MODULATION OF THE MICROBIOTA-GUT-BRAIN AXIS AS A THERAPEUTIC STRATEGY FOR ALZHEIMER AND PARKINSON'S DISEASE

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Abstract: Targeting the gut microbiota as part of the microbiota-gut-brain axis has been proposed as a potential interesting new therapeutic strategy for neurodegenerative disorders, such as Parkinson's and Alzheimer's disease. In this review, the original articles from April 2020 to March 2021 tackling this research topic, are discussed. Multiple research groups investigated the mechanisms involved in the altered microbiota-gut-brain axis in Parkinson's and Alzheimer's disease, pointing out correlations between the gut microbiome and specific (patho)physiological properties or gastrointestinal functions and the potential of gut microbial markers as novel diagnostic biomarkers. Furthermore, the interventions described to target the gut microbiota, included probiotics (e.g., VSL#3, *Bifidobacterium* strains), prebiotics (e.g., plant and yeast extracts), supplements (e.g., minerals), medication (e.g., acetylcholine esterase inhibitors, antibiotics) and alternative therapies (e.g., acupuncture). Positive effects on the different components of the microbiota-gut-brain axis were demonstrated, such as an improvement of gut microbiota dysbiosis (including a restoration of the *Bacteroidetes* to *Firmicutes ratio*, a decrease in *Clostridiales*, and an increase in *Lactobacillus* and short-chain fatty acids), intestinal barrier dysfunction, inflammation (central/systemic/intestinal), motor deficits, cognitive impairment, neurotoxicity, pathological lesions in the brain, and amyloid β (Aβ) deposition. These results show a major role for the modulation of the microbiota-gut-brain axis as a new therapeutic strategy for both Parkinson's and Alzheimer's disease. Since the available data predominantly resulted from preclinical studies, future research should be focused on translational studies with a bench-to-bedside approach in order to eventually incorporate new treatments targeting the microbiota-gut-brain axis in the clinic.

Keywords: Microbiota-gut-brain axis, Mechanism, Biomarker, Animal models, Probiotics, Prebiotics, Supplements, Parkinson's disease, Alzheimer's disease.

INTRODUCTION

The concept of the gut-brain axis, encompassing the bidirectional communication between the nervous system and the gastrointestinal tract, has long been acknowledged. Furthermore, evidence has also been provided for the involvement of the microbiota as one of the key regulators of gut-brain function which led to the appreciation of the importance of a distinct microbiota-gut-brain axis. Preclinical and clinical studies revealed exciting potential for novel treatments targeting the gut microbiota in neurodegenerative diseases such as Parkinson and Alzheimer's disease[1].

MATERIALS AND METHODS

A literature search was performed on PubMed with the following search terms: "microbiota" AND "gut" AND "brain" AND "Alzheimer" OR "Parkinson". Results were limited to research articles published between April 2020 and March 2021. The following inclusion criteria were used: (1) studies in English and (2) only original research papers (no reviews). Based on these criteria, 47 studies were eventually included in this review.

PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disease with an increasing prevalence world-wide. It is characterized by the presence of bradykinesia combined with either rest tremor and/or rigidity, as well as non-motor symptoms, such as gastrointestinal complaints. The pathophysiology encompasses a complex interplay of aberrant α-synuclein aggregation, dysfunction of mitochondria, lysosomes or vesicle transport, synaptic transport issues, and neuroinflammation. The current first-line therapy consists of levodopa, but a treatment that can slow down or stop the progression of PD has yet to be found. This highlights the need for further research towards new therapeutic strategies and a more personalized treatment of PD patients[2]. Hence, the role of the microbiota-gut-brain axis in PD has been intensively studied, both in animals and humans.

Mechanistic Studies

Dendritic cell factor 1 (Dcf1) is a membrane protein that plays a key role in the development of the nervous system. Li et al[3] highlighted that the changes observed in the gut microbiota of Dcf1^{-/-} knockout (KO) mice compared to wildtype animals were similar to the human situation in PD patients, with an increase in *Proteobacteria* (phylum-level) and a decrease in *Prevotellaceae* (family-level). More specifically, on a species level, a decline in *Prevotellaceae UCG-001* and a rise in *Helicobacter ganmani* was observed in KO mice, which associated with glycolipid metabolism disorders and inflammatory lesions, respectively. Furthermore, Dcf1^{-/-} mice showed typical PD-like behavioral and pathological changes[3]. The gut microbiota in PD patients was also investigated using metagenomics and serum metabolomics, uncovering the contribution of the gut microbiome to the degradation of mucin and host glycans, folate deficiency and homocysteine metabolism in PD patients[4]. Previous studies[5,6] have demonstrated that short-chain fatty acids (SCFA) are reduced in fecal samples of PD patients. Surprisingly, a more recent study from Shin et al[7] reported that an increase in plasma SCFA in PD patients was associated with disease severity and anti-PD medication. Other studies[8] reported correlations between gut microbiota alterations and specific (patho)physiological functions. Firstly, gut microbiota dysbiosis, as characterized by elevated *Peptostreptococcaceae, Lachnospiraceae* and *Burkholderiales* and a decline in *Methanobacteriales, Odoribacter, Clostridium*, unclassified *Sutterellaceae* and *Escherichia*, resulted in increased bile acids in PD patients[8]. An increase in *Ruminococcus, Parabacteroides* and *Parasutterella* and a decrease in *Coriobacteriaceae, Flavonifractor, Lachnospiraceae, Lactobacillaceae,* and *Rikenellaceae*, was correlated with the disturbance of specific neurotransmitter pathways (dopamine, kynurenine, serotonin) in an 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced PD mouse model[9] whereas a reduction of the *Clostridium* genus associated with the genetic variant of the bitter taste receptor TAS2R38 (a genetic risk factor for the development of PD) in PD patients, possibly resulting in reduced activation of protective signaling molecules and thus gut homeostasis[10]. Furthermore, two studies[11,12] demonstrated an association between gut microbiota alterations on the one hand and gastrointestinal functions on the other hand. In a rotenone-induced conventional PD model, an increase in the bacterial genera *Lactobacillus, Bifidobacterium, Akkermansia,* and *Bacteroides spp.* and a decrease in *Lachnospiraceae, Ruminococcaceae UCG-014, Turicibacter, Faecalibaculum*, and *Clostridium spp* was observed. These changes in gut microbiota composition could be linked to an increased intestinal permeability and motor deficits, which were only observed in rotenone-treated conventionally-raised mice and not in rotenone-treated germ-free mice[11]. The second study[12] in PD patients identified microbial alter-

ations characterized by a higher abundance of *Christensenellaceae, Desulfovibrionaceae, Bifidobacterium, Collinsella, Bilophila* and *Akkermansia* and a lower abundance of *Lachnospiraceae, Roseburia,* an unclassified *Lachnospiraceae* genus and *Faecalibacterium*. These shifts in microbial composition strongly associated with stool consistency and constipation in PD patients[12]. Also, the effect of two common infections was tested in different PD mouse models. An oral infection with *Porphyromonas gingivalis* (the most common bacterium causing periodontitis) in leucine-rich repeat kinase 2 (LRRK2)-mutated PD mice resulted in an inflammatory response, an altered intestinal permeability and neurodegenerative lesions, such as a decline in dopaminergic neurons in the substantia nigra and activated microglial cells[13]. Cannon et al[14] characterized the intestinal microbiota during a *Citrobacter rodentium* infection in a Pink1^{-/-} KO mouse model for PD, with no major differences in fecal microbial diversity but a remarkable increase in the SCFA butyric acid at the peak of infection and post infection. Of note, butyric acid levels were not different in WT *vs.* Pink1^{-/-} KO mice prior to infection. These results contrast to the findings in humans, where fecal butyric acid levels in PD patients are lower[14]. Finally, two studies[15,16] identified novel gut microbial factors as potentially interesting diagnostic biomarkers for PD. More specifically, Qian et al[15] identified 25 gut microbial gene markers distinguishing PD patients from healthy controls (ROC curve: AUC 0.896, confidence interval: 83.1-96.1%), as well as discriminating between PD and multiple system atrophy and between PD and Alzheimer's disease[15]. The 25 microbial gene markers consist of different species from the genera *Bacteroides, Escherichia, Enterobacteriaceae, Proteobacteria, Klebsiella, Akkermansia* and *Alistipes*. For a complete overview, we refer to the Supplementary Table 12 published by Qian et al[15]. Another study[16] identified a subset of 22 bacterial families (*Lachnospiraceae, Ruminococcaceae, Bacteroidaceae, Verrumicrobiaceae, Rikellaceae, Bifidobacteriaceae, Porphyromonadaceae, Veillonaceae, Enterobacteriaceae, Alcaligenaceae, Christensenellaceae, Streptococcaceae, Erysipelotrichaceae, Odoribacteriaceae, Prevotellacaea, Desulfovibrionaceae, Coriobacteriaceae, Clostridiaceae, Barnesiellaceae, Lactobacillaceae, Tissierellaceae, Streptococcaceae*) to predict PD by using machine learning algorithms analyzing 846 metagenomic samples from PD patients and healthy controls[16].

Intervention Studies

Other studies have investigated whether specific interventions targeting the microbiota-gut-brain axis could affect PD symptoms in different animal models.

The effect of probiotics in PD animal models showed predominantly positive effects on PD pathology in different studies. A 4-week oral treatment of MPTP-induced PD mice with *C. butyricum* improved motor deficits and neurotoxicity and reversed gut microbiota dysbiosis[17]. Similar results were observed after a 4-week oral treatment with *L. plantarum PS128* in MPTP-induced PD mice[18]. Also, a 4-day oral administration of *B. breve* strain A1 in MPTP-induced mice resulted in an enhanced cognitive performance, as demonstrated by a restored abnormal hippocampal synaptic plasticity and the facilitation of fear extinction[19]. Exposure of rats to manganese (a transition metal) resulted in neurotoxicity, as demonstrated by an increased Aβ and Tau production in the brain, hippocampal degeneration and necrosis, which could be improved after manganese-exposed rats received a fecal microbiota transplantation (FMT) from normal rats[20]. Furthermore, oral gavage of *Enterococcus faecalis* or *E. faecium* in an MPTP + probenecid (medication that increases uric acid excretion in the urine) mouse model increased brain dopamine and ameliorated PD manifestation whereas supplementation with oral berberine (a phytonutrient) even showed a better therapeutic effect than with bacteria alone[21]. This interesting therapeutic effect could be explained by the fact that *Enterococcus* administration resulted in the synthesis of dopa/dopamine in the intestinal tract, thereby elevating dopamine levels in the blood and brain. Moreover, berberine is an agonist of tyrosine hydroxylase in *Enterococcus* and the combination of *Enterococcus* with berberine could thereby lead to the production of L-dopa in the gut and an amelioration of PD symptoms. This study[21] suggests that *E. faecalis* and *E. faecium* might ameliorate PD symptoms via dopa/dopamine production in the intestine, and that drug regulation of this process might further improve brain function. On the other hand, a pre-treatment with the probiotic VSL#3 (containing *Bifidobacteria, Lactobacillus, Streptococcus thermophilus BT01*) did not influence the PD-like pathology provoked by a dual hit toxin model using lipopolysaccharide (LPS) and

paraquat exposure[22]. Taken together, these studies suggest the potential of probiotics to improve PD pathological symptoms, such as motor and cognitive impairment, neurotoxicity and gut microbiota dysbiosis.

Prebiotics are also seen as a possible therapeutic option for PD patients. The plant flavonoid fisetin was demonstrated to have neuroprotective effects in an MPTP-induced PD mouse model by altering the number, diversity and distribution of gut microbiota[23]. More specifically, the *Lachnospiraceae* family was more abundant whereas the *Bifidobacteriaceae, Enterobacteriaceae* and *Bacillaceae* families were depleted. At the genus level, the treated animals displayed an increase in *uncultured_bacterium_f_Lachnospiraceae, [Eubacterium]_ruminantium_group*, and *Marvinbryantia*, and a decrease in *Bifidobacterium, Escherichia, Shigella* and *Bacillus*[23]. Neuroprotective effects were also observed after a 2-month oral treatment of 6-hydroxydopamine-induced PD mice with propionate or its receptor agonist (FFAR3-agonist, AR420626)[24]. Furthermore, a 4-week oral preventive treatment with the brown seaweed polysaccharide of polymannuronic acid (chosen for its low toxicity and easy biodegradability) showed neuroprotective effects (i.e., improved motor functions by preventing dopaminergic neuronal loss in the substantia nigra and increased levels of striatal neurotransmitters) in the same PD mouse model[25]. In addition, inflammation was significantly reduced in the gut, brain and systemic circulation and the integrity of the intestinal barrier and the blood brain barrier was enhanced. Treatment also resulted in an altered gut microbiota composition, with a suppression of *Lactobacillus* and *Turicibacter* and an increase in *Coprococcus* and *Ruminococcus*, which were respectively increased and decreased in untreated MPTP-mice. Finally, also alterations in the digestion and metabolism of dietary proteins and fats were noticed, leading to an increased level of SCFA (total SCFA, acetic acid, propionic acid and butyric acid) in the colon[25]. The abovementioned studies clearly highlight the beneficial effects of prebiotics on different parts of the microbiota-gut-brain axis in PD-like pathology, as shown by an improvement of the gut microbiota composition, neurotoxicity, inflammation, intestinal and blood brain barrier.

The mercury-sulfide-containing supplements Hua-Feng-Dan and 70 Wei-Zhen-Zhu-Wan (Rannasangpei) showed promising results in an MPTP + lipopolysaccharide (LPS)-induced two-hit PD mouse model[26]. More specifically, treatment improved motor activity and ameliorated pathological lesions in the brain (microglia and dopaminergic neurons), as well as altered the gut microbiota composition, which was characterized by a depletion of *Verrucomicrobiaceae, Methanobacteriaceae, Pronicromonosporaceae* and *Clostridaceae*[26]. Mercury sulfide is presumed to assist therapeutic effects of other ingredients in polyherb-metallic preparations[26]. Similar results were observed in an MPTP mouse model after a 12-day oral treatment with Korean red ginseng. In this study, beneficial effects were observed on motor activity, brain lesions and the gut microbiota composition, typified by a lower abundance of *Verrucomicrobiaceae, Ruminococcus* and *Akkermansia* and an increased abundance of *Eubacterium*[27]. A 2-month intraperitoneal treatment with osteocalcin (protein secreted by osteoblasts) ameliorated motor deficits and dopaminergic loss in a 6-hydroxydopamine-induced PD mouse model, which was mediated by propionate-producing gut microbiota[24].

Other therapeutic options include, e.g., acupuncture treatment, which was demonstrated to improve motor functions and anxiety, protected dopaminergic neurons as well as alter gut microbiota composition in MPTP-induced PD mice[28]. 16S rRNA sequence analysis further revealed a significant enrichment of *Rikenellaceae, Vallitaleaceae, Alistipes, Vallitalea, Lachnoclostridium, Pseudoclostridium, B. xylanolyticus, V. pronyensis, C. aerotolerans, P. thermosuccinogenes* and *R. faecis*. Some of them were even correlated with motor functions and/or anxiety[28].

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a chronic neurodegenerative disorder with an estimated prevalence of 10-30% in the population of >65 years. The underlying disease mechanism consists of the failure to clear Aβ from the interstices of the brain. The FDA-approved medication results in symptom improvement, but it does not affect the underlying disease mechanisms, thereby highlighting the need for novel therapeutic targets. The modulation of the microbiota-gut-brain axis is one possibility, that has received increased attention in the latest years[29].

Mechanistic Studies

Multiple studies have investigated associations between the gut microbiota composition and some typical pathophysiological features of AD. A mouse study demonstrated a sex-dependent relationship between the gut microbiota composition (with a decreased abundance of *Ruminococcaceae*) and cognitive dysfunction, which was only observed in female transgenic AD mice[30]. Interestingly, another research group also reported gender-dependent differences in APP/PS1 transgenic mice. They found that the bile acid (BA) profile (based on the levels of 28 different BAs) was significantly different in male compared to female mice, with decreased levels of taurine-conjugated primary BAs (i.e., tauroursodeoxycholic acid, taurocholic acid and muricholic acid) and increased levels of secondary BA (iso-deoxycholic acid) in plasma and liver extracts in female mice. In contrast, increased levels of taurodeoxycholic acid in liver extracts and decreased levels of muricholic acid in jejunal content were observed in male AD mice[31]. Of note, sex differences are also observed in the epidemiology of Alzheimer's disease in humans[32]. Another study[33] demonstrated an altered composition of intestinal bacterial communities in 5-month-old APP^{swe}/PS1$^{\Delta E9}$ (PAP) transgenic mice characterized by an upregulation of *Acinetobacter guillouiae* and *B. coprocola* and a downregulation of *C. methylpentosum, Aminipila butyrica, Lawsonibacter asaccharolyticus, Kineothrix alysoides, Flintibacter butyricus* and *A. finegoldii*. These microbial changes in the gut of 5-month-old PAP mice were correlated with the impairment of cognitive functioning and might stimulate amyloid deposition by promoting the MAPK signaling pathway in the brain. Besides, two different mouse studies showed the occurrence of gut microbial changes before the presence of typical features of AD. Chen and colleagues demonstrated the presence of differences in microbiome composition between WT and APP/PS1 starting from an early age and increasing with age. Of note, WT and their age-matched WT littermates were housed together under specific pathogen-free conditions (n=4 mice/cage). Specifically, at 2 months of age, there was already an increased abundance in APP/PS1 mice compared to age-matched WT mice of the phyla *Verrucomicrobia, Actinobacteria* and *Proteobacteria* and the families *Verrucomicrobiaceae, Prevotellaceae, Erysipelotrichaceae,* and *Bifidobacteriaceae*. At the genus level, *Akkermansia, P. UCG-001, Bifidobacterium, Erysipelatoclostridium, Allobaculum* and *Alloprevotella* were significantly elevated. At later ages (i.e., 6 and 9 months), inflammation-related bacterial taxa such as *Escherichia, Shigella, Desulfovibrio, Akkermansia*, and *Blautia* were more abundant in APP/PS1 mice compared to age-matched WT mice. Interestingly, key pathological features of AD, such as amyloid deposition and plaque-localized neuroinflammation, were only seen at later ages, starting at 3 months, thereby indicating that microbial alterations in the gut precede typical pathological features of AD[34]. A second study proposed a possible mechanism behind the gut microbial alterations eventually leading to AD. In brief, Wei et al[35] found that outer membrane vesicles, produced by gut microbiota, could increase the blood brain barrier permeability and activate astrocytes and microglia, thereby inducing an inflammatory response and tau hyperphosphorylation by stimulating the GSK-3 pathway, eventually leading to cognitive dysfunction[35]. Another research group demonstrated an altered microbial composition in APP/PS1 mice after chronic noise exposure with a decrease of *Muribaculaceae* and an increase of *Bacteroidaceae* at the family level, as well as decreased levels of *Rikenella* and *Anaerovorax* at the genus level. These microbial alterations were related to detrimental effects on oxidation, systemic inflammation and tight junction expression levels in the brain and intestines[36].

Intervention Studies

Research in the field of AD has also been dedicated to the effects of specific interventions targeting the microbiota-gut-brain axis in animal models and humans.

The effect of probiotics has also been investigated in AD. A 6-month oral treatment of APP/PS1 double transgenic mice with *B. longum 1714* resulted in a reduced Aβ deposition in the brain, a reduced microglial activation and reduced levels of pro-inflammatory cytokines in the brain[37]. Interestingly, these positive results were confirmed in a randomized double-blind, and placebo-controlled multicenter trial in healthy 65+ volunteers that were

treated with *Bifidobacterium* strains, including *B. bifidum BGN4* and *B. longum BORI,* for 12 weeks. Compared to the placebo group, the treated group showed a greater improvement in the mental flexibility test and stress score, a significant reduction in inflammation-causing gut bacteria (*Eubacterium, Allisonella, Clostridiales*, and *Prevotellaceae*), a significant increase in brain-derived neurotrophic factor (BDNF) serum levels which were negatively correlated with *Eubacterium* and *Clostridiales*[38]. Food containing seven different lactic acid bacteria strains reversed the malformation of eye structures (frequently observed in AD) in the transgenic GMR-Aβ42 Drosophila melanogaster animal model. Moreover, these lactic acid bacteria ameliorated the gut microbiota profile with a reduction of *Wolbachia* and an increase of *Stenotrophomonas* and *Acetobacter* (resembling the microbial profile of the control group)[39]. Probiotic supplementation of App^{NL-G-F} mice with VSL#3 resulted in a significant increase in both bacterial diversity and species richness, with an increased abundance of the bacteria phyla *Verrucomicrobia* and *Actinobacteria*, but no change in the overall *Firmicutes*/*Bacteroidetes* ratio. Furthermore, a decreased intestinal inflammation and gut permeability as well as minimal effects on Aβ, cytokine and gliosis levels in the brain were observed[40]. Finally, the clinical relevance of FMT in AD was demonstrated in a case report showing symptom improvement in a patient with AD following FMT for treating a *C. difficile* infection[41]. Altogether, these studies suggest an interesting role for probiotics as a therapeutic option for AD patients with favorable effects on Aβ deposition and inflammation in the brain, microglial activation, gut microbiota composition and even intestinal inflammation and barrier function.

The prebiotic R13 (7,8-Dihydroxyflavone prodrug) had positive effects, when given once a day from 12 weeks of age through 24 to 25 weeks of age in a 5XFAD mouse model. More specifically, it suppressed amyloid aggregates in the gut, alleviated gut dysbiosis and induced probiotic *L. salivarius* that suppressed C/EBPβ/AEP signaling, thereby decreasing gut leakage and oxidative stress[42]. Also yeast β-glucans administration in Aβ_{1-42}-induced AD mice resulted in alterations of the composition of the gut microbiota. At the phylum level, it restored the Bacteroidetes to Firmicutes ratio. At the genus level, inflammatory-related bacteria such as *Oscillibacter, Mucispirillum, Alistipes, Anaerotruncus, Rikenella* were decreased whereas beneficial bacteria such as *Lactobacillus, Bifidobacterium, Saccharibacteria_genera_incertae_sedis* and *Desulfovibrio* increased. Besides, yeast β-glucans ameliorated cognitive defects (by alleviating neuroinflammation and brain insulin resistance), increased SCFA levels and restored gut microbiota dysbiosis[43].

The effects of different supplements were also investigated in preclinical mouse and rat models for AD. Poria cocos (a wood-decay fungus) improved the cognitive function, reduced Aβ deposition and improved gut dysbiosis in APP/PS1 mice[44]. Similar effects were observed after supplementation with salidroside (a plant extract) in SAMP8 mice[45], quercetin-3-O-glucuronide in Aβ_{1-42}-induced AD-like mice[46], Tetragonia tetragonioides Kuntze (TTK; New Zealand spinach) Aβ_{25-35}-induced rats[47] and Camellia oil in aluminium chloride-treated rats[48]. With regard to the improved gut dysbiosis, salidroside restored the Bacteroidetes to Firmicutes ratio and reduced both *Clostridiales* and *Streptococcaceae*[45]. Similarly, quercetin-3-O-glucuronide supplementation also restored the *Bacteroidetes* to *Firmicutes* ratio and elevated short-chain fatty acids (SCFA)[46]. Administration of TTK resulted in a reduction of *Clostridiales*, *Erysipelotrichales, Desulfovibrionales* and an increase in *Lactobacilales* and *Bacteroidales*[47]. *Lactobacilales* were also increased after treatment with Camellia oil[48]. Interestingly, these supplements also exerted other specific effects. Quercetin-3-O-glucuronide and TTK improved insulin signaling and ameliorated insulin resistance in the brain[46,47]. Moreover, salidroside and camellia oil attenuated pro-inflammatory cytokine expression levels in the blood and brain[45,48]. In addition, salidroside improved intestinal barrier homeostasis and reduced microglial activation[45], whereas camellia oil also decreased multiple AD-related proteins (APP, BACE1 and TAU-5), enhanced antioxidant enzyme levels and the expression of autophagy-related proteins (Atg5, Beclin-1, and LC3II)[48].

On the contrary, two other supplements, trimethylamine N-oxide (TMAO; a gut microbe-dependent metabolite)[49] and wheat amylase trypsin inhibitors (ATIs) (dietary protein component of gluten-containing cereals)[50] both aggravated AD pathology in a 3×Tg and a 5xFAD AD mouse model, respectively. At the gut microbial level, ATIs induced a lowered *Bacteroidetes* to *Firmicutes* ratio and a reduction in *Bifidobacteria*[50]. These data point towards TMAO inhibition and an ATI-depleted diet as potential therapeutic options[49,50].

Finally, the effects of some classic medication were also investigated in preclinical mouse models for AD. Both a 3-week subcutaneous treatment with anastrozole (27-hydroxycholesterol inhibitor) and an oral treatment from postnatal day 14-21 with an antibiotic cocktail (containing kanamycin, gentamicin, colistin, metronidazole, vancomycin) in APP/PS1 transgenic mice significantly reduced the brain Aβ-amyloidosis and altered the microbiota profile[51,52]. Antibiotic cocktail-treated mice showed changes in *s_Uniformis*, the *Lachnospiraceae* family and the genera of *Parabacteroides* and *Ruminococcus*[52]. Treatment with anastrozole demonstrated an increase in *Roseburia*, which are butyrate-producing bacteria that can metabolize dietary fibers and exhibit anti-inflammatory effects in the gut[51]. Anastrozole also reduced intestinal and systemic inflammation, improved intestinal barrier function and alleviated cognitive deficits[51]. Another study investigated the effect of FDA-approved medication for AD on intestinal properties in mice. The acetylcholine esterase inhibitors donepezil, rivastigmine and galantamine had no effect on fecal bacteria viability, while a high dose of memantine led to a reduced biofilm formation of *E. coli*. Furthermore, the acetylcholinesterase inhibitors prolonged the colonic propulsion time and memantine increased calcium influx in enteric neurons. Taken together, these results indicate that all FDA-approved drugs for AD could potentially affect different intestinal properties and thereby also the microbiome[53].

LIMITATIONS

The literature with regard to the role of the microbiota-gut-brain axis, PD and AD is getting more attention in recent years. However, the currently available studies do have some limitations. Firstly, most studies were performed in animal models and therefore the transferability of the results to a human setting should be carefully considered, since the microbiota composition differs between animals and humans. Secondly, most studies report data from smaller groups and the results are mostly descriptive without mentioning a clear effect size. Finally, the few clinical studies that have been conducted report promising outcomes, but more translational and clinical studies in this domain are eagerly awaited.

CONCLUSIONS

In this review, we summarized the original research from April 2020 to March 2021 investigating the mechanisms behind microbiota-gut-brain alterations in neurodegenerative disorders such as PD and AD and the effect of modulating the microbiota-gut-brain axis as a potential new therapeutic target. Mechanistic studies pointed out specific associations between the gut microbiota composition on the one hand and gastrointestinal functions or pathophysiological properties of AD or PD on the other hand. An overview of the different microbial alterations in PD and AD models is given in Figure 1. Moreover, a panel of gut microbial markers was put forward as a potential interesting new diagnostic biomarker for PD. Remarkably, studies with regard to AD observed gender-related associations and demonstrated the presence of microbial changes before the onset of typical AD symptoms. The administration of probiotics, prebiotics, supplements, classic medication and alternative therapies showed interesting outcomes with beneficial effects on motor deficits, cognitive impairment, neurotoxicity, pathological lesions in the brain, Aβ deposition (AD), gut microbiota dysbiosis, inflammation (central/systemic/intestinal) and intestinal barrier dysfunction. Some specific effects on the gut microbiota composition seem to play an important role in the amelioration of the pathophysiology of PD and AD such as a decrease in *Clostridiales*, an improvement of the *Bacteroidetes* to *Firmicutes* ratio (increased *Bacteroidetes,* decreased *Firmicutes*) and an increase of *Lactobacillus* and SCFA. The effects of different interventions on the microbiota-gut-brain axis are summarized in table 1 for PD and table 2 for AD. These promising results are a major step forward towards the search for new therapeutic targets for PD and AD. However, most studies are performed in preclinical animal models and therefore more translational studies are eagerly awaited to be able to evaluate the clinical potential of these new targets for the management of PD and AD.
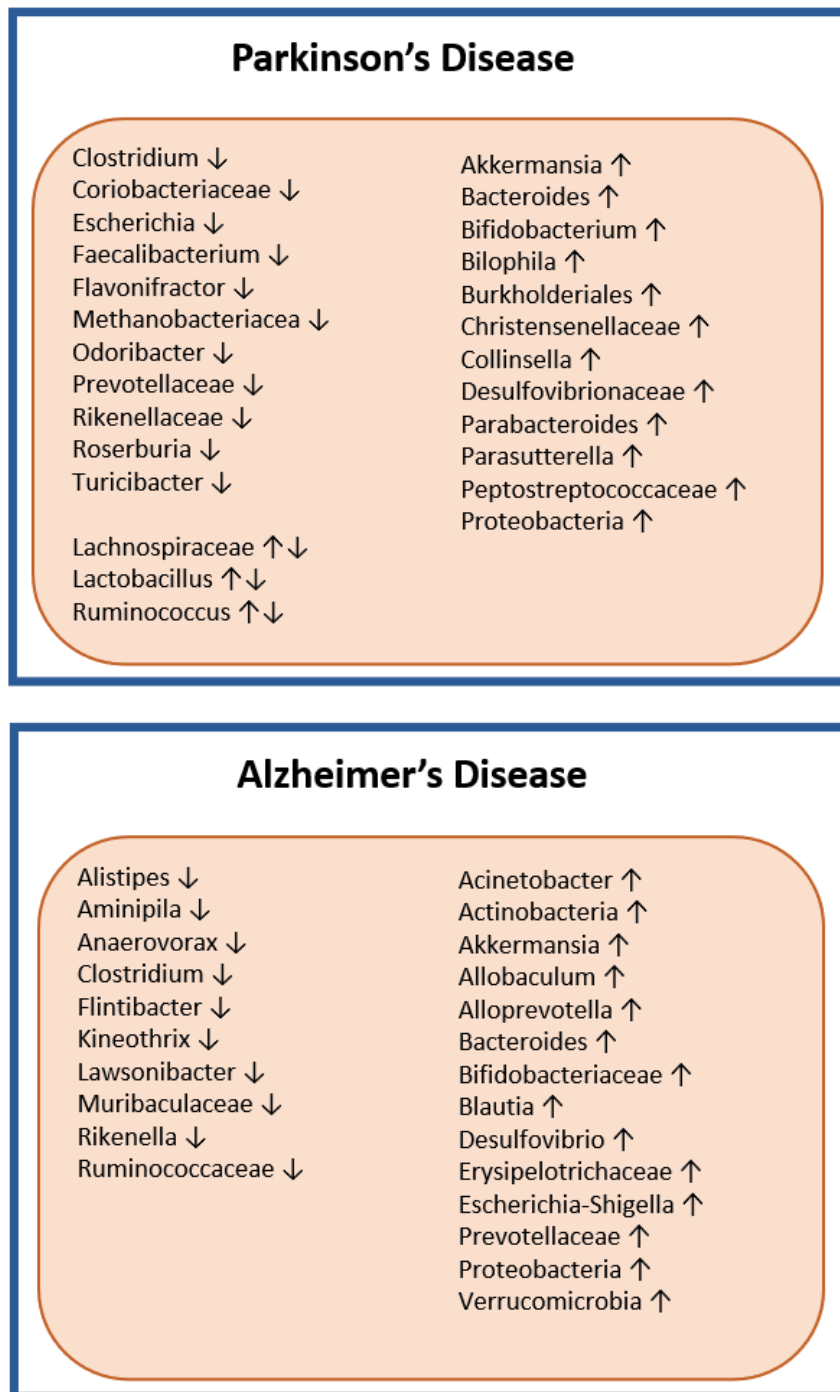
Parkinson's Disease

Clostridium ↓
Coriobacteriaceae ↓
Escherichia ↓
Faecalibacterium ↓
Flavonifractor ↓
Methanobacteriacea ↓
Odoribacter ↓
Prevotellaceae ↓
Rikenellaceae ↓
Roserburia ↓
Turicibacter ↓

Lachnospiraceae ↑↓
Lactobacillus ↑↓
Ruminococcus ↑↓

Akkermansia ↑
Bacteroides ↑
Bifidobacterium ↑
Bilophila ↑
Burkholderiales ↑
Christensenellaceae ↑
Collinsella ↑
Desulfovibrionaceae ↑
Parabacteroides ↑
Parasutterella ↑
Peptostreptococcaceae ↑
Proteobacteria ↑

Alzheimer's Disease

Alistipes ↓
Aminipila ↓
Anaerovorax ↓
Clostridium ↓
Flintibacter ↓
Kineothrix ↓
Lawsonibacter ↓
Muribaculaceae ↓
Rikenella ↓
Ruminococcaceae ↓

Acinetobacter ↑
Actinobacteria ↑
Akkermansia ↑
Allobaculum ↑
Alloprevotella ↑
Bacteroides ↑
Bifidobacteriaceae ↑
Blautia ↑
Desulfovibrio ↑
Erysipelotrichaceae ↑
Escherichia-Shigella ↑
Prevotellaceae ↑
Proteobacteria ↑
Verrucomicrobia ↑

Figure 1. Summary of the microbial changes seen in animal models and human studies of Parkinson's and Alzheimer's disease.

TABLE 1. SUMMARY OF THE EFFECTS OF DIFFERENT INTERVENTIONS IN PD MODELS ON THE MICROBIOTA-GUT-BRAIN AXIS.

Intervention	Study group	Microbiome	Gut functions	CNS/Brain	Reference
Probiotics					
Clostridium butyricum	MPTP mouse model	*Alistipes* ↓ *Odoribacter* ↓ *Prevotellaceae* ↓ *Akkermansia* ↑ *Verrucomicrobiaceae* ↑		Motor function ↑ Neurotoxicity ↓	Sun et al 2021
Lactobacillus plantarum PS128	MPTP mouse model	*Firmicutes/Bacteroidetes* ↓ *Enterobacteriaceae* ↓		Motor function ↑ Neurotoxicity ↓	Liao et al 2020
Bifidobacterium breve strain A1	MPTP mouse model			Cognitive function ↑	Ishi et al 2021
Fecal microbiota transplantation (FMT)	Manganese-exposed rat model			Neurotoxicity ↓ β-amyloid ↓ Tau protein ↓ Hippocampal degeneration & necrosis ↓	Wang et al 2020
Enterococcus faecalis	MPTP + probenecid mouse model	*Enterococcus* ↑ *Escherichia* ↑ *Lactobacillus* ↑ *Pseudomonas* ↑ *Shigella* ↑		Dopamine ↑ PD symptoms ↓	Wang et al 2021
VSL#3	LPS + paraquat mouse model	*Streptococcaceae* ↑		PD symptoms =	Dwyer et al 2021
Prebiotics					
Fisetin	MPTP mouse model	*Bacillaceae* ↓ *Bifidobacteriaceae* ↓ *Enterobacteriaceae* ↓ *Escherichia* ↓ *Shigella* ↓ *Lachnospiraceae* ↑ *Eubacterium* ↑ *Marvinbryantia* ↑		Neurotoxicity ↓	Chen et al 2020

TABLE 1 (*CONTINUED*). SUMMARY OF THE EFFECTS OF DIFFERENT INTERVENTIONS IN PD MODELS ON THE MICROBIOTA-GUT-BRAIN AXIS.

Intervention	Study group	Microbiome	Gut functions	CNS/Brain	Reference
Prebiotics (continued)					
Propionate or FFAR3-agonist AR420626	6-hydroxydopamine mouse model		Neurotoxicity ↓		Hou et al 2021
Brown seaweed polysaccharide of polymannuronic acid	MPTP mouse model	*Lactobacillus* ↓ *Turicibacter* ↓ *Coprococcus* ↑ *Ruminococcus* ↑	Inflammation ↓ Intestinal barrier ↑ SCFA ↑	Motor function ↑ Neurotoxicity ↓ Dopamine ↑ Striatal neurotransmitters ↑ Inflammation ↓ Blood brain barrier ↑	Dong et al 2020
Supplements					
Hua-Feng-Dan and 70 Wei-Zhen-Zhu-Wan (Rannasangpei)	MPTP + LPS mouse model	*Clostridaceae* ↓ *Methanobacteriaceae* ↓ *Pronicromonosporaceae* ↓ *Verrucomicrobiaceae* ↓		Motor function ↑ Brain lesions ↓	Hu et al 2020
Korean red ginseng	MPTP mouse model	*Akkermansia* ↓ *Ruminococcus* ↓ *Verrucomicrobiaceae* ↓ *Eubacterium* ↑		Motor function ↑ Brain lesions ↓	Jeon et al 2021
Osteocalcin	6-hydroxydopamine mouse model	Propionate-producing gut microbiota ↑		Motor function ↑ Dopamine ↑	Hou et al 2021
Other					
Acupuncture	MPTP mouse model	*Alistipes* ↑ *Bacteroides xylanolyticus* ↑ *Clostridium aerotolerans* ↑ *Lachnoclostridium* ↑ *Pseudoclostridium* ↑ *Rikenellaceae* ↑ *Roseburia faecis* ↑ *Vallitaleaceae* ↑		Motor function ↑ Dopamine ↑ Anxiety ↓	Jang et al 2020

The interventions that were studied include probiotics, prebiotics, supplements and acupuncture. The effects observed on the microbiota-gut-brain axis include the increase or decrease of specific microbial strains, a decrease in intestinal inflammation, an improved intestinal barrier function, an increase in SCFA, improvement of typical PD-related features (e.g., motor function, neurotoxicity, brain lesions) and beneficial effects on the expression levels of specific neurotransmitters (e.g., dopamine) and proteins (e.g., β-amyloid and tau-protein). FFAR3 = free fatty acid receptor 3; MPTP = 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; LPS = lipopolysaccharides; PD = Parkinson's Disease; SCFA = short-chain fatty acids.

TABLE 2. SUMMARY OF THE EFFECTS OF DIFFERENT INTERVENTIONS IN AD MODELS ON THE MICROBIOTA-GUT-BRAIN AXIS.

Intervention	Study group	Microbiome	Gut functions	CNS/Brain	Reference
Probiotics					
Bifidobacterium longum 1714	APP/PS1 double transgenic mice			β-amyloid ↓ Microglia activation ↓ Pro-inflammatory cytokines ↓	Wu et al 2020
Bifidobacterium longum BORI *Bifidobacterium bifidum* BGN4	Healthy 65+ volunteers	*Allisonella* ↓ *Clostridiales* ↓ *Eubacterium* ↓ *Prevotellaceae* ↓		Mental flexibility test and stress score ↑ BDNF ↑	Kim et al 2021
Lactic acid bacteria strains	Transgenic GMR-Aβ42 Drosophila melanogaster animal model	*Wolbachia* ↓ *Acetobacter* ↑ *Stenotrophomonas* ↑		Malformation of eye structures ↓	Liu et al 2020
VSL#3	App^NL-G-F mice	*Actinobacteria* ↑ *Verrucomicrobia* ↑ *Bacteroidetes/ Firmicutes* =	Inflammation ↓ Intestinal barrier ↑	β-amyloid ↓ Pro-inflammatory cytokines ↓ Gliosis levels ↑	Kaur et al 2020
Fecal microbiota transplantation	Case report AD patient with *Clostridium difficile* infection			AD symptoms ↓	Azan et al 2020
Prebiotics					
R13 (7,8-Dihydroxy-flavone prodrug)	5XFAD mouse model	*Lactobacillus salivarius* ↑	Intestinal barrier ↑	β-amyloid ↓ Oxidative stress ↓	Chen et al 2020
yeast β-glucans	Aβ$_{1-42}$-induced mice	*Alistipes* ↓ *Anaerotruncus* ↓ *Mucispirillum* ↓ *Oscillibacter* ↓ *Rikenella* ↓ *Bacteroidetes/Firmicutes* ↑ *Bifidobacterium* ↑ *Desulfovibrio* ↑ *Lactobacillus* ↑ *Saccharibacteria* ↑	SCFA ↑	Cognitive function ↑ Brain insulin resistance ↑	Xu et al 2020

TABLE 2 (*CONTINUED*). SUMMARY OF THE EFFECTS OF DIFFERENT INTERVENTIONS IN AD MODELS ON THE MICROBIOTA-GUT-BRAIN AXIS.

Intervention	Study group	Microbiome	Gut functions	CNS/Brain	Reference
Supplements					
Poria cocos	APP/PS1 double transgenic mice	Bacteroidetes/ Firmicutes ↑ Bacteroidaceae ↓ Cyanobacteria ↓ Deferribacteraceae ↓ Enterobacteriaceae ↓ Lactobacillaceae ↓ Lachnospiraceae ↓ Proteobacteria ↓ Ruminococcaceae ↓ Rikenellaceae ↓		Cognitive function ↑ β-amyloid ↓	Sun et al 2021
Salidroside	SAMP8 mice	Clostridiales ↓ Streptococcaceae ↓ Bacteroidetes/ Firmicutes ↑	Intestinal barrier ↑	Cognitive function ↑ β-amyloid ↓ Pro-inflammatory cytokines ↓ Microglial activation ↓	Xie et al 2020
Quercetin-3-O-glucuronide	$A\beta_{1-42}$-induced mice	Bacteroidetes/ Firmicutes ↑	SCFA ↑	Cognitive function ↑ β-amyloid ↓ Brain insulin signaling and resistance ↑	Xu et al 2021
Tetragonia tetragonioides Kuntze	$A\beta_{25-35}$-induced rats	Clostridiales ↓ Erysipelotrichales ↓ Desulfovibrionales ↓ Bacteroidales ↑ Lactobacilales ↑		Cognitive function ↑ β-amyloid ↓ Brain insulin signaling and resistance ↑	Kim et al 2020
Camellia oil	Aluminium chloride-treated rats	Lactobacilales ↑		Cognitive function ↑ β-amyloid ↓ Pro-inflammatory cytokines ↓ AD-related proteins (APP, BACE1, TAU-5) ↓ Antioxidant enzyme levels ↑ Autophagy-related proteins (Atg5, Beclin-1, LC3II) ↑	Weng et al 2020

TABLE 2 (*CONTINUED*). SUMMARY OF THE EFFECTS OF DIFFERENT INTERVENTIONS IN AD MODELS ON THE MICROBIOTA-GUT-BRAIN AXIS.

Intervention	Study group	Microbiome	Gut functions	CNS/Brain	Reference
Supplements (continued)					
Trimethylamine N-oxide	3×Tg mouse model			AD symptoms ↑	Govindarajulu et al 2020
Wheat amylase trypsin inhibitors	5XFAD mouse model	*Bacteroidetes/Firmicutes* ↓ *Bifidobacterium* ↓		AD symptoms ↑	Dos Santos Guilherme et al 2020
Medication					
Anastrozole	APP/PS1 double transgenic mice	*Roseburia* ↑	Inflammation ↓ Intestinal barrier ↑	β-amyloid ↓ Inflammation ↓ Cognitive function ↑	Wang et al 2020
Antibiotic cocktail	APP/PS1 double transgenic mice	s_*Uniformis* ↑ *Lachnospiraceae* ↑ *Parabacteroides* ↓ *Ruminococcus* ↓		β-amyloid ↓	Dodiya et al 2020
Acetylcholine esterase inhibitors	Mice	Fecal bacteria viability =	Colonic propulsion time ↑		Nguyen et al 2021
Memantine	Mice	*E. coli* biofilm ↓	Enteric neuron properties ↑		Nguyen et al 2021

The interventions that were studied include probiotics, prebiotics, supplements and medication. The effects observed on the microbiota-gut-brain axis include the increase or decrease of specific microbial strains, a decrease in intestinal inflammation, an improved intestinal barrier function, an increase in SCFA, improvement of typical AD-related features (e.g., cognitive function, brain insulin signaling and resistance) and beneficial effects on the expression levels of specific proteins (e.g., β-amyloid) and pro-inflammatory cytokines. AD = Alzheimer's Disease; SCFA = short-chain fatty acids; APP = amyloid-β precursor protein; BACE1 = β-secretase 1; Atg5 = autophagy-related 5; LC3II = Microtubule-associated proteins 1A/1B light chain 3B; BDNF = brain-derived neurotrophic factor.

Conflict of interest

The authors have no competing interests.

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