

Supplementary Table 1 | Systematic review of probiotics pre-clinical studies of Parkinson's disease.

PubMed Search Terms: "Probiotic" OR "Probiotics" OR "Pro-biotic" OR "Pro-biotics" AND "Parkinson" OR "Parkinsonism"						
Date of publications: 1 Jan 2000 to 05 Jan 2023						
Total: 90 references — 32 Pre-Clinical Studies (25 Probiotics and 7 Engineered Probiotics)						
Pre-clinical study of probiotics						
No	Pre-clinical study (listed chronologically and according to first author)	Objective of Investigation	Models	Parkinsonian Feature Induction Method	Characteristics & dosage of probiotic species	Study Outcome - Effects of probiotics
	First author (year of publication)	Aspect of probiotic investigation	Cell line/animal	Method, Substance	Probiotic preparation, Method of introduction, Dosage, Duration	Main study outcomes
					Number of probiotic; Species name	
1	Magistrelli et al. (2019) ¹	Effects in PBMCs isolated from PD patients vs. healthy donors (HD)	Human PBMCs, Caco-2 Cells	Isolation from heparinized blood of HD and PD patients	Suspension of probiotics in RPMI-1640 medium added to PBMCs cultures, incubation with PBMCs/pathogen for 24h 6; <i>Lactobacillus salivarius</i> LS01 DSM 22775, <i>L. plantarum</i> LP01 LMG P-21021, <i>L. acidophilus</i> LA02 DSM 21717, <i>L. rhamnosus</i> LR06 DSM 21981, <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BS01 LMG P-21384, <i>B. breve</i> BR03 DSM 16604	<u>All administered probiotics</u> • Restored epithelial damage in Caco-2 cells <u><i>Lactobacillus salivarius</i> and <i>L. acidophilus</i></u> • Decreased pro-inflammatory cytokines (TNF- α , IL-6, and IL-17A) in PD PBMCs • Increased anti-inflammatory cytokines (IL-4 and IL-10) in PD PBMCs • Reduced ROS production in both PD- and HD- PBMCs • Inhibited pathogen strains <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> <u><i>Lactobacillus plantarum</i> and <i>L. rhamnosus</i></u> • Exerted highest inhibition of pathogen strains <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i>
2	Srivastav et al. (2019) ²	Protective effects on dopaminergic neurodegeneration in two separate toxin models	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP or rotenone	Water suspension, oral administration, 0.002×10^9 CFU daily for 30d 3; <i>Lactobacillus rhamnosus</i> GG (L-GG), <i>Bifidobacterium animalis</i> <i>lactis</i> (BB-12), <i>L. acidophilus</i> (LA-5)	<u>MPTP model</u> • Prevented sensory motor impairments • Prevented dopaminergic neurodegeneration • Attenuated microglial and astrocyte activation after MPTP challenge • Upregulated neurotrophic factors (BDNF and GDNF) • Downregulated MAO-B levels <u>Rotenone model</u> • Prevented sensory motor impairments • Ameliorated dopaminergic neuronal loss • Prevented gliosis • Upregulated neurotrophic factors (BDNF and GDNF) • Increased levels of β -hydroxybutyrate and acetylated histone H3 <u>Comparative study of probiotics</u> • L-GG - most potent in dopaminergic neuronal protection
3	Castelli et al. (2020) ³	<i>In vitro</i> and <i>in vivo</i> effects on probiotic formulation (SLAB51)	SH-SY5Y cell line, C57BL/6 male mice	Toxin, stereotaxic injection of 6-OHDA	Cell line: filtrated bacterial lysates, 0.1 mg/ml for 2h Mice: water suspension, oral gavage, 5.4×10^9 CFU daily for 2w 9; <i>Bifidobacterium breve</i> , <i>B. infantis</i> , <i>B. longum</i> , <i>Lactobacillus acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>L. brevis</i> , <i>L. paracasei</i> , <i>L. plantarum</i> , <i>Streptococcus thermophilus</i>	<u>Cell line</u> • Exhibited neuroprotection by counteracting 6-OHDA induced cell injury • Reduced oxidative stress by restoring the BDNF, PI3K/Akt, neuronal death pathways, and PPAR γ and 4-HNE protein levels to control levels <u>Mice</u> • Counteracted behavioural and motor impairment • Rescued dopaminergic neurons in both SN and striatum • Restored PPAR γ , HO-1, p-Nrf2, NF- κ B protein levels to control levels • Reduced markers of neuroinflammation and microglial activation • Protected against 6-OHDA-induced apoptosis of dopaminergic neurons in the SN

4	Goya et al. (2020) ⁴	Effects on α -SYN aggregation	<i>Caenorhabditis elegans</i>	Animal model of synucleinopathy	Growth plate containing probiotic cell/spores on continuous feeding regime, changed 2x/d 1; <i>Bacillus subtilis</i> PXN21	<ul style="list-style-type: none"> Improved locomotion fitness after switching to the <i>B. subtilis</i> diet compared to animals continuously fed on <i>E. coli</i> Inhibited and reversed α-SYN aggregation through sphingolipid pathway Induced protective effects through both spores and vegetative cells, attributed in part to biofilm formation within the worms' gut and the release of bacterial metabolites
5	Hsieh et al. (2020) ⁵	Long term effects on nigrostriatal dopamine neurons and motor dysfunctions	Transgenic MitoPark PD mice	Animal model of neurodegeneration and motor deficit	Lieber-DeCarli liquid diet mixture, oral administration, 1×10^9 CFU daily for 16w 6; <i>Bifidobacterium bifidum</i> , <i>B. longum</i> , <i>Lactobacillus rhamnosus</i> , <i>L. rhamnosus</i> GG, <i>L. plantarum</i> LP28, <i>Lactococcus lactis</i> subsp. <i>Lactis</i>	<ul style="list-style-type: none"> Alleviated progressive deterioration of motor functions (balance, coordination and gait impairments) Preserved TH-positive cells in the SNpc
6	Marsova et al. (2020) ⁶	Effects of human biotopope derived probiotic	<i>Caenorhabditis elegans</i> , C57/BL6 male mice	Toxin, addition of paraquat solution into <i>C. elegans</i> S-medium, oral administration of paraquat solution into mice	<i>C. elegans</i> : growth plate containing probiotics and <i>E. coli</i> OP50 suspended in saline; 0.1×10^9 CFU/mL Mice: saline suspension, oral administration, 0.5 ml (0.1×10^9 CFU) of <i>L. fermentum</i> U-21 daily for 18d 14; <i>Lactobacillus fermentum</i> 279, <i>L. fermentum</i> 311, <i>L. fermentum</i> 103sk, <i>L. fermentum</i> U-21, <i>L. fermentum</i> 39zv, <i>L. rhamnosus</i> 40f, <i>L. rhamnosus</i> 313, <i>L. rhamnosus</i> GG, <i>L. brevis</i> 15f, <i>L. brevis</i> s47f, <i>L. plantarum</i> K13, <i>L. plantarum</i> 90sk, <i>L. plantarum</i> 106zv, <i>L. gasseri</i> k21	<p><i>L. fermentum</i> (U-21 & 39zv) and <i>L. plantarum</i> (90sk)</p> <ul style="list-style-type: none"> Increased lifespan of <i>C. elegans</i> <p><i>L. fermentum</i> (U-21)</p> <ul style="list-style-type: none"> Reduced paraquat's toxic effects in both <i>C. elegans</i> and mice models Most successful in increasing the life span of <i>C. elegans</i> and mice Preserved TH-positive cells in mice SN similar to control group in mice Preserved motor function similar to control group in mice
7	Perez Višňuk et al. (2020) ⁷	Neuroprotective effects of 2 vitamin-producing and 1 immune-modulating probiotic mixture	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	Saline suspension, oral administration, 100uL ($0.8 \pm 0.2 \times 10^9$ CFU/mL per strain) daily for 22d 3; <i>Lactobacillus plantarum</i> CRL 2130, <i>Streptococcus thermophilus</i> CRL 807, <i>Streptococcus thermophilus</i> CRL 808	<ul style="list-style-type: none"> Alleviated motor deficiencies and maintained performance similar to control groups without neurotoxins Maintained the number of TH-positive cells in the SNpc similar to control groups without neurotoxins Decreased serum proinflammatory cytokines (IL-6 and TNF-α) similar to the control group
8	Xie and Prasad (2020) ⁸	Effects on anxiety and memory	Sprague-Dawley male rats	Toxin, bilateral infusion of 6-OHDA into the striatum	Water suspension, oral administration, $0.1-1 \times 10^9$ CFU daily for 6w 1; <i>Lactocaseibacillus rhamnosus</i> HA-114	<ul style="list-style-type: none"> Reversed hippocampal dependent cognitive deficits by rescuing memory retention
9	Alipour Nosrani et al. (2021) ⁹	Effects on behavioural, biochemical, and histological parameters	Wistar male rats	Toxin, injection of 6-OHDA into the right SNpc	Probiotic preparation not specified, oral administration, 2×10^9 CFU/strain daily for 14d 4; <i>Lactobacillus acidophilus</i> , <i>Bifidobacterium bifidum</i> , <i>L. reuteri</i> , <i>L. fermentum</i>	<ul style="list-style-type: none"> Prevented the increase in number of apomorphine-induced contralateral rotation Prevented memory dysfunction Decreased MDA levels in midbrain Reduced number of 6-OHDA-injured neurons
10	Dwyer et al. (2021) ¹⁰	Probiotic or DSS effect on PD pathology in a dual hit toxin model	C57Bl6/J male mice	Toxin, injection of LPS above the SNpc, and intraperitoneal injection of paraquat	Water suspension, oral administration, 5.4×10^9 CFU daily for 12d 7; <i>Lactobacillus acidophilus</i> , <i>L. casei</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>L. plantarum</i> , <i>Bifidobacterium breve</i> , <i>B. infantis</i> , <i>B. longum</i>	<p><u>Probiotic VSL#3</u></p> <ul style="list-style-type: none"> Altered microbiome composition - increased abundance of <i>Streptococcaceae</i> Prevented LPS- and paraquat-induced weight loss
11	Ghyselinck et al. (2021) ¹¹	Effects on dynamic, multi-compartment gastrointestinal model	PD-derived gut microbiota enriched M-SHIME® system, Caco-2, THP1 & T84 cells	Multi-compartment gut model, <i>in vitro</i> bilayer tight-junction cell model, <i>in vitro</i> wound healing model	Aqueous suspension, 48h 4; <i>Lactobacillus acidophilus</i> NCIMB 30175, <i>Lactobacillus plantarum</i> NCIMB 30173, <i>Lactobacillus rhamnosus</i> NCIMB 30174, <i>Enterococcus faecium</i> NCIMB 30176	<ul style="list-style-type: none"> Altered microbiome composition - enriched proportions of Actinobacteria and Firmicutes Altered the production and consumption of lactate and SCFAs concentration at different incubation time Improved epithelial tight-junction integrity (based on TEER value) when supplemented with sodium butyrate Modulated secretion of pro-inflammatory cytokines and chemokines (NF-κB, TNFα,

						CXCL 10 and IL-8) • Increased wound healing in scratched T84 monolayer cells
12	Ishii et al. (2021) ¹²	Effects on the facilitation of hippocampal memory extinction	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	Saline suspension, oral gavage, 0.2 mL (1×10^9 CFU) daily for 4d 1; <i>Bifidobacterium breve</i> A1 (MCC1274)	• Restored the facilitation of contextual fear extinction via the prevention of abnormal changes in hippocampal synaptic plasticity • Prevented the MPTP-induced reduction of spine density to similar levels in control mice
13	Sun et al. (2021) ¹³	Effects on motor functions, neuroprotection and gut microbiota	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	PBS suspension, oral administration, 0.5×10^9 CFU/0.2 mL daily for 4w 1, <i>Clostridium butyricum</i> WZMC1016	• Improved motor deficits • Protected against dopaminergic neuronal loss • Reversed microglia activation and synaptic dysfunction • Reversed MPTP-induced abnormal microbial composition • Increased colonic GLP-1 and GPR41/43 levels • Upregulated the expression of cerebral GLP-1R
14	Cuevas-Carbonell et al. (2022) ¹⁴	Effects on neuroimmune and motor deficits	Wistar male rats	Toxin, injection of 6-OHDA into the striatum	Sunflower and tocopherol oil suspension, cannula drip, 1.2×10^9 CFU/strain daily for 5w (2w before and 3w after injecting 6-OHDA) 2; <i>Bifidobacterium animalis subsp. lactis</i> (BB-12 strain), <i>Lactocaseibacillus rhamnosus</i> (GG strain)	• Reduced loss of TH-positive area in striatum and SNpc • Attenuated bradykinesia and motor incoordination • Diminished recruitment of Iba1+ microglia
15	Ilie, Duta, Balmus, et al. (2022) ¹⁵	Neuroactive effects on sub-optimal toxin dose model	AB genetic line <i>Danio rerio</i>	Toxin, exposure of rotenone in <i>Danio rerio</i> environment	Dissolved mixture, oral administration, 3g/100mL daily for 32d 9; <i>Lactobacillus casei</i> W56, <i>L. acidophilus</i> W22, <i>L. paracasei</i> W20, <i>L. salivarius</i> W24, <i>L. lactis</i> W19, <i>L. plantarum</i> W62, <i>Bifidobacterium lactis</i> W51 & W52, <i>B. bifidum</i> W23	• Conferred slight neuroprotection against rotenone effect
16	Ilie, Duta, Jijie, et al. (2022) ¹⁶	Effects on social component and level of aggression	AB genetic line <i>Danio rerio</i>	Toxin, exposure of rotenone in <i>Danio rerio</i> environment	Dissolved mixture, oral administration, 3g/100mL daily for 32d 9; <i>Lactobacillus casei</i> W56, <i>L. acidophilus</i> W22, <i>L. paracasei</i> W20, <i>L. salivarius</i> W24, <i>Lactobacillus lactis</i> W19, <i>L. plantarum</i> W62, <i>Bifidobacterium lactis</i> W51 & W52, <i>B. bifidum</i> W23	• Probiotic treated fish exhibited less aggressivity but not shown in probiotic treated rotenone exposed fish
17	Li et al. (2022) ¹⁷	Effects on neuroprotection	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	Saline suspension, oral gavage, 10^9 CFU/200uL daily for 5w 1; <i>Bifidobacterium breve</i> CCFM1067	• Mitigated motor impairment • Reduced MPTP-induced neuropathological changes and glial activation • Restored levels of neurotransmitters • Suppressed pro-inflammatory gene and protein expression • Decreased inflammation in brain and colon and boosted anti-inflammation capabilities • Protected against MPTP-induced BBB damage and intestinal barrier dysfunction • Reversed the MPTP-induced reduction in microbial community richness and diversity • Increased pathways involved in the biosynthesis of carotenoids, terpenoids and steroids, sesquiterpenoids and triterpenoids, steroids, and insulin resistance • Increased the concentrations of colonic SCFAs
18	S. Pan et al. (2022) ¹⁸	Effects on motor functions and its mechanism	C57BL/6J male mice	Toxin, intraperitoneal injection of MPTP	Suspension, intragastrical administration, 0.2mL x 10^9 CFU/mL daily for 4w 1; <i>Pediococcus pentosaceus</i> WMU002	• Improved motor dysfunction • Attenuated MPTP-induced dopaminergic neuronal degeneration by reducing accumulation of α -SYN • Reversed the MPTP-induced decrease of GABA • Improved oxidative stress by regulating Nrf2 signalling pathway • Altered microbiota composition
19	Sancandi et al. (2022) ¹⁹	Effects on gut health	Albino male Wistar rats	Toxin, intraperitoneal	Aqueous solution, oral administration, 0.07×10^9 CFU daily for 24d	• Prevented toxins-induced weight loss • Reduced ileum tissue damage and inflammation by regulating occludin and $\text{I}\kappa\text{-B}\alpha$

				injection of DSP-4, bilateral injection of 6-OHDA to striatum	4; <i>Lactobacillus acidophilus</i> NCIMB 30175, <i>Lactobacillus plantarum</i> NCIMB 30173, <i>Lactobacillus rhamnosus</i> NCIMB 30174, <i>Enterococcus faecium</i> NCIMB 30176	expression levels <ul style="list-style-type: none"> • Decreased circulating plasma inflammatory markers (LPS, IL-6, TNF-α, and IL-1β) • Altered gut microbiota composition – increased α-diversity and modified β-diversity • Prevented decrease in faecal butyrate • Prevented neuroinflammation and the decrease in TH-positive cells in SNpc
20	Wang et al. (2022) ²⁰	Effects on α -SYN accumulation in the SN of PD mice	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	Saline suspension, oral administration, 0.2 ml (1×10^9 CFU/mL) daily for 14d 1; <i>Lactobacillus plantarum</i> PS128	<ul style="list-style-type: none"> • Increased the levels of antioxidants in the SN by reversing the decrease of SOD and GSH-Px and increase of MDA and ROS. • Reduced the increased expression of pro-inflammatory factors TNF-α, IL-6, and IL-1β in the SN • Increased expression of anti-inflammatory factor IL-10 in the SN • Decreased expression of α-SYN in the SN • Restored gut microbiota composition • Alleviated oxidative stress injury via the Nrf2/ARE pathway • Resisted MPTP-induced oxidative injury by upregulating the levels of antioxidant proteins (PGC-1α, UCP2, and MnSOD) • Inhibited inflammation by reducing expressions of NLRP3, cleaved caspase-1, and IL-1β
21	Chu et al. (2023) ²¹	Attenuating efficacy and potential mechanisms of probiotics	C57BL/6J mice	Toxin, oral administration of rotenone	Saline suspension, oral gavage, 10^9 CFU/200 μ L daily for 8w 1; <i>Lactobacillus plantarum</i> CCFM405	<ul style="list-style-type: none"> • Inhibited rotenone-induced weight loss • Alleviated constipation symptoms and colon shortening • Alleviated motor impairment • Regulated striatal neurotransmitter metabolism by inhibiting reductions in levels of dopamine, serotonin, and their related metabolites • Inhibited the rotenone-induced microglia and astrocyte activation • Reduced pro-inflammatory cytokine levels (IL-1β, IL-6, and TNF-α) in midbrain • Attenuated rotenone-induced histopathology features in colon • Reduced pro-inflammatory cytokine levels (IL-6, and TNF-α) in colon • Upregulated mRNA expression of ZO-1 and occludin protein in colon • Restored gut microbiota composition • Increased branched-chain amino acid synthesis and levels in faeces and serum
22	Fan et al. (2023) ²²	Neuroprotective effects of live and heat-killed probiotics and the possible mechanisms	Male Sprague-Dawley rats, Genetically identified mice	Toxin, unilateral injection of 6-OHDA or LPS into the SN, subcutaneous injection of rotenone	Water suspension, intragastric gavage, daily for 5w 1; Heat killed or Live <i>Lactobacillus murinus</i>	<p>6-OHDA-injected rat formed a gut microbial community different from the control group, while LPS and ROT did not form a significantly independent community</p> <p><u>Live probiotic</u></p> <ul style="list-style-type: none"> • No improvement in 6-OHDA induced motor dysfunction • No protective effects on 6-OHDA induced dopamine neuronal damage <p><u>Heat killed probiotic</u></p> <ul style="list-style-type: none"> • Improved 6-OHDA-induced motor dysfunction • Reduced 6-OHDA-induced dopamine neuronal loss • Reversed 6-OHDA-induced changes of TH and iba1 protein levels • Inhibited the 6-OHDA-induced protein expressions of inflammatory factors (TNF-α, IL-1β, and IL-18) • Suppressed 6-OHDA-induced activation of the microglial and NLRP3 inflammasome signalling (NLRP3, ASC, and caspase-1)
23	Hawrysh et al. (2023) ²³	Screening study of 49 probiotic strains and formulation on upregulation of mitophagy	HEK293 expressing GFP-PRKN, Male Canton-S <i>Drosophila</i>	Toxin, supplementation of paraquat in fly food	HEK293 expressing GFP-PRKN: Co-cultured with PBS probiotic suspension, 0.094×10^9 CFU/mL for 3h at 37°C and 5% CO2 using three MOIs: 100:1, 50:1, and 10:1 Male Canton-S <i>Drosophila</i> : low-melt agarose fly food supplemented with <i>Saccharomyces boulardii</i> CNCM-I-1079 (3.0×10^9 CFU/mL), <i>Lactococcus lactis</i> R1058 (10×10^9 CFU/mL) 6-7d or 2w depending on experiments	<p><u>In vitro</u></p> <ul style="list-style-type: none"> • 5/49 probiotics increased mitochondrial PRKN recruitment following CCCP-induced mitochondrial dysfunction • 4/5 probiotics elevated mitochondrial phospho-ubiquitination following CCCP-induced mitochondrial dysfunction • 2/5 probiotics (CNCM-I-1079 and R1058) facilitated MFN2 degradation to reduce integration of dysfunctional mitochondria into the healthy mitochondrial network <p><u>In vivo</u></p> <ul style="list-style-type: none"> • CNCM-I-1079 and R1058 mediated elevation in mitolysosomes during paraquat-

				Screening of 49 probiotic, resulted in 2 chosen probiotic strains, <i>Saccharomyces boulardii</i> CNCM-I-1079 and <i>Lactococcus lactis</i> R1058	induced mitochondrial stress is likely a PRKN-mediated phenomenon in park knockdown fly line <ul style="list-style-type: none"> • Heteroplasmic flies that were fed CNCM-I-1079, but not R1058, exhibited a marked recovery in motor function in comparison to heteroplasmic control flies that were fed fly food without probiotics • Flies that were exposed to paraquat and supernatant samples from either CNCM-I-1079 or R1058 showed a marked improvement in their motor ability compared to flies that were fed alone • UP-LCMS isolated MI6C; a small molecule that probiotics release that influenced mitochondrial autophagy 	
24	Nápoles-Medina et al. (2023) ²⁴	Effects on BBB and gastrointestinal barrier	C57/BL6 male mice	Toxin, unilateral injection of 6-OHDA into the striatum	Saline suspension, oral gavage, 100uL x 10 ⁹ CFU/mL for 4w 3; <i>Lactobacillus fermentum</i> LH01, <i>Lactobacillus reuteri</i> LH03, and <i>Lactobacillus plantarum</i> LH05	<ul style="list-style-type: none"> • Inhibited defects in motor coordination • Protected nigrostriatal dopamine neurons • Inhibited permeability in BBB and gut barrier • Inhibited lipid peroxidation
25	Parra et al. (2023) ²⁵	Effect of probiotics on inflammatory model	Wistar male rats	Toxin, intracranial injection of LPS into the striatum	Sunflower oil and vitamin E suspension, oral administration, 1 x 10 ⁹ CFU/strain daily for 15d 2; <i>Lactobacillus rhamnosus</i> GG, <i>Bifidobacterium animalis lactis</i> (BB-12)	<ul style="list-style-type: none"> • Countered several LPS-induced motor behaviour • Reduced microgliosis and aberrant activation of microglia in the striatum
Pre-clinical studies of engineered probiotics						
26	Fang et al. (2019) ²⁶	Effects of co- and pre-treatment of engineered probiotic that continuously express GLP-1 on nerve cells, inflammatory factors, and intestinal microbiota	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	Water suspension, oral administration, daily for 2w <ul style="list-style-type: none"> • PTL group: pre-treated with 0.01 x 10⁹ CFU probiotic, then treated with MPTP • TL group: treated with MPTP in combination with 0.01 x 10⁹ CFU probiotic • PTH group: pre-treated with 1 x 10⁹ CFU probiotic then treated with MPTP • TH group: treated with MPTP in combination with 1 x 10⁹ CFU probiotic 1; <i>Lactococcus lactis</i> subsp. <i>cremoris</i> (strain MG1363)	<u>PTL group</u> <ul style="list-style-type: none"> • Showed the best recovery effect on exploratory and locomotor function in MPTP-induced bradykinetic mice • Inhibited astrocyte and microglia activation in the SN • Reduced the abundance of pathogens of Enterobacteriaceae and <i>Alloprevotella</i> • Enhanced the abundance of probiotic <i>Lactobacillus</i> <u>TL group</u> <ul style="list-style-type: none"> • Enhanced α-diversity of gut microbiota composition <u>All groups (PTL, TL, PTH, TH)</u> <ul style="list-style-type: none"> • Inhibited the MPTP-induced loss of TH-positive neurons and further development of inflammatory response (TLR-4 and NF-κB) • Altered gut microbiota composition
27	Fang et al. (2020) ²⁷	<i>In vivo</i> effects of engineered probiotic that continuously express GLP-1	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP (PD Model)	Water suspension, oral administration, 1 x 10 ⁹ CFU daily for 3w (1w before MPTP, and 2w after MPTP) 1; <i>Lactococcus lactis</i> (strain MG1363)	<u>PD model</u> <ul style="list-style-type: none"> • Improved motor function • Reversed the MPTP-induced increase expression of TLR4, p-IκBα and p-p65 and reduce expression of p-AKT, p-GSK3β and β-catenin in brain tissue • Partially rescued MPTP-induced decreased of TH-positive neurons • Altered gut microbiome composition - reduced pathogens <i>Enterococcus</i> and <i>Proteus</i>
28	H. Pan et al. (2022) ²⁸	Effects of spatiotemporal regulation of engineered light sensitive probiotics in the gut	C57BL/6N male mice	Toxin, intraperitoneal injection of MPTP	Sodium alginate microdroplets, oral gavage, 200uL (1 x 10 ⁹ CFU/mL) for 10d 1; <i>Lactobacillus lactis</i> NZ9000	<u>NIR Light-Responsive GABA-secreting <i>L. lactis</i></u> <ul style="list-style-type: none"> • Relieved anxiety-like behaviour in anxiety mice model <u>NIR Light-Responsive GCSF-secreting <i>L. lactis</i></u> <ul style="list-style-type: none"> • Improved MPTP-induced cognitive deficit and brain inflammatory reaction • Influenced neuronal activity via GLP1-mediated stimulation of the vagus nerve
29	Yue et al. (2022) ²⁹	Neurotrophic effects of engineered GLP-1 producing probiotic strain	C57BL/6 male mice	Toxin, oral administration of MPTP	Saline suspension, oral gavage, 1 x 10 ⁹ CFU/mL for 7d 1: <i>Lactococcus lactis</i> MG1363-pMG36e-GLP-1	<ul style="list-style-type: none"> • Ameliorated motor deficit • Suppressed dopaminergic neuronal death and α-SYN aggregation • Increased expression levels of GLP-1 • Improved BBB integrity potentially by attenuating epithelial damage in the SN and reversing reduction of tight junction protein occludin and ZO-1 • Exhibited neurotrophic effect by regulating ferroptosis via activation of the keap1-

						<p>nrf2-gpx4 pathway</p> <ul style="list-style-type: none"> • Reduced systemic and SN oxidative stress by regulating the levels of oxidative-related factor (MDA, GSH-Px, and SOD) • Attenuated intestinal barrier damage • Reversed MPTP-induced dysbacteriosis
30	Wang et al. (2023) ³⁰	Neuroprotective effects of engineered GLP-1 producing probiotic strain	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	Saline suspension containing 0.01% gelatin, oral gavage, 1.0 x 10 ⁹ CFU/mL for 7d 1; <i>Clostridium butyricum</i> pMTL007-GLP-1	<ul style="list-style-type: none"> • Improved motor dysfunction • Ameliorated MPTP-induced neuropathology by downregulating nigral α-SYN level, and increasing TH and dopamine transporter level • Increased GLP-1 and GLP-1R concentration in SN • Promoted PINK1/Parkin mitophagy pathway to clear abnormal mitochondria • Alleviated oxidative stress • Altered gut microbiota composition - increased α-diversity and changed β-diversity • Recovered MPTP-induced reduction of GPR41/43 positive cells and intestinal tight junction proteins
31	Wu et al. (2023) ³¹	Neuroprotective effects of engineered GLP-1 producing probiotic strain	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	Saline suspension, oral gavage, 0.2mL (1.0 x 10 ⁹ CFU) daily for 7d 1; <i>Escherichia coli</i> Nissle 1917 (EcN-GLP-1)	<ul style="list-style-type: none"> • Improved motor coordination • Reversed the MPTP-induced pathological changes by reducing GFAP-positive astrocytes, Iba1-positive microglia, and α-SYN aggregation • Inhibited neuroinflammation by enhancing p-AKT/AKT expressions and inhibiting p-IκB-α, TLR4, and p-p65/p56 • Attenuated colonic inflammation by enhancing p-AKT/AKT expressions and inhibiting p-IκB-α, TLR4, and p-p65/p56 • Attenuated MPTP-induced colonic permeability by modulating the expression of tight junction proteins (occludin and ZO-1) and inhibiting the inflammatory response via NF-κB signaling pathway • Restored the imbalance of the microbiome
32	Zhang et al. (2023) ³²	Effects of engineered light sensitive probiotics in the gut	C57BL/6 male mice	Toxin, intraperitoneal injection of MPTP	PH-sensitive alginate hydrogel microcapsules in saline, oral gavage, 100mg probiotic preparation in 200uL saline (0.5 x 10 ⁹ bacteria) for 5d 1; <i>Escherichia coli</i> Nissle 1917 (Red-light Optogenetic; ROEN)	<ul style="list-style-type: none"> • Improved motor dysfunctions, spatial memory impairment and anxiety symptoms similar to healthy mice • Recovered MPTP-induced reduction in dopamine concentration • Slightly reduced inflammation and α-SYN aggregation
<p>4-HNE; 4-Hydroxynonenal, 6-OHDA; 6-hydroxydopamine, α-SYN; Alpha-synuclein, ASC; The Adaptor Molecule Apoptosis-Associated Speck-Like Protein Containing A CARD, BBB; Blood Brain Barrier, BDNF; Brain-derived neurotrophic factor, CFU; Colony Forming Unit, CCCP; protonophore carbonyl cyanide m-chlorophenyl hydrazone (CCCP), COX-2; Cyclooxygenase-2, CXCL 10; Chemokine (C-X-C motif) Ligand 10, DAF-16; Dauer Formation Abnormal 16, DSS; Dextran sodium sulphate, GABA; Gamma-aminobutyric Acid, GCSF; Granulocyte-Colony Stimulating Factor, GFAP; Glial Fibrillary Acidic Protein, GLP-1; Glucagon-Like Peptide-1, GLP-1R; Glucagon-Like Peptide-1 Receptor, GPR41/43; G protein-coupled receptors 41 & 43, GSH-Px; Glutathione Peroxidase, HO-1; Heme Oxygenase 1, Iba1; Ionized Calcium-Binding Adaptor Molecule 1, IL-; Interleukin, ILS; Insulin-like Signaling, iNOS; Inducible Nitric Oxide Synthase, Iκ-Bα; Inhibitor of Nuclear Factor Kappa-B Alpha, LPS; Lipopolysaccharide, MDA; Malondialdehyde, MFN2; Mitofusin-2, MnSOD; Manganese-Dependent Superoxide Dismutase, MPTP; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, NIR; Near-infrared, NF-κB; Nuclear factor-κB, NLRP3; NOD-, LRR- and pyrin domain-containing protein 3, Nrf2/ARE; Nuclear factor erythroid 2-related factor 2/Antioxidant Response Element, p-AKT; Phosphorylated Protein Kinase B, p-GSK3β; Phosphorylated Glycogen Synthase Kinase 3 Beta, p-IκBα; Phosphorylated Inhibitor of Nuclear Factor Kappa-B Alpha, p-Nrf2; Nuclear Factor Erythroid 2-Related Factor 2, p-p65; Phosphorylated p65 Subunit of NF-κB, Parkin; Parkin RBR E3 ubiquitin-protein ligase, PBMCs; Peripheral Blood Mononuclear Cells, PD; Parkinson's Disease, PGC-1α; Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha, PHA-4/DR; PHA-4: "GATA-type transcription factor" DR:"Daf-16 (FOXO) Regulator, PI3K/Akt; Phosphoinositide 3-Kinase/Protein Kinase B, PINK1; PTEN-induced Kinase 1, PPARγ; Peroxisome Proliferator Activated Receptor γ, SCFAs; Short-Chain Fatty Acids, SN; Substantia Nigra, SNpc; Substantia Nigra pars compacta, SOD; Superoxide Dismutase, TEER; Transepithelial Electrical Resistance, TH; Tyrosine Hydrolase, TNF-α; Tumour Necrosis Factor alpha, UCP2; Uncoupling Protein 2, UP-LCMS; ultraperformance liquid chromatography tandem mass spectrometry, ZO-1; Zonula Occludens-1.</p>						

Supplementary Table 2 | Systematic review of combined probiotics and other components in pre-clinical studies of Parkinson's disease.

PubMed Search Terms: "Probiotic" OR "Probiotics" OR "Pro-biotic" OR "Pro-biotics" AND "Parkinson" OR "Parkinsonism"						
Date of publications: 1 Jan 2000 to 05 Jan 2023						
Total: 90 references — 6 Pre-Clinical Studies						
Pre-clinical study of the combination of probiotics and other components						
No	Pre-clinical study (listed chronologically and according to first author)	Objective of Investigation	Models	Parkinsonian Feature Induction Method	Characteristics & dosage of probiotic strains and other components.	Study Outcome - Effects of probiotics
	First author (year of publication)	Aspect of probiotic investigation	Cell line/animal	Method, Substance	Probiotic preparation, Method of introduction, Dosage, Duration Total strains; Scientific name	Main study outcomes
1	Ilie et al. (2021) ³³	Effects in reducing oxidative status and motor impairment in a zebrafish PD model	<i>Danio rerio</i>	Toxin, exposure of rotenone in <i>Danio rerio</i> environment	Dissolved mixture, oral administration, 3.52mg/L daily for 21d Probiotic: 2 strains; <i>Bifidobacterium longum</i> BB536 (4 × 10 ⁹ CFU; 3mg/L), <i>Lactobacillus rhamnosus</i> HN001 (1 × 10 ⁹ CFU; 0.5mg/L) Vitamin: Vit B6 (0.02mg/L)	<u>Probiotic and vitamin B6</u> • No significant improvement in rotenone-induced motor function and oxidative stress <u>Probiotic</u> • Induced short boost of hyper-activity in rotenone free fish
2	Nurrahma et al. (2021) ³⁴	<i>In vitro</i> effect of probiotic, probiotic residual media and the combination of both	Sprague-Dawley male rats	Toxin, unilateral injection of 6-OHDA into the right medial forebrain bundle	Water suspension, oral gavage, daily for 8w Probiotic: 1 strain, <i>Lactobacillus salivarius</i> subsp. <i>salicinius</i> AP-32 (1.03 × 10 ⁹ CFU/kg/BW) Prebiotic: <i>L. salivarius</i> AP-32 residual media (62 mg/kg/BW)	<u>Probiotic and prebiotic</u> • Decreased apomorphine-induced contralateral rotation • Prevented loss of TH-positive intensity level in the striatum and SNpc • Improved gait dysfunction • Restored mitochondrial function and energy metabolism (glycolysis) • Prevented body weight lost, increased food consumption efficiency and maintained body composition • Enhanced antioxidative enzyme activities (GPx) • Elevated fecal SCFAs <u>Probiotic</u> • Best effect in preventing loss of TH-positive intensity level in the striatum and SNpc • Best effect in restoring mitochondrial function and energy metabolism (glycolysis) • Best effect in preventing body weight lost, increasing food consumption efficiency and maintaining body composition • Best effect in enhancing antioxidative enzyme activities (GPx and SOD) <u>Prebiotic</u> • Prevented loss of TH-positive intensity level in the SNpc
3	Tsao et al. (2021) ³⁵	Neuroprotective effects of probiotic, and/or prebiotic <i>in vivo</i>	Sprague-Dawley male rats	Toxin, injection of 6-OHDA into the right medial forebrain bundle	Water suspension, oral gavage, daily for 21d Probiotic: 1 strain; <i>Lactobacillus salivarius</i> subsp. <i>salicinius</i> AP-32 (1.03 × 10 ⁹ CFU/kg/BW) Prebiotic: <i>L. salivarius</i> AP-32 residual media (62 mg/kg/BW)	<u>Probiotic and prebiotic</u> • Alleviated motor dysfunction • Reduced severity of dopaminergic neuronal loss in SN and striatum • Reduced oxidative stress by increasing serum inflammatory markers levels (ROS, and TNF- α , SOD, GPX, and catalase activity) • Increased fecal propionate and butyrate • Altered microbiota composition <u>Probiotic</u> • Highest TH-positive signals in striatum and SNpc • Best effect in increasing fecal butyrate
4	Liu et al. (2022) ³⁶	Neuroprotective effects and	C57BL/6J male mice	Toxin, intraperitoneal	Water suspension, oral gavage, daily for 5w	<u>Probiotic and prebiotic</u> • Improved motor function

		mechanisms of probiotic with/or polymannuronic acid		injection of MPTP	Probiotic: 1 strain, <i>Lactocaseibacillus rhamnosus</i> GG (15×10^9 CFUs/kg/BW) Prebiotics: polymannuronic acid PM (30 mg/kg/BW)	<ul style="list-style-type: none"> Prevented dopaminergic neuronal loss by improving gene and protein expressions of striatal TH Improved BBB and neurotrophs via striatal ZO-1, occludin, BDNF and GDNF gene expression in the striatum Suppressed apoptosis by increasing striatal Bcl-2 mRNA levels and downregulating the ratio of Bax/Bcl-2 in the striatum Altered gut microbiota composition <p><u>Prebiotic</u></p> <ul style="list-style-type: none"> Increased faecal SCFA Inhibited striatal inflammation by reducing TNF-α mRNA levels
5	Ma et al. (2023) ³⁷	Effect with levodopa or DBS on advanced stage PD toxin model	Sprague-Dawley male rats	Toxin, unilateral injection of 6-OHDA	Saline suspension, oral administration, daily for 6w Probiotic: 1 strain; <i>Lactobacillus plantarum</i> PS128 (15×10^9 CFU) Other components: Levodopa (6mg/kg/BW)-benserazide (15 mg/kg/BW), DBS (STN)- bipolar stimulation	<p><u>Probiotic and levodopa/DBS</u></p> <ul style="list-style-type: none"> Exhibited better beta PSD suppression <p><u>Probiotic</u></p> <ul style="list-style-type: none"> Suppressed beta oscillation which correlated with improvement on motor function Exhibited neuroprotective effect with higher percentage of TH-positive regions in the striatum and midbrain Mitigated dopamine reduction in the striatum and midbrain Induced noradrenaline production in the striatum <p><u>Levodopa</u></p> <ul style="list-style-type: none"> Suppressed beta oscillation which correlated with improvement on motor function <p><u>DBS</u></p> <ul style="list-style-type: none"> Suppressed beta oscillation
6	Zhou et al. (2023) ³⁸	<i>In vitro</i> effect of probiotic and human mesenchymal stromal cells (hMSCs) on PD model	C57BL/6J male mice	Toxin, intraperitoneal injection of MPTP	Saline suspension, via gastrointestinal tract, daily for 6d Probiotic: 8; <i>Lactobacillus casei</i> , <i>L. plantarum</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> , <i>Bifidobacterium longum</i> , <i>B. breve</i> , <i>B. infantis</i> , <i>Streptococcus salivarius</i> (0.1 mL \times 4 \times 10 ⁹ CFU) Other component: human mesenchymal stromal cells (hMSCs) (0.2 mL \times 2 \times 10 ⁶ cells)	<p><u>Probiotic and hMSCs</u></p> <ul style="list-style-type: none"> Regulated dopamine and norepinephrine in the striatum Attenuated loss of dopaminergic neurons in the SN Restored the mRNA levels of inflammatory cytokines (TNF-α, IL-1β, caspase-1, and NLRP3) in striatum comparable to control Downregulated serum inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-17, GM-CSF, and IFN-γ) Restored mRNA expression of inflammatory cytokines in the liver (NLRP3) and intestine (caspase-1 and NLRP3)
<p>Bax/Bcl-2; Bax (Bcl-2-associated X protein) and Bcl-2 (B-cell lymphoma 2), BBB; Blood Brain Barrier, BDNF; Brain-derived neurotrophic factor, DBS; Deep Brain Stimulation, GDNF; Glial Cell Line-Derived Neurotrophic Factor, GM-CSF; Granulocyte-Macrophage Colony-Stimulating Factor, GPx; Glutathione peroxidase, IFN-γ; Interferon Gamma, IL-; Interleukin, NLRP3; NOD-, LRR- and pyrin domain-containing protein 3, PD; Parkinson's Disease, PSD; Power Spectral Density, ROS; Reactive Oxygen Species, SCFAs; Short-Chain Fatty Acids, SN; Substantia Nigra, SNpc; Substantia Nigra pars compacta, SOD; Superoxide Dismutase, TH; Tyrosine Hydrolase, TNF-α; Tumour Necrosis Factor alpha, ZO-1; Zonula Occludens-1.</p>						

Supplementary Table 3 | Systematic review of prebiotics pre-clinical studies of Parkinson's disease.

PubMed search terms: "Prebiotic" OR "Prebiotics" OR "Pre-biotic" OR "Pre-biotics" AND "Parkinson" OR "Parkinsonism"						
Date of publications: 1 Jan 2000 to 05 Jan 2024						
Total: 16 references — 7 pre-clinical studies						
Pre-clinical study of prebiotics						
No.	Pre-clinical study (listed chronologically and according to first author)	Objective of Investigation	Models	Parkinsonian Feature Induction Method	Characteristics & dosage of prebiotic	Study Outcome – Effects of prebiotics in the prebiotic group
	First author (year of publication)	Aspect of prebiotic investigation	Cell line/animal	Substance, Method	Method of introduction, Dosage, Duration	Main study outcomes
1	Perez-Pardo et al. (2017) ³⁹	Effects of uridine and DHA diet on motor, cognitive, and gastrointestinal symptoms	C57BL/6J mice (7 weeks old)	Toxin, infusion of rotenone into the right striatum	Oral administration, control diet/diet 1/diet 2 daily for 6w <ul style="list-style-type: none"> Control diet: standard animal food Diet 1: standard animal food + uridine (0.51/100g diet), fish oil providing DHA (0.75/100g diet), EPA (0.50/100g diet) Diet 2: standard animal food + prebiotic fibers, including GOS (1.5/100g diet), lcFOS (0.17/100g diet), scFOS (1.67/100g diet), and nutrose (1.67/100g diet) 	<u>Diet 2</u> <ul style="list-style-type: none"> More effective in normalizing motor and non-motor symptoms More effective in normalizing PD-like pathologies in brain and gut More effective in reducing rotenone-induced T-cell infiltration Restored striatal dopamine transporter levels <u>Diet 1 and Diet 2</u> <ul style="list-style-type: none"> Reduced α-synuclein levels in the striatum
2	Krishna and Muralidhara (2018) ⁴⁰	Effects of rotenone exposure during gestation on oxidative impairments in maternal rat brain and associated implications on foetal brain	Sprague-Dawley rats (pregnant)	Toxin, oral administration of rotenone	Oral administration, inulin (2g/kg BW/day) daily for 19d	<ul style="list-style-type: none"> Increased maternal caecal bacterial numbers that significantly corresponded with improved exploratory-related behaviour Alleviated gestational rotenone-induced oxidative impairments, mitochondrial dysfunction and dopamine alterations
3	Perez-Pardo et al. (2018) ⁴¹	Effects of levodopa in the rotenone model and interactions between prebiotic diet and levodopa	C57BL/6J mice (7 weeks old)	Toxin, infusion of rotenone into the right striatum	Oral administration, control diet/active diet daily for 9w <ul style="list-style-type: none"> Control diet: standard animal food Active diet: standard animal food + uridine (0.51g/100g diet), DHA (0.75g/100g diet), EPA (0.50g/100g diet), and prebiotic fibers including GOS (1.5g/100g diet), lcFOS (0.17g/100g diet), scFOS (1.67g/100g diet) and nutrose (1.67g / 100g diet) 	<ul style="list-style-type: none"> Alleviated rotenone-induced motor and non-motor problems Restored delayed intestinal transit and colon length Reduced spatial memory impairments Showed an additive beneficial effect on the motor function with levodopa
4	Ho et al. (2019) ⁴²	Influence of the gut microbiota's interpersonal heterogeneity on the production and bioavailability of flavonoid metabolite	<ul style="list-style-type: none"> Humanised gnotobiotic mice <i>Drosophila</i> line <i>elav^{C155}-GAL4, UAS- alpha-synuclein^{A53T}</i> 	<ul style="list-style-type: none"> Germ-free mice were colonised with microbiota culture collections from healthy human donors Female flies carrying the driver <i>elav^{C155}-GAL4</i> were crossed to males carrying the <i>UAS-alpha-synuclein^{A53T}</i> 	Oral administration, flavanol (40mg/kg BW/day) daily for 14d	<u>Humanised gnotobiotic mice</u> <ul style="list-style-type: none"> Interpersonal heterogeneity of the gut microbiota may differentially affect the generation, and thereby the bioavailability, of microbial-generated phenolic acid metabolites that have been derived from dietary flavanols Plasma-accumulating DHCA modulated inflammation Brain-accumulating 3-HBA, 3,4-diHBA and 3-HPPA inhibited α-synuclein misfolding <u>In vivo A53T mutant α-synuclein Drosophila model</u> <ul style="list-style-type: none"> Modulated the development and progression of motor dysfunction

5	Yamasaki et al. (2020) ⁴³	Effects of the interference of 3-HBA, 4-HBA, 3,4-diHBA, or 3-HPPA with α -synuclein spreading in a cell-based system	<ul style="list-style-type: none"> • HEK293 cells overexpressing α-syn-A53T-CFP/YFP • Post mortem PD or MSA brain specimens 	NA	Suspension of α -synuclein in aggregation buffer with or without the phenolic acid compounds 3-HBA, 4-HBA, 3,4-diHBA, and 3-HPPA (10:1 phenolic acid compounds: α -synuclein monomer) for 24h	<ul style="list-style-type: none"> • 3-HPPA, 3,4-diHBA, 3-HBA, and 4-HBA significantly attenuated intracellular α-synuclein seeding aggregation • Incubation of polyphenolic compounds with insoluble brain fractions showed that 3,4-diHBA and 3-HPPA effectively inhibited the generation of aggregation-prone forms in both PD and MSA
6	Abdel-Haq et al. (2022) ⁴⁴	Effects of prebiotic diet on gut microbiome and microglia in the ASO mouse model	Thy1- α -synuclein mouse line (male)	Male BDF1 mice were crossed with female ASO mice expressing the α -synuclein transgene on the X chromosome	Oral administration, wheat bran (50%) and resistant maltodextrin (50%) daily from 5-6 w of age until 22w of age	<ul style="list-style-type: none"> • Reduced PD-like symptoms and brain pathology • Restructured the microbiome towards increased relative abundances of taxa associated with potentially protective effects • Dampened microglial reactivity in brain regions • Dampened proinflammatory and neurotoxic signalling pathways • Promoted the expansion of protective disease-associated macrophage subsets of microglia
7	Mao et al. (2023) ⁴⁵	Evaluate the pharmacological effect of dioscin against PD	C57BL/6 J mice (4-6 weeks old, male)	Toxin, intraperitoneal injection of MPTP	Intragastric administration, dioscin (20, 40, and 80mg/kg) daily for 3w	<ul style="list-style-type: none"> • Improved motor behaviour, neuron viability and oxidative stress • Reversed gut dysbiosis • Regulated bile acid-mediated oxidative stress and neuroinflammation by targeting GLP-1 signalling
ASO; Antisense oligonucleotides, DHCA; dihydrocaffeic acid, 3,4-diHBA; 3,4-dihydroxybenzoic acid, 3-HPAA; 3-hydroxyphenylacetic acid, GLP-1; Glucagon-Like Peptide-1, DHA; Docosahexaenoic acid, GOS; galactooligosaccharides, lcFOS; long chain fructooligosaccharides, scFOS; short chain fructooligosaccharides, 4-HBA; 4-hydroxybenzoic acid.						

References for Supplementary Tables

1. Magistrelli L, Amoruso A, Mogna L, et al. Probiotics May Have Beneficial Effects in Parkinson's Disease: In vitro Evidence. *Front Immunol* 2019; 10: 969. 20190507. DOI: 10.3389/fimmu.2019.00969.
2. Srivastav S, Neupane S, Bhurtel S, et al. Probiotics mixture increases butyrate, and subsequently rescues the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity. *J Nutr Biochem* 2019; 69: 73-86. 20190406. DOI: 10.1016/j.jnutbio.2019.03.021.
3. Castelli V, d'Angelo M, Lombardi F, et al. Effects of the probiotic formulation SLAB51 in in vitro and in vivo Parkinson's disease models. *Aging (Albany N Y)* 2020; 12: 4641-4659. 20200309. DOI: 10.18632/aging.102927.
4. Goya ME, Xue F, Sampedro-Torres-Quevedo C, et al. Probiotic *Bacillus subtilis* Protects against α -Synuclein Aggregation in *C. elegans*. *Cell Rep* 2020; 30: 367-380.e367. DOI: 10.1016/j.celrep.2019.12.078.
5. Hsieh TH, Kuo CW, Hsieh KH, et al. Probiotics Alleviate the Progressive Deterioration of Motor Functions in a Mouse Model of Parkinson's Disease. *Brain Sci* 2020; 10 20200401. DOI: 10.3390/brainsci10040206.
6. Marsova M, Poluektova E, Odorskaya M, et al. Protective effects of *Lactobacillus fermentum* U-21 against paraquat-induced oxidative stress in *Caenorhabditis elegans* and mouse models. *World J Microbiol Biotechnol* 2020; 36: 104. 20200706. DOI: 10.1007/s11274-020-02879-2.
7. Perez Visňuk D, Savoy de Giori G, LeBlanc JG, et al. Neuroprotective effects associated with immune modulation by selected lactic acid bacteria in a Parkinson's disease model. *Nutrition* 2020; 79-80: 110995. 20200828. DOI: 10.1016/j.nut.2020.110995.

8. Xie C and Prasad AA. Probiotics Treatment Improves Hippocampal Dependent Cognition in a Rodent Model of Parkinson's Disease. *Microorganisms* 2020; 8 20201027. DOI: 10.3390/microorganisms8111661.
9. Alipour Nosrani E, Tamtaji OR, Alibolandi Z, et al. Neuroprotective effects of probiotics bacteria on animal model of Parkinson's disease induced by 6-hydroxydopamine: A behavioral, biochemical, and histological study. *J Immunoassay Immunochem* 2021; 42: 106-120. 20201020. DOI: 10.1080/15321819.2020.1833917.
10. Dwyer Z, Chaiquin M, Landrigan J, et al. The impact of dextran sodium sulphate and probiotic pre-treatment in a murine model of Parkinson's disease. *J Neuroinflammation* 2021; 18: 20. DOI: 10.1186/s12974-020-02062-2.
11. Ghyselinck J, Verstrepen L, Moens F, et al. Influence of probiotic bacteria on gut microbiota composition and gut wall function in an in-vitro model in patients with Parkinson's disease. *Int J Pharm X* 2021; 3: 100087. 20210702. DOI: 10.1016/j.ijpx.2021.100087.
12. Ishii T, Furuoka H, Kaya M, et al. Oral Administration of Probiotic Bifidobacterium breve Improves Facilitation of Hippocampal Memory Extinction via Restoration of Aberrant Higher Induction of Neuropsin in an MPTP-Induced Mouse Model of Parkinson's Disease. *Biomedicines* 2021; 9 20210208. DOI: 10.3390/biomedicines9020167.
13. Sun J, Li H, Jin Y, et al. Probiotic Clostridium butyricum ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. *Brain Behav Immun* 2021; 91: 703-715. 20201024. DOI: 10.1016/j.bbi.2020.10.014.
14. Cuevas-Carbonell SG, Vásquez-Celaya L, García-López D, et al. Chronic Treatment with the Probiotics Lacticaseibacillus rhamnosus GG and Bifidobacterium lactis BB12 Attenuates Motor Impairment, Striatal Microglial Activation, and Dopaminergic Loss in Rats

with 6-Hydroxydopamine-induced Hemiparkinsonism. *Neuroscience* 2022; 507: 79-98. 20221110. DOI: 10.1016/j.neuroscience.2022.11.004.

15. Ilie OD, Duta R, Balmus IM, et al. Assessing the Neurotoxicity of a Sub-Optimal Dose of Rotenone in Zebrafish (*Danio rerio*) and the Possible Neuroactive Potential of Valproic Acid, Combination of Levodopa and Carbidopa, and Lactic Acid Bacteria Strains. *Antioxidants (Basel)* 2022; 11 20221017. DOI: 10.3390/antiox11102040.

16. Ilie OD, Duta R, Jijie R, et al. Assessing Anti-Social and Aggressive Behavior in a Zebrafish (*Danio rerio*) Model of Parkinson's Disease Chronically Exposed to Rotenone. *Brain Sci* 2022; 12 20220708. DOI: 10.3390/brainsci12070898.

17. Li T, Chu C, Yu L, et al. Neuroprotective Effects of *Bifidobacterium breve* CCFM1067 in MPTP-Induced Mouse Models of Parkinson's Disease. *Nutrients* 2022; 14 20221104. DOI: 10.3390/nu14214678.

18. Pan S, Wei H, Yuan S, et al. Probiotic *Pediococcus pentosaceus* ameliorates MPTP-induced oxidative stress via regulating the gut microbiota-gut-brain axis. *Front Cell Infect Microbiol* 2022; 12: 1022879. 20221109. DOI: 10.3389/fcimb.2022.1022879.

19. Sancandi M, De Caro C, Cypaite N, et al. Effects of a probiotic suspension Symprove™ on a rat early-stage Parkinson's disease model. *Front Aging Neurosci* 2022; 14: 986127. 20230118. DOI: 10.3389/fnagi.2022.986127.

20. Wang L, Zhao Z, Zhao L, et al. *Lactobacillus plantarum* DP189 Reduces α -SYN Aggravation in MPTP-Induced Parkinson's Disease Mice via Regulating Oxidative Damage, Inflammation, and Gut Microbiota Disorder. *J Agric Food Chem* 2022; 70: 1163-1173. 20220124. DOI: 10.1021/acs.jafc.1c07711.

21. Chu C, Yu L, Li Y, et al. *Lactobacillus plantarum* CCFM405 against Rotenone-Induced Parkinson's Disease Mice via Regulating Gut Microbiota and Branched-Chain Amino Acids Biosynthesis. *Nutrients* 2023; 15 20230401. DOI: 10.3390/nu15071737.

22. Fan HX, Sheng S, Li DD, et al. Heat-killed *Lactobacillus murinus* confers neuroprotection against dopamine neuronal loss by targeting NLRP3 inflammasome. *Bioeng Transl Med* 2023; 8: e10455. 20221123. DOI: 10.1002/btm2.10455.
23. Hawrysh PJ, Gao J, Tan S, et al. PRKN/parkin-mediated mitophagy is induced by the probiotics *Saccharomyces boulardii* and *Lactococcus lactis*. *Autophagy* 2023; 19: 2094-2110. 20230205. DOI: 10.1080/15548627.2023.2172873.
24. Nápoles-Medina AY, Aguilar-Uscanga BR, Solís-Pacheco JR, et al. Oral Administration of *Lactobacillus* Inhibits the Permeability of Blood-Brain and Gut Barriers in a Parkinsonism Model. *Behav Neurol* 2023; 2023: 6686037. 20231109. DOI: 10.1155/2023/6686037.
25. Parra I, Martínez I, Vásquez-Celaya L, et al. Neuroprotective and Immunomodulatory Effects of Probiotics in a Rat Model of Parkinson's Disease. *Neurotox Res* 2023; 41: 187-200. 20230120. DOI: 10.1007/s12640-022-00627-y.
26. Fang X, Tian P, Zhao X, et al. Neuroprotective effects of an engineered commensal bacterium in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine Parkinson disease mouse model via producing glucagon-like peptide-1. *J Neurochem* 2019; 150: 441-452. 20190401. DOI: 10.1111/jnc.14694.
27. Fang X, Zhou X, Miao Y, et al. Therapeutic effect of GLP-1 engineered strain on mice model of Alzheimer's disease and Parkinson's disease. *AMB Express* 2020; 10: 80. 20200424. DOI: 10.1186/s13568-020-01014-6.
28. Pan H, Sun T, Cui M, et al. Light-Sensitive *Lactococcus lactis* for Microbe–Gut–Brain Axis Regulating via Upconversion Optogenetic Micro-Nano System. *ACS Nano* 2022; 16: 6049-6063. DOI: 10.1021/acsnano.1c11536.

29. Yue M, Wei J, Chen W, et al. Neurotrophic Role of the Next-Generation Probiotic Strain *L. lactis* MG1363-pMG36e-GLP-1 on Parkinson's Disease via Inhibiting Ferroptosis. *Nutrients* 2022; 14 20221118. DOI: 10.3390/nu14224886.
30. Wang Y, Chen WJ, Han YY, et al. Neuroprotective effect of engineered *Clostridium butyricum*-pMTL007-GLP-1 on Parkinson's disease mice models via promoting mitophagy. *Bioeng Transl Med* 2023; 8: e10505. 20230317. DOI: 10.1002/btm2.10505.
31. Wu H, Wei J, Zhao X, et al. Neuroprotective effects of an engineered *Escherichia coli* Nissle 1917 on Parkinson's disease in mice by delivering GLP-1 and modulating gut microbiota. *Bioeng Transl Med* 2023; 8: e10351. 20220618. DOI: 10.1002/btm2.10351.
32. Zhang X, Pang G, Sun T, et al. A red light-controlled probiotic bio-system for in-situ gut-brain axis regulation. *Biomaterials* 2023; 294: 122005. 20230120. DOI: 10.1016/j.biomaterials.2023.122005.
33. Ilie OD, Paduraru E, Robea MA, et al. The Possible Role of *Bifidobacterium longum* BB536 and *Lactobacillus rhamnosus* HN001 on Locomotor Activity and Oxidative Stress in a Rotenone-Induced Zebrafish Model of Parkinson's Disease. *Oxid Med Cell Longev* 2021; 2021: 9629102. 20211014. DOI: 10.1155/2021/9629102.
34. Nurrahma BA, Tsao SP, Wu CH, et al. Probiotic Supplementation Facilitates Recovery of 6-OHDA-Induced Motor Deficit via Improving Mitochondrial Function and Energy Metabolism. *Front Aging Neurosci* 2021; 13: 668775. 20210507. DOI: 10.3389/fnagi.2021.668775.
35. Tsao SP, Nurrahma BA, Kumar R, et al. Probiotic Enhancement of Antioxidant Capacity and Alterations of Gut Microbiota Composition in 6-Hydroxydopamin-Induced Parkinson's Disease Rats. *Antioxidants (Basel)* 2021; 10 20211117. DOI: 10.3390/antiox10111823.

36. Liu X, Du ZR, Wang X, et al. Polymannuronic acid prebiotic plus Lacticaseibacillus rhamnosus GG probiotic as a novel synbiotic promoted their separate neuroprotection against Parkinson's disease. *Food Res Int* 2022; 155: 111067. 20220224. DOI: 10.1016/j.foodres.2022.111067.
37. Ma YF, Lin YA, Huang CL, et al. Lactiplantibacillus plantarum PS128 Alleviates Exaggerated Cortical Beta Oscillations and Motor Deficits in the 6-Hydroxydopamine Rat Model of Parkinson's Disease. *Probiotics Antimicrob Proteins* 2023; 15: 312-325. 20210827. DOI: 10.1007/s12602-021-09828-x.
38. Zhou L, Han D, Wang X, et al. Probiotic Formulation VSL#3 Interacts with Mesenchymal Stromal Cells To Protect Dopaminergic Neurons via Centrally and Peripherally Suppressing NOD-Like Receptor Protein 3 Inflammasome-Mediated Inflammation in Parkinson's Disease Mice. *Microbiol Spectr* 2023; 11: e0320822. 20230202. DOI: 10.1128/spectrum.03208-22.
39. Perez-Pardo P, de Jong EM, Broersen LM, et al. Promising Effects of Neurorestorative Diets on Motor, Cognitive, and Gastrointestinal Dysfunction after Symptom Development in a Mouse Model of Parkinson's Disease. *Front Aging Neurosci* 2017; 9: 57. 20170320. DOI: 10.3389/fnagi.2017.00057.
40. Krishna G and Muralidhara. Oral supplements of inulin during gestation offsets rotenone-induced oxidative impairments and neurotoxicity in maternal and prenatal rat brain. *Biomed Pharmacother* 2018; 104: 751-762. 20180529. DOI: 10.1016/j.biopha.2018.05.107.
41. Perez-Pardo P, Broersen LM, Kliet T, et al. Additive Effects of Levodopa and a Neurorestorative Diet in a Mouse Model of Parkinson's Disease. *Front Aging Neurosci* 2018; 10: 237. 20180803. DOI: 10.3389/fnagi.2018.00237.

42. Ho L, Zhao D, Ono K, et al. Heterogeneity in gut microbiota drive polyphenol metabolism that influences α -synuclein misfolding and toxicity. *J Nutr Biochem* 2019; 64: 170-181. 20181114. DOI: 10.1016/j.jnutbio.2018.10.019.
43. Yamasaki TR, Ono K, Ho L, et al. Gut Microbiome-Modified Polyphenolic Compounds Inhibit α -Synuclein Seeding and Spreading in α -Synucleinopathies. *Front Neurosci* 2020; 14: 398. 20200504. DOI: 10.3389/fnins.2020.00398.
44. Abdel-Haq R, Schlachetzki JCM, Boktor JC, et al. A prebiotic diet modulates microglial states and motor deficits in α -synuclein overexpressing mice. *Elife* 2022; 11 20221108. DOI: 10.7554/eLife.81453.
45. Mao Z, Hui H, Zhao X, et al. Protective effects of dioscin against Parkinson's disease via regulating bile acid metabolism through remodeling gut microbiome/GLP-1 signaling. *J Pharm Anal* 2023; 13: 1153-1167. 20230616. DOI: 10.1016/j.jpha.2023.06.007.
46. Zheng J, Wittouck S, Salvetti E, et al. A taxonomic note on the genus *Lactobacillus*: Description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*. *Int J Syst Evol Microbiol* 2020; 70: 2782-2858. 20200415. DOI: 10.1099/ijsem.0.004107.