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8. Probióticos, prebióticos, psicobióticos, simbióticos, postbióticos.

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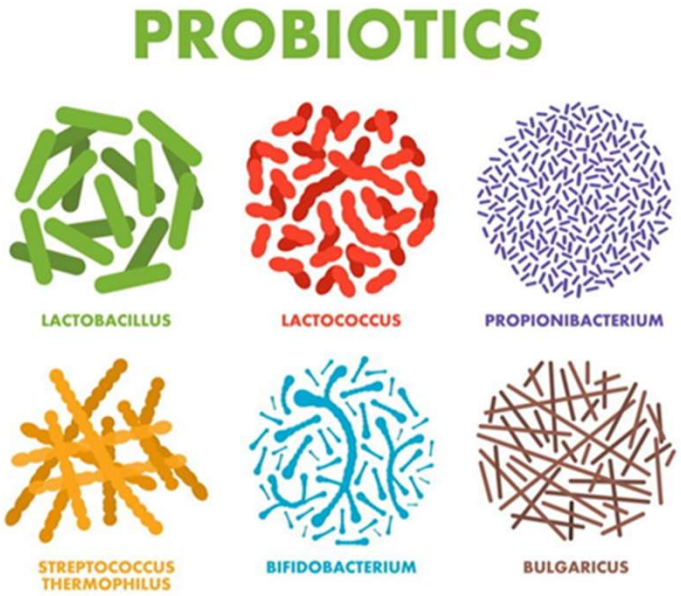
Introducción

- Antiguos egipcios de Oriente Medio
- Principios s. XX:
  - Asociación: longevidad y yogur
  - -Fermentos, microflora, toxinas
  - -Aislamiento *Bifidobacterium*
- 1960: probiótico
- 2001: la OMS define probiótico
- Avances secuenciación
- Prevenir antes que curar.

PROBIÓTICOS

"Microorganismos vivos que, administrados en cantidades adecuadas, ejercen un efecto beneficioso sobre la salud del consumidor".

- Vía oral
- Polvo o líquido



PROBIÓTICOS

Requisitos:

1) Los microorganismos deben estar **vivos** y en cantidades adecuadas (**suficientes**) cuando se administren.

2) Las cepas deben **identificarse** genéticamente y **clasificarse** de acuerdo con la terminología más reciente y designarse con números, letras o nombres.

3) Se deben realizar estudios con un **tamaño muestral y diseño adecuados** para poder designar una cepa como un probiótico y usarla en el hospedador al que va dirigido (puede ser humanos o animales).

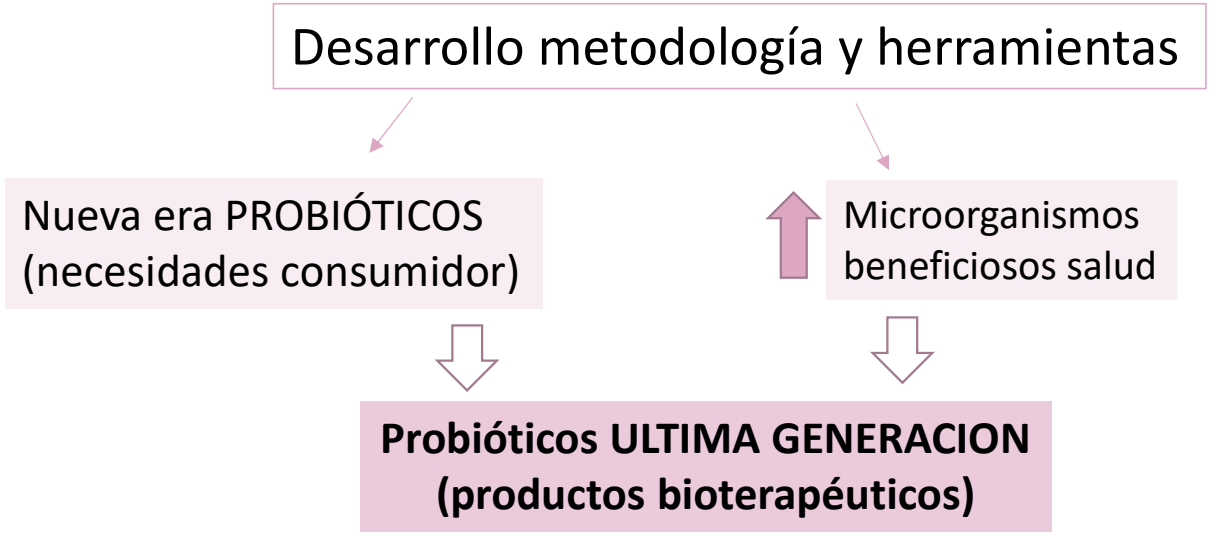
4) Las cepas beneficiosas para una condición (enfermedad) pueden no ser probióticas para otra aplicación. Es decir que existe **especificidad.**

5) Para que las cepas que han demostrado ser probióticas en modelos animales se puedan utilizar **en humanos** deben superar los **ensayos clínicos** correspondientes según la normativa vigente.

Probióticos clásicos y probióticos de última generación

Clásicos: *Lactobacillus* spp. y *Bifidobacterium* spp

- Seguras (EEUU)
- Presuntamente seguras (EFSA)



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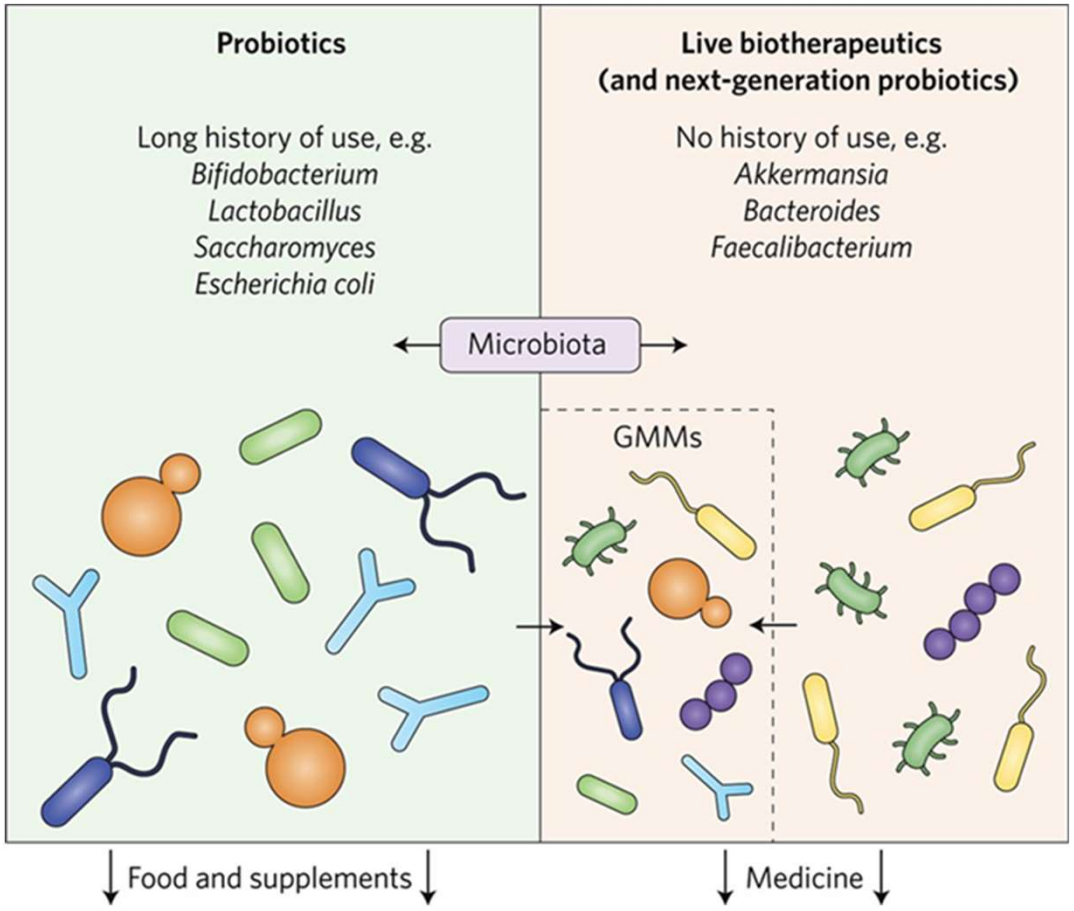
Probióticos clásicos y Probióticos de última generación



microorganismos genéticamente modificados (GMMs)

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Alimentos que contienen probióticos

- Yogur
- Kéfir
- Queso fresco
- Chucrut (col fermentada en salmuera típico de Centroeuropa)
- Kimchi (plato coreano a base de repollo fermentado)
- Jocoque (leche de vaca fermentada típica en México)
- Kombucha (bebida a base de té fermentado)
- Encurtidos (aunque no todos)
- Miso (soja, cebada o arroz integral fermentados con un hongo)
- Natto (soja fermentada, típico de Japón)
- Kvass (remolacha fermentada, típico de Europa del este)
- Tempeh (soja fermentada típico en Indonesia)

Prebióticos

Los **prebióticos** son componentes dietéticos **no digeribles** que benefician la salud del huésped mediante la estimulación selectiva del crecimiento y/o actividad de ciertos microorganismos.

- **Hidratos de carbono** (olisacáridos y polisacáridos) **no digeribles**
- **Fibra:** celulosa, hemicelulosa, pectinas, mucilago y goma, así como el almidón resistente

Características:

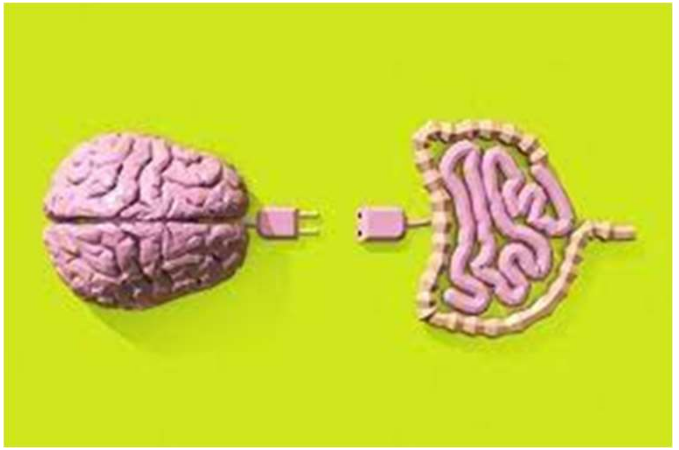
1. **No** ser **digeribles** por las enzimas del tracto gastrointestinal
2. **No** ser **absorbibles**
3. Mejorar la **inmunidad** del hospedador impidiendo la invasión por patógenos.
4. Estimular el **crecimiento selectivo** de algunas cepas bacterianas.
5. Se capaz de **modular la microbiota** intestinal

Psicobióticos

Los **psicobióticos** son bacterias beneficiosas (probióticos) o el sustrato para dichas bacterias (prebióticos) que influyen en las relaciones bacteria-cerebro y que confieren beneficios para la salud mental a través de la microbiota intestinal.

- Ansiolíticos y antidepresivos
- Eje intestino-cerebro
- Incógnitas

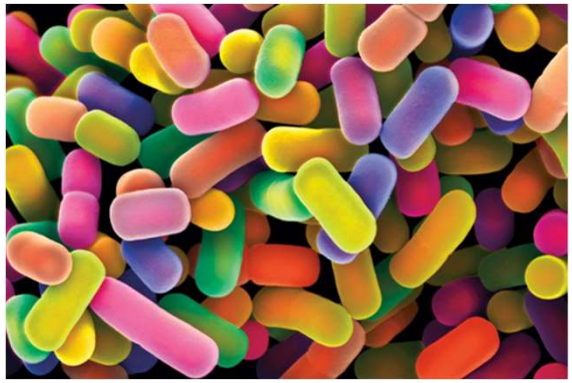
Dosis-respuesta
Efectos largo plazo
Mecanismos



Investigaciones actuales:
Alzheimer, Esclerosis Amiotrófica Lateral, Trastorno del Espectro Autista, depresión, ansiedad, estrés, Encefalopatía Hepática, Diabetes

Postbióticos

Un postbiótico es una preparación de microorganismos inanimados y/o sus componentes que confiere un beneficio para la salud del huésped. En definitiva, son **microrganismos muertos** pero que sí tienen **acción sobre la salud**



Se han hecho diferentes estudios en humanos empleando postbióticos en enfermedades como diarrea crónica, enfermedad inflamatoria intestinal, infección por *Helicobacter pylory*, asma, tuberculosis o estrés entre otras.

Simbióticos

Un simbiótico es una **mezcla** que contiene microorganismos vivos y sustrato/s utilizado/s selectivamente por los microorganismos del huésped que confiere un beneficio a la salud del huésped.

1) **Los simbióticos complementarios**: tanto el probiótico como el prebiótico que componen el simbiótico funcionan **independientemente** para aportar beneficios para la salud.
2) **Simbióticos sinérgicos**: probiótico y prebiótico trabajan como un **equipo** para aportar beneficios a nuestra salud. Es decir, que el prebiótico es el sustrato del probiótico.

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Probióticos como tratamiento de diferentes enfermedades: Depresión

Reference	Sample characteristics	Strain	Study design	Duration of intervention	Measurement	Key findings and conclusions
Akkasheh et al. [46]	40 MDD patients. Ages 20–55 years	*Lactobacillus acidophilus, L. casei, and Bifidobacterium bifidum*	Double-blind, randomized, placebo-controlled trial	8 weeks	BDI	Consumption of probiotic supplement improved BDI scores
Benton et al. [42]	124 healthy humans. Avg. age 62 years	*L. casei*	Double-blind, randomized, placebo-controlled trial	3 weeks	POMS, self-rated mood	No effect of probiotic on POMS results. Consumption of probiotic-containing yogurt improved self-reported mood of those whose mood was initially poor
Chung et al. [44]	36 healthy humans. Age 60–75 years	*L. helveticus*	Double-blind, randomized, placebo-controlled trial	12 weeks	PSS, GDS-SF, DST, SRT, VLT, RVIP, Stroop Task	No significant effects of probiotics on the PSS, GDS-SF. Consumption of probiotics did improve DST, SRT, VLT, RVIP, and stroop tasks scores.
Gruenwald et al. [48]	34 adults suffering from stress or exhaustion. Mean age 44 years	*L. acidophilus* and *B. bifidum* and *longum*	Pre- and post-intervention assessment	6 months	PNQ, EWL	Subjects' general condition improved by 40.7%. 73% of participants rated the effect of treatment as "good" or "very good"
Hilimire et al. [50]	710 young adults. Mean age 19 years	Unknown	Self-report questionnaires on fermented food consumption, neuroticism and social anxiety	N/A	BFI, SPAI-23	Consumption of fermented foods containing probiotics was negatively associated with symptoms of social anxiety and interacts with neuroticism to predict social anxiety symptoms. Those at higher genetic risk for social anxiety disorder (indexed by high neuroticism) show fewer social anxiety symptoms when they consume more fermented foods.
Marcos et al. [49]	136 healthy students. Age 18–23 years	*L. casei*	Prospective, randomized, controlled, parallel study	6 weeks	STAI	No significant effects of probiotics on anxiety levels. Probiotics did modulate lymphocyte and CD56 cell counts
Messaoudi et al. [36]	55 healthy Caucasians. Mean age 43 years	*L. helveticus* and *B. longum*	Double-blind, randomized, controlled, parallel study	30 days	HADS, HSCL-90, PSS, CCL	Consumption of probiotics reduced global severity index of the HSCL-90 due to lower somatization, depression, and anger-hostility and also reduced HADS global scores. Consumption of probiotic reduced self-blame score on CCL and increased focus on problem solving. No effect on PSS
Messaoudi et al. [47]	Sub-population of above sample of 25 with lowest UFC levels	*L. helveticus* and *B. longum*	Double-blind, randomized, controlled, parallel study	30 days	HADS, HSCL-90	Consumption of probiotics reduced HADS and HSCL-90 scores
Rao et al. [43]	35 CFS patients. Age 18–65 years	*L. casei*	Double-blind, randomized, placebo-controlled pilot study	2 months	BDI, BAI	Consumption of probiotics significantly improved BAI scores. No effect on BDI scores
Steenbergen et al. [45]	40 non-smoking healthy young adults. Mean age 20 years	*B. lactis* and *L. acidophilus, brevis, casei, lactis,* and *salivarius*	Triple-blind, randomized, placebo-controlled, pre- and post-intervention assessment	4 weeks	LEIDS-r	Consumption of multispecies probiotic significantly reduced overall cognitive reactivity to depression (in particular aggressive and ruminative thoughts)

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Probióticos como tratamiento de diferentes enfermedades: estrés

Authors and year	Sample size and characteristics	Study design	Duration	Strains and cell-density (Colony-Forming Units, CFU)	Modality of administration	Psychological symptom / Scale	Outcome/key findings
Marcos et al., 2004 [19]	155 Healthy students aged 18–23 years old	Prospective, randomized, placebo controlled and parallel study	6 weeks	$1x10^7$ CFU/ml of *L. delbrueckii* subsp. bulgaricus, *St. salivarius* subsp. *thermophilus* ($1x\ 10^8$ /ml), *L. casei* DN114001 ($1x10^8$ /ml)	Milk	Stress / STAI	Unchanged
Diop et al., 2008 [22]	37 Healthy volunteers 18-60 years old	Randomized double blind placebo-controlled study	3 weeks	$3x10^9$ CFU/g of *L. acidophilus* Rosell-52 and *B. longum* Rosell-175 (all same cell-density)	Sachets	Stress / SI (VAS)	Unchanged
Langkamp-Henken et al., 2015 [17]	583 Healthy undergraduate students average age 20 years	Randomized double blind placebo-controlled study	6 weeks	$3x10^9$ CFU/g of: *B. bifidum* R0071, *B. longum* ssp. *infantis* R0033 and *L. helveticus* R0052 (all same cell-density)	Capsule	Stress / SI (VAS)	Improved
Rao et al., 2009 [25]	39 Patients with CFS aged 18-65 years old	Randomized double blind placebo-controlled study	8 weeks	2.4×10^{10} CFU/g of *L. casei* Shirota 9029	Sachet	Anxiety / HAD	Improved
Simren et al., 2010 [28]	74 Adults with IBS; average age 44	Randomized, double-blind, controlled study	8 weeks	$5x10^7$ CFU/ml of: *L. paracasei* subsp. paracasei F19, *L. acidophilus* La5, and *B. lactis* Bb12 (all same	Milk	Anxiety / HAD	Improved

Probióticos como tratamiento de diferentes enfermedades: TDAH

En la siguiente tabla se muestran diferentes estudios en los que se muestran qué cepas se encuentran alteradas respecto a pacientes control.

No.	Study	Gut microbiota profiles
1	Aarts et al. [12]	Phylum: ↑: *Actinobacteria* Order: ↓: *Clostridiales* Family: ↑: *Rikenellaceae, Porphyromonadaceae* Genus: ↑: *Bifidobacterium, Eggerthella*
2	Jiang et al. [9]	Family: ↑: *Peptostreptococcaceae*[a], *Moraxellaceae*[b], *Xanthomonadaceae*[b], *Peptococcaceae*[b] ↓: *Alcaligenaceae*[a] Genus: ↓: *Faecalibacterium*[a], *Dialister*[a], *Lachnoclostridium*[c], *Sutterella*[b]
3	Prehn-Kristensen et al. [14]	Family: ↑: *Neisseria, Bacteroidaceae* Genus: ↑: *Neisseria* ↓: *Prevotella* OTU level: ↑: *Bacteroides OTU_7, Bacteroides OTU_577*
4	Wang et al. [10]	Phylum: ↑: *Fusobacteria* Genus: ↑: *Fusobacterium* Species: ↑: *Bacteroides uniformis, Bacteroides ovatus, Sutterella stercoricanis* ↓: *Bacteroides coprocola*

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Probióticos como tratamiento de diferentes enfermedades: obesidad

Table 1. Detailed summary of the selected studies included in the revision.

Author	Year, Country	Population	Design	Intervention	Control	Strains & Doses	Inter Period	Results
Kadooka et al. [23]	2010, Japan	$n = 87$ n(IG) = 43 n(CG) = 44 Adults (male and female) Visceral fat 81.2–178.5 cm^2 BMI: 24.2–30.7 kg/m^2 Age: 33–63 years	Multi-center RCT-DB	200 g/day of fermented milk	200 g/day of fermented milk without *Lactobacillus gasseri* SBT2055	*Lactobacillus gasseri* SBT2055 (5×10^{10} CFU/100 g)	12 weeks	Body weight, BMI, waist and hip circumferences decreased significantly ($p \leq 0.001$). In the active group the visceral and abdominal subcutaneous fat areas decreased significantly ($p \leq 0.01$)
Omar et al. [24]	2013, Canada	$n = 28$ n(IG) = 14 n(GC) = 14 Adults (male and female) BMI: 25–32 kg/m^2 Age: 18–60 years	Cross-over RCT-DB	(i) Yogurt with probiotic 1 (ii) Yogurt with probiotic 2 Both groups were put on diet	Control yogurt	(i) 100 g of control yogurt + 10 g of 1.39×10^9 CFU microencapsulated BSH-active *Lactobacillus acidophilus* (ii) 100 g of control yogurt + 10 g of 1.08×10^9 CFU microencapsulated FAE-active *Lactobacillus fermentum*	13 weeks	No significant differences in body weight were observed at baseline or endpoint across the three treatments. Significant reductions in total fat mass by 3% from baseline ($p = 0.05$)
Sanchez et al. [25]	2013, Canada	$n = 125$ n(IG) = 62 n(GC) = 63 Healthy adults (male and female) BMI: 29–41 kg/m^2 Age:18–55 years	RCT-DB	2 capsules/day of probiotic + moderate restriction of energy in the first 12 weeks followed by 12 weeks of maintenance	Placebo	*Lactobacillus rhamnosus* CGMCC1.3724 (LPR) (1.62×10^8 CFU) with 300 mg of one mix of oligofructose and inulin (70:30, vv)	24 weeks	No significant reduction in weight among the comparison groups. Significant interaction between sex and intervention. Weight loss in female in the intervention group was significantly higher than those of placebo group ($p = 0.02$)

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Probióticos como tratamiento de diferentes enfermedades: Alzheimer

References	Study design	N	Diagnostic criteria	Age (M ± SD)		Sex ratio (M/F)		Type of Probiotics	Duration (weeks)	Dose	Primary outcome	Secondary outcome
				PRO	CON	PRO	CON					
Akbari et al. (2016)	Randomized Double-blind Placebo-Controlled Trial	60	AD(NINDS-ADRDA criteria)	77.67± 2.62	82.00 ± 1.69	6/24	6/24	Multiple (Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, Lactobacillus fermentum)	12	8×10^9 (CFU/g)	MMSE	TAC GSH MDA hs-CRP NO
Agahi et al. (2018)	Randomized Double-blind Placebo-Controlled Trial	48	AD (NINDS-ADRDA criteria)	79.70 ± 1.72	80.57 ± 1.79	7/18	10/13	Multiple (*Lactobacillus fermentum, Lactobacillus plantarum, Bifidobacterium lactis Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum*)	12	3×10^9 (CFU/d)	TYM	TAC GSH MDA NO
Tamtaji et al. (2019a)	Randomized Double-blind Placebo-Controlled Trial	90	AD (NINDS-ADRDA criteria)	76.2 ± 8.1	78.5 ± 8.0	/	/	Multiple (Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum)	12	6×10^9 (CFU/d)	MMSE	TAC GSH MDA hs-CRP NO
Kobayashi et al. (2019)	Randomized Double-blind Placebo-Controlled Trial	121	Subjective memory complaints (MMSE, 22–27)	61.5 ± 6.83	61.6 ± 6.37	30/31	30/30	Sole (*Bifidobacterium breve* A1)	12	$>2.0 \times 10^{10}$ (CFU/d)	RBANS MMSE	hs-CRP
		44	MCI (RBANS <41)					Sole (*Bifidobacterium breve* A1)	12	$>2.0 \times 10^{10}$ (CFU/d)	RBANS MMSE	
Hwang et al. (2019)	Randomized Double-blind Placebo-Controlled Trial	100	MCI (DSM-5)	68.0 ±5.12	69.2 ± 7.00	20/30	14/36	Sole (*Lactobacillus plantarum* C29)	12	$>1.0 \times 10^{10}$ (CFU/d)	VLT ACPT DST	
Xiao et al. (2020)	Randomized Double-blind Placebo-Controlled Trial	80	MCI (MMSE ≥22)	61.3 ± 7.7	60.9 ± 6.9	19/21	20/20	Sole (*Bifidobacterium breve*A1)	16	$>2.0 \times 10^{10}$ (CFU/d)	RBANS	JMCIS

PRO, probiotics group; CON, control group; AD, Alzheimer's disease; MCI, mild cognitive impairment; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; CFU, colony-forming units; MMSE, Mini-Mental State Examination; TAC, total anti-oxidant capacity; GSH, total glutathione; MDA, malondialdehyde; hs-CRP, high-sensitivity C-reactive protein; NO, nitric oxide; TYM, test your memory; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; VLT, verbal learning test; ACPT, auditory continuous performance test; DST, digit span test; JMCIS, Japanese version of the MCI Screen.

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Probióticos como tratamiento de diferentes enfermedades: Parkinson

Study	Study design	N	Diagnostic criteria	Age (M ± SD)		Sex ratio (M/F)		Type of Probiotics	Duration (weeks)	Dose	Primary outcome	Secondary outcome	Main findings
				PRO	CON	PRO	CON						
Georgescu et al. (2016)	Randomized Double-blind Placebo- Controlled Trial	40	PD (modified Hoehn–Yars scale)	69.80 ± 5.64	75.65 ± 9.66	/	/	Multiple (*Lactobacillus acidophilus*, *Bifidobacterium infantis*)	12	120 mg/d	Abdominal pain; Bloating; Constipation	Non-motor symptoms	Treatment with probiotics could improve abdominal pain and bloating as much as with trimebutine, but less for constipation with incomplete evacuation, where trimebutine showed better results.
Barichella et al. (2016)	Randomized Double-blind Placebo- Controlled Trial	120	PD (UK Brain Bank criteria and Rome III criteria)	71.8 ± 7.7	69.5 ± 10.3	41/39	24/16	Multiple (*Streptococcus salivarius subsp thermophilus*, *Enterococcus faecium*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*)	4	2.5×10^{11} (CFU/d)	CBMs	3 or more CBMs; CBMs during weeks 3 and 4; stool frequency; stool consistency; the frequency of laxative use; satisfaction with treatment	The consumption of a fermented milk containing multiple probiotic strains and prebiotic fiber was superior to placebo in improving constipation in patients with PD.

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