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REVIEW ARTICLE

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Influence of gut microbiota on the development of most prevalent neurodegenerative dementias and the potential effect of probiotics in elderly: A scoping review

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Abstract

Dementia is one of today's greatest public health challenges. Its high socio-economic impact and difficulties in diagnosis and treatment are of increasing concern to an aging world population. In recent years, the study of the relationship between gut microbiota and different neurocognitive disorders has gained a considerable interest. Several studies have reported associations between gut microbiota dysbiosis and some types of dementia. Probiotics have been suggested to restore dysbiosis and to improve neurocognitive symptomatology in these dementias. Based on these previous findings, the available scientific evidence on the gut microbiota in humans affected by the most prevalent dementias, as well as the probiotic trials conducted in these patients in recent years, have been here reviewed. Decreased concentrations of short-chain fatty acids (SCFA) and other bacterial metabolites appear to play a major role in the onset of neurocognitive symptoms in Alzheimer disease (AD) and Parkinson disease dementia (PDD). Increased abundance of proinflammatory taxa could be closely related to the more severe clinical symptoms in both, as well as in Lewy Bodies dementia. Important lack of information was noted in Frontotemporal dementia behavioral variant. Moreover, geographical differences in the composition of the gut microbiota have been reported in AD. Some potential beneficial effects of probiotics in AD and PDD have been reported. However, due to the controversial results further investigations are clearly necessary.

KEYWORDS
Alzheimer disease, dementia, gut microbiota, Parkinson disease dementia, probiotics

1 | INTRODUCTION

Dementia is a syndrome characterized by impairment of cognitive functions. Around 55 million people suffer from dementia worldwide, being estimated that this figure could triple by 2050 due to the increase in the life expectancy, but also the lack of effective treatments (WHO, 2019).

Alzheimer's disease (AD) is the leading cause of dementia worldwide. As the disease progresses, three periods can be identified: the early preclinical phase, the mild cognitive impairment phase (MCI, which may promote the onset of dementia) and the final phase, when dementia is observed (Scarabino et al., 2016). Although the etiology of the disease is unknown, several distinctive and common signs are

described. The accumulation of proteins that can cause neurotoxic damage, such as β-amyloid and hyper-phosphorylated tau protein stands out. The β-amyloid protein accumulates in brain tissue forming the extracellular plaques characteristic of the disease (Pistollato et al., 2016). When Tau protein is hyper-phosphorylated, it forms intracellular neurofibrillary tangles that accumulate in neurons and cause cell death (Lionnet et al., 2018).

On the other hand, Lewy body dementia (LBD) and Parkinson's disease dementia (PDD) are neurodegenerative diseases involving loss of dopaminergic neurons in the *Substantia nigra*. Both have similar symptomatology that worsen over time as neuronal loss increases. Although the etiology of both diseases is unknown, the presence of Lewy bodies has been observed in the enteric nervous system (ENS) and CNS (Sezgin et al., 2019). These structures are formed by misfolding of α-synuclein protein, mainly due to inflammatory processes induced by oxidative stress (Surendranathan et al., 2015).

Frontotemporal dementia (FTD) is characterized by a progressive atrophy of the frontal and anterior temporal lobes, associated with the accumulation of Tau protein. The most prevalent form is the behavioral variant (bvFTD), which includes deficit in social skills and personality disorders.

Most proteins likely to be related to the etiology of dementia are produced or modulated by the gut microbiota (GMB), which is described as the group of microorganisms that inhabit our intestines. In recent years, the scientific community is paying a notable attention to the gut microbiota, because it contains about 10 times more genes than the rest of the human genome (Johnstone et al., 2019; Sherwin et al., 2018). Several studies have demonstrated its relevance in different vital processes, including the production of metabolites, the regulation of the immune response and its role in modulating the CNS. This modulation is carried out through a bidirectional communication channel: the gut-brain axis (Alkasir et al., 2017; Benakis et al., 2020; Generoso et al., 2020). The gut-brain axis (GBA) collects information from peripheral organs and modulates their activity by three main pathways. The vagus nerve is the most direct physical way, consisting of a nerve that links viscera directly to the CNS. Furthermore, gut microbial populations secrete numerous small substances and metabolites that can reach the CNS, as lipopolysaccharide (LPS) and short-chain fatty acids (SCFA). On the other hand, the gut microbiota can modulate the immune system through circulating cytokines produced in the gut, which probably influence the CNS.

Several studies, both in animals and humans, have shown differences in the composition of the gut microbiota in patients with PD and AD (González-Domínguez et al., 2021; Scheperjans et al., 2015). Similar differences have also been observed in animal models of other neurocognitive disorders, such as Huntington's disease (HD) and multiple sclerosis (Kong et al., 2020). For instance, a study by Wasser et al. (2020) found changes in the diversity of microbial species (β-diversity) and a decrease in the variety within a microbial community (α-diversity) in human patients with HD. These disorders share common characteristics of inflammatory processes and metabolites produced by the gut microbiota. However, the potential distinction between them may reside in the presence of a specific profile of intestinal microbiota associated with each type of dementia.

Dysregulation in the homeostasis of gut microbiota has been associated with risks for human health. This dysregulation is known as dysbiosis. Several investigations suggest that an intervention on microbial populations to correct dysbiosis could lead to a restoration of body functions (Arteaga-Henríquez et al., 2020; Wallace et al., 2020). In dementia, there has been growing interest in the use of probiotics, which are a kind of active microorganisms that are beneficial to the host by colonizing the human body and by modifying the composition of the microbiota. They have been proposed as therapeutic alternative to restore microbiota homeostasis and to reduce the symptomatology of different types of dementia (Bonfili et al., 2017; Leblhuber et al., 2018; Lombardi et al., 2018).

The main objective of this scoping review was to explore the research conducted to date on the role of gut microbiota in the development of AD, FTD, DLB, and PDD, as well as in MCI, in the elderly population (aged 60 years and older). In addition, clinical trials of probiotics conducted in the target population were reviewed to assess their potential inclusion as a therapeutic alternative for the aforementioned dementias. Although both topics are calling the attention of the scientific community and they are being investigated, to our knowledge none has still reviewed the available scientific literature.

2 | METHODS

2.1 | Search strategy

PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com) were used as the databases to find the available studies in the scientific literature. The literature search was conducted following the PRISMA checklist for scoping reviews (Tricco et al., 2018). We used the following sets of keywords to investigate the profile of gut microbiota in the most prevalent neurodegenerative dementias: (1) *microbiota* OR *gastrointestinal microbiome* OR *gut brain axis* AND (2) *human* OR *patient* OR *subject* OR *participants*, *volunteer* OR *people*, *person*, *population* OR *individual* AND (3) *dementia* OR *mental health* OR *frontotemporal dementia* OR *Alzheimer Disease* OR *Parkinson Disease* OR *Lewy Body Disease* OR *cognitive dysfunction* OR *mild cognitive impairment*. Additionally, we included a fourth set of keywords to assess the impact of probiotics in treating the aforementioned dementias: AND (4) *probiotics*. The literature search was limited to publications from January 2015 onwards up to May 2023 due to the lack of relevant data prior to this period. Duplicate entries between the two databases were removed. Search equation can be referenced within Table S1.

2.2 | Inclusion criteria

All peer-reviewed research articles based on in vivo and clinical trials are selected for further reviewed. The chosen articles must be written

in English or Spanish, and include an abstract. The selected articles were further screened for compatibility, ensuring that they met the following criteria: (1) inclusion of human population, (2) inclusion of elderly individuals aged 60 or older, and (3) diagnostic information regarding the aforementioned dementias. In the case of probiotic studies, the following measures are also taken into consideration: (1) probiotic composition, (2) duration of treatment, and (3) findings.

2.3 | Exclusion criteria

Review articles, systematic reviews, and methodological reports were excluded from being further reviewed. Those articles published before year 2015 or those that did not meet the inclusion criteria were been excluded from further analysis. Besides, studies that discuss other forms of dementia or other neurological diseases were been excluded too. Articles based on other microbiological approaches, such as prebiotics or fecal transplants, were been excluded from the analysis.

2.4 | Data extraction and management

Figure 1 illustrates the search strategy. The results of the selected articles will be classified by type of dementia and recorded in tables. Probiotic-related articles will have their own separate table.

3 | RESULTS

Figure 2 summarizes up to 56 studies of the microbiota in the different types of dementias and mild cognitive impairment (MCI) patients reviewed, including those articles where probiotics have been tested.

3.1 | Alzheimer disease and mild cognitive impairment

Tables 1 and 2 summarize the studies reviewed on the microbiota of AD and MCI patients and their main contributions.

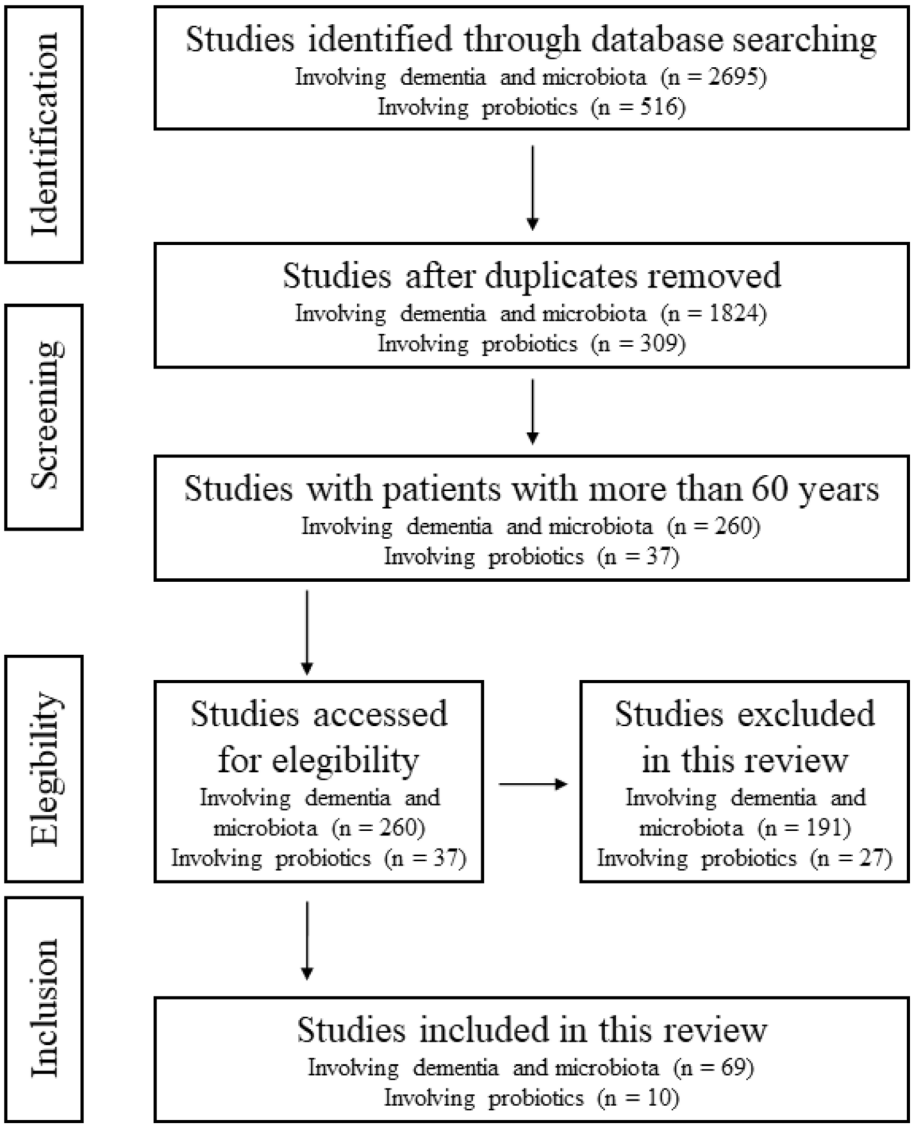

FIGURE 1 Flow chart of the search strategy.

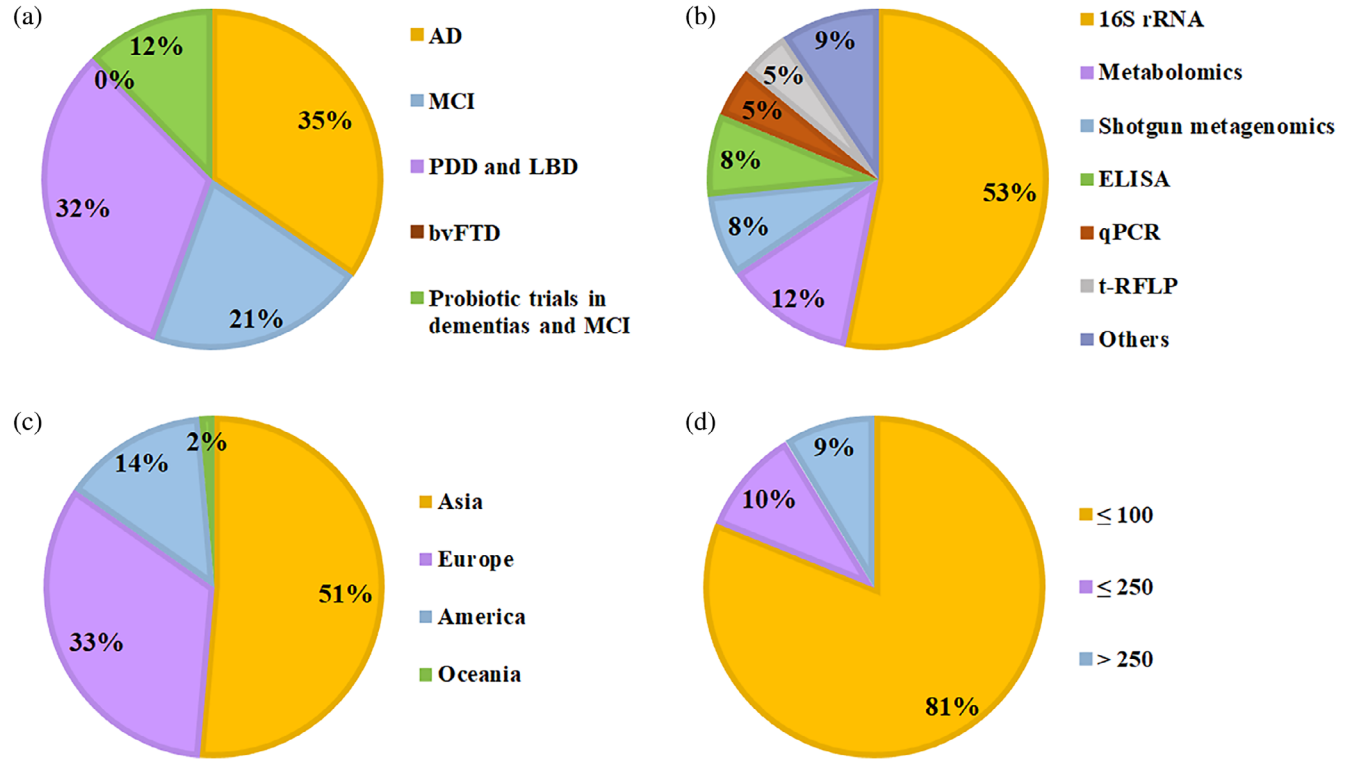

FIGURE 2 Distribution of the studies and probiotic trials reviewed, categorized by: (a) type of disease; (b) methodological approach; (c) geographical distribution of the studied populations; and (d) number of patients recruited. AD, Alzheimer disease; bvFTD, frontotemporal dementia behavioral variant; ELISA, enzyme-linked immunosorbent assay; LBD, Lewy bodies dementia; MCI, mild cognitive impairment; PDD, Parkinson disease dementia; qPCR, quantitative polymerase chain reaction; rRNA, ribosomal RNA; t-RFLP, terminal restriction fragment length polymorphism.

Although the formation of amyloid plaques and tau-phosphorylated neurofibrillary tangles are two of the hallmarks of AD, more molecules are studied in order to find the etiology of the disease. In recent years, numerous metabolites (especially related to GMB) have been analyzed to explore the relationship with the progression of the disease (González-Domínguez et al., 2021).

For example, the concentration of rhamnolipids (RL) in serum and cerebrospinal fluid (CSF) is higher in MCI and AD patients than healthy individuals (Andreadou et al., 2017). Rhamnolipids are microbial virulence factors secreted by GMB under conditions of dysbiosis, being susceptible to induce inflammatory responses. In addition, RL levels of MCI patients are lower than RL concentrations of AD patients. This correlation between RL levels and disease progression is consistent with the consideration of MCI as an early stage prior to AD.

A special attention has been paid at bile acids (BA), which result from cholesterol metabolism and further metabolized by GMB. In a study with 1464 volunteers divided into an early MCI group, a late MCI group, and an AD group, an increased concentration of secondary BA in the serum of the AD group was reported (MahmoudianDehkordi et al., 2019). No differences between the MCI groups and controls were observed. In a subsequent investigation conducted by the same research group, the obtained profile of six bile acids was associated with the presence of amyloid and Tau protein in CSF, both biomarkers of AD (Nho et al., 2019).

Similarly, Wei et al. (2020) found that outer membrane vesicles (OMVs), which are produced by the GMB, promote cognitive deficit by causing BBB ruptures, as well as inducing Tau protein phosphorylation in the hippocampus. In addition, OMVs contribute to inflammatory processes through activation of astrocytes and microglia in the CNS, and secretion of inflammatory cytokines. Breaks in the BBB allow other metabolites secreted by the GMB, such as LPS and *Escherichia coli* fragments, to reach the CNS and to contribute to the amyloidosis process (Li, He, et al., 2019). In relation to this, some gut barrier modulators such as zonulin or platelet activation have been studied, and AD and MCI patients have shown alterations (Wang et al., 2020). Interestingly, both zonulin and platelet C-type lectin-like receptor 2 (CLEC-2) levels are increased in MCI and AD patients because of the progression of neurodegeneration. Both parameters are significantly correlated with reduced mini-mental state examination (MMSE) scores.

Among the metabolites produced by GMB, short-chain fatty acids (SCFA) such as acetate, propionate and butyrate play a prominent role. SCFA are the result of anaerobic fermentation by GMB on indigestible polysaccharides, such as fiber, being characterized by their anti-inflammatory properties. Specifically, butyrate levels have been associated with the maintenance of cognitive ability, given its

TABLE 1 Summary of Alzheimer disease studies with their most relevant goals.

Number of samples	Methods	Country	Results	Reference
59	ELISA assays	Greece	Concentration of RL in serum and CSF correlates with the progression of the MCI to AD.	Andreadou et al. (2017)
30	16S rRNA	China	The abundance of *Lactobacillus*, *Akkermansia*, *Dorea*, *Bifidobacterium*, *Streptococcus*, *Acinetobacter* and *Blautia* was increased in AD patients.	Li, He, et al. (2019)
73	qPCR assays	Italy	The abundance of *Escherichia/Shigella* and *Eubacterium rectale* was associated with a peripheral inflammatory state in patients with cognitive impairment.	Cattaneo et al. (2017)
74	16S rRNA	Spain	Relative abundance of *Actinobacteria* and *Peptostreptococcaceae* may be useful to predict quality life in presenior populations.	de Cuevillas et al. (2022)
842	Metabolomics	Spain	Early metabolic events are associated with the later risk to develop cognitive decline.	González-Domínguez et al. (2021)
18	16S rRNA	China	AD patients had decreased *Bacteroides*, *Lachnospira*, and *Ruminiclostridium* and increased *Prevotella* at the genus level compared with healthy controls. Its abundances correlated with worse cognitive function.	Guo et al. (2021)
108	*Shotgun* metagenomics	United States	AD elders show a lower proportion and prevalence of bacteria with the potential to synthesize butyrate, as well as higher abundances of taxa that are known to cause proinflammatory states.	Haran et al. (2019)
48	Metabolomics	Taiwan	Indole-3-propionic acid was identified as a predictor of AD progression from MCI.	Huang et al. (2021)
78	16S rRNA	Republic of Korea	Alterations in gut bacterial taxa may precede cognitive decline in MCI and AD patients.	Jung et al. (2022)
41	16S rRNA	Kazakhstan	GMB alterations were related with disease severity in AD patients.	Kaiyrlykyzy et al. (2022)
33	16S rRNA	China	Distinct microbial communities were associated with patients with AD when compared with predementia stage aMCI and healthy subjects.	Liu et al. (2019)
305	Whole-genome sequencing (WGS)	United States Netherlands	AD patients have an increased concentration of secondary BA in serum.	MahmoudianDehkordi et al. (2019)
34	qPCR assays	Italy	Gut microbiota-related products and systemic inflammation are associated with brain amyloidosis.	Marizzoni et al. (2020)
838	Metabolomics	France	Propionate, a SCFA produced by GMB, was associated with cognitive impairment.	Neuffer et al. (2022)
4	16S rRNA	Japan	Up to 16 butyrate-producing bacteria were isolated from AD patients.	Nguyen et al. (2018)
305	Metabolomics	United States Netherlands	Six BA are associated with levels of amyloid and Tau protein in CSF.	Nho et al. (2019)
34	t-RFLP	Japan	Populations of enterotype I and enterotype III bacteria were strongly associated with dementia.	Saji, Niida, et al. (2019)
25	t-RFLP	Japan	A combination of higher fecal ammonia and lactic acid concentrations was indicative of the presence of dementia.	Saji et al. (2020)
56	16S rRNA	United Kingdom	APOE genotype is associated with specific gut microbiome profiles in humans.	Tran et al. (2019)
170	16S rRNA	Netherlands	Lower abundances of SCFA-producing microbes were associated with amyloid and Tau.	Verhaar et al. (2022)

(Continues)

TABLE 1 (Continued)

Number of samples	Methods	Country	Results	Reference
25	16S rRNA	United States	The abundance of Firmicutes and *Bifidobacterium* was decreased, whereas the abundance of Bacteroidetes was increased in AD patients.	Vogt et al. (2017)
40	ELISA assays Metabolomics	United States	High concentration of TMAO in patients with MCI and AD was associated with biomarkers of AD pathology.	Vogt et al. (2018)
20	16S rRNA	Thailand	AD Thai patients showed higher abundances of *Escherichia-Shigella*, *Bacteroides*, *Holdemanella*, *Romboutsia*, and *Megamonas* than healthy controls and MCI groups.	Wanapaisan et al. (2022)
110	ELISA assays	China	Increased CLEC-2 and zonulin are the significant factors for reduced MMSE score in MCI and AD.	Wang et al. (2020)
16	Western blot analysis Immunofluorescence	China	OMVs promote increase the permeability of the BBB, induce inflammatory response and Tau hyperphosphorylation.	Wei et al. (2020)
27	Metabolomics	China	Indole-3-pyruvic acid was identified as a signature for discrimination and prediction of AD, and five SCFA for pre-onset and progression of AD.	Wu et al. (2021)
21	16S rRNA Metabolomics	China	Bacterial alterations and related metabolic changes may be associated with pathogenesis of AD.	Xi et al. (2021)
43	16S rRNA	China	Gut microbiota is altered in AD patients and may be involved in the pathogenesis of AD.	Zhuang et al. (2018)

Abbreviations: AD, Alzheimer disease; aMCI, amnesic mild cognitive impairment; APOE, apolipoprotein E; BA, bile acids; BBB, blood brain barrier; CLEC-2, C-type lectin-like receptor 2; CSF, cerebrospinal fluid; GMB, gut microbiota; MCI, mild cognitive impairment; MMSE, mini-mental state examination; OMVs, outer membrane vesicles; RL, rhamnolipids; SCFA, short-chain fatty acids; t-RFLP, terminal restriction fragment length polymorphism; TMAO, trimethylamine N-oxide.

attenuating effect on inflammatory reactions. Nguyen et al. (2018) assessed the presence of butyrate-producing bacteria in the gut microbiota of AD patients. Surprisingly, up to 16 butyrate-producing bacteria belonging to the phyla Firmicutes (Order *Costridials*) and Bacteroidetes were isolated and identified. Similarly, Haran et al. (2019) reported that the number of butyrate-producing bacteria was reduced in AD patients, with an increased presence of bacteria involved in inflammatory responses. Interestingly, amyloid accumulation in the CNS correlates positively with levels of SCFA acetate and valerate, proinflammatory cytokines, biomarkers of endothelial dysfunction and circulating LPS in blood, but correlates negatively with butyrate levels (Marizzoni et al., 2020). Recently, other metabolites such as indole-3-propionic acid (IPA) and indole-3-pyruvic acid (IPyA), whose are generated by GMB from tryptophan, were identified as predictors of AD progression (Huang et al., 2021; Wu et al., 2021). Notably, Wu et al. (2021) observed tryptophan disorders and reduced SCFA in amnesic MCI (aMCI) patients. These disorders decreased progressively from aMCI to AD. However, the positive association of propionate with cognitive impairment has been also reported. Thus, the role of SCFA requires further investigations (Neuffer et al., 2022).

The interest in the process of amyloidosis and the role of inflammatory processes in the development of AD is not new. In a study conducted in MCI patients, the abundances of certain bacterial taxa known for their proinflammatory (*Escherichia/Shigella*) and anti-inflammatory (*Eubacterium*) activity, as well as the levels of some cytokines related to inflammatory processes were determined (Cattaneo et al., 2017). An increase in proinflammatory genera (*Escherichia/Shigella*) was observed with respect to healthy controls, correlating also with circulating cytokine levels. Wanapaisan et al. (2022) described elevated abundances of *Escherichia/Shigella*, *Bacteroides*, *Holdemanella*, *Romboutsia*, and *Megamonas* in a Thai population of AD patients. Furthermore, a lower abundance of *Eubacterium* was associated with higher odds of amyloid positivity in MCI and AD patients (Verhaar et al., 2022). In a study with obese African American MCI patients, cognitive scores were positively correlated with relative abundance of *Akkermansia muciniphila*, a bacterium associated with reduction of inflammatory processes (McLeod et al., 2023).

Consistent with these results, Vogt et al. (2017) reported that the GMB of American AD patients was different from that of healthy controls, with a decrease in microbial diversity. The abundance of Bacteroidetes increased while Firmicutes and the genus *Bifidobacterium* decreased. These abundances correlated with AD biomarkers measured in CSF, thus associating the phylum Bacteroidetes with inflammatory processes, and Firmicutes and the genus *Bifidobacterium* as

TABLE 2 Summary of mild cognitive impairment studies with their most relevant goals.

Number of samples	Methods	Country	Results	Reference
30	16S rRNA	China	Patients of MCI and AD were not shown significative differences in α-diversity and β-diversity.	Li, Wang, et al. (2019)
74	16S rRNA	Spain	Relative abundance of *Actinobacteria* and *Peptostreptococcaceae* may be useful to predict quality life in presenior populations.	de Cuevillas et al. (2022)
18	16S rRNA	China	The abundance of Bacteroidetes was increased and Firmicutes was decreased in MCI patients.	Duan et al. (2021)
842	Metabolomics	Spain	Early metabolic events are associated with the later risk to develop cognitive decline.	González-Domínguez et al. (2021)
20	16S rRNA	China	MCI patients had dramatically decreased *Lachnospira* at the genus level compared with healthy controls. Its abundance correlated with worse cognitive function.	Guo et al. (2021)
48	Metabolomics	Taiwan	Indole-3-propionic acid was identified as a predictor of AD progression from MCI.	Huang et al. (2021)
78	16S rRNA	Republic of Korea	Alterations in gut bacterial taxa may precede cognitive decline in MCI and AD patients.	Jung et al. (2022)
32	16S rRNA	China	Distinct microbial communities were associated with patients with AD when compared with predementia stage aMCI and healthy subjects.	Liu et al. (2019)
60	16S rRNA	United States	Gut microbial composition may be associated with inflammation and oxidative stress in African American MCI patients.	McLeod et al. (2023)
838	Metabolomics	France	Propionate, a SCFA produced by GMB, was associated with cognitive impairment.	Neuffer et al. (2022)
22	16S rRNA	China	GMB differed between controls and MCI patients.	Pan et al. (2021)
61	t-RFLP	Japan	An increased prevalence of Bacteroides is independently associated with the presence of MCI in patients without dementia.	Saji, Murotani, et al. (2019)
170	16S rRNA	Netherlands	Lower abundances of SCFA-producing microbes were associated with amyloid and Tau.	Verhaar et al. (2022)
12	16S rRNA	Thailand	Reduction of *Clostridiaceae* and increases in *Enterobacteriaceae* and *Bacteroides* were associated with MCI and AD Thai patients.	Wanapaisan et al. (2022)
110	ELISA assays	China	Increased CLEC-2 and zonulin are the significant factors for reduced MMSE score in MCI and AD.	Wang et al. (2020)
22	Metabolomics	China	Tryptophan disorders presented in aMCI and SCFA decreased progressively from aMCI to AD.	Wu et al. (2021)
81	16S rRNA	China	Genus *Bifidobacterium* may be associated with cognition in T2DM.	Zhang et al. (2021)

Abbreviations: AD, Alzheimer disease; aMCI, amnesic mild cognitive impairment; CLEC-2, C-type lectin-like receptor 2; GMB, gut microbiota; MCI, mild cognitive impairment; MMSE, mini-mental state examination; SCFA, short-chain fatty acids; t-RFLP, terminal restriction fragment length polymorphism; T2DM, type 2 diabetes mellitus.

protective against these processes. Later, this same group showed that the concentration of another AD-related microbial derivative, trimethylamine N-oxide (TMAO), increased progressively in MCI and AD patients (Vogt et al., 2018). Similar results were obtained in Chinese patients with cognitive deficits, in which the abundance of Bacteroidetes increased and Firmicutes decreased (Duan et al., 2021). More importantly, the abundance of the genus *Bifidobacterium* is found to be decreased in patients with type 2 diabetes, one of the risk factors for dementia (Zhang et al., 2021). This depletion of *Bifidobacterium* and other bacteria of the *Lactobacillaceae* family has been also reported in Kazakh AD patients (Kaiyrlykyzy et al., 2022). Controversially, a Japanese study in patients without dementia and with dementia found a decrease in the genus *Bacteroides*, which belongs to the phylum Bacteroidetes and has endothelial regulatory and anti-inflammatory functions. However, these discrepancies were attributed to the different lifestyle and diet of the American and Japanese populations (Saji, Niida, et al., 2019). The possible role of the genus *Bacteroides* as a protector against cognitive impairment was also

reported by the same group (Saji, Murotani, et al., 2019), who highlighted the value of fecal ammonium and lactic acid concentration as new biomarkers of dementia (Saji et al., 2020).

In recent years, several studies have reported differences between the GMB of healthy patients and that of MCI and AD patients, with very heterogeneous results. In a study conducted in Chinese AD patients, significant increases in Actinobacteria and *Ruminococcus*, and decreases in *Bacteroides* and *Lachnospiraceae*, were found compared to healthy patients (Zhuang et al., 2018). However, increases in relative abundance of Actinobacteria have been related to a better quality of life in healthy Spanish elders (de Cuevillas et al., 2022). Moreover, family *Lachnospiraceae* has been negatively associated with MMSE score and positively associated with the development of type 2 diabetes (Xi et al., 2021). Another Chinese study found that microbial diversity decreased in AD patients in comparison to MCI patients and healthy controls (Liu et al., 2019). In that study, a reduction in Firmicutes and an increase in Proteobacteria in AD patients compared to the control group were detected, while Gammaproteobacteria, *Enterobacteriales* and *Enterobacteriaceae* increased as cognitive impairment increased. Moreover, Liu et al. (2019) found a correlation between the severity of clinical assessment of AD and the abundance of altered microbiota, suggesting a model based on GMB profiles to discriminate between controls and AD, but also between MCI and AD by examining the abundance of *Enterobacteriaceae*. This difference in the GMB profile of different types of dementia has also been suggested by assessing the β-diversity of healthy patients, with AD or with other types of dementia (Haran et al., 2019). More recently, another study revealed a decrease in the abundance of Bacteroidetes and an increase in Fusobacteria in Japanese MCI patients (Pan et al., 2021). These changes were reflected in the analysis of β-diversity, discriminating MCI patients from healthy controls. Guo et al. (2021) found increased β-diversity in patients with AD or MCI compared with healthy controls. In their study, patients with AD and MCI exhibited reduced abundances of *Bacteroides*, *Lachnospira*, and *Ruminiclostridium_9*. However, they observed elevated abundances of genus *Prevotella* correlated with worse cognitive function. In contrast, Li, He, et al. (2019) reported a lack of significant differences between the GMB of MCI and AD patients. These differences may occur even before the onset of cognitive deficits. Patients with cerebral amyloidosis without cognitive deficit showed higher abundance of *Megamonas*, *Serratia*, *Leptotrichia*, and *Clostridiaceae*, and lower abundance of *CF231*, *Victivallis*, *Enterococcus*, *Mitsuokella*, and *Erysipelotrichaceae* in comparison to healthy patients (Jung et al., 2022). These results suggest the potential role of GMB in the development of these diseases.

Finally, the impact of genetics on GMB composition has also been investigated. Apolipoprotein E (APOE) genotype is the best characterized genetic risk factor for AD. No differences in microbial diversity were found in healthy patients with different APOE genotypes, measured using the Mann–Whitney *U* test for α-diversity and permutational multivariate ANOVA (PERMANOVA) for β-diversity. However, correlations have been observed between the abundance of butyrate-producing genera, such as *Prevotellaceae* and *Ruminococcaceae*, and different APOE genotypes (Tran et al., 2019).

3.2 | Lewy bodies dementias: Lewy bodies dementia and Parkinson disease dementia

Table 3 shows the studies reviewed on the microbiota of LBD and PDD patients and their main contributions.

Lewy bodies dementias is an umbrella term that includes LBD and PDD. Although both conditions have very similar clinical symptomatology, most of the published studies focuses on PD (with and without dementia) and the effects of GMB on different aspects of the disease.

In a Finnish study, the relative abundance of *Prevotellaceae* in the feces of PD patients was found to be lower than that of healthy controls, while the abundance of *Enterobacteriaceae* was positively associated with the severity of postural instability and gait difficulties (Scheperjans et al., 2015). These results highlight the role of GMB in both gastrointestinal and motor symptoms. Consistent with this, Unger et al. (2016) reported the same alterations in the microbial abundance of *Prevotellaceae* and *Enterobacteriaceae*, adding the observation that the phylum Bacteroidetes was also diminished. Another paper comparing healthy controls with PD patients was also published (Keshavarzian et al., 2015). It reported some genera associated with anti-inflammatory processes, such as *Blautia*, *Coprococcus*, and *Roseburia*, as well as *Faecalibacterium*, which suffered from decreased abundance in PD patients. In accordance with these findings, the abundance of *Ralstonia* was increased, as well the expression of genes involved in LPS biosynthesis, suggesting a role for this genus in proinflammatory processes. Lower abundance of *Roseburia* was associated with worse evolution of motor, non-motor and cognitive functions at 3-year follow-up cohort of Italian de novo PD patients (Cilia et al., 2021). Similar results were obtained by Li et al. (2017), who found a reduction in the abundance of *Ruminococcus*, *Blautia*, and *Faecalibacterium* and an increase in *Escherichia/Shigella*, *Proteus*, and *Enterococcus* compared to that in the control group. In addition, this study detected an increase in the concentration of neurotoxins, which are involved in inflammatory processes that may promote α-synuclein misfolding. Interestingly, a Russian investigation obtained similar results, with reductions in the abundance of *Dorea*, *Bacteroides*, *Prevotella*, and *Faecalibacterium*, and increases in *Christensenella*, *Catabacter*, *Lactobacillus*, *Oscillopira*, and *Bifidobacterium*, in line with the profiles described to date (Petrov et al., 2017).

Over the years, different studies have described further changes in the GMB profile of PD. In a German cohort, no changes were found at the level of alpha diversity. However, changes in some bacterial families were detected, being the abundance of *Lactobacillaceae*, *Barnesiellaceae*, and *Enterococcacea* higher in PD patients (Hopfner et al., 2017). Another study conducted in Germany described a higher abundance of *Verrucomicrobiaceae*, while *Prevotellaceae* and *Erysipelotrichaceae* were less abundant (Bedarf et al., 2017). In turn, Heintz-Buschart et al. (2018) studied changes in the GMB and nasal microbiota of PD patients, finding only changes in the GMB profile consisting of an increase in the genus *Akkermansia*, belonging to the *Verrucomicrobiaceae*. This increase of *Akkermansia*, together with the

TABLE 3 Summary of Parkinson disease dementia and Lewy bodies dementia studies with their most relevant goals.

Number of samples	Methods	Country	Results	Reference
64	16S rRNA	Finland	The previously detected gut microbiota differences between PD patients and controls persisted after 2 years.	Aho et al. (2019)
75	16S rRNA	China	PD is accompanied by alterations in the abundance of specific gut microbes.	Lin et al. (2018)
193	16S rRNA	Italy	Gut microbiota may be an environmental modulator of the pathogenesis of PD and contribute to the interindividual variability of clinical features.	Barichella et al. (2019)
31	*Shotgun* metagenomics	Germany	Differences of colonic microbiota and microbiota metabolism between PD patients and healthy controls are reported.	Bedarf et al. (2017)
80	16S rRNA	Taiwan	Altered gut microbiota in PD is correlated with clinical phenotypes and severity in PD patients.	Lin et al. (2019)
25	16S rRNA	Italy	Lower abundance of *Roseburia*, *Ruminococcaceae*, and Actinobacteria was associated with fester and worse evolution of cognitive functions at 3-year follow-up in de novo patients of PD.	Cilia et al. (2021)
10	16S rRNA	China	The abundance of *Ruminococcaceae*, *Verrucomicrobiaceae*, *Porphyromondaceae*, *Hydrogenoanaerobacterium* and *Lachnospiraceae NK4A* were enriched in patients with PD.	Li, Wang, et al. (2019)
41	ELISA assays	Slovakia	CgA analysis may be relevant in distinguishing LBD from PDD patients and presumably early stages of PD.	Gmitterova et al. (2020)
76	16S rRNA 18S rRNA	Luxembourg	Differential abundances of gut microbial taxa in PD are reported.	Heintz-Buschart et al. (2018)
30	Metabolomics	Germany	PD-specific patterns in microbial-host sulfur co-metabolism may contribute to PD severity.	Hertel et al. (2019)
29	16S rRNA	Germany	Beta diversity analyses revealed significant differences between cases and controls for four bacterial families.	Hopfner et al. (2017)
423	Multilevel models	United States	The presence of GI symptoms may serve as an early marker of cognitive impairment in PD.	Jones et al. (2020)
38	16S rRNA	United States	Proinflammatory dysbiosis is present in PD patients and could trigger inflammation-induced misfolding of α-synuclein and development of PD.	Keshavarzian et al. (2015)
313	*Shotgun* metagenomics	China	PD patients shown increments in the abundance of Actinobacteria and inflammatory indicators.	Li et al. (2021)
36	ELISA assays qRT-PCR assays	Japan	The total counts of intestinal bacterial decrease during PD progression.	Minato et al. (2017)
20	16S rRNA	Finland	The concentration of *Desulfovibrio* species correlated with the severity of PD.	Murros et al. (2021)
18	*Shotgun* metagenomics	Australia	Lower abundance of *Butyricimonas synergistica* was associated with worse PD non-motor symptoms in PD patients.	Nuzum et al. (2023)
89	16S rRNA	Russia	Gut microbiota can trigger local inflammation followed by aggregation of α-synuclein and generation of Lewy bodies.	Petrov et al. (2017)
80	16S rRNA	Italy	PD showed a distinctive microbiota composition.	Pietrucci et al. (2019)
45	16S rRNA	China	Differences in the fecal microbiome may explain the pathogenesis of PD.	Qian et al. (2018)
78	*Shotgun* metagenomics	China	Identified PD index based on the gene set from the gut microbiome may be a potential diagnostic biomarker of Parkinson's disease.	Qian et al. (2020)
72	16S rRNA	Finland	Intestinal microbiome is altered in PD and is related to motor phenotype.	Scheperjans et al. (2015)

(Continues)

TABLE 3 (Continued)

Number of samples	Methods	Country	Results	Reference
104	16S rRNA	Malaysia	Gut microbial function is altered in PD, characterized by differentially abundant metabolic features that provide important biological insights into gut–brain pathophysiology.	Tan et al. (2021)
34	qPCR assays	Germany	Association between PD and the abundance of certain gut microbiota shows a reduction in fecal SCFA concentrations.	Unger et al. (2016)
9	16S rRNA	United States	*Akkermansia* and *Prevotellaceae* as potential biomarkers for PD diagnosis.	Vidal-Martinez et al. (2020)
24	16S rRNA	China	Changes of gut microbiota in PD are characterized by the decreases of SCFA and production of neurotoxins.	Li et al. (2017)

Abbreviations: CgA, chromogranin A; GI, gastrointestinal; LBD, Lewy bodies dementia; PD, Parkinson disease; PDD, Parkinson disease dementia; SCFA, short-chain fatty acids.

increase of *Bifidobacterium* and the decrease of *Prevotella*, have been suggested as biomarkers of PD (Vidal-Martinez et al., 2020).

Compared to studies in Asian populations, the results do not differ much from those obtained in Europe. For example, *Bifidobacteriaceae* is more abundant in Chinese PD patients, while *Lachnospiraceae* is found to be reduced by almost 50% (Lin et al., 2018). Similar results were obtained by Li et al. (2021), who reported increases in the abundance of *Collinsella*, *Oscillibacter*, and *Subdoligranulum*, among others. *Collinsella* was increased in other diseases, such as type 2 diabetes, and *Subdoligranulum*, showing to be associated with constipation, a common symptom of PD. In fact, the reduction of *Lachnospiraceae* and the increase of *Enterobacteriaceae* are associated with an increase in disease severity and motor symptoms (Barichella et al., 2019; Pietrucci et al., 2019). In accordance with these results, reduced abundance of *Ruminococcoccaceae*, *Verrucomicrobiaceae*, and *Lachnospiraceae* was again found in Chinese population (Li, Wang, et al., 2019). Lower abundance of *Ruminococcaceae* was associated with faster worsening of global cognitive functions (Cilia et al., 2021). The genera *Butyricicoccus* and *Clostridium XIVb* have been associated with cognitive impairment in China (Qian et al., 2018). A PD profile characterization study was also conducted in Taiwan, incorporating cytokine analysis to assess their impact on inflammatory responses. Previously described alterations were found, including a reduction of *Prevotella* and an increase of *Bacteroides*, which correlated with some cytokines detected in plasma, as well as with the severity of patients' motor symptoms (Lin et al., 2019). The results of that study support the potential involvement of inflammatory processes on the etiology of the disease.

Although changes in GMB composition in PD have been studied, the functional consequences have not been especially taken into consideration. Baldini et al. (2020) reported an increase in the secretion of methionine and cysteinylglycine and the ability to produce large amounts of pantothenic acid, related to the presence of specific motor symptoms. Previously, the same research group showed that the methionine and cysteine conversion pathway is altered in PD patients, while taurine-conjugated bile acids are associated with increased severity of motor symptomatology (Hertel et al., 2019).

Other studies have investigated the evolution of PD over time, analyzing different symptomatology. For example, low *Bifidobacterium* counts are associated with worse prognosis of hallucinations, while low *Bacteroides* counts are associated with motivational problems at 2-year follow-up (Minato et al., 2017). Aho et al. (2019) reported alterations of *Roseburia*, *Prevotella*, and *Bifidobacterium* genera in PD patients when compared to a control group. Furthermore, the severity of gastrointestinal symptoms (constipation, loss of control of stools, hard stools) prior to neurodegeneration is associated with scores on different cognitive tests, and therefore, they can be used as indicators of cognitive deficits typical of PDD (Jones et al., 2020). In turn, Barichella et al. (2019) found a lower abundance of *Lachnospiraceae* and an increase of *Lactobacillaceae* and *Christensenellaceae* in PD patients, in line with the results above described, which are associated with worse clinical profile of the patients.

Finally, some studies have tried to describe metabolites produced by GMB, which might be amenable to use as biomarkers. This is the case of SCFA, which as in other types of dementia are found to be reduced in PD patients, being associated with a decline in cognitive abilities (Li et al., 2017; Unger et al., 2016). Specifically, low butyrate levels correlate with severity of instability and postural problems (Tan et al., 2021). Lower abundance of *Butyricimonas synergistica*, a butyrate-producer, was associated with worse PD non-motor symptoms (Nuzum et al., 2023). On the other hand, Gmitterova et al. (2020) have investigated endocrine cell markers, such as chromogranin A (CgA), which gradually increases in serum concentration from PD to PDD and LBD. This highlights the value of metabolomics approaches, especially to find candidate microbial species to produce compounds that correlate better with the disease symptomatology (Murros et al., 2021; Tan et al., 2021). This is the case of *Desulfovibrio*, whose abundance increases in PD patients, being associated with the disease severity (Murros et al., 2021). This bacterial genus produces hydrogen sulfide, LPS, and magnetite, all related to the oligomerization and aggregation of α-synuclein.

TABLE 4 Summary of the probiotic trial studies.

Diagnostic	Number of samples	Probiotic	Country	Results	Reference
Alzheimer disease	25	*Lactobacillus fermentum*, *Lactobacillus plantarum* and *Bifidobacterium lactis* *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Bifidobacterium longum*	Iran	Cognition and inflammation biomarkers show no differences after the probiotic consumption.	Agahi et al. (2018)
	60	*Bifidobacterium bifidum*, *Lactobacillus casei*, *Lactobacillus acidophilus* and *Lactobacillus fermentum*	Iran	Probiotic improved memory and learning activities in AD patients.	Akbari et al. (2016)
	27	*Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI	Republic of Korea	Probiotics alleviate stress in older adults, along with causing changes in gut microbiota.	Kim et al. (2021)
	20	*Lactobacillus casei*, *Lactococcus lactis*, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Lactobacillus paracasei*, *Lactobacillus plantarum*, *Bifidobacterium bifidum* and *Lactobacillus salivarus*	Austria	Multispecies probiotic increased abundance of *Faecalibacterium prausnitzii* and improved tryptophan metabolism.	Leblhuber et al. (2018)
Mild cognitive impairment	169	*Lactobacillus rhamnosus* GG	United States	Decreases in the relative abundance of *Prevotella* and *Dehalobacteriumin* response to probiotic was correlated with an improved cognitive score in MCI patients.	Aljumaah et al. (2022)
	115	*Bifidobacterium breve* MCC1274 (AI)	Japan	MCC1274 could help to prevent brain atrophy progression and cognitive impairment in MCI patients.	Asaoka et al. (2022)
	50	*Lactobacillus plantarum* C29 (DW2009)	Republic of Korea	DW2009 can be safely administered to enhance cognitive function in individuals with MCI.	Hwang et al. (2019)
	42	*Lactobacillus plantarum* BioF-228, *Lactococcus lactis* BioF-224, Bifidobacterium lactis CP-9, *Lactobacillus rhamnosus* Bv-77, *Lactobacillus johnsonii* MH-68, *Lactobacillus paracasei* MP137, *Lactobacillus salivarius* AP-32, *Lactobacillus acidophilus* TYCA06, *Lactococcus lactis* LY-66, *Bifidobacterium lactis* HNO19, *Lactobacillus rhamnosus* HNO01, *Lactobacillus paracasei* GL-156, *Bifidobacterium animalis* BB-115, *Lactobacillus casei* CS-773, *Lactobacillus reuteri* TSR332, *Lactobacillus fermentum* TSF331, *Bifidobacterium infantis* BLI-02 and *Lactobacillus plantarum* CN2018	China	Multispecies probiotic improved cognitive function and sleep quality through changes in microbiota composition after 12 weeks of treatment in MCI patients.	Fei et al. (2023)
	78	*Lactiplantibacillus plantarum* OLL2712 (OLL2712)	Japan	OLL2712 ingestion has protective effects against memory function decline in elders.	Sakurai et al. (2022)
Parkinson disease dementia	22	*Lactobacillus* sp. and *Bifidobacterium* sp.	Malaysia	Probiotic improved bowel opening frequency and whole gut transit time in PD patients with constipation.	Ibrahim et al. (2020)

Abbreviations: MCI, mild cognitive impairment; PD, Parkinson disease.

The genetic component of PD is also receiving some attention. In the search for new biomarkers of the disease, Qian et al. (2020) identified in Chinese population the first catalogue of specific microbial genes to diagnose PD patients compared to healthy controls.

3.3 | Frontotemporal dementia behavioral variant

The search conducted for this review did not yield any reports of articles in which the role of gut microbiota and frontotemporal dementia behavioral variant were studied. It is expected that bvFTD will show alterations in the composition of the GMB, as it also occurs in other types of dementia. AD and FTD overlap clinically and pathologically, Thus, it is acceptable to assume that bvFTD will have an altered GMB composition.

Despite being one of the most common types of dementia, this lack of in-depth studies may be due to several reasons. One of them could be the difficulty in obtaining a large group of bvFTD patients. On the other hand, the socio-economic impact of bvFTD is much lower than that in other more limiting dementias. Thus, these studies may not be considered as priority as other dementias such as AD or LBD.

3.4 | Probiotics

Probiotics are used to restore GMB homeostasis. Specifically, numerous animal studies support their efficacy in restoring microbial populations that have declined in abundance. Nevertheless, studies on human population are still scarce. Table 4 summarizes the probiotic studies in humans here reviewed.

Kim et al. (2021) performed a randomized, double-blind, placebo-controlled trial in Korean AD patients. The consumption of *Bifidobacterium bifidum BGN4* and *Bifidobacterium longum BORI* for 12 weeks reduced bacterial taxa involved in inflammatory processes, showing mental flexibility and stress improvement. In turn, brain-derived neurotrophic factor (BDNF) levels increased in blood. Similarly, Lee et al. (2021) found decreases of depression and anxiety symptoms in healthy adults consuming a mixture of *Lactobacillus reuteri NK33* and *Bifidobacterium adolescentis NK98* for 8 weeks. Furthermore, this mixture decreased *Enterobacteriaceae* in GMB, which has been associated with cognitive improvements (Barichella et al., 2019; Scheperjans et al., 2015). On the other hand, Leblhuber et al. (2018) examined the effect of a multi-species probiotic in AD patients. The consumption of *Lactobacillus casei*, *Lactococcus lactis*, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Lactobacillus paracasei*, *Lactobacillus plantarum*, *Bifidobacterium bifidum*, and *Lactobacillus salivarus* for 4 weeks, increased the abundance of *Faecalibacterium prausnitzii*, as well as improvements in tryptophan metabolism. *Faecalibacterium* had been found to be decreased in PD and MCI patients, being associated with anti-inflammatory processes and mitochondrial function (Keshavarzian et al., 2015; Ueda et al., 2021).

Akbari et al. (2016) performed a randomized, double-blind, placebo-controlled trial in Iranian AD patients. The consumption for 12 weeks of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* showed improvements in MMSE score, but probiotics had no remarkable effects on biomarkers of oxidative stress and inflammation. However, another randomized, placebo-controlled trial of the same group did not show sensitivity to the probiotic supplementation (Agahi et al., 2018). In that study, the effects of two different multispecies probiotics for 12 weeks (*Lactobacillus fermentum*, *Lactobacillus plantarum*, and *Bifidobacterium lactis* in the first one, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum* in the second) were tested.

Hwang et al. (2019) conducted a randomized, placebo-controlled trial in MCI patients. After consumption of *Lactobacillus plantarum* for 12 weeks, an improvement in cognitive symptoms was detected, as well as an increase in BDNF blood levels. On the other hand, consumption of *Lactiplantibacillus plantarum* OLL2712 for 12 weeks showed improvements in composite and visual memory and a reduction in the abundance of taxa related to inflammatory processes in patients with MCI (Sakurai et al., 2022). In turn, Asaoka et al. (2022) found that probiotic supplementation of *Bifidobacterium breve MCC1274 (A1)* for 24 weeks improved orientation, orientation in time, and writing tests in Japanese patients of MCI. Fei et al. (2023) described the effects of a multi-species probiotic in MCI Chinese patients. After 12 weeks of consumption, the probiotic group exhibited better cognitive function and sleep quality related to differences in β-diversity. More interestingly, Aljumaah et al. (2022) described higher prevalences of the genus *Prevotella* associated with MCI American patients. In their study, the consumption of *Lactobacillus rhamnosus* GG for 12 weeks reduced the abundance of *Prevotella* and *Dehalobacterium* in the MCI group, correlating with better cognitive scores. High abundances of *Prevotella* have been associated with cognitive impairment in MCI and AD patients (Guo et al., 2022).

On the other hand, Ibrahim et al. (2020) performed a multispecies probiotic trial in PD patients with constipation. The consumption of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus lactis*, *Bifidobacterium infantis*, and *Bifidobacterium longum*–twice daily for 8 weeks—showed improvements in intestinal transit, but some patients reported mild side effects.

The use of probiotics as a therapeutic option has also been investigated in other neurological diseases, showing a slight impact (Arteaga-Henríquez et al., 2020; Severance et al., 2017; Wallace et al., 2020; Zhang et al., 2019). However, these recent results are still too premature to become a treatment option in the dementia symptomatology.

4 | CONCLUSIONS AND FUTURE RECOMMENDATIONS

The gut microbiota plays a key role in the development of different forms of dementia, which has been demonstrated by the large number of studies reporting associations between the abundance of certain

taxa and specific aspects of the diseases. However, there is a high heterogeneity among the approaches that consider the metabolome and its functions in the organism, especially regarding the role of bacterial products secreted by the gut microbiota. Decreased concentrations of some of these molecules, such as SCFA, appear to play a major role in the onset of neurocognitive symptoms. This, together with the increased abundance of proinflammatory taxa, could be closely related to the more severe clinical symptoms in AD and PDD.

Moreover, geographical differences in the composition of the gut microbiota have been reported in AD. It shows the importance of regional studies to assess whether other factors, such as lifestyle or diet, play a major role in the development of dementias.

Hence, we call the attention to develop standardized protocols to facilitate the comparison among neuropsychological, neuropsychiatric, and functional assessments, as well as between the geographical particularities of different patients around the world.

Finally, there is a clear gap in the use of probiotics as a therapeutic alternative. It needs to be further explored to confirm its potential usefulness.

AUTHOR CONTRIBUTIONS

David Mateo: Conceptualization, Investigation, Writing – Original draft preparation. Montse Marquès: Conceptualization, Writing – Review and Editing, Supervision. José L. Domingo: Writing – Review and Editing, Supervision. Margarita Torrente: Conceptualization, Writing – Review and Editing, Supervision, Project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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