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THE USE OF MICROBIOTA-MODULATING AGENTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS BY INFLUENCING THE MICROBIOTA-GUT-BRAIN AXIS

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Abstract: Currently, no curative treatments exist for most neurological disorders. Nevertheless, the involvement of the gut microbiota has gained increasing interest over the last years. In this review, we summarize the main findings published between April 2019 and March 2020 that are related to the use of microbiota-modulating agents to treat depression, Alzheimer's disease (AD), and Parkinson's disease (PD). These 'psychobiotics' were investigated individually or in combination and included probiotics (e.g., *Bifidobacterium* and *Lactobacillus strains*), prebiotics (e.g., polysaccharides and plant extracts), medicinal products (e.g., antidepressants and vitamins), as well as physical activity or infrared red-light treatment. All agents improved disease-related abnormalities to some extent. Their main effects involved the restoration of gut homeostasis by altering gut microbiota composition and suppressing intestinal inflammation. Disease symptoms improved associated with a reduction in cytokine levels, microglia activation, plaque deposition and neuronal cell death and with an increase in neurotrophic factors and glucose uptake in the brain. Furthermore, the 5-HT, TLR, NLRP3 and PPARγ signaling pathways were highlighted as major bidirectional communication routes between the gut and the brain. In addition, whereas *Bifidobacterium longum*, *Bifidobacterium lactis* and *Lactobacillus plantarum* improved the symptom severity and affected pathophysiological pathways of both depression and AD, *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* were shown to ameliorate PD as well as depression or AD. Although most studies have been performed in animal models and the exact underlying mechanisms and pathways need further investigation, influencing the microbiota-gut-brain communication has major potential for the future treatment of depression, AD and PD.

Keywords: Microbiota-gut-brain axis, Psychobiotics, Probiotics, Prebiotics, Depression, Alzheimer's disease, Parkinson's disease.

METHODS

A literature search was performed on PubMed with the search terms "microbiota" AND "gut" AND "brain", limiting results to research papers published between April 2019 and March 2020. Additional filters were applied for "microbiota" AND "depression" OR "Alzheimer" OR "Parkinson" OR "brain" OR "colitis". 161 abstracts were selected for further review. Studies were included if they (1) contained original research considering the administration of probiotics and other gut microbiota-modulating agents in order to treat depression, Alzheimer's

disease (AD) or Parkinson's disease (PD); (2) investigated/discussed potential molecular mechanisms involved; and (3) were written in English. Eventually, 45 papers were selected.

DEPRESSION

Depression is a mental illness affecting more than 264 million people worldwide[1]. Chronic stress and anxiety are both major risk factors. As previous studies have emphasized the importance of microbial dysbiosis in patients with depression, modulation of the microbiota could thus be a potential strategy to influence several key brain signaling pathways[2].

Many probiotics (i.e., live or heat-killed micro-organisms that are claimed to be beneficial for health when consumed or applied to the body) exert general anti-inflammatory effects on the intestinal, systemic and brain level (Figure 1 and Table 1). In the following studies, mice were exposed to chronic immobilization stress (IS) to induce anxious and depressive symptoms, which were associated with both neural and intestinal inflammation. Upon treatment with *Lactobacillus reuteri*, *Bifidobacterium adolescentis*, *L. mucosae* or *B. longum,* mice showed improved performance in the elevated plus maze, light/dark transition, tail suspension and forced swimming tests. Furthermore, NFκB activation and infiltration of microglial cells were reduced in the hippocampus, whereas brain-derived neurotrophic factor (BDNF) levels were elevated (Figure 1)[3-5]. These effects are suggested to result from suppressing intestinal inflammation and reducing the levels of interleukin (IL)-6, corticosterone, and lipopolysaccharide (LPS) in the blood (Figure 1)[3,4]. Evaluation of fecal microbiota composition showed that treatment with the probiotics reversed the effects of IS by re-increasing the levels of *Firmicutes* and re-suppressing *Proteobacteria* and *Bacteroidetes*, which decreased intestinal LPS production (Figure 1)[3-5]. At the genus level, treatment with *B. adolescentis* increased *Lactobacillus* and decreased *Bacteroides*[5]. In addition, *L. mucosae* treatment was also shown to restore intestinal homeostasis and improve cognitive decline and signs of anxiety and depression during *Escherichia coli*-induced murine colitis[6]. Furthermore, the use of probiotic cocktails containing *Lactobacillus* and *Bifidobacterium* strains were able to improve depressive behavior by restoring gut and brain homeostasis[3,7,8].

Secondly, probiotic treatment can also affect the 5-hydroxytryptophan (5-HT) signaling pathway in the brain in rodents (Figure 1). The emergence of depression by chronic mild stress could largely be prevented in mice by the treatment with several *Bifidobacterium* strains (Table 1)[9,10]. This effect was also observed in rats treated with *B. longum*, *L. rhamnosus* or the prebiotics (i.e., food compounds that enhance the growth or activity of beneficial microorganisms) fructo-oligosaccharide or galacto-oligosaccharide (Table 1)[8]. Their mechanism of action was related to restoring 5-HT synthesis in the hippocampus and prefrontal cortex. More specifically, treatment affected tryptophan hydroxylase (TPH)1 expression in the colon and TPH2 and indoleamine-2,3-dioxygenase (IDO) levels in the brain (Figure 1)[8-10]. Although both the prebiotic and probiotic treatments affected microbiota composition, the study findings were not consistent[8-10].

Thirdly, the beneficial effect of several gut microbiota likely involves Toll-like receptor (TLR) signaling and the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome (Figure 1). Takahashi et al[11] investigated the effect of administering *Enterococcus faecalis* 2001 (EF-2001) to dextran sodium sulphate (DSS)-treated mice on the colon and the brain. The preventive treatment with EF-2001 improved the disease severity and histopathological changes of the colon induced by DSS-treatment. In addition, the protein levels of the proinflammatory cytokines IL-6 and tumor necrosis factor (TNF)-α were reduced in the colon and brain (Figure 1). EF-2001 treatment also resulted in specific changes in the hippocampus, including the reversal of reduced neurogenesis, an elevated activation of the NFκB p65/XIAP pathway, a decreased caspase-3 activity, as well as an increased expression of TLR2 (Figure 1). Hence, they suggested that EF-2001 could exert this antidepressant effect by decreasing cytokine expression and regulating cell death in the hippocampus *via* TLR2 activation, besides its protective effect on the intestines. A study performed by Kambe et al[12], further showed an anxiolytic effect of *E. faecalis* strain 12 on behavioral tests in healthy mice. Zhang et al[13] also highlighted an important role for the inflammasome in shaping the microbiota-gut-brain axis. In their study, fecal microbiota transplantation (FMT) of NLRP3 knockout mice improved depressive-like behaviors in mice. Alteration of the microbiota profile was shown to partially restore astrocyte function by inhibiting the increase of the circular RNA HIPK2.

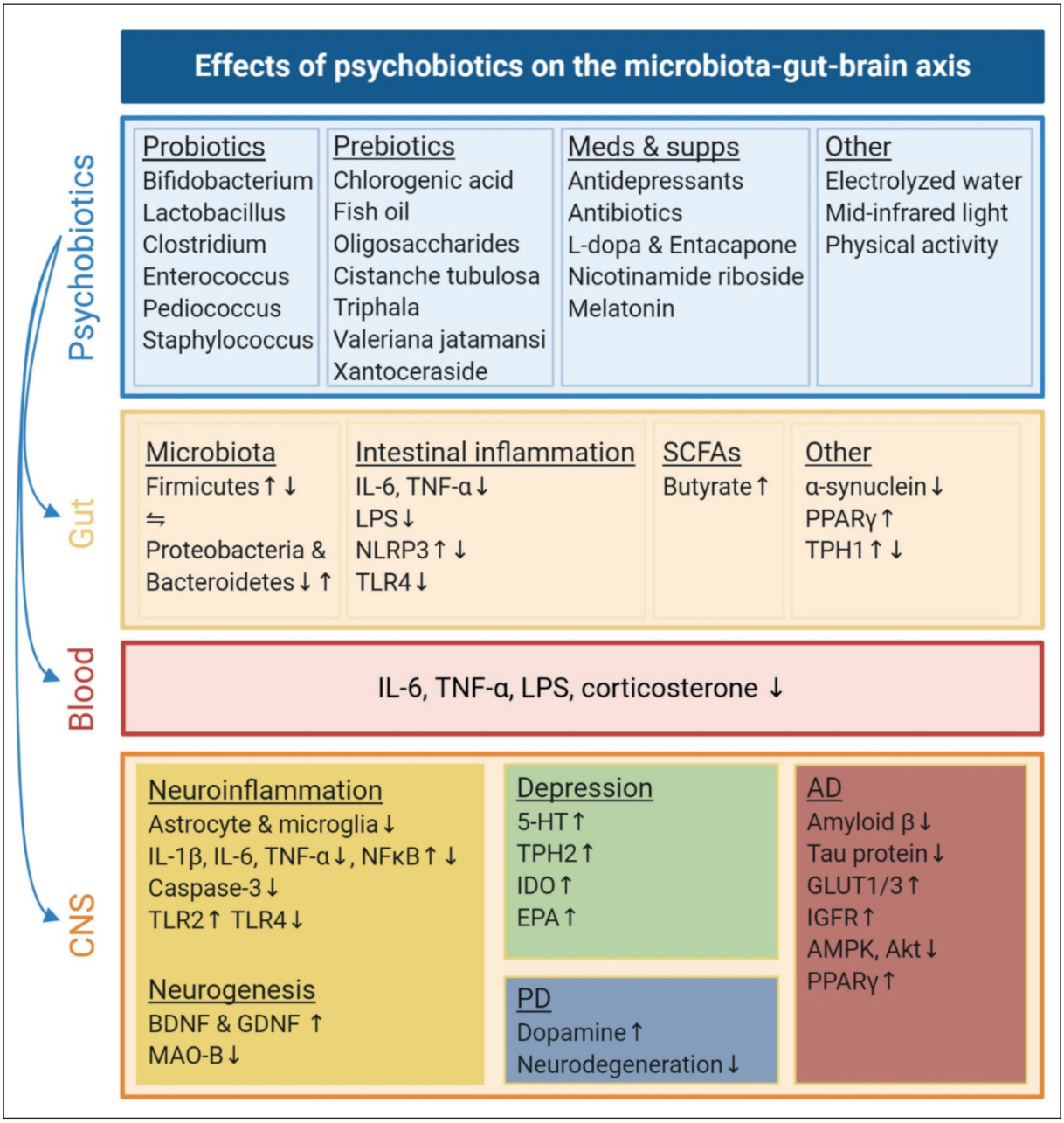

Figure 1. Summary of the effects of psychobiotics on the microbiota-gut-brain axis. The psychobiotics that were investigated individually or in combination included several probiotics, prebiotics, medication and supplements, as well as physical activity. Bifidobacterium and Lactobacillus strains are the most potent bacteria to affect gut-brain communication. The therapeutic effect of psychobiotic administration involves their effect on gut microbiota composition and inflammatory parameters in the gut, blood and central nerve system (CNS). In addition, they are able to affect the expression of neurotransmitters (dopamine & serotonin (5-HT)), glucose transporters (GLUT1/3) and protein accumulation (amyloid β & Tau protein) in the brain. IL = interleukin; TNF = tumour necrosis factor; LPS = lipopolysaccharide, TLR = toll-like receptor; NLRP3 = NOD-, LRR- and pyrin domain-containing protein 3; TPH = tryptophan hydroxylase; PPARγ = peroxisome proliferator-activated receptor γ; BDNF = brain derived neurotrophic factor; GDNF = glial derived neurotrophic factor; MAO-B = monoamino-oxidase; 5-HT = 5-hydroxytryptophan; IDO = indoleamine-2,3-dioxygenase; EPA = eicosapentaenoic acid; IGFR = insulin-like growth factor receptor; AMPK = monophosphate-activated protein kinase, Akt = protein kinase B. The figure was created with BioRender.com.

TABLE 1. MAIN PSYCHOBIOTIC AGENTS USED AND THEIR IMPLICATIONS. THE NUMBERS INDICATE THE REFERENCES OF THE CORRESPONDING STUDIES.

Class	Agent	Anxiety/ Depression	Alzheimer's disease	Parkinson's disease
Other	Electrolyzed reduced water			47
	Mid-infrared light		35	
	Voluntary running			49
Medication and supplements	Nicotinamide riboside (Vit B3)	14		
	Melatonin	17		
	L-Dopa			40
	Entacapone			40
	Broad-spectrum antibiotics	25		44, 45
	Antidepressants	22, 24		
Prebiotics	Xanthoceraside		34	
	Valeriana jatamansi (iridoids)	20		
	Triphala plant extract		32	
	Polysaccharides from okra	17		
	Galacto-oligosaccharide	8		
	Fructo-oligosaccharide	8, 23		
	Fish oil	18		
	Chlorogenic acid	19		
	Cistanche tubulosa	21		
Probiotics	FMT	13, 14	29	
	S. thermophilus		38	
	P. pentosaceus	7		
	L. rhamnosus	7, 8		46
	L. reuteri	3		
	L. plantarum	7	32, 38	
	L. paracasei		38	
	L. mucosae	4, 6		
	L. helveticus		38	
	L. fermentum		32	
	L. brevis		38	
	L. acidophilus		33, 38	46
	E. faecalis	11, 12		
	C. butyricum		31	
	B. longum	4, 8, 9, 10	30, 32, 33	
	B. lactis	7	38	
	B. breve	7, 10		
	B. bifidum		33	
	B. animalis lactis			46
	B. adolescentis	3, 5		

Finally, specific medications, supplements or foods also possess antidepressant properties by reshaping the gut microbiota (Figure 1 and Table 1). In an alcohol-induced depression model, the treatment with nicotinamide riboside (NR), a form of Vitamin B3, alleviated depressive-like behavior in mice. NR treatment suppressed microglia activation and cytokine secretion and restored BDNF levels in the brain (Figure 1). The AKT/GSK3β/β-catenin signaling pathway was also affected, which is involved in neuronal cell survival and apoptosis and is suggested to be a downstream target of BDNF. Interestingly, these effects could be confirmed by FMT of stool from NR-treated mice to depressed mice. Furthermore, significant correlations were found between neuronal changes, NR treatment and microbial composition. Specifically, *Akkermansia* and *Clostridium* XVIII were mainly enriched in the alcohol-exposed group, whereas *Barnesiella* and *Alloprevotella* were the most abundant post treatment group with NR[14]. Kim et al[15] showed a healing effect of melatonin on colitis by modulating TLR4, which has been suggested to play a key role in depression and PD (Figure 1)[16]. In particular, mela-

tonin treatment increased goblet cells and reduced pro-inflammatory cytokine levels in the colon *via* TLR4 activation. Moreover, the ratio of Firmicutes to Bacteroidetes was increased, which could result from TLR4-mediated Reg3β activation[15]. In addition, the antidepressant effects of a polysaccharide isolated from okra involved the partial suppression of TLR4 and NFκB activation in the murine hippocampus by reshaping the microbiota and the levels of short chain fatty acids in the gut (Table 1)[17]. Food supplementation of depressive rats with olive or fish oil, also showed improvements on gut dysbiosis (Table 1). Nevertheless, only fish oil supplementation had mild preventive and curative effects on depressive behavior which could be related to increased brain levels of phospholipid EPA (Figure 1)[18]. Chlorogenic acid, a phenolic acid present in fruit, vegetables and coffee, also exerted antidepressant effects in rats by restoring microbial diversity, specifically the abundance of Firmicutes and Proteobacteria (Table 1). Moreover, serum analysis by ELISA showed reduced levels of IL-6 and TNF-α, as well as an inhibitory effect on dopamine and 5-HT decrease (Figure 1)[19]. In addition, *Valeriana jatamansi* and *Cistanche tubulosa*, two plants widely used in traditional Chinese medicine, were also shown to alleviate depressive-like symptoms in rodents that were exposed to chronic unpredictable mild stress, which was associated with changes in gut microbial composition[20,21]. Interestingly, the main antidepressants seem to exert parts of their beneficial effects by influencing the gut microbiota composition, stressing the bidirectional communication between the gut and the brain (Table 1). Fluoxetine, a selective serotonin reuptake inhibitor, was shown to restore the microbiota composition to a similar extent as the administration of fructo-oligosaccharides in rodents[22,23]. Lukic et al[24] further confirmed the effect of fluoxetine and four other main antidepressants (escitalopram, venlafaxine, duloxetine and desipramine) on the murine gut microbiota. The simultaneous treatment of mice with duloxetine and *Ruminococcus flavefaciens*, a microbial species that was reduced by antidepressant treatment, ameliorated the effects of duloxetine on murine behavior. Gene expression analysis in the prefrontal cortex revealed that *R. flavefaciens* treatment increased expression of genes related to mitochondrial processes, whereas neural plasticity-related genes were downregulated. Moreover, it also affected serotonin levels in the brain. On the other hand, Schmidtner et al[25] showed that the anxiolytic effects of antibiotic treatment of high-anxiety breeded male Wistar rats, was abolished by simultaneous short-term treatment with escitalopram.

ALZHEIMER'S DISEASE

AD is a progressive neurodegenerative disorder mainly affecting the elderly and is the main cause of dementia. The pathophysiology of AD is characterized by the accumulation of amyloid β (AB) and hyperphosphorylated tau protein in the brain in combination with neuroinflammation. Interestingly, increasing evidence highlights a key role for the gut microbiota[26]. Accordingly, two recent studies[27,28] showed that alterations in microbial composition could even distinguish different stages of AD.

Probiotics seem to improve cognitive function by influencing aggregate formation and inflammation in the brain (Table 1 and Figure 1). In this way, FMT from healthy to AD mice alleviated both the accumulation of AB and tau protein and gliosis in the brain which was associated with improved memory, as well as restoring intestinal homeostasis and systemic immune cell populations (Figure 1)[29]. Lee et al[30] explored the therapeutic potential of 25 *Lactobacillus* and 25 *Bifidobacterium* species. The most potent one was *B. longum* NK46, of which treatment suppressed intestinal inflammation which was associated with a decrease of *Firmicutes* and *Proteobacteria* and an increase of *Bacteroidetes* populations in the 5XFAD-Tg mouse model (Table 1). Furthermore, probiotic treatment attenuated cognitive decline based on their improved performance in the novel object recognition, Y-maze, passive avoidance and Morris water maze tasks (Figure 1). Similar effects were observed during the administration of *Clostridium butyricum* which restored microbiota composition and increased butyrate production in the gut (Table 1)[31]. Remarkably, Westfall et al[32] showed the potential of a symbiotic treatment to affect multiple aspects of the pathogenesis. By combining three probiotic strains and a Triphala plant extract, they were able to simultaneously improve survival, immune signaling, metabolism, oxidative, and mitochondrial stress in a Drosophila model of AD (Figure 1 and Table 1). By using a specific inhibitor, they further showed the major in-

volvement of peroxisome proliferator-activated receptor (PPAR) γ, which is a lipid sensor that is expressed in many tissues, including the gut and the brain and is involved in inflammatory, metabolic and oxidative stress-related pathways. As this receptor can be modulated directly or indirectly by the gut microbiota, it is suggested as a potential mechanism of gut-brain communication (Figure 1). Besides these molecular effects, Rezaei et al[33] studied the effect of probiotics on neuronal activity. Preventive treatment with a mixture of *L. acidophilus, B. bifidum, B. longum* improved the induction of long term potentiation, a key mechanism involved in long-term memory storage, in the hippocampal CA1 region of the rat's brain (Table 1).

The gut microbiota could also be modulated by using specific plant extracts or other non-invasive methods (Table 1 and Figure 1). The neuroprotective effect of Xanthoceraside, a triterpenoid extracted from the husks of *Xantocheras sorbifolia*, was evaluated by investigating alterations in the gut microbiota as it could not pass the blood-brain-barrier of AD mice. They found a decreased ratio of Firmicutes to Bacteroidetes. Interestingly, changes in microbial composition could be linked to changes in brain metabolites and FMT transplantation of Xanthoceraside-treated to untreated AD mice improved disease phenotype[34]. In addition, Wang et al[35] observed reduced AB plaque deposition and improved cognitive functioning upon whole-body mid-infrared light treatment in AD mice. Interestingly, microbial homeostasis was also restored.

Additionally, some other potential mediators of gut-brain communication reached attention. Shen et al[36] confirmed the role of NLRP3 in gut-brain communication in the pathogenesis of AD (Figure 1). The transplantation of AD fecal microbiota into healthy mice, did upregulate NLRP3 and induced inflammation in the intestines and brain. Another surprising mechanism of the bidirectional gut-brain communication was proposed by Diling et al[37], who identified interactions between the expression of circular RNAs and microbial changes in AD. Accordingly, injection of circNF1-419 in the cerebral cortex also influenced microbial composition and exerted healing effects on the intestine of AD mice models. In addition, probiotic treatment could also restore glucose metabolism in the brain. In a triple transgenic mice model of AD, Bonfili et al[38] showed that the administration of a probiotic cocktail containing five *Lactobacillus* strains, two *Bifidobacterium* strains and one *Streptococcus* strain improved glucose uptake in the brain by upregulating the transporters GLUT1 and GLUT3 and insulin-like growth factor receptor (IGFR) β, in accordance to the reduced phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and protein kinase B (Akt) (Figure 1).

PARKINSON'S DISEASE

PD is a progressive neurodegenerative disease with the highest prevalence in people older than 65 years. The pathophysiology involves the loss of dopaminergic neurons in the substantia nigra and the formation of α-synuclein which is reflected in a decreased motor function and is also often associated with gastrointestinal complaints. The Braak hypothesis suggests that PD development may start in the gut by α-synuclein build-up in the enteric nerve system, which propagates to the brain via the vagus nerve[39]. Although it remains unclear which triggers are responsible for altering the microbiota composition, and whether changes in microbiota composition precede disease development, several recent studies further highlighted the differences in microbiome composition in PD patients that could even distinguish between different stages of disease[40-43].

As PD development is associated with a pro-inflammatory environment and the disturbance of the dopamine signaling pathways in the dorsal striatum of the brain, several studies investigated the potential of microbiota modulation on these biological processes (Figure 1 and Table 1). The most drastic way to study the role of the gut microbiota in the pathogenesis of PD, was highlighted by Koutzoumis et al[44], who treated rats with broad-spectrum antibiotics resulting in a 90% reduction of microbial richness. Considering microbial diversity, Firmicutes were decreased and *Proteobacteria*, *Bacteroidetes*, *Verrucomicrobia* and *Cyanobacteria* increased. After injection of oxidopamine to induce PD development, antibiotic treatment alleviated motor deficits and dopaminergic cell loss, as well as decreasing the levels of IL-1β and TNF-α in the striatum (Figure 1). Similar results were obtained by Pu et al[45] in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. Other animal studies investigated the

effects of probiotic treatment on dopaminergic neurodegeneration. Srivastav et al[46] indicated that the pretreatment with a probiotic mixture containing *L. rhamnosus GG*, *B. animalis lactis* and *L. acidophilus* exerted neuroprotective effects in two models of PD, which potentially resulted from the butyrate-induced upregulation of BDNF and glial cell line-derived neurotrophic factor (GDNF), as well as the inhibition of monoamino-oxidase (MAO)-B in the brain (Figure 1 and Table 1). More specifically, pretreatment greatly counteracted the loss of dopaminergic neurons, as well as the levels of dopamine and its metabolites. The activation of inflammatory cells in the brain was also alleviated (Figure 1).

Butyrate-producing bacteria are likely interesting candidates for PD treatment (Table 1 and Figure 1). In a pesticide-induced rat model of PD, the anti-oxidant treatment with electrolyzed water increased the abundance of butyrate-producing bacteria in the gut, preventing intestinal barrier dysfunction and decreasing striatal dopamine levels[47]. Furthermore, Qiao et al[48] highlighted the potential working mechanism of sodium butyrate in the gut. According to the Braak hypothesis, butyrate stimulation of enteroendocrine cells, which are in proximity to α-synuclein-containing nerves, induced α-synuclein degradation potentially by inducing autophagy in an Atg5- and PI3K/Akt/mTOR-related way.

Brain to gut communication seems to be important in PD pathology as well. Intranigral overexpression of α-synuclein in rats was associated with an altered gut microbiome, decreased neuronal density in the intestinal submucosa, elevated enteric glial cell expression in the myenteric plexus and affected myenteric and submucosal tyrosine hydroxylase levels. Interestingly, physical activity, in the means of voluntary running, exerted beneficial effects on all these factors, including alterations in microbial genera that are related to gut health[49].

CONCLUSIONS

In this review, we show evidence that the modulation of the gut microbiota greatly affects the symptoms and physiological pathways related to major neurological disorders, including depression, AD and PD (Table 1). The psychobiotics mainly exerted their effects by restoring gut homeostasis and pro-inflammatory molecules in the blood. As a result in the brain, disease symptoms improved associated with a reduction in cytokine levels, microglia activation, plaque deposition and neuronal cell death and with an increase in neurotrophic factors and glucose uptake in the brain. Additionally, the 5-HT, TLR, NLRP3 and PPARγ signaling pathways, as well as several circular RNAs, were highlighted as major bidirectional communication routes between the gut and the brain (Figure 1). Interestingly, *Lactobacillus* and *Bifidobacterium* seem to be the most potent genera to influence the microbiota-gut-brain axis. Unfortunately, most studies are performed in animal models and the exact mechanisms and pathways connecting the microbiome-gut-brain axis need further investigation to prove their causality. Nevertheless, influencing the microbiota-gut-brain communication has major potential for the future treatment of depression, AD and PD.

Conflict of Interest

The authors have no competing interests.

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