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Effects of probiotics and postbiotics against cognitive frailty *in vivo*: A narrative review

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ABSTRACT

Cognitive frailty (CF), a geriatric syndrome that is marked by the coexistence of frailty and cognitive impairments without the presence of dementia, increases the risk of harmful health outcomes especially amongst the older adults. Given that there remains no approved therapy that addresses CF, the continuous growth of global ageing population raises the need for non-pharmacological approach that is able to address both cognitive and physical vulnerability together rather than in isolation. There is growing evidence that positions the gut as the biological interface that influences the brain and the muscles through interconnected immune, endocrine, metabolic, and barrier-related pathways. In this context, dietary modifications using probiotics or postbiotics have gained considerable attention for their potential in attenuating processes underlying CF by reshaping gut microbial composition and function. The present review aimed at uncovering the roles probiotics and postbiotics against CF (including its individual cognitive and physical components) along with their mechanisms that are mediated through the gut-brain axis and gut-muscle axis based on the current evidence. This review featured *in vivo* studies on various probiotic strains and postbiotic preparations that conferred a measurable improvement in neuroprotection, memory and behavioural changes, muscle/ bone function and homeostasis, anti-/pro-inflammatory biomarkers, gut health amongst others. The consolidated evidence supports probiotics or postbiotics as supportive or adjunctive therapy to prevent or mitigate the progression of CF. More importantly, this review provides a framework to inform future translational research and rational development of targeted interventions aimed at promoting healthy ageing.

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INTRODUCTION

Both cognitive impairment and physical frailty are increasingly recognised as clinical conditions amongst older adults. Whilst they have been historically studied as distinct phenomena, there is mounting evidence that indicates the interconnection between cognitive impairment and physical frailty (Kelaiditi *et al*., 2013). In fact, both cognitive impairment and physical frailty can coexist [yet without meeting the diagnostic criteria for dementia] as a clinical syndrome known as cognitive frailty (CF) (Ruan *et al*., 2019). CF exists on a spectrum that begins with a presymptomatic stage, which is a reversible process with appropriate intervention (Murukesu *et al*., 2024). However, CF can deteriorate into dementia if left unmanaged (Sugimoto *et al*., 2018).

The pooled prevalence of CF is approximately 5% (95% CI: 4-6%) of older adults across multiples community-based studies (Bian *et al*., 2026). In a Malaysian community-dwelling cohort, for instance, the reported prevalence varies substantially between 2.2%-12.1%, depending on diagnostic criteria, frailty framework, and whether pre-frail states were included. (Malek Rivan *et al*., 2019; Ponvel *et al*., 2024). This condition is rather concerning given that many countries including Malaysia are already an ageing nation and soon will enter the status of aged nation (DOSM, 2026). This is expected to heighten the risk of CF and other age-related health challenges.

Currently, there remain no FDA-approved pharmacological interventions that address CF. As such, management of CF relies on non-pharmacological interventions and early detection (Prakopimaite *et al*., 2026). Amongst these non-pharmacological interventions, dietary modifications have been increasingly hailed as being effective in maintaining cognitive and physical functions by modulating gut health, which is linked to neuroprotection and overall well-being (Lauria *et al*., 2026). In this regard, probiotics have garnered attention not only for their positive effects on mental and physical well-being, but also for their influence on gut microbiota composition and function. In addition, probiotics can be processed to harvest their postbiotics consisting of inactivated cells and/or their bioactive components. Probiotic-derived bioactive metabolites such as short-chain fatty acids (SCFA) regulate brain and physical health by modulating inflammatory responses (Kaya *et al*., 2026). Furthermore, the lack of viable microorganisms in postbiotics confers a better safety profile and extended shelf life when compared to probiotics (Mishra *et al*., 2024).

The present narrative review aimed at consolidating the existing preclinical evidence that is relevant to the effects of probiotics and postbiotics against CF but scattered across multiple disciplines, models and domain outcomes. To this end, a thorough literature search was conducted using electronic databases, which included PubMed and ScienceDirect. A combination of Medical Subject Headings (MeSH), Text Words (tw) field qualifier and a wildcard search were used to maximise the search efficiency. The keywords included “cognitive frailty”, “cognitive impairment”, “cognitive dysfunction”, “cognition”, “memory impairment”, “cognitive decline”, “cognitive function”, “probiotics”, “lactic acid bacteria”, “*lactobacillus*”, “*bifidobacterium*”, “postbiotics” “cell-free supernatant”, “inactivated cell”, “parabiotics” “frailty”, “physical frailty”, “muscle wasting”, “muscle loss”, “sarcopenia”, “frailty syndrome”, “pre-frail”, “physical function”, “gut brain axis”, “gut muscle axis”, “gut-brain axis”, “gut-muscle axis”, “gut microbiota”, “microbiome”, “microbiota” and their synonyms. These terms were combined with Boolean operators and manually adjusted for each e-database's requirement. The search was limited to studies published in English. Additional studies were screened through relevant systematic reviews. The last search was carried out on the 13th of November 2025. Basically, this review featured the common outcomes in relation to probiotic and postbiotic interventions against CF, including its individual cognitive and physical components. The concepts and mechanistic insights that arise from the present review may be translated into future experimental and translational studies.

PROBIOTICS AND POSTBIOTICS: OVERVIEW

Probiotics are *live microorganisms that support health when consumed in adequate amounts* (FAO/WHO, 2001). Being “good bacteria”, probiotics confer strain-dependent beneficial effects primarily by promoting

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gut health, enhancing immune function, and improving metabolic balance (Hill *et al*., 2014). In general, these beneficial microbes restore microbiota balance, providing relief from digestive issues such as antibiotic-associated diarrhoea and irritable bowel syndrome (Arunavarsini *et al*., 2024). Probiotics also prevent infections by activating immune responses. Their roles in metabolic regulation (e.g., improving insulin sensitivity and reducing cholesterol levels) may lower the risk of metabolic disorders (Sharma *et al*., 2024). Probiotics counteract dysbiosis by inhibiting pathogen adherence in the gut (Oladipo and Ogunleke, 2023). Interestingly, probiotics produce essential vitamins and metabolites (collectively known as postbiotics), which support overall health. Basically, postbiotics are *preparations of inanimate microorganisms and/ or their components that confers a health benefit on the host* (Salminen *et al*., 2021). *L. plantarum* FP48 (Aiello *et al*., 2023) and *L. brevis* CRL 2013 (Cataldo *et al*., 2020), for example, could reportedly produce B-vitamins, SCFA (acetate, propionate, butyrate), antimicrobial peptides (bacteriocins) and neurotransmitters (GABA). These bioactive metabolites could confer health benefits, including anti-inflammatory effects and enhanced gut barrier function, making them valuable in the development of functional foods.

EFFECTS OF PROBIOTICS AND POSTBIOTICS AGAINST COGNITIVE IMPAIRMENT *IN VIVO*

There is now growing evidence that implicates probiotics and postbiotics as potential modulators of cognitive function. Table 1 summarizes the effects of probiotics and postbiotics against cognitive impairment *in vivo*. In general, probiotics and postbiotics improved cognitive function in a strain-dependent manner, regardless of multi-strain or single-strain. The probiotic- and postbiotic-based interventions varied across the preclinical studies. The doses at which these beneficial effects were observed ranged between 5×10^6 and 1×10^{10} CFU/mL. The shortest duration of the said interventions was 2 weeks, whereas the longest was 40 weeks. The impact of probiotics and postbiotics against cognitive impairment has been validated in a variety of animal models of cognitive impairment, including those that were induced, transgenic, or naturally occurring. Probiotics and postbiotics appear to improve cognitive function through neuroprotection, memory and behavioural changes, modulation of anti-/ pro-inflammatory biomarkers, improved gut health, amongst others.

Neuroprotection

Probiotics and postbiotics consistently conferred neuroprotection across multiple animal models of cognitive impairment by modulating neuroplasticity, synaptic integrity, neurotrophic factors, and neurotransmission. In terms of ageing-related models, including the SAMP8 transgenic, natural and D-galactose-induced ageing models, probiotics enhanced synaptic markers such as synaptophysin and PSD-95, increased neurotrophic factors including BDNF, NGF, Nrf2 and improved neurotransmission and reduced neuronal apoptosis markers (Bax, cleaved-caspase 1, caspase 11) (Cheng *et al*., 2022; Nie *et al*., 2024; Shi *et al*., 2024; Wuttisa *et al*., 2025; Yang *et al*., 2023; Zeng *et al*., 2024; Zhang *et al*., 2025a). Besides, probiotics also protected the blood-brain barrier (BBB) via the AMPK/ Sirt1 (Zeng *et al*., 2024). In terms of the stress- and pain-induced cognitive deficit models, probiotics elevated hippocampal BDNF, serotonin, dopamine, NPY, and Trk-B and reduced Aβ, contributing to enhanced neuroprotection and neurotransmitter balance (Abazari-Bozhgani *et al*., 2025; Dandekar *et al*., 2022; Eladawy *et al*., 2025). In terms of the pathogen- or toxin-induced cognitive impairment models, including the E. coli K1 and LPS-challenged models, probiotics increased mitochondrial Complex III enzyme activity, 5-HT ghrelin levels, enhanced BDNF expression, and reduced ApoE levels. (Lee *et al*., 2021b; Muhammad *et al*., 2023). In terms of the blunt chest trauma model, autoimmune encephalomyelitis model, vaginitis and osteoporosis models, and high cholesterol diets model, probiotics increased neuron survival by restoring BDNF, TrkB, and serotonin while simultaneously lowering microglia activation such as IBA1 and apoptosis as well as neurodegeneration markers like Aβ, p-tau, α-synuclein, cleaved caspase-1 and ASC (Li *et al*., 2025; Liu *et al*., 2025b; Shahin *et al*., 2025; Shin *et al*., 2024). Postbiotics, on the other hand, increased neuroactive

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molecules such as ACh and its precursor ChAT while lowering AChE. This effect extends towards stronger neuroplasticity and suppressed brain injury as indicated by higher levels of BDNF, CREB, p-CREB and β-secretase (Cheng *et al*., 2022; Lee *et al*., 2025; Wu *et al*., 2022).

Memory and behavioural changes

Probiotics and postbiotics consistently improved memory and behavioural outcomes across diverse experimental conditions. In terms of the chronic stress models, probiotics improved depressive and anhedonia-related outcomes, which were reflected by the decreased passivity in Forced Swim Test (FST) and anxiety-like behaviour in Elevated Plus Maze (EPM) but increased sucrose intake in Sucrose Preference Test (SPT) (Dandekar *et al*., 2022). Similar improvements were also observed in the autoimmune encephalomyelitis model and vaginitis and osteoporosis models, whereby probiotics attenuated depressive behaviour (Li *et al*., 2025; Shin *et al*., 2024). In terms of ageing-related paradigms, probiotics resulted in comparable benefits, including improved memory performance in MWM, Y-maze, Passive Avoidance Test (PAT) and Novel Object Recognition (NOR), nesting behaviour and improved motor function. (Cheng *et al*., 2022; Nie *et al*., 2024; Shi *et al*., 2024; Wang *et al*., 2025; Wuttisa *et al*., 2025; Yang *et al*., 2023; Zeng *et al*., 2024; Zhang *et al*., 2025a). In terms of the infection and inflammation-driven cognitive deficit models, supplementation of probiotics reduced escape latency and depressive behaviour (Muhammad *et al*., 2023; Yun *et al*., 2020). In terms of the blunt chest trauma animal model, probiotics also reduced anxiety-like behaviour. Other models characterised by neurotoxicity-, pain-, noise-, trauma- and dietary-induced cognitive deficits also exhibited parallel improvements in memory and learning behaviour including fewer errors in the reverse Y-maze, reduced nociceptive responses and anxiety-like behaviour following probiotic supplementations (Abazari-Bozhgani *et al*., 2025; Li *et al*., 2023; Lim *et al*., 2017; Liu *et al*., 2025b; Zhang *et al*., 2023a). Postbiotics, on the other hand, improved recognition index and learning as well as motor function but reduced anxiety and depression-like behaviour (Cheng *et al*., 2022; Lee *et al*., 2025; Wu *et al*., 2022; Yun *et al*., 2020).

Anti-/Pro-inflammatory biomarkers

Probiotics and postbiotics consistently modulated oxidative stress and inflammation across multiple animal models. In terms of the ageing and natural cognitive decline animal models, probiotic supplementations was generally associated with lower levels of pro-inflammatory markers (IL-1β, IL-6, TNF-α, NF-κB, ALPK1), oxidative stress and lipid peroxidation while boosting antioxidant markers (SOD and CAT) (Cheng *et al*., 2022; Nie *et al*., 2024; Shi *et al*., 2024; Wang *et al*., 2025; Wuttisa *et al*., 2025; Yang *et al*., 2023; Zeng *et al*., 2024; Zhang *et al*., 2025a). In terms of the stress- and pain-induced cognitive impairment models, probiotics reduced TNF-α, IL-1β, CRP, COX-2 and other inflammatory mediators in central and peripheral tissues (Abazari-Bozhgani *et al*., 2025; Dandekar *et al*., 2022; Eladawy *et al*., 2025). In terms of the pathogen- or toxin-induced memory deficit models, probiotics attenuated inflammatory signaling and immune cell activation, reflected by lower levels of IL-1β, IL-6, TNF-α, MPO, and NF-κB activity, and a lower percentage of active microglia (NF-κB$^+$/Iba1$^+$ and LPS$^+$/Iba1 (Lee *et al*., 2021b; Yun *et al*., 2020). In terms of the environmentally and dietary challenged animal models, probiotics decreased inflammatory mediators and oxidative stress markers but enhanced antioxidant systems, supporting systemic and neuronal resilience (Li *et al*., 2023; Shahin *et al*., 2025; Zhao *et al*., 2025). In terms of the autoimmune encephalomyelitis model, trauma-related neuroinflammation models and vaginitis and osteoporosis models, probiotics reduced TNF-α and IL-6 levels and suppressed NF-κB activation, alongside decreases in IL-18 and phosphorylated NF-κB (Li *et al*., 2025; Liu *et al*., 2025b; Shin *et al*., 2024). Postbiotics, on the other hand, elevated the expression of anti-inflammatory genes and antioxidant properties, decreased NF-κB signaling, MPO activity, IL-1β, IL-6, TNF-α expression, and NF-κB+CD11c+ cells within the immune cell population (Cheng *et al*., 2022; Wu *et al*., 2022; Yun *et al*., 2020).

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Gut health

Probiotics and postbiotics improved gut health across diverse animal models, primarily through modulation of microbial composition, enhancement of intestinal barrier integrity, and promotion of beneficial metabolites. Previous studies reported on the positive effects of probiotics on gut structure and barrier function, which were evidenced by the upregulated Occludin and ZO-1 proteins. Probiotics also increased beneficial gut microbes, such as SCFAs-producing bacteria and caecal butyrate, but decreased pathogens like *C. perfringens* and *E. coli*. These resulted in the normalisation of the microbiota balance in gut and vaginal dysbiosis (Eladawy *et al*., 2025; Li *et al*., 2025; Li *et al*., 2023; Li *et al*., 2022; Liu *et al*., 2025b; Nie *et al*., 2024; Shahin *et al*., 2025; Shin *et al*., 2024; Wang *et al*., 2025; Wuttisa *et al*., 2025; Yang *et al*., 2023; Yun *et al*., 2020; Zeng *et al*., 2024; Zhang *et al*., 2025a; Zhao *et al*., 2025). Postbiotic supplementation, on the other hand, reduced colon shortening (Yun *et al*., 2020).

Other effects

Interestingly, probiotics produced additional systemic and organ-specific benefits. These included extended lifespan in ageing models (Shi *et al*., 2024), lowered brain cholesterol pathway activity (Lim *et al*., 2017), and improved hepatic structure but reduced fibrosis, leukocyte infiltration, and better glycogen distribution (Wuttisa *et al*., 2025). Probiotics also modulated metabolic outcomes, which included improved energy balance, normalisation of lipid profiles, and mitigation of energy deficits (Shahin *et al*., 2025). The probiotic-induced immunomodulatory effects were observed through reduced Th17 responses with a stable Treg population (Li *et al*., 2025) accompanied by modulation of neuroendocrine mediators such as cholecystokinin (Eladawy *et al*., 2025). Beyond that, probiotics also reduced vaginitis- and osteoporosis-associated symptoms (Shin *et al*., 2024).

EFFECTS OF PROBIOTICS AND POSTBIOTICS AGAINST PHYSICAL FRAILTY *IN VIVO*

With regard to physical frailty, probiotics and postbiotics have also been increasingly implied of their potential in mitigating the frailty syndrome. Table 2 summarises the effects of probiotics and postbiotics against physical frailty *in vivo*. Probiotics and postbiotics yielded their beneficial effects in a strain-dependent manner, be it multi-strain or single-strain. Except for *B. adolescentis*-derived nicotinic acid which was administered at 150 mg/kg, the doses at which the probiotics and postbiotics were administered ranged between 1×10^8 - 2×10^{10}. The experimental duration varied between studies, ranging from 5 weeks up to 12 weeks. The effects of probiotics and postbiotics against physical frailty were demonstrated in induced or naturally occurring physical frailty models. These beneficial effects are mediated through maintenance of muscle/bone function and homeostasis, modulation of anti-/ pro-inflammatory biomarkers and improved gut health, amongst others.

Anti-/Pro-inflammatory biomarkers

Probiotics exerted anti-inflammatory effects and reduced oxidative stress in preclinical models of muscle ageing and atrophy. In terms of the dexamethasone-induced muscle atrophy models, probiotic supplementations increased anti-inflammatory cytokines but reduced pro-inflammatory mediators (Lee *et al*., 2023). In terms of the SAMP8 transgenic ageing mice, probiotics lowered levels of IL-1β, TNF-α, IL-6, and MCP-1, and reduced overall inflammation and reactive oxygen species (Chen *et al*., 2022; Park *et al*., 2025). In terms of the female frailty model and sarcopenic faecal microbiota transplant model, probiotics increased irisin levels but decreased inflammatory markers including IL-6, PGE2, CRP and TNF-α, supporting both anti-inflammatory and muscle-protective outcomes (Dong *et al*., 2024; Liu *et al*., 2025a). In contrast to other animal models, probiotics increased anti-inflammatory metabolites in the natural ageing model (Zhang *et al*., 2024).

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Gut health

Probiotic- and postbiotic-based interventions could reportedly improve gut health across multiple preclinical models. In terms of the natural ageing mice, probiotics increased tight junction protein expression and BSH activity, supporting barrier integrity (Ahmadi *et al*., 2020). On the other hand, the ovariectomised and HFD mice supplemented with multi-strain probiotics (*L. paracasei* and *L. plantarum*) elicited elevated caecal lactic acid levels (Ohlsson *et al*., 2025). Besides, the high-cholesterol diet models supplemented with probiotics also displayed enhanced beneficial bacterial population, improved intestinal epithelial integrity, increased microbiota diversity, elevated *Bacteroidota,* but decreased *Firmicutes/Bacteroidota* ratio (Karekezi *et al*., 2025; Kim *et al*., 2025). In terms of the dexamethasone-induced muscle atrophy models, probiotics promoted BCAAs production and improved gut microbial composition (Kang *et al*., 2024). In terms of the DSS-induced gut dysfunction and antibiotic-treated mice, probiotics increased *Bifidobacterium* abundance, increased colorectal length, enhanced tight junction protein expression (ZO-1, Occludin, Claudin-1), but reduced intestinal permeability as well as decreased colonic TNF-α, IL-6, and IL-1β gene expression (Chen *et al*., 2025). In terms of the SAMP8 transgenic mice, probiotics increased Shannon and Chao indices, raised ZO-1 and Occludin levels, but reduced colon TNF-α, COX-2, and Claudin-1 (Park *et al*., 2025). In terms of the sarcopenic FMT models, probiotics improved epithelial markers (E-cadherin, Occludin), reduced CD8+ IFNγ+ T cells, and decreased colonic TNF-α and IL-1β (Liu *et al*., 2025a). Interestingly, postbiotic supplementation increased SCFAs production in natural ageing mice (Kim *et al*., 2024).

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Table 1. Effects of probiotics and postbiotics against cognitive impairment *in vivo*.

Probiotics	Dose	Duration	Animal Models	Neuroprotection	Memory and Behavioural Change	Anti-/ Pro-inflammatory Biomarkers	Gut Health	Other Effects	Reference
Multi-strain									
L. paracasei MSMC39-1 *Bifidobacterium animalis* MSMC83.	1×10^9 CFU/mL	24 - 40 weeks depending on groups	Natural ageing model	↑ Brain neurogenesis ↓ mRNA expression of app and tau	↑ Escape latency	↑ SOD ↓ IL-1β, TNF-α, MDA	↑ Colonic structure, Occludin, ZO-1	↑ HDL ↓ LDL, Liver fibrosis, triglycerides	(Wuttis*a et al*., 2025)
L. kefiranofaciens HL1 *L. lactis* subsp *cremoris* APL015	1×10^9 CFU/mL	8 weeks	D-galactose induced ageing model		Cognitive behaviou (Y-maze, MWM)	↑ SOD ↓ MDA ↓ IL-1β, TNF-α	↑ SCFAs producers ↑ Cecal butyrate *Clostridium perfringen*		(Wang *et al*., 2025)
L. acidophilus (LA-5) *L. paracasei* (*L. casei* 431) *B. lactis* (BB12)	1×10^9 CFU/mL	12 weeks	Pain induced cognitive impairments model	↑ BDNF, NPY, Trk-B	↑ Learning and memory ↓ Nociceptive behaviour	↓ IL-1β, TNF-α, COX-2			(Abazari-Bozhgan*i et al*., 2025)
L. delbrukii *L. fermentum* Or *Bacillus clausii*	1×10^{10} CFU/mL Or 1×10^9 CFU/mL	3 weeks	Chronically stressed rat model	↑ BDNF ↓ Aβ		↓ Systemic inflammation ↓ Colonic inflammation (via NLRP3 inflammasome inhibition	Gut microbiota balanc Gut membrane integrit	↑ CCK levels	(Eladaw*y et al*., 2025)
L. plantarum 20174 And/ Or *Asparagus officinalis*	1×10^9 CFU/mL	12weeks	High cholesterol diet model	↑ BDNF ↓Aβ, p-tau, α-synuclein,		↓ Oxidative stress ↓ Inflammation	lodulated gut microbiot	↑ Energy metabolism ↑ Lipid profile	(Shahi*n et al*., 2025)
L. lactis P32 (PL) *B. bifidum* P45 (PB)	5×10^8 CFU/mL	2 weeks	Gv- vaginitis and Ov-osteoporosis model	↑ Serotonin, BDNF	↓ Depression-	↓ TNF-α, IL-6, NF-κB activation	↓ Vaginal and gut dysbiosis, *Proteobacteria*	↑ Osteoprotegerin ↓ Vaginitis, RANK, RANKL	(Shi*n et al*., 2024)
L. acidophilus *L.* casei *B. bifidum* *B. lactis*	2×10^9 CFU/mL	12 weeks	SAMP8: transgenic mouse model of ageing	↓ Synaptic deficits and cerebral neuronal injuries, caspase-11, cleaved caspase-1,	↑ Memory performance	↓ IL-1β, ALPK1	↑ Expression of tight junction proteins		(Yang *et al*., 2023)
Bacillus coagulans Unique IS-2 *L. plantarum* UBLP-40 *L. rhamnosus* UBLR-58 *B. lactis* UBBLa-70 *B. breve* UBBr-01 *B. infantis* UBBI-01	1-2 × 10^9 CFU/mL	6 weeks	Chronic unpredictable mild stress model	↑ BDNF ↑ Serotonin ↑ Dopamine	Normalised anhedonia ↓ Passivity ↓ Anxiety-like behaviour	↓ CRP ↓ TNF-α			(Dandekar *et al*., 2022)

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Single-strain									
A. muciniphila	$5 \times 10^{6-8}$ CFU/mL	3 weeks	Autoimmune encephalomyelitis model	↓ Cleaved caspase-1, ASC	↑ Cognitive function	↓ IL-18, NF-κB, p-NF-κB (NLRP3-mediated neuroinflammation)	Modulated gut microbiota ↑ IEB function ↓ *Firmicute to /Bacteroidetes* ratio	Modulated Treg response ↓ Disease severity, Th17 responses	(Li *et al*., 2025)
A. muciniphila	2×10^{9} CFU/mL	3 weeks	Blunt-chest trauma induced model	↑ BDNF ↑ TrkB ↓ IBA1	↓ Anxiety-like behaviour	↓ Pro-inflammatory cytokines	↑ Beneficial gut microbiota		(Liu *et al*., 2025b)
L. johnsonii HL79	1×10^{9} CFU/mL	20 weeks	High-altitude exposure model		↑ Working memory	↑SOD, CAT ↓MDA	↑ Beneficial gut microbiota		(Zhao *et al*., 2025)
B. longum 300	6×10^{9} CFU/mL	12 weeks	D-galactose-induced ageing model	↓ AChE	↑ Nesting, Escape latency ↓ PAT error	↓TNF-α, IL-6	Modulated gut content		(Zhang *et al*., 2025a)
B. pseudocatenulatum NCU-08	1×10^{9} CFU/mL	10 weeks	D-galactose-induced ageing	↑ BBB integrity (via AMPK/Sirt1 pathway) ↓ Neuronal apoptosis (via PI3K/AKT pathway activation)	↑ Motor function ↓ Anxiety-like behaviour	↓ Neuronal oxidative stress ↑ Antioxidant enzyme activity	↑ Restored microbiota homeostasis		(Zeng *et al*., 2024)
L. plantarum LLY-60[6]	1×10^{9} CFU/mL	24 weeks	Natural ageing model	↑ Synaptic plasticity ↑ Eurotrophic factor levels	↑ Improve age-related cognitive impairment	↑ Antioxidant capacity ↓ Inflammatory cytokines		↑ Lifespan	(Shi *et al*., 2024)
L. plantarum MWFLp-182	1×10^{9} CFU/mL	8 weeks	Natural ageing model	↑ PSD-95, Nrf2, NGF, BDNF ↓ Bax	↑ Recognition memory ↑ Spatial learning and memory	↑ SOD ↓ MDA	↑ Tight junction protein expression ↑ Gut microbiota modulation ↑ SCFAs		(Nie *et al*., 2024)
L. paracasei PS23	1×10^{9} CFU/0.2 mL/day	9 weeks	Natural ageing model	↑ Neuroplasticity	↑ Motor function ↓ Memory deficits, anxiety-like behaviour	↑ Anti-inflammatory gene ↑ Antioxidant activity			(Cheng *et al*., 2022)
L. rhamnosus GG	1×10^{8} CFU/mL	8 weeks	Noise-induced memory deficits model		↑ Memory function	↓ Inflammatory cytokines	↑ Beneficial metabolites		(Li *et al*., 2023)

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Lacticaseibacillus rhamnosus GR-1	1×10^9 CFU/mL	Pregnancy: ~21 days Lactation ~21 days Post-Weaning ~35 days.	Lead-acetate induced neurobehavioural injury model		↑ Memory performance (MWM and Y-maze)		↓ *E. coli*		(Zhang *et al*., 2023a)
L. plantarum WSJ-06	1×10^9 CFU/mL	10 weeks	Lead-acetate induced neurobehavioural injury model		↑ Memory function	↓ Inflammatory cytokines	↑ Beneficial metabolites		(Li *et al*., 2022)
L. plantarum LAB12	1×10^9 CFU/mL	33 days	LPS-challenged rats' model	↑ Mitochondrial Complex III enzyme activity, 5HT, Ghrelin	↑ Escape latency (MWM)				(Muhammad *et al*., 2023)
L. plantarum NK151 *B. longum* NK173	1×10^9 CFU/mL	5 days	*E. coli* K1-induced CI model, LPS-induced CI model	↑ BDNF expression ↓ ApoE level		↓ IL-1β, IL-6, TNF-α, NF-κB+/Iba1+, and LPS+/Iba1+			(Lee *et al*., 2021b)
L. gasseri NK109	1×10^9 CFU/mL	5 days	*E. coli* K1-induced CI model		↓ Depressive behaviour	↓ NF-κB, MPO, IL-1β, IL-6, TNF-α, NF-κB+/CD11c+ (immune cell populations)	↓ Colitis & gut dysbiosis		(Yun *et al*., 2020)
L. plantarum LAB12	1×10^9 CFU/mL	7 weeks	High cholesterol diet model		↑ Spatial learning & memory			↓ appa (brain cholesterol pathway)	(Lim *et al*., 2017)
Postbiotics									
Heat-killed *L. lactis* KC24	1-2 × 10^9 CFU/mL equivalent	2 weeks	Scopolamine-induced memory impairment model	↑ ACh, ChAT, BDNF, CREB, p-CREB, β-Secretase ↓ Amyloid β, AChE	↑ Recognition index and learning (NOR, Y-maze)				(Lee *et al*., 2025)
Heat killed *L. paracasei* PS23	1×10^9 CFU/mL equivalent	9 weeks	Natural ageing model	↑ Neuroplasticity	↑ Memory function motor function ↓ Memory deficits, anxiety-like behaviour	Anti-inflammatory gene ↑ Antioxidant activity			(Cheng *et al*., 2022)
L. plantarum HJZW0 postbiotics	1×10^9 CFU/mL	2 weeks	*Salmonella*-induced neurological dysfunction model	↑ Neuroactive molecules ↓ Suppressed brain injuries	↑ Memory function ↓ Anxiety, depression	↓ Neuroinflammation			(Wu *et al*., 2022)
Heat killed *L. gasseri* NK109 and lysates (NC & NM)	1×10^9 CFU/mL equivalent	5 days	*E. coli* K1-induced CI model		↓ Depressive behaviour	↓ NF-κB activation ↓MPO activity ↓ IL-1β, IL-6, TNF-α ↓ NF-κB+/CD11c+ immune cell population	↓ Colon shortening		(Yun *et al*., 2020)

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Muscle/Bone function and homeostasis

Probiotic and postbiotic supplementations could reportedly improve muscle function across diverse preclinical models. In terms of natural ageing animal models, probiotics increased grip strength and maximum running distance (Ahmadi *et al*., 2020; Zhang *et al*., 2024). In terms of the dexamethasone-induced muscle atrophy models, probiotics enhanced lean muscle mass and muscle strength (Kang *et al*., 2024). In terms of the high-cholesterol diet (HCD) models, probiotics increased muscle and grip strength (Karekezi *et al*., 2025; Kim *et al*., 2025). In terms of the SAMP8 ageing mice, probiotics enhanced grip strength, ATP content, mitochondrial DNA, Pgc1α and mitochondrial dynamics markers (Mfn2, Drp1, Fis1), leading to improved strength and mitochondrial function (Chen *et al*., 2022; Park *et al*., 2025). In terms of the female frailty and sarcopenic FMT models, probiotics enhanced mitochondrial function (Dong *et al*., 2024; Liu *et al*., 2025a). Postbiotics, on the other hand, increased muscle mass and improved grip strength in the hindlimb-immobilised mouse model (Han *et al*., 2023). Postbiotics also improved physical function, as indicated by longer maximum running distance, increased muscle mass, and enhanced exercise capacity (Jeong *et al*., 2024; Kim *et al*., 2024; Zhang *et al*., 2025b).

Additionally, probiotic and postbiotic supplementations also supported muscle and bone homeostasis. In terms of the ovariectomised mice fed with a high-fat diet, probiotics increased the total body BMD and Runx2 expression (Ohlsson *et al*., 2025). In terms of the dexamethasone-induced muscle atrophy models, probiotics enhanced myofibril size, elevated expression of myosin heavy chain genes, and increased muscle mass, but reduced atrophy and degradation markers (Atrogin-1, MuRF-1) (Kang *et al*., 2024; Lee *et al*., 2023). In the gut-compromised and antibiotic-treated mice, probiotics increased muscle mass, type IIB fibers, BMD, trabecular microarchitecture (BV/TV, Tb.Th, Tb.N) and anabolic markers (P1NP) but reduced CTX and atrophic markers (Chen *et al*., 2025). In terms of the HCD animal models, probiotics increased myofibril size, myogenic protein expression, muscle mass, fiber size and hind leg thickness, but reduced atrophy markers (Karekezi *et al*., 2025; Kim *et al*., 2025). In terms of the SAMP8 transgenic mice, probiotics improved muscle mass, enhanced Myh2 and MyoD expression, activated mTORC1 signalling, but decreased Myh7 and muscle loss (Chen *et al*., 2022; Park *et al*., 2025). In terms of the natural ageing and sarcopenic models, probiotics and postbiotics increased muscle mass, PAX7, dystrophin, but reduced in FoXO3, Atrogin-1, and MuRF-1 (Liu *et al*., 2025a; Zhang *et al*., 2025b). In terms of the female frailty and other natural ageing models, probiotics and postbiotics demonstrated similar trends, suggesting their broad benefits for muscle maintenance (Dong *et al*., 2024). In terms of the hindlimb-immobilised mice and dexamethasone-induced muscle atrophy models, postbiotics also increased muscle mass, upregulated MyoD expression, and activated anabolic signalling pathways (FoxO3a, Akt, mTOR) (Han *et al*., 2023; Jeong *et al*., 2024).

Other effects

Probiotics could reportedly modulate lipid metabolism by increasing lipid excretion in faeces, suppressing fat-absorption genes, decreasing plasma lipid levels, and limiting lipid accumulation in white adipose tissue and ectopic sites in the SAMP8: transgenic mouse model (Kim *et al*., 2025). There was also evidence that indicated a reduction in eWAT in probiotic- and postbiotic-supplemented aged mice (Zhang *et al*., 2025b). On another note, probiotics intervention was associated with increased lifespan in the naturally ageing mice model (Ahmadi *et al*., 2020). Elsewhere, probiotics have also been shown to reduce cellular senescence markers such as SA-β-gal, p16, and p21, along with lowering SASP-related genes including Mcp1, TNF-α, and Il1b in aged and SAMP8 transgenic mice, respectively (Park *et al*., 2025; Zhang *et al*., 2024). Moreover, probiotics reduced spleen swelling and disease activity index in the DSS-induced gut dysfunction model (Chen *et al*., 2025). Furthermore, postbiotics resulted in higher serum lactate dehydrogenase levels in the dexamethasone-induced muscle atrophy model (Jeong *et al*., 2024). On the other hand, another previous study that utilised postbiotics reported an increase of serum NA levels and fasting glucose levels in aged mice (Kim *et al*., 2024; Zhang *et al*., 2025b).

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Table 2. Effects of probiotics and postbiotics on frailty syndrome *in vivo*.

Probiotics	Dose	Duration	Animal Models	Muscle/ Bone Function and Homeostasis	Anti-/ Pro-inflammatory Biomarkers	Gut Health	Other Effects	References
Multi-strain								
L. paracasei 8700:2® *L. plantarum* DSM 15312 (HEAL9®) *L. plantarum* DSM 15313 (HEAL19)	1×10^9 CFU/mL	12 weeks	Ovariectomy and HFD model	↑ Total body BMD ↑ Runx2		↑ *L.* paracasei and *L.* plantarum. ↑ Ceacal lactic acid		(Ohlsson *et al*., 2025)
L. paracasei D3-5 *L. rhamnosus* D4-4 *L. plantarum* D6-2 *L. rhamnosus* D7-5 *L. plantarum* D13-4 *E. raffinosus* D24-1 *E.* INBio D24-2 *E. avium* D25-1 *E. avium* D25-2 *E. avium* D26-1	1×10^9 CFU/mL	10 weeks	Natural ageing model	↑ Physical function ↓ Adiposity		↑ Tight junction protein ↑ BSH activity	↑ Lifespan	(Ahmad*i et al*., 2020)
Single-strain								
B. animalis subsp. *lactis* A6	2×10^{10} CFU/mL	10 weeks	DSS-induced gut dysfunction and ABX-treated model	↑ Type IIB fibers, BMD, BV/TV, T*B.* Th, T*B.* N, P1NP ↓ Type I fibers, Atrogin-1 & Murf-1, CTX	↓ TNF-α, IL-6, IL-1β	↑ *B. animalis* & *Bifidobacterium*, Colorectum length, ZO-1, Occludin, Claudin-1 ↓ FITC-dextran permeability	↓ Spleen swelling ↓ Disease activity index.	(Chen *et al*., 2025)
L. plantarum LM1001	5×10^9 CFU/mL	20 weeks	High cholesterol diet model	↑ Myofibril size, Myogenic protein expression, Muscle strength ↓ Muscle atrophy markers		↑ Beneficial gut bacteria ↑ Integrity of large intestine epithelium		(Karekezi *et al*., 2025)
L. paragasseri SBT2055	1×10^8 CFU/mL 1×10^{10} CFU/mL	12 weeks	High cholesterol diet model	↑ Muscle mass ↑ Hind leg thickness ↑ Muscle protein levels ↑ Muscle fiber size ↑ Grip strength		↑ Gut microbiota diversity ↑ *Bacteroidota* ↓ *Firmicutes to Bacteroidota* ratio	↑ Lipid excretion ↓ Fat absorption genes, Plasma lipid, WAT and ectopic lipid	(Kim *et al*., 2025)
L. rhamnosus *F. prausnitzii*	1×10^9 CFU/mL	12 weeks	Sarcopenic FMT model	↑ Muscle mass, mitochondrial function ↓ Atrophic markers	↓ TNF-α and IL-1β	↑ E-cadherin and Occludin ↓ CD8+ IFNγ+ T cells		(Liu *et al*., 2025a)
A. muciniphila	1.8×10^8 CFU/mL	12 weeks	SAMP8: transgenic mouse model	↑ Muscle mass, Myh2, mTORC1 signalling, MyoD, Grip strength, ATP content, mtDNA and Pgc1α, Mfn2, Drp1, Fis1 ↓ Myh7	↓ IL-1β ↓ MCP-1 ↓ TNF-α ↓ IL-6	↑ Shannon & Chao indices ZO-1 and Occludin ↓ colon.TNF-α & COX-2, Claudin-1	↓ SA-β-gal, p16, p21	(Park *et al*., 2025)

Table continued overleaf

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L. casei Shirota	$1 \times 10^{8-9}$ CFU/mL	12 weeks	SAMP8: transgenic mouse model	↑ Grip strength ↑ Mitochondrial function ↓ Muscle loss	↓ ROS			(Chen *et al*., 2022)
B. adolescentis	5×10^{8} CFU/mL	5 weeks	Natural ageing model	↑ Muscle mass, PAX7, Dystrophin, Grip strength, Maximum running distance ↓ FoXO3, Atrogin-1 & Murf-1			↓ eWAT	(Zhang *et al*., 2025b)
B. animalis Probio-M8	1.8×10^{8} CFU/mL	4 weeks	Natural ageing model	↑ Muscle function	↑ Antioxidant metabolites		↓ Senescence score	(Zhang *et al*., 2024)
L. plantarum BFS1243	1×10^{9} CFU/mL	9 weeks	Female frailty model	↑ Muscle endurance	↑ Irisin ↓ PGE2, CRP and TNF-α			(Dong *et al*., 2024)
L. rhamnosus IDCC3201	1×10^{8} CFU/mL	5 weeks	Dexamethasone-induced muscle atrophy model	↑ Expression of MHC1, MHC1b, MHC2A, 2bB, Lean muscle mass, Muscle strength, Myofibril size ↓ Atrogin-1, MuRF-1		↑ BCAAs ↑ gut microbiota composition		(Kang *et al*., 2024)
L. rhamnosus JY02	1×10^{8} CFU/mL	5 weeks	Dexamethasone-induced muscle atrophy model	↑ MHC Iβ, MHC IIα, and Myo-D ↓ Muscle degradation marker	Modulate inflammatory cytokines			(Lee *et al*., 2023)
Postbiotics								
B. adolescentis-derived nicotinic acid	150 mg/kg	5 weeks	Natural ageing model	↑ Muscle mass, PAX7, Dystrophin, maximum running distance, grip strength ↓ FoXO3, Atrogin-1 & Murf-1			↑ Serum NA levels ↓ eWAT	(Zhang *et al*., 2025b)
KL-Biome (CSF and HK *L. plantarum)*	900 mg/kg	8 weeks	Dexamethasone-induced muscle atrophy model	↑ Muscle mass ↑ Anabolic phosphorylation FoxO3a, Akt, Mtor			↑ LDH levels	(Jeong *et al*., 2024)
DL-3-Phenyllactic acid (PLA)	-	4 weeks	Natural ageing model	↑ Exercise capacity ↑ Physical function		↑ SCFAs	↑ Fasting glucose levels	(Kim *et al*., 2024)
WDK postbiotics	1×10^{8} CFU/mL	3 weeks	Hindlimb-immobilised mouse model	↑ Muscle mass ↑ Myod gene expression ↑ Grip strength				(Han *et al*., 2023)

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EFFECTS OF PROBIOTICS AGAINST CF *IN VIVO*

Recent evidence has started to uncover the potential of probiotics in addressing both cognitive and physical aspects of CF in tandem. Table 3 summarises the effects of probiotics against CF *in vivo*. Probiotics yielded their beneficial effects in a strain-dependent manner, be it multi-strain or single-strain. The dose at which the probiotics were administered was 1 x 10^9 CFU/mL, with the experimental period ranging between 8 weeks and 12 weeks. The previous studies mainly adopted the naturally ageing models given ageing is associated with cognitive and physical deficits. The beneficial effects of probiotics seemed to be mediated through neuroprotective effects, behavioural changes, modulation of inflammatory response, regulation of muscle and bone health as well as lipid metabolism.

Neuroprotection

Probiotics mitigated brain degeneration in the naturally ageing model by reducing the activation of FOXO3a and NF-κB-positive cell population, both of which are linked to neuroinflammation and neuronal damage. Additionally, probiotics also resulted in higher levels of BDNF, suggesting enhanced neuroplasticity, which is essential for maintaining cognitive function and neuronal survival (Baek *et al*., 2023). Similarly, probiotics also elevated neurotrophic factors such as glial cell line-derived neurotrophic factor (GDNF) and NGF, indicating improved neuronal support and protection. The probiotic-induced neuroprotection was further complemented by the expression of regulatory proteins, including Sirt1, FoxO1, and Wisp1 (Ni *et al*., 2019).

Memory and behavioural changes

The cognitive and neurological benefits of probiotics against CF were further supported by evidence of memory and behavioural improvement. Probiotics reduced escape latency of the naturally ageing model in the Morris Water Maze (MWM) Test, suggesting enhanced spatial memory and learning ability (Ni *et al*., 2019). Similarly, probiotics improved recognition memory in the naturally ageing model, which was evidenced by the increased performance in the Novel Object Recognition (NOR) Test (Ni *et al*., 2019). There were also other studies that reported an improvement in cognitive function and learning behaviour in the naturally ageing model supplemented with probiotics (Baek *et al*., 2023; Lee *et al*., 2021a).

Anti-/Pro-inflammatory biomarkers

Probiotics were found to be effective against inflammation and oxidative stress in CF, both of which are contributors to cognitive and physical decline. Probiotic-based intervention effectively suppressed pro-inflammatory cytokines but enhanced oxidative stress resistance through the upregulation of antioxidant enzymes (SOD1, Gpx, Gsr) (Ni *et al*., 2019). Additionally, probiotics also reduced IL-6 expression in the naturally ageing model, further supporting their anti-inflammatory potential (Baek *et al*., 2023; Lee *et al*., 2021a).

Muscle/Bone function and homeostasis

Probiotics could reportedly improve muscle performance of the naturally ageing model, which was evidenced by the increased grip strength and enhanced treadmill running time and distance (Baek *et al*., 2023). Additionally, probiotics also increased muscle weight and elevated levels of muscle growth markers such as AKT, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), silent mating-type information regulation 2 homolog 1 (SIRT1), and myosin heavy chain (MyH) in the naturally ageing model, suggesting that probiotics could promote muscle growth and repair (Baek *et al*., 2023). Furthermore, evidence from the animal studies indicated that probiotics could prevent age-related muscle deterioration. Probiotics were associated with increased muscle strength in the young mice but prevented ageing-related muscle loss and decline in bone mass in aged mice (Lee *et al*., 2021a). At the molecular level, probiotics reduced muscle atrophy markers, including FOXO3a, NF-κB, muscle RING-finger protein-1 (MuRF1), and p16, further reinforcing their protective effects against muscle degradation (Ni *et al*., 2019).

Lipid metabolism

Dysregulated lipid metabolism is a common feature of ageing and metabolic disorders. Probiotics could reduce lipid accumulation, triglyceride (TG) and total cholesterol (TC) levels, thereby promoting cardiovascular and metabolic health (Ni *et al*., 2019). Additionally, it was reported that both aged and young mice exhibited increased muscle glycogen levels, suggesting improved energy storage and endurance (Lee *et al*., 2021a).

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Table 3. Effects of probiotics against CF *in vivo*.

Probiotics/Postbiotics	Dose	Duration	Animal model	Cognitive Domain			Physical Domain		References
				Neuroprotective effect	Behavioural assessment	Anti/proinflammatory Biomarker	Muscle/Bone Health	Lipid metabolism	
Multi-strain									
B. bifidum P61 *L. paracasei* P62	1×10^9 CFU/mL	8 weeks	Natural ageing model	↑ BDNF ↓ Brain degeneration (FOXO3a activation, NF-κB+ cell populations)	↓ Cognitive impairments-like behaviours	↓ IL-6 expression	↑ Muscle weight ↑ AKT, PGC1α, SIRT1, MyH, cell size ↑ Grip strength ↑ Treadmill running time and distance ↓FOXO3a, NF-κB, MuRF1, p16, NF-κB+CD11c+		(Baek *et al*., 2023)
Single strain									
L. plantarum TWK10	1×10^9 CFU/mL	8 weeks	Natural ageing model		Aged mice: ↑ Improve age learning and memory abilities.		Aged mice: ↑ Preserve muscle strength. ↑ Preserve bone mass Young mice: ↑ Muscle strength	Aged and young mice: ↑ Muscle glycogen levels.	(Lee *et al*., 2021a)
L. casei LC122 & *B. longum* BL986,	1×10^9 CFU/mL	12 weeks	Natural ageing model	↑ Neurotrophic Factors (BDNF, GDNF, NGF) ↑ Neuroprotection (Sirt1, FoxO1, Wisp1)	↑ Escape latency ↑Recognition index	↑ Oxidative Stress Resistance (SOD1, Gpx, Gsr) ↓ Proinflammatory cytokines	↑ Sik1, Pgc1a4 ↑ GM & TM weight ↑ Grip strength, Endurance ↓ FOXO3a, NF-κB, MuRF1, p16	↓ Lipid accumulation ↓ TG & TC levels	(Ni *et al*., 2019)

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EFFECTS OF PROBIOTICS AND POSTBIOTICS ON GUT MICROBIOTA COMPOSITION

Recent evidence indicated that probiotics and postbiotics significantly influenced the gut microbiota composition in both cognitive impairment- and physical frailty-related models. Table 4 summarises the effects of probiotics and postbiotics on gut microbiota composition *in vivo*. The effects of probiotics and postbiotics were dependent upon the specific strain used, regardless of single- or multi-strain. The probiotic- and postbiotic-based interventions varied between studies, with the shortest duration being 2 weeks while the longest duration being 12 weeks. The doses at which probiotics and postbiotics were administered ranged between 1×10^8 - 1×10^9 CFU/mL. Probiotics and postbiotics primarily affect the gut by shifting the gut microbiota composition in favour of the growth of commensal bacteria.

Gut microbiota composition

Probiotic and postbiotic interventions appear to influence the gut microbiota composition in a heterogeneous manner. This is tied to the complex structure revolving around the gut and its environmental factors (Mille*r et al*., 2021). However, the general pattern surrounding the specific context of each study can still be observed whereby probiotic and postbiotic supplementations seemed to be able to shift the gut microbiota in favour of good health. In the ageing-related models, namely the SAMP-8 transgenic model, D-galactose-induced ageing model and naturally aged model, the most common taxa influenced by probiotics belong to the *Bacillota* (formerly known as *Firmicutes*) phylum, which could be one of the factors that mediated the beneficial effects in the ageing-related context (Ahmadi *et al*., 2020; Chen *et al*., 2022; Cheng *et al*., 2022; Park *et al*., 2025; Zeng *et al*., 2024; Zhang *et al*., 2023a). *Bacillota* is often associated with gut health, as the *Bacillota-to-Bacteroidota* ratio could potentially be an indicator of gut microbiota balance (Tsa*i et al*., 2025). Bacteria from *Bacillota* often possess numerous genes that are associated with fermentation of dietary fibres, which could confer health benefits and contribute towards gut homeostasis (Sun *et al*., 2023). In contrast, the most commonly reduced taxa belong to the *Bacteroidota* (formerly *Bacteroidetes*) phylum. Likewise, postbiotics also enriched *Firmicutes* in the naturally ageing model (Cheng *et al*., 2022). In terms of cognitive-deficit-related models such as the lead-acetate- and noise-induced and memory deficits model, the *Bacillota* phylum was enriched in parallel to probiotic supplementations whereas taxa under both the *Bacteroidota* and *Gammaproteobacteria* phyla were reduced (Li *et al*., 2023; Li *et al*., 2022). Interestingly, in terms of the female frailty model, the *Verrucomicrobia* phylum was enriched (Dong *et al*., 2024). On the other hand, postbiotics enriched the *Bacillota* phylum in the dexamethasone-induced muscle atrophy model and *Salmonella*-induced neurological dysfunction model (Jeong *et al*., 2024; Wu *et al*., 2022).

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Table 4. Effects of probiotics and postbiotics on gut microbiota composition *in vivo*.

Probiotic/Postbiotic	Dose	Duration	Sequencing Platform	Animal Model	Increased	Decreased	References
Multi-strain							
L. plantarum WSJ-06 *L. reuteri* YLR-01 *E. hirae* YEH04 *E. faecalis* YEF-02	1×10^9 CFU/mL	10 weeks	16S rRNA	Lead-acetate induced neurobehavioural injury model	Phylum: ↑ *Bacillota* (formerly *Firmicutes*) Genus: ↑ *Lactobacillus, Roseburia, Lachnospiraceae*_NK4A136_group, *[Eubacterium]_siraeum*_group	Genus: ↓ *Parabacteroides, Alloprevotella, Rikenellaceae_RC9_gut*_group	(Li *et al*., 2022)
L. paracasei D3-5 *L. rhamnosus* D4-4 *L. plantarum* D6-2 *L. rhamnosus* D7-5 *L. plantarum* D13-4 *E. raffinosus* D24-1 *E.* INBio D24-2 *E. avium* D25-1 *E. avium* D25-2 *E. avium* D26-1	1×10^9 CFU/mL	10 weeks	16S rRNA	Natural ageing model with HFD	Phylum: ↑ *Bacillota* (formerly *Firmicutes*) Genus: ↑ *Clostridiales* (unclassified*), Oscillospira, Allobaculum, Roseburia, Desulfovibrio, Dorea*	Phylum: ↓ *Verrucomicrobia* Genus: ↓ *Lactococcus, Ruminococcus, Coprobacillus, Lactobacillus, Akkermansia, S24-7, SMB53*	(Ahmadi *et al*., 2020)
Single strain							
A. muciniphila	1.8×10^8 CFU/mL	12 weeks	16S rRNA	SAMP8: transgenic mouse model of ageing	Phylum: ↑ *Bacillota* (formerly *Firmicutes*) Genus: ↑ *Coprococcus, Jutongia, Sporofaciens, Berryella, Inhubacter, Zhenpiania*	Phylum: ↓ *Bacteroidota* (formerly *Bacteroidetes*)	(Park *et al*., 2025)
L. casei Shirota	1×10^9 CFU/mL	12 weeks	16S rRNA	SAMP8: transgenic mouse model of ageing	Genus: ↑ *Lachnospiraceae* UCG_006, *Erysipelatoclostridium*		(Chen *et al*., 2022)
B. pseudocatenulatum NCU-08	1×10^9 CFU/mL	10 weeks	16S rRNA	D-galactose-induced ageing	Phylum: ↑ *Bacillota,Actinobacteria* Family: ↑ *Lachnospiraceae* Genus: ↑ *Bifidobacterium, Coprococcus*	Phylum: ↓ *Bacteroidota* Family: ↓ *Paraprevotellaceae, Clostridiaceae* Genus: ↓ *Helicobacter*	(Zeng *et al*., 2024)
L. plantarum BFS1243	1×10^9 CFU/mL	9 weeks	16S rRNA	Female frailty model	Phylum: ↑ *Verrucomicrobia* Species: ↑ *A. muciniphila, Fournierella massiliensis, Faecalimonas phoceensis, F. umbilicata*	Species: ↓ *Eisenbergiella massiliensis, E. tayi, Blautia coccoides, Flavonifractor plautii*	(Dong *et al*., 2024);

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L. rhamnosus GG	1×10^8 CFU/mL	8 weeks	16S rRNA	Noise-induced memory deficits model	Phylum: ↑ *Bacillota* Genus: ↑ *Alloprevotella, Lachnoclostridium, Peptococcus,* Species: *Clostridiales_bacterium*_42_27, *Oscillibacter*_sp_1-3, *L. gasseri,*	Phylum: ↓ *Gammaproteobacteria, Bacteroidota* Genus: ↓ *Dubosiella* Species: ↓ *Bacteroides sartorii*	(Li *et al*., 2023)
B. animalis Probio-M8	1.8×10^8 CFU/mL	4 weeks	16S rRNA	Natural ageing model	Family: ↑ *Erysipelotrichaceae* *Erysipelotrichales* *Clostridia* *Succinivibrionaceae*	-	(Zhang *et al*., 2023a)
L. paracasei PS23	1×10^9 CFU/mL	9 weeks	16S rRNA	Natural ageing model	Phylum: ↑ *Bacillota* *Mycoplasmatota* *Bacteroidota* Family: ↑ *Erysipelotrichaceae* Genus: ↑ *Dubosiella*	Family: ↓ *Coriobacteriaceae*_UCG_002 Genus: ↓ *Oscillibacter, Ruminiclostridium_9*	(Cheng *et al*., 2022)
Postbiotics							
KL-Biome (CSF and HK *L. plantarum)*	900 mg/kg	8 weeks	Shotgun	Dexamethasone-induced muscle atrophy model	Phylum: ↑ *Bacillota* (formerly *Firmicutes*) Genus: ↑ *Subdologranulum, Alistipes* Species: ↑ *F. prausnitzii*		(Jeong *et al*., 2024)
L. plantarum HJZW08 derived postbiotic	1×10^9 CFU/mL	2 weeks	16S rRNA	C57BL/6: *Salmonella*-induced neurological dysfunction model	Genus: ↑ *Helicobacter, Lactobacillus, Dubosiella*	Family: ↓ *norank_f_Oscillospiraceae* Genus: ↓ *Mucispirillum, Eubacterium_siraeum*_group	(Wu *et al*., 2022)
Heat killed *L. paracasei* PS23	1×10^9 CFU/mL	9 weeks	16S rRNA	Natural ageing model	Phylum: ↑ *Bacillota* (formerly *Firmicutes*) *Mycoplasmatota* (formerly *Tenerictes*), *Bacteroidota* (formerly *Bacteroidetes*) Family: ↑ *Muribaculaceae*	Genus: ↓ *Dubosiella,*	(Cheng *et al*., 2022)

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CONCLUSION

The current evidence supports the potential of probiotics and postbiotics in conferring beneficial effects on both the cognitive and physical domains of CF. These effects are mainly mediated through broad neuroprotective effects, regulation of memory and behaviour changes, improvement of muscle and bone function and homeostasis, suppression of local and systemic inflammation, and maintenance or restoration of a functional gut microbiota (Fig. 1). The gut emerges as the central organ through which the beneficial effects of probiotics and postbiotics improve cognitive and motor functions via the gut-brain and the gut-muscle/ bone axes. As such, probiotics and postbiotics should be considered as useful non-pharmacological approaches in CF management.

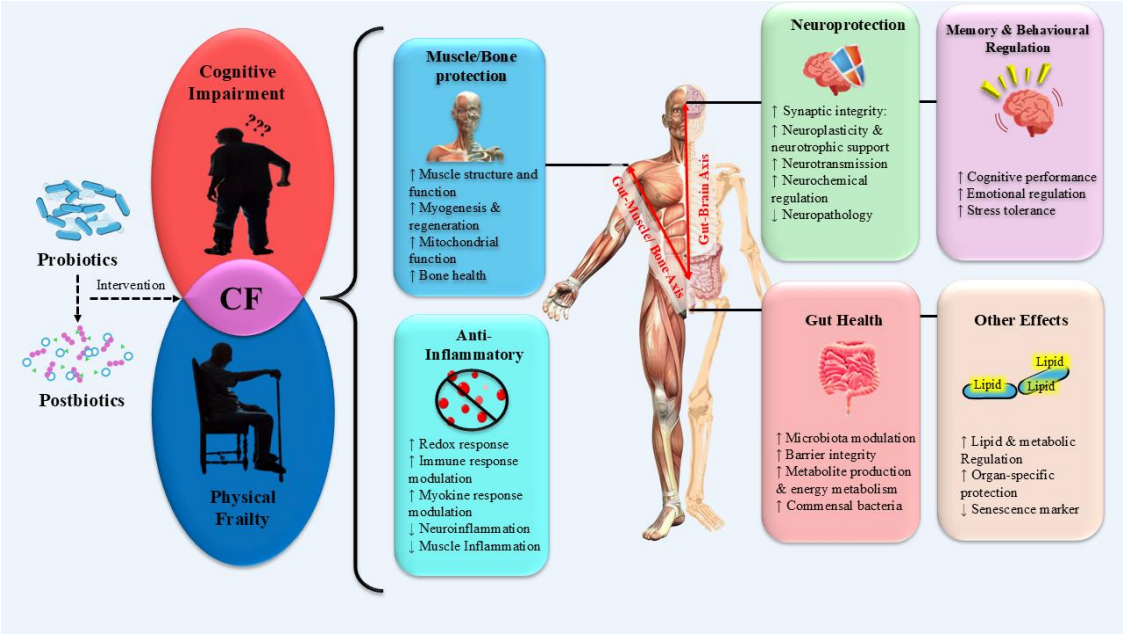

Fig 1. Overview of probiotic- and postbiotic-induced beneficial effects in relation to CF and its related cognitive and physical domains. Part of this diagram were designed using Freepik.

LIMITATIONS AND FUTURE PERSPECTIVES

It is important to acknowledge the limitations of these potential probiotics- and postbiotics-based interventions. Firstly, the beneficial effects of probiotics and postbiotics are highly strain-dependent. Different probiotic strains, be it multi-strain or single-strain, produce varying postbiotic composition and exhibit distinct mechanisms of action (Khalsom *et al*., 2025). Therefore, strain-level evaluation is a necessary prerequisite for future developments of probiotics and postbiotics as non-pharmacological interventions against CF. Furthermore, manufacturing regulations for probiotics could be formed to standardise probiotics variability and facilitate a smooth transition from research findings to clinical and commercial applications (Churin et al., 2026). Secondly, the efficacy of probiotics is inherently constrained by their viability. In fact, the maintenance of the viability of probiotics at the industrial level has been proven to be a significant challenge (Khalsom *et al*., 2025). Amongst the strategies that can be implemented to address this issue is improving the probiotics formulation. Encapsulation methods that involve various matrices (e.g., alginate, starch, chitosan), for instance, could maintain the efficacy of probiotics and improve their delivery (Ramírez *et al*., 2025). In contrast, postbiotics, which are composed of inanimate microbial components, are highly stable and do not require strict storage conditions. They are also presented with improved reproducibility across studies and have greater suitability for vulnerable populations (Calvanese *et al*., 2025). Thirdly, probiotics are primarily classified as dietary supplements rather than therapeutic agents in the market. This classification limits their integration into standard medical treatments and results in differing regulatory requirements across regions, creating inconsistencies in approval processes (Gottlieb, 2020). Future studies on probiotics and postbiotics should essentially elucidate their mechanisms holistically to enable a rational translation into therapeutic strategies against CF and ageing-related domains. Fourthly, the majority of previous studies on gut microbiota composition had mainly adopted the 16S rRNA gene sequencing platform. This approach, however, offers limited taxonomic resolution especially with regard to species-level identification (Poretsky *et al*., 2014). In this regard, shotgun metagenomic sequencing may be utilized given

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it offers a higher resolution for a finer species-based identification. Fifthly, even though current *in vivo* evidence supported that probiotics and postbiotics are associated with improved cognitive and muscle functions as well as gut-microbiota composition, limitations in terms of animal models and experimental design constrained the interpretations of the findings. Owing to the fact that the pathological construct of CF in animal models is still a developing field (Mladenovic & Pracer, 2025), previous studies that investigated cognitive and physical deficits relied on ageing or ageing-related models as a proxy for CF phenotype. Although CF is inherently related to ageing, it represents a vulnerability rather than direct consequences of ageing (Aravindhan *et al*., 2025). Furthermore, these studies did not incorporate specific tools to measure deficit accumulation, such as the frailty index, which limited the characterisation of frailty (Rockwood *et al*., 2017). While existing *in vivo* evidence provided proof-of-concept that supported the relevance of probiotics and postbiotics in CF and CF-related contexts, further clinical investigations are required to validate their mechanisms and therapeutic suitability. Thus far, probiotics and postbiotics have been primarily investigated clinically in the context of dementia, MCI, or physical frailty with CF remains largely unexplored (Rolland *et al*., 2024; Ticinesi *et al*., 2018). Probiotics and postbiotics demonstrated the potential in improving cognition in patients with MCI and AD (Hwang *et al*., 2019; Peng *et al*., 2025) and enhancing muscle functions in patients with sarcopenia and frailty-related syndrome (Lee *et al*., 2025; Zhang *et al*., 2024). Clinical studies of non-pharmacological interventions against CF appear to focus on other lifestyle-based approaches that included exercise, psychosocial, nutritional management and cardiovascular risk management (Murukesu *et al*., 2024). These interventions were implemented either in isolation or as a part of a multidomain approach (Cozza & Boccardi, 2025; Zheng *et al*., 2022). This raises the need for a well-designed translational study on probiotics and postbiotics against CF. Such a framework is in line with the vision of the UN Decade of Healthy Ageing (2021–2030) that focuses on developing and maintaining the functional ability of the elderly population amidst the rising global population (WHO, 2022).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

AUTHOR'S CONTRIBUTION

Adam Azmihan wrote the original draft. Kalavathy Ramasamy was involved in conceptualisation, supervision, review and editing of the manuscript. Abu Bakar Abdul Majeed was involved in supervision, review and editing of the manuscript. Siong Meng Lim was involved in conceptualisation, supervision, review and editing of the manuscript. All authors read and approved the final manuscript.

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