axis symptoms have also received increased interest in recent years. It has been reported that gastrointestinal symptoms can precede the development of motor and cognitive symptoms by many years (Chapelet et al., 2019; Liang et al., 2018; Nair et al., 2018).

In addition, the impact of the microbiota on the CNS is being investigated in ADHD, which is a neurodevelopmental disorder characterized by inattention, impulsivity, and hyperactivity (Boonchooduang et al., 2020). It has been suggested that ADHD may be associated with "unhealthy" diets, with suboptimal levels of iron, zinc, and magnesium, and that dietary habits play a key role in modulating the composition of the gut microbiota (Sinn, 2008). Therefore, a potential role has been given to the gut microbiota in the pathophysiology of ADHD.

Understanding the early interaction between the gut microbiota and the occurrence of the mentioned diseases will open new avenues for intervention, particularly for early diagnosis and early therapy. Regarding possible therapies, research is focusing on the role of psychobiotics in cognition. The term psychobiotic was used for the first time by Dinan et al. (2013) who defined it as 'a living organism that, when ingested in adequate amounts, produces a benefit for the health of patients suffering from psychiatric illnesses'. Currently, studies in humans and rodents are analyzing how dietary interventions with psychobiotic may have the potential to modulate psychiatric symptoms associated with gut–brain axis dysfunction (Castillo-Álvarez and Marzo-Sola, 2019; Oriach et al., 2016).

Given these factors, the aim of this systematic review is to examine the relationship between the gut microbiota and its involvement in the different pathologies presented, as well as to verify the benefit of psychobiotics supplementation (probiotics and prebiotics) in humans. A more detailed understanding of the pathophysiology of the different disorders presented can serve as the basis for an early diagnosis, better evolution of symptoms, and better treatment options.

2. Methods

2.1. Search strategy

A systematic literature review was conducted following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) in order to adjust the review methodology to quality criteria (Liberati et al., 2009; Moher et al., 2009). The research question was formulated with the PICOS tool, that was used to identify components of clinical evidence for systematic reviews in evidence-based medicine and is endorsed by the Cochrane Collaboration (Table 1).

The databases used to search for articles were PubMed and PsycINFO. Both were chosen because they are databases of articles related to Neuroscience in general (PubMed) and Psychology specifically (PsycINFO).

The search process was carried out systematically in both databases,

Table 1
Criteria of the research question formulation strategy according to PICOS.

P	Population	Patients with altered microbiota or healthy
I	Intervention	Dietary treatment or microbiota composition analysis
C	Comparison	Control group or placebo
O	Outcomes	Cognitive functions
S	Study type	Symptom study

with the words and the Boolean terms: 'gut microbiota' AND 'brain' AND 'human' AND 'cognitive disorders'. The results were limited to articles published in academic journals in the last 10 years (2011–2021) because it is a recent study topic, especially in the field of neuroscience. The search in both databases was carried out in March 2021, obtaining a total of 193 articles in PubMed and 66 in PsycINFO.

2.2. Study selection

The titles and abstracts were screened according to their affinity with the study with these inclusion and exclusion criteria: 1) Articles had to be empirical studies, thus excluding systematic reviews, case studies and study protocols; 2) The studies had to be conducted with human participants with any pathology related to this topic, or with healthy patients if they were considered the comparison group, and 3) Studies conducted only in non-human animals were discarded. After this first screening, 32 articles met the criteria described. Specifically, the first search was carried out in the PubMed database, where 19 articles were selected, and the second search in PsycINFO, where 13 articles were selected. In these two databases, nine articles were duplicated.

The second phase of screening consisted of an exhaustive reading of the 23 full articles in order to check in the method sections the most important variables related to our research question: the number of subjects studied, their age, the country of residence of the subjects, the procedure followed, the pathologies of the participants and the measuring instruments informed. This first analysis revealed that some articles could not met the eligibility criteria, and six publications were finally discarded due to inconclusive results or not having completed the study due to the high dropout rate. In the Fig. 1 is presented the complete study selection process which ended with 17 articles finally chosen for the systematic review, and in Table 2 are specified their titles, first authors, journals, countries, number of citations according to Google Scholar in April 2021, and a code per publication.

For the analysis of these articles, in addition to the information presented in Table 2, a two-phases procedure was conducted. In the first phase, the methodological characteristics of the 17 articles were systematically evaluated, specifying the characteristics of the samples, the instruments used and the research designs. In the second phase, as presented below, the information presented in the results sections of each article was synthesized.

3. Results

As can be seen in Table 2, the 17 articles selected for this systematic review were very recent, being the oldest from 2017, and the most recent from this year, 2021. The different studies were carried out mainly in Europe (7) and Asia (6), the rest being in the United States (3) and Australia (1).

In Table 3 the main methodological information is synthesized, differentiating two types of studies: from 1 to 13 these are investigations where data on the composition of the intestinal microbiota are collected in order to study its relationship with the severity of a certain pathologies. The exception is study 7, which collects data on the frequency of gastrointestinal symptoms rather than the composition of the microbiota. From 14–17 are studies investigating the effect of the consumption of dietary supplements (prebiotics and probiotics) both in healthy patients and in patients with depression. The first type of study are observational research, where data were collected at a single point in time, and the relationship between the variables of interest (microbiota and severity of symptoms) is examined. Exceptionally, 7 is longitudinal, with patient follow-up for five years. The second type of study tracks 1, 4, or 8 weeks of dietary supplementation, and the variation of cognitive

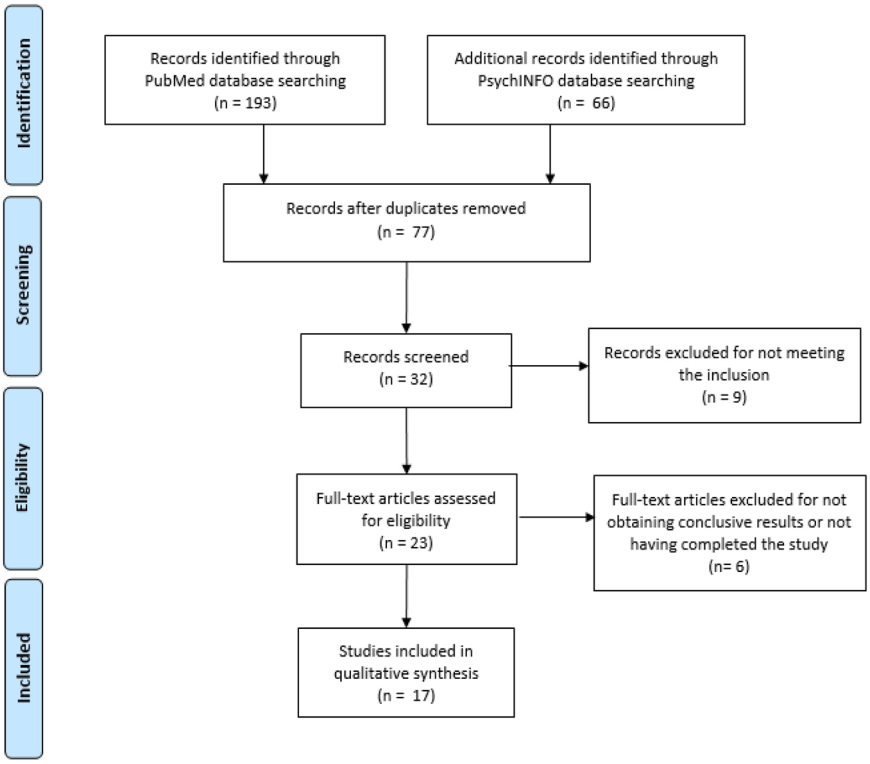

Fig. 1. PRISMA Flow diagram of the study selection.

Table 2
Articles included in the systematic review.

Code.	First author & year	Journal	Cites	Country
1	(MahmoudianDehkordi et al., 2020)	Alzheimers and Dementia	136	U.S.A.
2	(Nho et al., 2019)	Alzheimers and Dementia	60	U.S.A.
3	(Liu et al., 2019)	Brain, Behavior and Immunity	82	China
4	(Saji et al., 2019b)	Scientific Reports	67	Japan
5	(Cattaneo et al., 2017)	Neurobiology of Aging	387	Italy
6	(Liu et al., 2021)	CNS Neuroscience y Therapeutics	4	China
7	(Jones et al., 2020)	Parkinsonism and Related Disorders	9	U.S.A.
8	(Szopinska-Tokov et al., 2020)	Microorganisms	17	Netherlands
9	(Li et al., 2019)	Alzheimers and Dementia	58	China
10	(Saji et al., 2020)	Scientific Reports	7	Japan
11	(Saji et al., 2019b)	Scientific Reports	15	Japan
12	(Heym et al., 2019)	Psychopharmacology	30	U.K.
13	(Barichella et al., 2019)	Movement Disorders	94	Italy
14	(Dalile et al., 2020)	Neuropsychopharmacology	13	Belgium
15	(Chahwan et al., 2019)	Journal of Affective Disorders	42	Australia
16	(Berding et al., 2021)	Psychopharmacology	4	Ireland
17	(Rudzki et al., 2019)	Psychoneuroendocrinology	123	Poland

Table 3
Main methodological information of the reviewed studies.

Code.	n	Age ($\bar{x}$)	Procedure	Pathology (follow-up weeks / years)	Comparison group
1	1464	74.6	Analysis of the GM, clinical evaluation and DNA	Early MCI, late MCI and AD	Control (no pathology)
2	1562	73.3	Analysis of the GM, biomarkers AD and neuroimaging	Early MCI, late MCI and AD	Control (no pathology)
3	97	74 ± 10.6	Analysis of the GM and clinical evaluation	AD	MCI and control (no pathology)
4	128	76	Analysis of the GM, daily living activities, cognitive function and neuroimaging	Dementia	Control (no dementia)
5	83	69.7	Analysis of the GM and level blood expression of cytokines	MCI	Control (no MCI)
6	42	70.7 ± 9.6	Analysis of the GM and neuroimaging	MCI	Control (no MCI)
7	423	61.2	Frequency of GI symptoms and neuropsychological tests every year	PD (5 years)	MCI and control (no MCI)
8	107	20.3	Analysis of the GM and ADHD symptom scores	ADHD	Control (no ADHD)
9	90	65.2	Analysis of the GM, blood and cognitive function	MCI and AD	Control (no MCI)
10	107	76	Analysis of the GM, daily living activities, cognitive function and neuroimaging	Dementia	Control (no dementia)
11	82	76	Analysis of the GM, cognitive function and neuroimaging	MCI	Control (no MCI)
12	40	36.5	Analysis of the GM and blood and psychometric parameters	Healthy patients	–
13	350	67.9	Analysis of the GM, clinical and nutritional evaluation	PD	Control (no PD)
14	66	23.6	Dietary fiber (prebiotic SCFAs) or placebo	Healthy patients (1 week)	Placebo
15	71	36	Probiotic (Ecologic © Barrier) or placebo	Depression (8 weeks)	Placebo, control (no depression)
16	18	26 ± 1.3	Dietary fiber (PDX prebiotic) or placebo	Healthy patients (4 weeks)	Placebo
17	60	39	SSRI with probiotic LP299v or placebo	Depression (8 weeks)	Placebo

Note: AD: Alzheimer's disease; ADHD: Attention deficit hyperactivity disorder; BA: Bilic Acid; GI: gastrointestinal; GM: Gut Microbiota; Lactobacillus Plantarum 299v; n: total number of participants in the study; MCI: Mild Cognitive Impairment; PD: Parkinson's disease; PDX: polydextrose; SCFAs: Short Chain Fatty Acids; SSRI: Selective Serotonin Reuptake Inhibitor.

symptoms evaluated.

The *n* in Table 3 indicates the number of subjects who have participated in each study. The total number of participants included in this review is 4790, although it has been found that most studies have a sample of less than 150 participants, and only two publications evaluate more than 1000 cases. As could be expected, the mean age is higher in studies with participants with some pathology related to cognitive impairment (CI), and lower in patients with ADHD or depression. Another feature to highlight is that all the studies compare an experimental group (with pathology) with a control or placebo group, except for study 12, which compares between the results of the only group studied.

Finally, the studies found mostly investigate cognitive decline, Alzheimer's disease, dementia and Parkinson's disease, and to a lesser extent ADHD and mood disorders. The studies with healthy patients will be used in the discussion to compare them with patients with some pathology.

Table 4 shows the most significant results found in the studies analyzed. Considering the large number of comparisons presented in all the studies, we have decided to only present those whose results have been considered by the authors as statistically significant and were more relevant for the purpose of this systematic review.

On the other hand, the measurement instruments used for the studies varied according to the pathology, but in general, in the studies where there were patients with cognitive impairment, the MMSE, the ADAS-cog or the MoCA, among others, were used. For the studies with healthy or depressed patients, questionnaires were used that measured different cognitive functions and biochemical parameters such as cortisol or cytokines, among others. For those performing neuroimaging, the most common techniques are VSRAD, SLI, and RM. The composition of the microbiota was measured using next-generation sequencing (NGS) approaches.

Finally, the results showed that dysbiosis affects the different pathologies mentioned and their clinical severity, as well as the progression towards other pathologies. Dysbiosis is regularly characterized by an abundance of pro-inflammatory bacteria (*Lactobacillus*, *Escherichia*) and a shortage of anti-inflammatory bacteria (*Bacteroides*). In the results of studies with psychobiotics, the subjects showed improvement in some cognitive functions and reduction of biochemical parameters such as cortisol or kynurenine.

Table 4
Relevant results of the reviewed studies.

Code	Measure	Most significant results
1	GM composition: BA profile ADAS-cog	Altered BA profile in AD ($p < .001$) BA profile associated with progression from MCI (a) to AD ($p < .001$)
2	GM composition: BA profile Biomarkers EA: CSF	BA profile associated with AD biomarkers ($p < .05$)
3	GM composition CDR, MMSE, MoCA	Differences GM in EA group compared with group MCI (a) and CG Correlation between clinical severity scores in the AD group and altered GM ($p < .05$)
4	GM composition MMSE, CDR-SB, ADAS-cog SLI, CMBs, VSRAD	Dementia group < *Bacteroides* prevalence and > prevalence of other bacteria (*Lactobacillum* and *Bifidobacterium*) ($p < .001$) Brain disorders (SLI $p = .002$, CMBs $p = .014$ y VSRAD $p < .001$) dementia group
5	GM composition Citokine blood level MMSE	↑ *Escherichia* (pro-inflammatory) and ↓ *E. rectale* (anti-inflammatory) associated with peripheral inflammatory status in the MCI(a) group
6	GM composition FMRI resting state and amplitud fALFF	GM alteration and spontaneous local brain activity ($p < .05$) MCI(a) group compared with CG
7	MoCA, LNS, SDMT, AF, JLG, HVLT-R SCOPA-AUT	All cognitive outcomes predicted by GI symptom effect ($p < .005$) > frequency of symptoms associated with poorer cognitive performance
8	GM composition Seriousness IA e HI: CAARS, CTRS	Differences in the composition of GM in the ADHD and CG groups; 7 Bacterial genera associated with IA and HI symptom scores ($p < .05$)
9	GM composition and blood MMSE	Similar GM results between MCI and AD (↑ *Escherichia* $p < .001$ and *Lactobacillus* $p = .022$, ↓ *Bacteroides* $p < .001$)
10	GM composition MMSE, CDR-SB SLI, VSRAD	*Ammonia* ($p = .026$), *phenol* ($p = .029$) and *p-cresol* (p = .014) concentrations > dementia group compared to CG Dementia associated with high VSRAD scores ($p < .001$)
11	GM composition MMSE, CDR-SB, ADAS-cog WMH, VSRAD	MCI group (a) > *Bacteroides* prevalence ($p = .009$) Patients with more *Bacteroides* are more likely to present WMH ($p = .009$) and high VSRAD scores ($p = .01$)
12	GM composition and blood (pro-inflammatory molecules) Psychometric parameters: depression (BDI-II), self-judgment and empathy (CAE)	↑ *Lactobacillus* indirect. related to cognitive depression and <affective empathy ($p < .001$) Pro-inflammatory molecules predict < cognitive empathy ($p = .001$)
13	GM composition MMSE	GM group PD novo < proportion *Lachnospiraceae* compared to CG ($p < .05$) ↓ *Lachnospiraceae* and ↑ *Lactobacillus* associated with worse clinical profile
14	Psychosocial stress: MAST, VAS Fear conditioning: SCRs DASS-21, GSRS Biological parameters: salivary cortisol	↓ cortisol response to acute stress prebiotic group compared with GP ($p = .013$)
15	Psychological tests: MINI, DAS-21, BDI-II	< cognitive reactivity probiotic group compared to PG ($p = .04$)
16	Cognitive performance: CANTAB Mood: Test Stress response: cortisol Inflammatory markers	↑ PDX group cognitive performance in CANTAB test (IED and RVP) compared to PG ($p = .03$, $p = .003$)
17	Affective functions: depression and anxiety symptoms Cognitive functions Biochemical parameters: cytokines, quinurenine and cortisol	Improves cognitive functions group LP299v in AP and CLV tests ($p = .024$) compared with PG ↓ kynurenine concentration group LP299v (p = .017) compared to PG

Note (in alphabetical order): ↑: increase; ↓: decrease; AD: Alzheimer's disease; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; AF: Animal Fluency; AP: Attention and Perceptivity; BA: Bile Acids; BDI-II: Beck Depression Index Second Edition; CAARS: Conners Adult; ADHD: Attention-Deficit/Hyperactivity Disorder; CAE: cognitive and affective empathy; CANTAB: Cambridge Neuropsychological Test Automated Battery; CDR-SB: Clinical Dementia Rating Sum of Boxes; CF: cognitive flexibility; CG: Control group; CMBs: cerebral microbleeds; CSF: cerebrospinal fluid; CTRS: Conners Teacher Rating Scale; CVL: Californian Verbal Learning; DASS-21: Depression Anxiety Stress Scale - 21 Items; fALFF: fractional amplitude of the low frequency fluctuations; FMRI: functional magnetic resonance; GI: gastrointestinal; GM: Gut microbiota; GSRS: Gastrointestinal Symptom Rating Scale; HI: hyperactivity / impulsivity; HVLT-R: Hopkins Verbal Learning Test - Revised; IA: inattention; JLG: Judgment of Line Orientation; LNS: Letter-Number Sequencing; LP299v: Lactobacillus Plantarum 299v; MAST: Maastricht Acute Stress Test; MCI(a): Mild Cognitive Impairment (amnesic); MINI: Mini International Neuropsychiatric Interview; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease; PDX: polydextrose; PG: placebo group; RVP: sustained attention; SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Autonomic; SCRs: skin conductance responses; SDMT: Symbol Digit Modalities Test; SLI: Silent lacunar infarct; VAS: visual analogue scale; VSRAD: voxel-based specific regional analysis system for Alzheimer's disease; WMH: White matter hyperintensity.

Our analysis highlights the influence of the microbiome on the development and pathogenesis of different pathologies, as well as the advantages of different dietary supplements with psychobiotics in the improvement of cognitive symptoms in humans. Almost every study has shown how dysbiosis (that occur when there is increased deconjugation of primary bile acids) affects the development of CI, AD, PD or ADHD. Moreover, the possibility of an early diagnosis and improvement of cognitive symptoms, such as memory loss, stress, or inattention, is associated with different dietary supplements. Dietary supplementation with psychobiotics (mainly dietary fibers and probiotics of the *Lactobacillus* family) has proven to improve different cognitive functions and a reduce the response to stress.

4. Discussion

In the present work, a systematic review has been carried out on studies that present the influence of the gut microbiota in the development and pathogenesis of mild cognitive impairment, dementia, Alzheimer's disease, Parkinson's disease, ADHD and depression. Differences were found between the microbiota of the patients with some pathology in comparison with the control groups, whose identification would allow for an early diagnosis. In addition, studies have demonstrated the benefits that different psychobiotics have, mainly dietary fibers and probiotics of the *Lactobacillus* family, in the improvement of different cognitive functions.

Based on the results obtained, we can observe three lines of research in the 17 selected studies. In the first line of research, some researchers focus on collecting data on the composition of the gut microbiota and the severity of the pathology to be studied in order to know their relationship. In the second line of research, researchers will collect data on the frequency of gastrointestinal symptoms, analyzing their evolution in relation to the results of different neuropsychological tests in patients with PD. In the third line of research, other researchers carry out follow-up studies of the effects of the consumption of psychobiotics (prebiotics and probiotics).

4.1. Composition of the microbiota and effects on cognitive functions

During the last 15 years, it has been recognized that the microbiota is one of the key regulators of gut-brain function (Cryan et al., 2019). The most of the studies in this review about this line of research focus on MCI, AD, and dementia, as well as PD, ADHD, and depression. All the empirical studies analyzed, associated a state of dysbiosis with a worse

progression of the disease, compared with other states of the disease or with healthy patients. Specifically, a higher proportion of *Lactobacillus* and *Escherichia* (pro-inflammatory bacteria) and a lower proportion of *Bacteroides* (anti-inflammatory bacteria) were found (Cattaneo et al., 2017; Li et al., 2019).

Dysbiosis is also known to occur when there is increased deconjugation of primary bile acids. The host's bile acids are often modified by bacteria into secondary bile acids (Needham et al., 2020). Further, all the secondary bile acids produced by the bacteria were detected in patients with Alzheimer's disease, and the increase in the proportions of secondary bile acids correlated with MCI and with changes in brain images (Nho et al., 2019; MahmoudianDehkordi et al., 2020).

In other studies, which were carried out with the same sample of patients, gut imbalance was associated with dementia, MCI, and AD (Saji et al., 2019b, 2019a, 2020); and also correlated clinical severity scores in patients with AD and altered microbiota (Liu et al., 2019). In addition, brain abnormalities, such as cortical and hippocampal atrophy, were found in patients with MCI and a higher prevalence of *Bacteroides* (Saji et al., 2019a), producing results similar to other studies in animal models such as that of Luczynski et al. (2016) or in human models such as that of Fernandez-Real et al. (2015), demonstrating that the microbiota could influence the microstructure and morphology of the brain.

Another finding on the early diagnosis of AD and its relationship with the microbiota is related to amnestic MCI, which mainly affects memory, and has been shown to have a high risk of progression to dementia, especially the type that appears in patients with Alzheimer's (Gauthier et al., 2006). Results in neuroimaging tests showed that, in addition to differences in the microbiota, there were cognitive and intrinsic brain activity differences related to the gut microbial composition in subjects with amnesic MCI (Liu et al., 2021). Specifically, the fractional amplitude value of the cerebellar IV-V vermis low frequency fluctuations was negatively associated with *Bacteroides* abundance. Previous studies have reported lesions in the cerebellum of patients with AD (Guo et al., 2016), so the analysis of intrinsic brain activity could be a tool to understand the pathogenesis and early detection of amnesic MCI.

Inflammation, an adaptive physiological process, is activated in response to pathogens (Turner et al., 2014), and some microbes of the microbiota, when there is decompensation, trigger cytokines and cause inflammation in the CNS (Zhu et al., 2020), contributing to the origin and development of MCI and AD. Certain bacterial taxa, known for their pro- or anti-inflammatory profile along with certain cytokines have been studied in patients with cognitive impairment, divided according to the presence of amyloid deposit. The presence of amyloid was associated with a greater abundance of inflammatory taxa (*Escherichia*) and a correlation between these and inflammatory cytokines. A lower abundance of *Bacteroides*, taxa with an anti-inflammatory profile, was also demonstrated (Cattaneo et al., 2017). This state of dysbiosis and inflammation in the CNS in patients with cognitive impairment could give an early diagnosis of AD, since it is considered a possible prodromal stage of AD (De Simone et al., 2019), and dysbiosis in the microbiota has been associated with the progression from MCI to AD (Liu et al., 2019; Nho et al., 2019; Li et al., 2019; MahmoudianDehkordi et al., 2020).

Another disorder studied in relation to dysbiosis is PD, which has linked the alteration of the gut-brain axis to specific bacteria related to gut and neuronal inflammation. Groups of PD patients demonstrated differences in the composition of the microbiota compared to healthy subjects, and certain bacteria were associated with a worse clinical profile, such as a higher frequency of cognitive impairment and postural instability (Barichella et al., 2019). This imbalance can affect the host's immune system, which is partly responsible for motor and non-motor symptoms in PD, so these changes in the microbiota could be explored as early biomarkers to identify individuals at higher risk of developing PD. (Sun and Shen, 2018).

In addition, differences in the composition of the microbiota compared to controls have been studied in patients with ADHD, as well as their role in inattention and hyperactivity/impulsivity. In addition to significant differences, seven- bacterial genera were associated with inattention and hyperactivity/impulsivity symptom scores (Szopinska-Tokov et al., 2020). These findings would support the potential role of the gut microbiota in the pathophysiology of ADHD.

Finally, the physiological process of inflammation in the face of pathogens has been studied in mood disorders, studying the effects it can have on the psychological factors that make people susceptible to depression or the effects that offer protection against it. In this case, different healthy patients gave significant results regarding the composition of the microbiota, inflammatory molecules and the prediction of some psychological factors. The results suggest that *Lactobacillus* and inflammation could be differentially associated with mood disorder through brain mechanisms that support self-judgment and empathy (Heym et al., 2019).

Based on these scientific findings, it is shown that any form of gut dysbiosis is capable of favoring the development of these pathologies, so its study and understanding is of great importance in the advancement of new therapies for its treatment.

4.2. Gastrointestinal symptoms and evolution of PD

Two of the non-motor symptoms in PD are cognitive impairment and gastrointestinal symptoms (Hayes, 2019), and they could predict the development of motor symptoms over many years (Nair et al., 2018). In a 5-year follow-up study with PD patients, the frequency of gastrointestinal symptoms and the results of different neuropsychological tests each year were measured, where all cognitive results of the neuropsychological tests were predicted by the main effect of gastrointestinal symptoms, associating a higher frequency of these symptoms with poorer cognitive performance (Jones et al., 2020). Despite the fact that this study showed significant results, it has major limitations since it only collects data on gastrointestinal symptoms, without analyzing the microbiota of the patients as the study progresses. This could be a variable to study in future research since the existence of dysbiosis would surely be evident.

The study by Jones et al. (2020) focuses on non-motor symptoms, but motor symptoms could also be predicted by dysbiosis in the microbiota. Although it is not in the same line of research, another study associated dysbiosis with a worse clinical profile, giving results in patients with a higher frequency of cognitive impairment, gait disturbances and postural instability (Barichella et al., 2019). With this, it can be seen how the microbiota could be an environmental modulator of the pathogenesis of PD and contribute to the interindividual variability of the clinical characteristics of the disease.

4.3. Effects of psychobiotics on cognitive functions

Diet is considered one of the most important factors influencing the human gut microbiota from infancy to old age, therefore, dietary interventions may have the potential to modulate psychological symptoms associated with gut-brain dysfunction (Oriach et al., 2016). Since the use of psychobiotics to improve the mental health of the host organism began to be investigated, it was hypothesized that one of the benefits could be related to anti-inflammatory actions and the ability to reduce the activity of the HHA axis, involved in stress (Dinan al. et al., 2013).

In a follow-up study of the effects of a prebiotic (dietary fiber) with healthy patients, a reduction in the cortisol response to acute stress was observed compared to the placebo group (Dalile et al., 2020), which would imply the influence of dietary intervention on the modulation of the reactivity of the HPA axis. In another study, a reduction in cognitive reactivity towards mood changes, in particular sadness, marked the vulnerability to depression (Chahwan et al., 2019). Other studies with psychobiotics found improvements in the cognitive functions of the subjects compared to the placebo groups, finding improvement in cognitive performance in different tests (Rudzki et al., 2019) and improvement in attention, in addition to a decrease in the concentration

of kynurenine (Berding et al., 2021). All these results are similar to previous studies with animal models with psychobiotics, which found improved mood, decreased anxiety, and improved memory and cognitive performance (Oriach et al., 2016).

5. Conclusion

In the present systematic review, the influence of the microbiome on the development and pathogenesis of different pathologies has been analyzed, as well as the advantages of dietary supplements with psychobiotics in the improvement of cognitive symptoms in humans. It has been demonstrated how dysbiosis affects the development of cognitive impairment, Alzheimer's disease, Parkinson's disease, mood disorders and ADHD. Furthermore, it has been proven how psychobiotics supplementation induce improvement in different cognitive functions and facilitate a reduction in the response to stress.

Although these results are encouraging, more research is needed to obtain evidence-based recommendations for the development of dietary strategies to improve mental health. In studies on psychobiotic supplementation, the dropout rate is high, especially in patients with depression. Eating habits and diet have proven to be very important factors for the microbiota, so having diet as a variable to study would have been very helpful to be able to deduce better results, being surely more effective in long-term studies. Currently, longitudinal studies are being carried out where the participants are followed (Stobernack et al., 2019, Arteaga-Henríquez et al., 2020), which will surely present enlightening results.

The study of the gut microbiota is a promising field with great insights, although much remains to be discovered. Most of the literature to date focuses on studies with animal models, so it is important to continue researching, especially with human models, to obtain more meaningful conclusions.

Understanding how communication is established between the gut and the CNS, the importance of maintaining a good balance between the bacteria that reside in our gut, and why it is important for the pathogenesis of different neurological and neuropsychiatric pathologies, is key to finding new strategies to improve cognition in our patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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