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REVIEW

Paradigm Shift of Microbiota-gut-brain Axis During Aging: Potential Role of Probiotics to Improve Cognitive Decline

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Abstract

Population aging is a global demographic inevitability, driven by advancements in healthcare, increased life expectancy, and declining fertility rates. Growing evidence implicates gut microbiota dysbiosis in the pathogenesis of cognitive impairments and neurodegenerative disorders commonly associated with aging, primarily through disruptions in immune, metabolic, and neuroendocrine signaling along the gut–brain axis. This review synthesizes current literature on the therapeutic potential of probiotic bacteria, such as *Lactobacillus* and *Bifidobacterium*, to enhance glial function, maintain blood-brain barrier integrity, and neurocognitive performance in older adults. However, probiotic efficacy is highly strain-specific and context-dependent, necessitating individualized evaluation of each microbial strain's therapeutic profile. Future research should prioritize precision microbiome-based strategies to elucidate mechanisms of action, optimal strain combinations, and their effectiveness across varying degrees of cognitive decline in the aging population. Furthermore, diet, physical activity, and microbial exposures represent essential, non-pharmacological tools for maintaining microbiota eubiosis and supporting neurocognitive health in aging populations.

Highlights

- Focus on the microbiota gut-brain axis in "Paradigm Shift" in aging
- Emphasis on sex and socioeconomic disparities in cognitive impairment
- Mechanistic pathways of probiotic action in the aging gut
- Strain-specific and context-dependent efficacy of probiotics on mitigating cognitive decline
- Inclusion of emerging concepts: "Neurobiotic Sense" and postbiotics on the gut-brain axis

Keywords Probiotics · Microbiota · Gut-brain-axis · Elderly · Cognitive function · Postbiotics · Lactobacillus

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Introduction

Population aging is an unavoidable global demographic shift, marked by a steadily increasing number and proportion of older individuals across societies. This shift is primarily driven by three factors: advancements in healthcare, rising life expectancy, and lower birth rates. A significant indicator is the drop in fertility below the replacement level of approximately 2.1 births per woman, which is essential for maintaining a stable population size. Between 2005 and 2010, nearly half of the global population resided in countries where fertility had fallen below this level [1]. In particular, low rates were observed in Europe (1.5) and Japan (1.4). When fertility remains this low for an extended period, a society will eventually experience an overall population decline accompanied by a rapidly aging demographic structure [2]. Consequently, the population sector aged 60 and over is expanding more quickly than any other group worldwide. This rapid demographic change presents profound socio-economic and public health challenges, necessitating significant policy and healthcare system adaptations to meet the needs of older adults (NSO, 2021) [3].

Global populations are aging, yet a critical challenge has emerged: gains in life expectancy do not reliably translate into equivalent gains in healthy life expectancy for everyone [4, 5]. Significant health disparities, influenced by socioeconomic factors, are prevalent within nations, and are further exacerbated across countries with varying levels of economic development [6]. A notable paradox in longevity: women generally live longer than men, but frequently report a higher burden of morbidity and poorer overall health in later life [7]. This is particularly evident in age-related neurodegenerative diseases like dementia [8]. The cognitive impairment characteristic of dementia is a primary driver behind the loss of independence and a decline in quality of life among the elderly [9]. Research indicates consistent sex differences in cognitive function [10], but the magnitude of these differences is not universal. It appears to be influenced by the country's economic status [11]. Education plays a vital role in shaping cognitive function, and sex disparities in educational attainment, shaped by economic development, may explain cross-country variations in cognitive function disparities among older adults. Historically, disparities in educational attainment between sexes have been more pronounced in many middle-income countries than in high-income nations. Consequently, older women in these settings often exhibit a greater relative cognitive disadvantage [12].

An imbalance in gut microbiota, commonly referred to as dysbiosis, has been strongly linked to detrimental changes in brain architecture, vascular physiology, and the permeability of the blood-brain barrier (BBB), thereby contributing to the pathogenesis of neurological disorders and cognitive decline [13]. Modulating the gut microbiota is emerging as a highly promising therapeutic strategy for preventing and treating cognitive impairments [14, 15]. The gut microbiome regulates neurodevelopment and function, including microglial and astrocyte polarization, neurogenesis, synaptic neurotransmission, and myelination [16]. Gut microbiota modulation can influence hippocampal function via bacterial metabolites and toxins, such as lipopolysaccharides (LPS) and amyloid-β that affect the vagus nerve, immune cytokine signaling, and neuroendocrine pathways [17]. Disruption of gut microbiota can adversely affect mental health, and its restoration may offer a novel strategy to enhance psychological well-being through the gut-brain axis [18]. The gut-brain axis encompasses the central, autonomic, and enteric nervous system, which work in concert with the immune and endocrine systems to facilitate crosstalk between the GI tract and the brain [19]. Biological mechanisms underlying depression, such as hypothalamic-pituitary-adrenal (HPA) axis dysregulation, neuroinflammation, and altered neurochemistry, further support the pivotal role of gut microbiota in the disorder [20–22].

Probiotics can beneficially modulate the gut microbiota, and this modulation is linked with improvements in cognitive dysfunction [23, 24]. For example, the administration of *Lactiplantibacillus plantarum* and *Asparagus officinalis* significantly modulated gut microbiota composition by increasing the abundance of *Lactobacillus* species and reducing populations of undesirable microbes, such as coliforms, staphylococci, and fungi. This information indicates that oral supplementation with *A. officinalis*-derived prebiotics and/or *L. plantarum* probiotics can counteract neurodegeneration and cognitive deficits by modulating the gut-brain axis, with synbiotic intervention showing the most pronounced neuroprotective effects [25]. Furthermore, probiotics can mitigate oxidative stress by inducing antioxidant enzymes and generating antioxidant metabolites (e.g., butyrate, folate, glutathione) and metal-ion chelators. They also suppress inflammatory signaling by downregulating Toll-like receptor (TLR) pathways, thereby preserving BBB function and enhancing neurological health [26, 27]. In individuals experiencing depressive states, probiotics have shown potential to improve cognitive function by modulating the HPA-axis and facilitating neurochemical processes, including monoamine synthesis and neuroplasticity [26]. Additionally, probiotics strengthen the intestinal barrier, prevent bacterial translocation, and decrease subsequent neuroinflammatory responses, including the production of inflammatory cytokines and activation of microglial cells [28].

Probiotic supplementation can modulate the gut microbiota and, consequently, reduce cortisol levels, likely

through regulation of the HPA axis. Evidence from various studies suggests that psychological stress and depressive symptoms may be alleviated in individuals consuming *Lactobacillus* strains, as indicated by decreases in salivary and urinary cortisol measurements [29, 30]. A study involving 33 participants who consumed a multispecies probiotic containing *Lacticaseibacillus rhamnosus* and *Bifidobacterium lactis* demonstrated marked improvements in cognitive abilities, memory, and depressive symptoms. Executive functions, including planning, problem-solving, mental flexibility, selective attention, impulse control, and inhibition, also showed notable enhancement, indicating an overall improvement in cognitive and emotional functioning among older adults following probiotic supplementation [31]. Symptoms of depression, including melancholy, malaise, insomnia, reduced interest, and neuroses, have been associated with improvement through lactobacilli formulations [32]. Moreover, probiotic consumption has been associated with improvements in sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), suggesting additional benefits for the management and prevention of neurodegenerative and mental health disorders [31, 33].

Considering the above factors, this systematic review provides a focused synthesis of current evidence on the potential of probiotics to prevent and manage cognitive impairments among older adults. Through an extensive review of peer-reviewed literature, we sought to address the following key research questions to elucidate the microbiota-gut-brain axis as a viable target for improved neurocognitive health in aging:

- How does the gut microbiota composition shift during healthy versus pathological aging?
- What mechanistic roles does gut microbiota play in modulating cognitive functions in elderly individuals?
- How do probiotics influence gut microbiota dysbiosis in older adults, and what are the implications for cognitive health?
- Do probiotics exert specific biological effects that alleviate depressive symptoms and cognitive decline associated with aging?

Methodology

This article presents a systematic review based on clearly defined inclusion and exclusion criteria. Studies were excluded if they did not include participants aged ≥ 60 years (for human studies), did not report cognitive or microbiota–gut–brain axis (MGBA)-related outcomes, lacked primary data, or did not meet the population or outcome eligibility criteria. The review follows a narrative design with systematic elements. The literature search and screening procedures were systematically conducted. The review provides a narrative synthesis of evidence on the association between probiotic-induced alterations in gut microbiota composition and depressive symptoms in the elderly population. Key biological and mechanistic pathways were summarized to enhance understanding of the advances over the past decade and to elucidate the potential mediating role of probiotics in the MGBA and mental health regulation. Only English-language, peer-reviewed articles were included. Additional relevant information was collected from reputable international organizations, including the United Nations (UN) and the World Health Organization (WHO). Articles were selected based on their examination of gut microbiota composition and its relationship with anxiety, depression, and cognitive function. The literature search employed keywords such as "aged persons," "aging," "unhealthy aging," "gut microbiota," "microbiota–gut–brain axis," "cognitive impairment," "anxiety," "depression," "probiotics," "prebiotics," "dysbiosis," "hypothalamic–pituitary–adrenal axis," "inflammation," and "blood–brain barrier". Searches were conducted across PubMed, Google Scholar, and the National Center for Biotechnology Information (NCBI) databases. A total of 2,245 articles were initially identified. Of these, approximately 825 were prioritized for detailed evaluation, and 537 were ultimately cited. The majority of included studies were published after 2015, except for a few seminal references predating 2015. Preference was given to double- and triple-blind study designs to ensure methodological rigor. Titles and abstracts were screened independently by two authors, followed by a full-text assessment of 750 articles. Studies were excluded if they did not include participants aged ≥ 60 years (for human), failed to report cognitive, affective, or MGBA-related outcomes, lacked primary data, or did not meet specific eligibility criteria. In total, 539 articles were included, with emphasis on randomized controlled trials (RCTs) and mechanistic studies in aging where available. Overall, this review aims to provide a concise yet comprehensive summary of the therapeutic potential of probiotics in preventing and treating cognitive impairments in older adults. It further discusses the potential roles of probiotics in modulating the immune and nervous systems, and their possible applications in the control and treatment of mental disorders.

Aging-Global Population

The global population is expected to peak at approximately 10.3 billion around the mid-2080s, up from the present 8.2 billion. A gradual decline to 10.2 billion is projected by 2100. There is now an 80% probability that this peak will

occur within the century, a significant increase from the 30% chance estimated in 2013. Current projections for 2100 are approximately 700 million lower than earlier forecasts, primarily due to declining fertility rates in major countries such as China [34]. A major demographic aging will accompany the growth. The population aged 65 and over is expected to reach 2.2 billion by the late 2070s, surpassing that of those under 18. Furthermore, by the mid-2030s, the global population of people aged 80 and over is projected to exceed the number of infants, reaching 265 million. These shifts necessitate that countries prepare by strengthening health and long-term care systems, ensuring sustainable social protections, and investing in new technologies [35].

Population aging is occurring worldwide, and the number of people aged 80 and over is projected to reach 426 million by 2050. Although this trend began in high-income countries (for example, in Japan, 30% of the population is already over 60), low- and middle-income countries are now experiencing the most rapid changes. By 2050, it is expected that 80% of all older adults will reside in these regions [36]. Regional variations are significant. For example, the United States anticipates its population aged 85 and over will triple by 2050. By the end of 2022, 14.9% of the Chinese population was aged 65 and over. Japan has the world's oldest population, with 28% of its citizens aged 65 or older, followed by Italy (23%) and several European countries, all of which have populations of just under 22%. In contrast, this age group represents 16% of the U.S. population, 6% of India's, and 3% of Nigeria's [37]. This demographic transformation underscores the urgent need for policy reforms tailored to support aging populations globally. Figure 1 illustrates the total population alongside the proportion of individuals aged 65 years and older across the top 25 countries [35, 38]. This demographic trend underscores the urgent need for country-specific policy adjustments to address the aging population.

The research has increasingly addressed key challenges faced by older adults, including social isolation, low self-confidence, limited access to health information, and unhealthy lifestyles. Numerous programs have been developed to enhance communication skills, self-management abilities, health literacy, physical activity, nutritional knowledge, understanding of medication, and overall quality of life [41]. With growing recognition of the role of a healthy lifestyle in promoting well-being among older populations, many countries have implemented interventions to foster health literacy [42, 43]. Inequalities in diet-related non-communicable diseases are well established [44, 45]. Individuals in lower socioeconomic positions exhibit higher rates of excess weight, cardio-metabolic disorders [46], and are at increased risk for preventable cancers such as lung and cervical [47]. Moreover, ethnic and racial disparities in non-communicable disease prevalence, such as type 2 diabetes, hypertension, and cancer, are shaped by gene–environment interactions, health behaviors, socioeconomic conditions, and unequal healthcare access [48]. Variations in living conditions create a social gradient in diet quality, contributing to persistent health inequalities [49]. Hence, strengthening understanding of these interrelationships is essential for health policies aimed at reducing diet-related inequities. Additionally, research on probiotic supplementation and cognition faces methodological limitations due to differences in cognitive assessment tools, probiotic strains, and study designs, as well as small sample sizes and dosage inconsistencies. Nevertheless, evidence suggests that

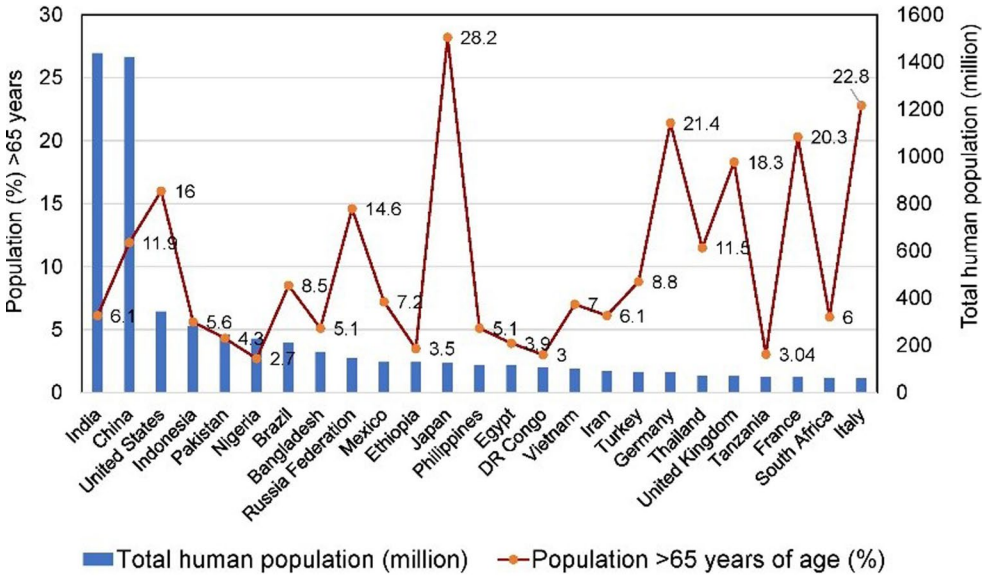


Fig. 1 Total population (million) in the top 25 countries and their population (in %) aging more than 65 years [39, 40]

12 weeks of probiotic use can enhance cognitive function, as demonstrated by the Montreal Cognitive Assessment test [50].

The rapid global increase in the older adult population poses a significant challenge for healthcare systems, families, and society. Aging is often accompanied by chronic diseases, loneliness, isolation, and social deprivation, all of which negatively impact well-being. The lack of social support further increases vulnerability to psychological problems in later life [51]. Older adults with low health literacy tend to use more emergency services, incur higher healthcare costs, and underutilize preventive services such as vaccinations and screenings, contributing to higher mortality rates [52]. Therefore, promoting self-care practices and effective communication with healthcare providers is crucial for improving outcomes among older adults [53]. Improving healthy lifestyles requires the development of community-based interventions that integrate technology, account for engagement duration, and adopt multidimensional approaches tailored to older populations [41].

Additionally, accurate assessment of socioeconomic status is vital to ensure equitable access to basic healthcare and social services. However, the current healthcare system remains ill-equipped to meet the growing demand, leading to a mismatch between service capacity and patient needs [54]. Addressing this challenge requires strengthening geriatric and gerontological education and ensuring the availability of affordable, quality, and accessible long-term care for all older individuals.

Dietary habits are another major determinant of health among older populations. In 2017, diet-related risks were responsible for 11 million deaths and 255 million disability-adjusted life years (DALYs) worldwide, surpassing all other global risk factors [55]. Socially disadvantaged groups often face barriers to maintaining a healthy diet, including financial constraints, food deserts, and adverse living and working conditions, leading to poorer diet quality. Individuals from lower socioeconomic backgrounds are disproportionately affected, which further exacerbates health inequalities. To mitigate these disparities, culturally tailored interventions addressing racial, ethnic, and socioeconomic differences are essential [48]. Enhancing dietary quality and health outcomes for all population segments requires coordinated action among policymakers, researchers, and public health professionals, emphasizing equity-focused strategies to promote healthy aging and reduce health inequities across diverse populations.

With the rapid global increase in the aging population, the proportion of older adults using five or more medications concurrently, a condition known as polypharmacy, has risen substantially [56, 57]. This trend is primarily driven by the high prevalence of multiple chronic diseases and the clinical guidelines recommending various therapeutic agents for their management. Polypharmacy often leads to a higher anticholinergic burden [58], which has been associated with cognitive impairment, increased fall risk, and poor oral health [59]. Age-related changes also occur in the oral microbiome, reflecting cumulative health exposures and biological aging. These microbial shifts are linked to chronic diseases, such as cardiovascular disease, diabetes, and cancer [60]. Recent research highlights complex bidirectional interactions between prescription medications and the gut microbiota, influencing both drug metabolism and microbial composition [61]. Specifically, polypharmacy has been correlated with reduced microbial diversity and altered gut community structures, likely due to the antimicrobial effects of certain drugs [62]. A study by Xiao et al. [63] showed that proton pump inhibitor (PPI) use promoted the translocation of oral-origin *Streptococcus* into the gut microbiota, indicating medication-induced barrier disruption. Both polypharmacy and high anticholinergic drug burden were negatively associated with oral microbiome diversity, and specific taxa were differentially linked to these variables [60]. A multivariate analysis revealed a negative correlation between the number of medications and microbiome biodiversity (Chao1 Index). The number of drugs influenced the relative abundance of 15 microbial taxa, with proton-pump inhibitors (PPIs), antidepressants, and antipsychotics showing the strongest associations. Interestingly, frailty and multimorbidity were not significantly related to gut microbial diversity, whereas a low Chao1 index predicted mortality but not rehospitalization or sepsis [64]. In addition, institutionalized older adults showed reduced abundance of short-chain fatty acid (SCFA)–producing bacteria and increased abundance of *Parabacteroides*, *Eubacterium*, *Coprococcus*, and *Anaerotruncus* [65], possibly reflecting dietary differences among nursing home residents [66]. Moreover, immunological aging may alter probiotic responsiveness, leading to age-specific effects on microbial and immune systems [67].

Influence of Aging on the Brain Structure and Function

The brain has high metabolic and nutrient demands, consuming approximately 20% of daily caloric intake. Its structure is highly dependent on lipids, which comprise 60% of its mass, including high levels of cholesterol and polyunsaturated fatty acids such as Omega-3. Neurotransmitters such as serotonin, norepinephrine, and dopamine are synthesized from amino acids and require B vitamins and mineral-dependent cofactors. B vitamins, including folate, support the methylation cycle, which is crucial for neurotransmitter synthesis and for regulating homocysteine, a compound

linked to cardiovascular disease and depression [68]. Fatty acids, especially Omega-3, are vital in maintaining neuronal structure, neurotransmission, gene expression, neurogenesis, and neuronal survival, in addition to providing anti-inflammatory properties and antioxidant benefits [69]. Modern Western diets often lack the vital balance between omega-6 and omega-3 fatty acids, being excessively higher in the former and lower in the latter [70].

Aging induces changes in brain structure at both macroscopic and microscopic levels. Macroscopically, these include cerebral atrophy, widening of sulci, and cerebrovascular alterations [71]. In contrast, microscopic changes involve the accumulation of lipofuscin pigments [72] and neurotoxic proteins such as neurofibrillary tangles and amyloid-beta [73]. These accumulations contribute to neuronal dysfunction and cognitive decline, with significant degeneration occurring in memory and the emotion-related regions, such as the limbic system [73]. Aging also alters biochemical and metabolic pathways, including neurotransmitter dysregulation involving acetylcholine, monoamines, and neurosteroids, which in turn affects enzymes, receptors, and protein functions [73].

At the cellular and molecular levels, aging affects nearly all the organelles and processes [73]. Mitochondria suffer dysfunction due to DNA damage, oxidative stress from reactive oxygen species (ROS), and calcium imbalance, which reduces energy (ATP) production and can trigger cell death [73, 74]. This mitochondrial impairment creates a destructive cycle that worsens neurodegenerative diseases. Furthermore, the cell's waste disposal systems, the lysosomes and proteasomes, become less efficient with age, leading to the harmful buildup of abnormal proteins seen in Alzheimer's and Parkinson's diseases [73]. Finally, aging disrupts the brain's electrical signaling by altering ion channels and critically impairing calcium homeostasis, a key regulator of neuronal communication and health, leading to widespread neuronal dysfunction. Changes (structural, microscopic, cellular, molecular, biochemical, and metabolic) in the brain due to aging are highlighted in Fig. 2.

Aging and Disease Occurrence

Biologically, aging is characterized by the cumulative effects of diverse molecular and cellular damage over time, which progressively impair physical and cognitive functions, heighten vulnerability to disease, and ultimately lead to death. This process is neither linear nor uniform, and it varies significantly among individuals, influenced by genetics, environment, and lifestyle. Aging is a major contributor to the global burden of diseases, with nearly 23% of all health conditions occurring in those aged 60 and older [36]. With advancing age, individuals may suffer from multiple health issues, collectively known as geriatric syndromes. These complex conditions arise from the convergence of numerous underlying factors and include frailty, pressure ulcers, urinary incontinence, falls, and delirium [36].

Although the overall burden of disease is significant in high-income countries, the rate of disability-adjusted life years (DALYs) per capita is actually 40% higher in low- and middle-income regions. The leading causes of illness in older adults are consistent globally, dominated by non-communicable diseases such as cardiovascular disease (30.3%), malignant cancers (15.1%), chronic respiratory diseases (9.5%), musculoskeletal diseases (7.5%), and neurological/mental disorders (6.6%) [37, 75]. These chronic conditions are primary drivers of illness and death among the elderly [76]. A key distinction exists in the distribution of certain conditions. The burden of infectious and parasitic diseases remains higher in lower-income regions. Conversely, mental, neurological, and musculoskeletal disorders represent a more prominent share of the disease burden in high-income areas [75].

Aging: Cognition-Dementia-Depression

Dementia currently affects over 50 million people globally, and it is projected to triple in the coming decades [77, 78]. This progressive neurodegenerative disorder, which evolves from mild cognitive impairment (MCI) to a significant neurocognitive disability, including Alzheimer's Disease, in which patients lose independence and quality of life deteriorates [79–81]. Mental health is deeply intertwined with cognitive decline. Approximately 14% of adults aged 60 and over live with a mental disorder, accounting for 10.6% of the total disability burden (DALYs) in this age group [82].

Depression is particularly significant; it is a risk factor for potential dementia, with 30–50% of affected individuals experiencing it [83, 84]. Depression, even in sub-diagnostic forms, exacerbates cognitive decline, reduces quality of life, and increases dementia risk [85, 86]. The consequences are severe, with older adults accounting for 27.2% of global suicide deaths, underscoring a critical treatment gap often widened by stigma [36, 82, 87].

Several modifiable and non-modifiable factors influence cognitive trajectories. Key predictors include education level, baseline cognitive function, depressive symptoms, anxiety, and physical health metrics like diabetes and body mass index [88–91]. Moreover, significant gender disparities exist. While women generally live longer, they experience worse cognitive health outcomes, a disparity exacerbated in middle-income countries by economic and educational inequalities [7, 10, 12]. Additionally, women

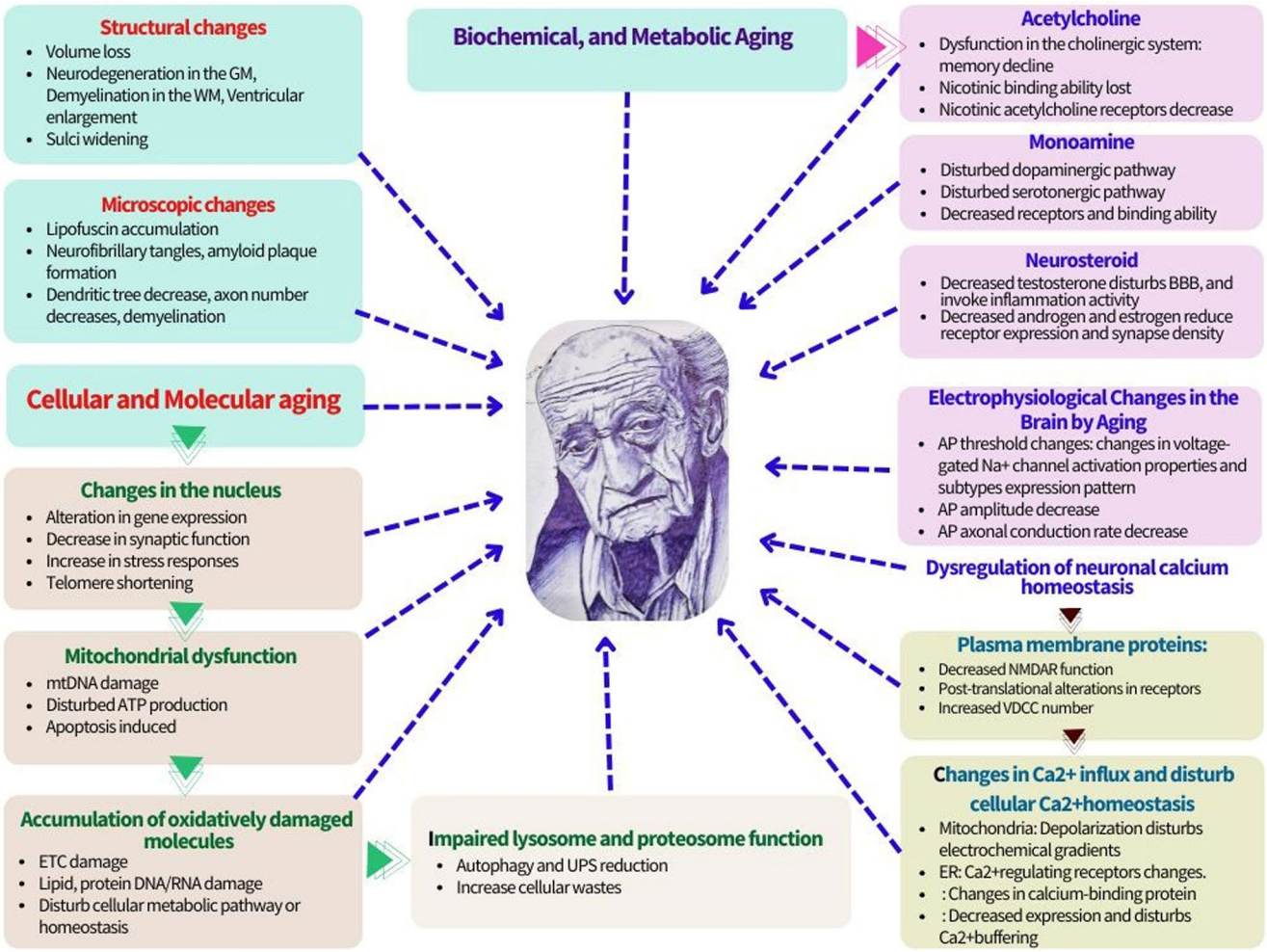


Fig. 2 Structural, microscopic, cellular, molecular, biochemical, and metabolic changes in the brain due to aging (Photo image of an aged person drawn by Surya Sekhar Dutta, graduating student (Bachelor of Technology-Electronics and Computer Science) GM = Gray matter, WM = White matter, mtDNA = mitochondrial DNA, ATP = Adenosine triphosphate, ETC = Electron transport complex, UPS = ubiquitin proteasome system, BBB = Blood-brain barrier, AP = action potential, NMDAR = N-methyl-D-aspartate Receptor, VDCC = Voltage-dependent calcium channel, ER = Endoplasmic reticulum

exhibit a noticeable age-related decline in complex psychomotor coordination and convergent thinking [92].

The cognitive reserve (the brain's resilience to pathology) is central to understanding these variations. It is quantified using indirect assessments, including education, work-related complexity, and leisure activities, as well as residual approaches that account for variance in cognition unexplained by demographic and brain measures or by identifying functional networks underlying reserve [93, 94].

Dementia and delirium often coexist, and a critical concern is the interplay between them. Older adults with dementia have a 15-fold increased risk of delirium, which in turn can accelerate cognitive decline and may even precipitate future dementia diagnosis [95–97]. Any presentation of delirium should therefore prompt an investigation for underlying cognitive impairment. Globally, the burden is shifting. Dementia prevalence is rising fastest in low- and middle-income countries (LMICs), because of increased life expectancy and a higher burden of modifiable risk factors [98]. It is projected that up to 40% of dementia cases could be avoided by addressing factors such as less education, hypertension, hearing loss, depression, and social isolation. However, population attributable risks may be even higher in specific regions, such as Latin America (56%) [99, 100]. Therefore, there is an urgent need for novel diagnostic, prognostic, and treatment strategies that address the intertwined paths of cognitive decline and mental health in aging populations.

Diet and Cognitive Function

The diet and its relationship with cognitive function (dementia) are complex. While observational studies have suggested potential protective effects from specific micronutrients such

as folate, B vitamins, vitamin C, vitamin D, vitamin E, and selenium, recent research has shifted towards whole dietary patterns rather than individual supplements [83]. Evidence increasingly supports the benefits of Mediterranean diets, which include cereals, nuts, vegetables, fruits, legumes, and olive oil, while limiting the consumption of saturated fats and red meat [101]. A meta-analysis of randomized controlled trials found that this diet was associated with modest improvements in global cognition. Still, it failed to show any meaningful reduction in the incidence of dementia [102, 103]. Supporting these findings, a longitudinal study found that a greater intake of green leafy vegetables was associated with a slower rate of cognitive decline, comparable to being 11 years cognitively younger [104]. In contrast, systematic reviews found no strong evidence that vitamins (A, B, C, D, E, or multivitamins), mineral supplements (Ca, Zn, Cu) or other supplements (n-3 fatty acids, antioxidants, herbs) prevent cognitive decline or dementia [105]. Cochrane reviews also found no cognitive benefits of B vitamin supplementation for 6–24 months [106], or vitamin E in preventing cognitive decline or dementia [107]. This is further supported by a 24-month trial of a multi-nutrient drink, which found no significant slowing of cognitive deterioration in individuals with prodromal Alzheimer's disease [108]. As a result, the WHO [109] guidelines recommend adopting a Mediterranean-style diet to support cognitive health but advise against the use of vitamins, fatty acids, or multivitamin complexes, due to insufficient evidence.

Diet is one of the primary determinants of the composition, diversity, and functionality of the gut microbiota, as demonstrated by recent research [110]. Lifelong dietary habits significantly contribute to inter-individual variability in gut microbial composition and enterotype distribution. Evidence indicates that a balanced dietary intervention positively influences both nutritional and inflammatory biomarkers, including fasting glucose, HbA1C (hemoglobin A1C), albumin, γ-GT (gamma-glutamyl transferase), total cholesterol, HDL (high-density lipoproteins) cholesterol, and IgE, while also modulating gut microbiota composition. Specifically, a balanced diet has been associated with favorable alterations in the microbiota, including a reduced *Firmicutes*/*Bacteroidetes* (F/B) ratio and increased abundances of *Bacteroidaceae*, as well as the genera *Prevotella* and *Faecalibacterium*. These microbial changes are linked to improved metabolic and immune health. Moreover, probiotic supplementation has been shown to enhance and complement these dietary effects, indicating a synergistic interaction that further supports the growth of beneficial gut bacteria. Together, these findings suggest that a balanced diet combined with probiotics may serve as an effective strategy to optimize gut microbiota composition and improve metabolic outcomes in older adults [67]. According to the 2020 Dietary Reference Intakes for Koreans (KDRIs), established by the Korean Nutrition Society and the Ministry of Health and Welfare, adults aged 65 years and older are advised to consume 2,000 kcal/day for men and 1,600 kcal/day for women, with recommended macronutrient ratios of carbohydrates (55–60%), protein (7–20%), and fat (15–30%), and daily protein intakes of 60 g for men and 50 g for women [111].

Hormonal Aging and Cognition

Hormones from the hypothalamic-pituitary-gonadal (HPG) axis, which regulate reproduction, also function as neurosteroids that significantly influence brain development, maintenance, and cognitive function [112]. This highlights the role of sex hormones in contributing to cognitive sex differences and varying susceptibilities to Alzheimer's disease [113]. The HPG axis also regulates the release of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), which then prompt the gonads to produce androgens and estrogens [113]. Menopause involves reduced estrogen and progesterone levels and increased serum FSH, often linked to cognitive impairment [114]. Cognitive declines during natural menopause include reduced verbal memory and fluency [115], with subjective complaints also correlating with objective deficits in attention and working memory [116]. Hormonal changes with aging contribute to cognitive decline, with estrogen and progesterone dropping significantly in postmenopausal females. Estrogen types include estriol, estradiol, and estrone, with a postmenopausal shift favoring estrone over estradiol [117]. Cognitive decline is associated with aging in both males and females; however, research has yielded mixed results regarding sex-based trajectories of cognitive aging [118]. The Baltimore Longitudinal Study of Aging found that females outperformed males at baseline in verbal memory and fluency, but both sexes showed similar rates of verbal cognitive decline with age. Males excelled in visual-spatial tasks at baseline but experienced steeper declines in spatial ability and psychomotor speed with age [119]. In males, aging is characterized by a gradual decline in testosterone and dehydroepiandrosterone, alongside increases in LH, FSH, and sex hormone-binding globulin [120]. A similar gradual decrease in androgens occurs in females from their thirties or forties onward [121].

Aging: Paradigm Shift of Gut Microbiomes

López-Otín et al. [122] identify twelve hallmarks of mammalian aging, including genetic instability, loss of proteostasis, mitochondrial dysfunction, impaired macroautophagy,

altered intercellular communication, dysbiosis, and chronic inflammation. Mattson and Arumugam [123] highlight brain-specific aging features, including excessive glial activation, leading to neuroinflammation, oxidative stress, disrupted calcium homeostasis, and impaired clearance of waste products. Emerging evidence emphasizes the microbiota's role in maintaining systemic homeostasis and its involvement in aging-related disorders, notably neurodegenerative diseases [124]. Though the contribution of gut microbiota has been the primary focus towards neurodegenerative diseases, oral commensals may also contribute to cognitive decline [125]. Dysbiosis triggers low-grade chronic inflammation that spreads systemically, compromising the BBB and promoting neuroinflammation. Additionally, microbiota-induced oxidative stress exacerbates neuronal aging. However, due to the scarcity of longitudinal research, causal links between alterations in microbiota and specific cellular mechanisms remain tentative [124].

The human body and its resident microbial communities form a complex super meta-organism [126]. While distinct ecological niches within various body habitats determine the distribution of these microbes [127], factors like genetics, socioeconomic status, age, diet, medications, and environment also modulate this ecosystem, particularly along the gut-microbiome-brain axis [128, 129]. This microbial community, comprising bacteria, fungi, archaea, parasites, and viruses, functions as an integrated unit, and disruptions to it are increasingly linked to human health and disease [130, 131]. The human gastrointestinal (GI) tract is the most densely colonized organ, hosting approximately 100 trillion microorganisms at a near 1:1 ratio with human cells [132, 133]. The microbiota is dominated by the bacterial phyla *Firmicutes* (*Bacillota*) and *Bacteroidetes* (*Bacteroidota*), which together constitute approximately 90% of the microbiota [134]. The *Firmicutes* include both beneficial genera (e.g., *Lactobacillus*) and potential pathogens (e.g., *Clostridium*), while *Bacteroidota* consists primarily of *Bacteroides* and *Prevotella*. Less abundant phyla include health-promoting *Actinobacteria* (e.g., *Bifidobacterium*) and often pathogenic *Proteobacteria* (e.g., *Escherichia*, *Salmonella*) [134]. This diverse microbial consortium plays essential roles in food fermentation, vitamin synthesis, pathogen defense, and immune regulation [135, 136]. Microbiota composition is dynamic, evolving through three key life stages: infancy, post-weaning, and old age [132]. Beyond bacteria, the gut also hosts fungi (e.g., *Candida*, *Saccharomyces*), viruses, and archaea such as *Methanobrevibacter smithii*, forming a multi-kingdom interactive network essential for host health [137, 138].

Analysis of 21,041 fecal microbiomes across diverse geographical regions (Europe, North and South America, and Asia) demonstrated that unhealthy aging correlates with an elevated Kendall Uniqueness score, characterized by diminished dominant taxa and enrichment of subdominant taxa [139]. Studies in older adults in the USA and Europe generally reveal reduced microbiome taxonomic diversity and an increased abundance of *Bacteroidetes* compared to younger individuals [140]. This observation suggests an age-associated decline in microbiome integrity, analogous to the deterioration of other biological processes. This age-related shift in the microbiome is independent of concurrent health conditions [141]. An extensive cross-sectional study in China found that the overall microbiome profiles of healthy older adults, including those 94 years and older, are comparable to those of healthy younger individuals [142]. The composition of the microbiome in very elderly individuals (≥ 90 years) is strongly influenced by health status, with healthy, long-lived individuals exhibiting distinct microbiome signatures [143]. In fact, some research indicates that these healthy, long-lived individuals can possess even greater gut microbiome diversity than their younger counterparts [144]. This supports the theory that a resilient and diverse gut ecosystem may help protect against age-related diseases and promote a longer, healthier lifespan.

The diversity of gut microbiota follows a distinct life-course, increasing from childhood to adulthood, before declining in older age (≥ 70 years) [145]. Initial colonization at birth is shaped by delivery mode. Birthing via the vaginal route allows infants to acquire microbiota from the mother's vaginal and fecal flora. In contrast, Caesarean-born infants are exposed to skin and environmental microbiota [146]. Early-life diet also plays a vital role; breastfed babies exhibit a more stable, *Bifidobacterium*-rich microbiota but a less diverse one [147]. The introduction of solid food drives a shift towards an adult-like profile, which is typically established by age three and dominated by the phyla *Firmicutes* (*Bacillota*), *Bacteroidetes* (*Bacteroidota*), and *Actinobacteria* (*Actinomycetota*) [148]. Older age is associated with alterations in diet and immune function, which significantly alter gut microbiota by decreasing *Bifidobacteria* and increasing *Enterobacteriaceae*, *Proteobacteria*, and *Clostridiaceae* [65]. Decreased *Bifidobacteria* are associated with increased inflammation as they play a role in immune stimulation. These disparities highlight the intricate relationship between the gut microbiome, diet, environment, and aging. A common feature of aging is a shift in the dominant phyla, characterized by increased abundance of *Bacteroidetes* and decreased abundance of *Firmicutes* [65, 149]. These changes contribute to a state of microbial dysbiosis, which is linked to intestinal barrier dysfunction, systemic inflammation, and elevated risk of age-related diseases like atherosclerosis and stroke [150, 151]. Notably, specific microbial signatures are associated with healthier aging. For instance, higher abundance of *Akkermansia*

muciniphila and the family *Christensenellaceae*, the latter of which is enriched in super-centenarians, are correlated with longevity and improved health outcomes [152, 153]. This underscores the gut microbiome's role as a dynamic interface between aging, diet, and host health. Changes in gut microbiota diversity associated with unhealthy aging have been summarized in Fig. 3.

Centenarians and other long-lived individuals exhibit a highly diverse gut microbial profile, with an abundance of specific bacterial families, including *Lachnospiraceae*, *Ruminococcaceae*, and *Akkermansia* [154]. *Coprococcus* is generally associated with healthy aging, but its level can decrease in very advanced age [139, 155]. *Ruminococcus*, a strong SCFA producer, is increased in centenarians and is also associated with frailty [152, 156]. *Lachnospiraceae* is associated with healthy aging and increased BMI in children [157]. *Alistipes* increases with age and is associated with dementia [158]. A decrease in *Faecalibacterium prausnitzii* and an increase in *Eggerthella* and *Eubacteria* are correlated with frailty [159]. Super-centenarians exhibit a high diversity and abundance of *Christensenellaceae* and *Akkermansia* [160]. While *Bacteroidetes* are generally reported to increase with age, this trend was not observed in healthy older Indonesians [161]. Healthy centenarians in India exhibited lower levels of *Bacteroidetes* and higher levels of *Enterobacteriaceae* compared to cohorts from Italy, China, and Japan [162]. *Akkermansia*, typically associated with healthy aging, has been linked to frailty in older Chinese adults [163]. These patterns of dysbiosis, often quantified by higher "Uniqueness" scores, correlate with an increased abundance of potential pathobionts such as *Klebsiella* and *Clostridium* [139]. Environmental factors exacerbate this dysbiosis. Older adults in nursing homes, who often have reduced dietary fiber intake, exhibit lower overall microbial diversity, fewer commensal bacteria, and increased prevalence of pathobionts [65, 140, 164]. Antibiotic use can significantly reduce microbial diversity and increase the risk of infection with antibiotic-resistant pathogens, and *Clostridioides difficile* colonization [165, 166]. *C. difficile* infection in older adults exhibits similar microbiome changes to those associated with general aging, characterized by an increase in pathobionts and a decrease in beneficial commensals [140]. Key takeaways include a lower abundance of *Bifidobacterium* and a higher abundance of *Bacteroidota* [167], which are linked to cognitive impairment, Parkinson's disease, and Alzheimer's disease [168, 169], potentially by increasing amyloid load via immune-mediated mechanisms. In contrast, *Bifidobacterium* is beneficial, as it reduces inflammation and amyloid accumulation [170]. Supplementation with this bacterium improves cognition in both animals and humans [171, 172].

Gut Microbiota and Longevity

Research on Italian individuals aged 99–109 years shows that extreme aging is associated with reduced diversity among core microbiota families, specifically *Ruminococcaceae*, *Lachnospiraceae*, and *Bacteroidaceae* [153]. A parallel study of Chinese centenarians corroborates this finding, noting a negative correlation between advanced age and beneficial genera *Coprococcus*, *Roseburia*, and *Faecalibacterium*, which belong to the *Lachnospiraceae* and *Ruminococcaceae* families [144, 173]. Despite significant differences in geography, race, diet, and lifestyle, both studies identified 11 shared microbial features among the top 50, including shifts in *Blautia*, *Clostridium* cluster XIVa, *Faecalibacterium*, *Escherichia*, *Shigella*, unclassified

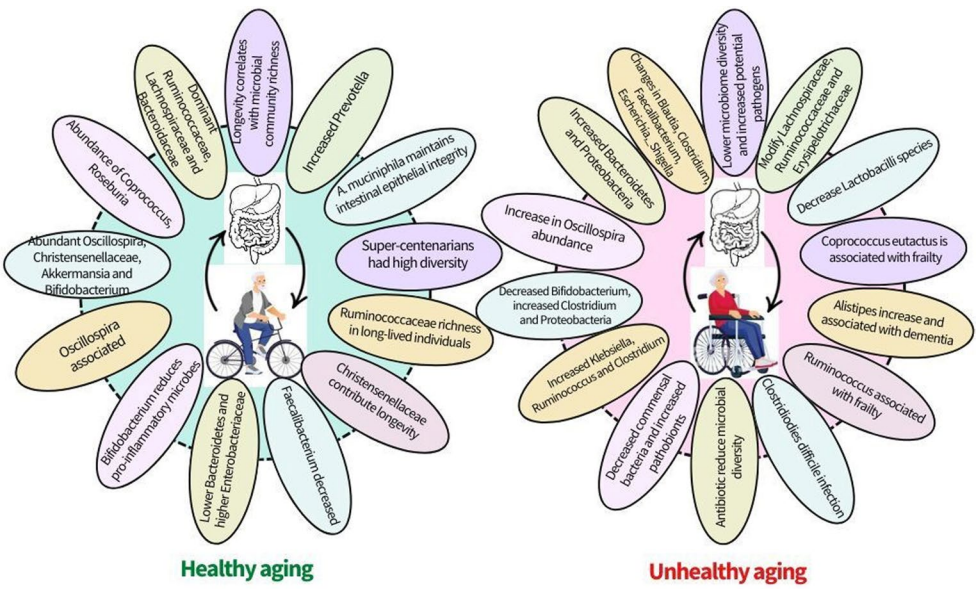


Fig. 3 Comparison of the gut microbiota diversity during healthy and unhealthy aging

Lachnospiraceae and *Ruminococcaceae*, and *Erysipelotrichaceae* [144, 173]. Conversely, longevity is positively correlated with increased overall microbial richness (measured by Chao and OTU indices) and a higher abundance of specific health-promoting, subdominant taxa. These include *Oscillospira*, *Christensenellaceae*, *Akkermansia*, and *Bifidobacterium* [144, 153]. *Oscillospira* and *Christensenellaceae* are linked to leanness and reduced inflammation [174]. *A. muciniphila* maintains gut barrier integrity, enriches SCFA-producing bacteria, and suppresses inflammatory response and metabolic impairments [175]. *Bifidobacteria* produce beneficial metabolites that inhibit pro-inflammatory microbes [176]. Supporting this, a reanalysis of lifespan sequencing data confirmed that *Oscillospira* abundance increases with age, from infancy through centenarian age [177].

Gut bacterial communities in centenarians exhibit distinct clustering, suggesting that age shapes these communities along a consistent trajectory. For example, Centenarians have been found to exhibit reduced levels of *Faecalibacterium* and *Roseburia* species [144, 173]. *Parabacteroides* spp. is enriched in centenarians on the island of Sardinia, Italy, and in Sichuan Province, China, but decreased in Guangxi Province, China [144, 178]. *Bifidobacterium* and *Lactobacillus* spp., known for their probiotic properties, are often found in low abundance in older adults [65]. However, a high abundance of these genera was detected in centenarians from Sardinia, Italy, and other regions, suggesting a link to human longevity [153, 178]. Furthermore, *Penicillium* and *Debaryomyces* spp., commonly associated with fermented foods, were more prevalent among Sardinians, possibly due to their high cheese consumption [179]. A high abundance of *Debaryomyces* spp. in young individuals than in older adults, as well as centenarians, could be attributed to dietary preferences [180].

Cognitive decline has been linked to reduced levels of *Intestinibacter*, suggesting that dysbiosis and inflammation-driven brain aging may be involved [181, 182]. The combined impact of such age-related conditions can advance dementia and frailty in older individuals [183]. Taxonomic profiling provides a compositional snapshot of the microbiome, whereas a functional understanding of the metabiome represents the functional potential of its metabolic capacity and metabolome. These microbiome-derived compounds can act within the gut or enter the bloodstream to affect distant organs, including the brain [184]. Measuring these metabolites in stool or serum is a window into these host-microbiome interactions and their systemic effects [185].

Due to the immense influence of microbiota on human health, research is being carried out beyond compositional studies to investigate functional associations. The composition and function of the human microbiota are intimately connected to health, necessitating a lifespan perspective to fully understand this dynamic relationship. Furthermore, the oral microbiome is now considered an emerging and valuable health indicator [186], while age-related changes in the microbiome are associated with disease development. Studies on "super-agers" may thus provide critical insights into how microbial populations can promote extended health spans and protect against age-related conditions [183].

Mood and Cognition Disorder: Neurological Pathway through Microbiota-Gut-Brain Axis

Most human aging studies rely on fecal samples, which mainly represent luminal communities. In contrast, mucosal biopsies capture adherent and mucus-associated taxa that are more directly engaged in epithelial and immune interactions. Differences between fecal and mucosal communities may partly explain inconsistencies in reported age-associated dysbiosis and in associations with systemic inflammation and cognitive outcomes [187]. Experimental rodent models, often using inbred strains, standardized diets, and gnotobiotic designs, show robust and reproducible probiotic effects on neuroinflammation and cognition that do not always translate to heterogeneous human populations exposed to multiple medications, comorbidities, and variable diets [188].

Furthermore, longitudinal study designs are likely superior to cross-sectional snapshots for aging-related microbiome dynamics, because repeated intra-individual sampling can capture temporal instability, microbiome 'trajectories', and time-lagged relationships between microbial change and cognitive decline. Large, longitudinal multi-omics cohorts have already highlighted the value of such approaches for other chronic diseases and could be adapted to cognitive aging studies [143, 189].

Research over the past decade has established that the gut microbiome is a central component of a bidirectional communication system, the microbiota-gut-brain axis (MGBA) linking the gut and brain [190]. This system enables central neural processes to regulate gut functions, including immune activity, while the gut can modulate mood, cognition, and mental health [191]. The enteric microbiota coordinates this interaction through neural, endocrine, and immune pathways, affecting stress response via the hypothalamic-pituitary-adrenal axis and supporting neuronal development early in life [192–194]. Diet further modulates this relationship by altering microbial composition and function, thereby influencing brain activity and behavior [195, 196]. Supported by brain imaging, the gut-brain axis is now established as a central regulator of homeostasis,

solidifying scientific consensus on this critical, bidirectional relationship [197].

Dysbiosis also disrupts MGBA-signaling and is implicated in the development of neurodegenerative diseases, such as Alzheimer's disease, as well as Parkinson's disease [190]. The MGBA also helps recovery from acute neurological injuries such as stroke, including traumatic brain injury [190]. This complex network integrates autonomic, enteric, and central nervous systems, along with the immune and endocrine systems, with the vagus nerve serving as a vital communication pathway. Gut microbes modulate this axis by producing and regulating neurotransmitters, including γ-aminobutyric acid (GABA), serotonin, melatonin, histamine, and catecholamines, which influence both gut and brain function [196, 197]. The autonomic nervous system can further shape gut immune responses by modulating macrophages and mast cells activity. A healthy gut microbiome is vital for the excitability of enteric primary afferent neurons [198].

The autonomic nervous system triggers physiological changes in the gut. It mediates enteric neural system-microbiota interactions, facilitating the delivery of nutrients, absorption, and the delivery of prebiotics and probiotics in the GI tract [199]. Jaglin et al. [200] found that specific microbial metabolites, such as tryptophan-derived indoles, can activate the vagus nerve and alter behavior. Whereas De Vadder et al. [201] revealed that microbiota-driven activation of the enteric neural system happens through 5-hydroxytryptamine (5-HT) receptors, thus further illustrating their roles in gut-brain communication.

Studies suggest that the gut microbiota directly influences brain function and behavior [202]. For example, antibiotics, administered to mice, altered the composition of the gut microbiota, increased exploratory behavior, and elevated hippocampal brain-derived neurotrophic factor (BDNF), a protein crucial for learning and memory, independent of neural or inflammatory pathways [203]. Specific microbial shifts are also associated with neurological and psychological conditions: depression and anxiety are linked with increased *Actinobacteria* and *Proteobacteria*, and decreased *Faecalibacterium* and *Bifidobacteria*, while fatigue correlates with increased *Enterococcus* and *Lactobacillus*, and decreased *Escherichia coli* and *Bifidobacterium* [204]. Similarly, sleep quality is impaired by increases in *Lachnospiraceae*, *Blautia*, *Parasutterella*, *Coprococcus*, and *Oribacterium*, and a reduction in *Bacteroidetes*, *Actinobacteria*, *Firmicutes*, *Corynebacterium*, *Sutterella*, and *Brevibacterium*. These microbial shifts diminish sleep-supporting neurotransmitters, such as GABA and serotonin [205].

Beyond bacteria, fungal overgrowth, such as *Candida*, may contribute to fatigue, suggesting a broader microbial influence on health [204, 206]. Various mood disorders, including anxiety and autism, are strongly associated with gastrointestinal dysfunction [191] and gut-brain pathways are also activated in conditions like irritable bowel syndrome (IBS) [207]. Importantly, microbiota transplants from Parkinson's patients worsen motor symptoms in mice [208], while probiotic supplementation (e.g., *B. longum* 1714) may improve memory and reduce stress in humans [209]. These findings indicate that the gut microbiome may serve as both a biomarker and a modulator of cognitive and psychiatric health [210]. The relationship between the gut microbiota with mental disorders is highlighted in Table 1.

Accumulating evidence shows that modifications in gut microbiota associated with metabolic diseases differ between men and women, influencing sex-specific patterns in disease development and prevalence. Key factors implicated in these pathologies include LPS-induced inflammation, microbiota-derived metabolites, gut barrier integrity, and gut–brain axis interactions. Sex steroids, mainly estrogens and testosterone, play a crucial role in shaping the sexual dimorphism of

Table 1 The relationship between gut microbiota and mental disorders

Mental disorders	Positive relationship with microbiota	Negative relationship with microbiota	References
Depression	*Streptococcus*, *Prevotella*, *Parapprevotella*, *Klebsiella*, *Clostridium*	*Streptococcaceae*, *Bacteroidetes*, *Gemella*	Xiong et al. [211]
Frailty	*Eggerthella*, *Eubacteria*, *Coprococcus eutactus*	*Faecalibacterium prausnitzii*	Lim et al. [212]
Anxiety	*Fusobacteria*, *Prevotella*, *Bacteroidetes*, *Lactobacillales*, *Sellimonus*, *Enterococcus*, *Streptococcus*	*Bacteroidetes/Firmicutes*, *Faecalibacterium*, *Lachnosprira*, *Sutterella*, *Butyricicoccus*	Xiong et al. [211]
Autism Spectrum Disorder	*Actinobacteria*, *Proteobacteria*, *Bacilli*, *Clostridium*, *Gammaproteobacteria*, *Erysipelotrichi*	*Agathobacter*, *Faecalibacterium*, *Akkermansia miciniphila*	Plaza-Díaz et al. [213]
Schizophrenia	*Veillonella*, *Lachnospiraceae*, *Collinsella*, *Lactobacillus*, *Succinivibrio*, *Corynebacterium*, *Mogibacetrium*	*Ruminococcus*, *Roseburia*, *Coprococcus*, *Faecalibacterium*, *Adlerereutzia*, *Abaerostipes*	Ma et al. [214]
Bipolar disorder	*Clostridiaceae*, *Flavonifractor*, *Collinsella*, *Curiobacteria*, *Actinobacteria*	*Faecalibacterium*, *Ruminococcaseae*	Lai et al. [215]

gut microbiota, with effects evident both between sexes and among women across menopausal transitions [216]. Microbial metabolites such as SCFAs, bile acids, polyamines, and indole derivatives act as molecular mediators linking microbial activity to host metabolic and immune regulation during aging [217]. Their production is influenced by diet, age, and sex-related hormonal factors [218]. Studies indicate that bile acid profiles and indole metabolites vary with sex and age, while SCFAs exhibit more context-dependent changes [219, 220]. Mechanistic insights highlight sex-dependent pathways involving SCFA decline, estrobolome activity, trimethylamine N-oxide (TMAO) production, and bile acid remodeling. However, human data remain limited by the lack of sex-stratified and hormone-informed analyses. From a precision-nutrition perspective, postmenopausal women, characterized by reduced estrobolome activity and SCFA production, may benefit from high-fiber, plant-based, and polyphenol-rich diets that enhance microbial diversity and anti-inflammatory capacity. In contrast, older men, with higher TMAO and phenylacetylglutamine (PAGln) levels, may benefit from reducing red meat and choline-rich foods while increasing omega-3 and fermentable fiber intake to lower cardiometabolic risk [221]. Sex influences how diet and the gut microbiota interact to shape metabolic and immune processes that drive aging. Integrating sex-specific biology into nutritional research is essential for designing tailored dietary strategies to promote longevity and health span [221].

Effect of Diets on Microbiota-gut-brain Axis

Diet significantly modulates inflammation; diets high in fiber, such as the Mediterranean diet, are associated with reduced inflammatory markers [141]. This diet is rich in whole grains, nuts, vegetables, fruits, and limited animal products such as fish and poultry. It is associated with lower risks of neurovegetative, psychiatric, cardiovascular diseases, and cancer [222, 223]. Maternal high-fat diets can alter microbiota and brain development in offspring [224], while generally high-fat diets reduce *Bacteroidetes* and increase *Proteobacteria* and *Firmicutes* [225]. Conversely, ketogenic diets may inhibit neurodegenerative diseases by elevating serum ketone, which enhances mitochondrial function. These increased levels of *Akkermansia*, *Parabacteroides*, *Sutterella*, and *Erysipelotrichaceae* improve mitochondrial function and seizure resistance [226, 227]. The introduction of solid foods for infants provides diverse substrates that support the microbial development of enzymatic systems [228]. Microbial fermentation of dietary fiber produces short-chain fatty acids, which have anti-inflammatory properties [229] and may mitigate age-related chronic inflammation. Microbiome studies of older adults, particularly those residing in long-term care facilities, have shown lower fiber intake [65], suggesting a diet-related loss of several beneficial taxa, including *Akkermansia* and *Christensenellaceae*, potential producers of SCFAs [152, 153]. This reduction may contribute to the inflammation associated with aging [230]. Moreover, the microbial metabolism of dietary compounds significantly influences health and age-related diseases. Additionally, gut microbes metabolize dietary polyphenols found in nuts, fruits, and chocolate into bioactive compounds. A dietary intervention involving polyphenol supplementation in older adults has been shown to improve gut barrier integrity and reduce inflammation [231].

Microbiota-Gut-Brain Axis Modulating Gene Expression

Bravo et al. [232] demonstrated that prolonged feeding of *Lacticaseibacillus rhamnosus* in mice altered brain GABA gene expression in a region-dependent manner. Hoban et al. [233] observed dysregulated microRNAs in the amygdala and prefrontal cortex of germ-free (GF) mice, linking microbiota to brain function. Chen et al. [234] found that while the re-colonization of gut microbiota restored microRNA/mRNA expression, it did not reverse behavioral changes in GF mice. A Danish study introduced the concepts of high-gene-count (HGC) and low-gene- count (LGC) microbiomes, both of which are associated with digestive health [235]. The HGC group, with a more functionally diverse microbiome, showed a reduced risk of metabolic disease and obesity. Key features include increased butyrate-producing organisms, greater hydrogen production capacity, and reduced hydrogen sulfide production. In contrast, the LGC group had a higher abundance of pro-inflammatory bacteria, which predisposed individuals to inflammatory bowel disease (IBD) and related disorders [236]. These gut-brain interactions are conserved across species, as demonstrated by *L. rhamnosus* modulating brain-derived neurotrophic factor and serotonin-related genes in zebrafish [237]. Additionally, the functional profile of the gut microbiome changes with age, reflecting shifts in metabolic pathway activities [230].

Microbiota-Gut-Brain Axis Regulating Immunity

The human body hosts trillions of microbes, primarily in the gut, that maintain a symbiotic relationship with the host. Microbiota also regulate immunity and metabolism via the microbiota-gut-brain axis [238]. Aging significantly alters the gut microbiome composition [239], promoting chronic low-grade inflammation known as inflammaging [239, 240]. This inflammatory state is associated with compromised gut

and blood-brain barrier integrity, allowing for the translocation of antigen and systemic inflammation [241, 242]. Inflammaging, which is further marked by oxidative stress and cellular senescence, underlies numerous age-related conditions such as cardiovascular disease, metabolic syndrome, and chronic kidney disease [243–245]. These processes are modulated through signaling pathways within the microbiota-gut-brain axis [246].

Chronic, age-related inflammation also affects physiological processes, such as the body's ability to maintain muscle protein synthesis, and insulin sensitivity, which contribute to conditions like sarcopenia and frailty [247, 248]. This inflammatory condition often begins in the gut. In disorders like IBS, an abnormal microbiome can trigger immune responses that damage the intestinal lining, heightened pain sensitivity, and disrupt the gut's own nervous system [196, 249, 250]. Dysfunction of the gut-brain axis compromises gastrointestinal motility and secretory processes, leading to enteroendocrine and immune dysregulation [196, 251]. GI tract inflammation in the gut releases cytokines and neurotransmitters into the bloodstream, particularly when intestinal permeability, or "leaky gut," is present. These inflammatory molecules can then compromise the blood-brain barrier, thereby affecting brain function [252, 253]. This process is now strongly linked to neuropsychiatric symptoms, including anxiety, depression, and memory loss [253–255]. The connection is so direct that inducing inflammation in healthy people can provoke depressive symptoms, tying cytokines like IL-6 and TNF-α directly to mood disorders [256], which can be mitigated by gut microbes. Gut bacteria produce metabolites such as SCFAs during the fermentation of dietary fibers and possess anti-inflammatory properties [229]. These compounds are believed to play a key role in counteracting chronic inflammaging in older adults.

Gut microbiota stimulate intestinal epithelial cells (IECs), which maintain immunity by eliminating pathogens and supporting commensals and mutualists [257]. IECs produce secretory IgA (sIgA), the dominant antigen-specific antibody in the gut, which coats pathogenic bacteria, preventing adhesion and disease [257, 258]. Symbionts such as *Lactobacillus* and *Dorea* receive less sIgA coating compared to pathobionts, allowing for selective immune tolerance [259]. In cases of increased gut permeability, systemic IgG enters the lumen and mounts immune responses primarily during inflammation [260]. IgG targets both pathogens (*Trichuris trichiura*, *Entamoeba histolytica*, *Salmonella*) and commensals (*Bacteroides fragilis*, *E. coli*), providing defense against microbial invasion [261]. Elevated systemic IgG may indicate microbial species capable of breaching the gut barrier and triggering immune activation, serving as potential markers of disease [206, 261]. IgA prevents translocation of symbiotic microbes, thereby reducing IgG-mediated systemic responses [261]. The gut microbiota play a critical role in localized gut immunity, systemic immune response, host neurodevelopment, and behavior. With age, changes in microbiota composition have been increasingly associated with age-related neurodegenerative diseases. Preclinical studies suggest that therapies targeting gut microbiota can improve behavioral outcomes by modulating microbial communities, metabolic outputs, and immune profiles [238].

Microbiota-gut-brain Axis Altering Metabolism

The gut microbiome acts as a vital partner in our metabolism, and its disruption (dysbiosis) has consequences that extend far beyond digestive comfort. By altering the microbial community, dysbiosis alters the levels of key metabolites, influencing overall health [206]. Key bacterial metabolites, like SCFAs, function much like hormones. SCFAs, mainly acetate, propionate, and butyrate, are principal metabolites derived from microbial fermentation of dietary fiber [262]. Beyond their intestinal roles, SCFAs act as critical signaling mediators within the gut–brain axis (GBA), regulating immune, metabolic, and barrier functions through interactions with enteroendocrine and immune cell receptors. By activating G-protein-coupled receptors (GPR43/FFAR2, GPR41/FFAR3, and GPR109A), SCFAs modulate anti-inflammatory signaling, lipid metabolism, and neuroplasticity [263–265]. At the epithelial level, butyrate enhances ATP production and triggers the cAMP– protein kinase A–CREB and Ca^{2+} pathways, leading to inositol 1,4,5-trisphosphate (IP_3)-mediated secretion of glucagon-like peptide-1 (GLP-1), PYY, and 5-HT [266–268]. This cascade increases vagal afferent excitability, enabling SCFAs to dynamically regulate autonomic and stress-related brain circuits in response to gut microbial metabolic activity [269]. They help regulate the immune system, communicate with nerves, and even cross the blood-brain barrier to support microglial cells [270]. When the SCFA balance is disrupted, it can impair these microglial cells, which have been linked to conditions such as autism [271, 272]. SCFAs also influence the production of serotonin by 95% of the body's supply and help maintain a healthy blood-brain [273, 274]. Altered gut serotonin levels can affect brain signaling and are observed in autistic children [275].

Tryptophan is primarily metabolized through three interconnected pathways, the serotonin (5-HT), kynurenine (Kyn), and indole pathways, each contributing to immune, metabolic, and neural regulation [276]. Approximately 95% of 5-HT is synthesized by enterochromaffin cells in the gut, where its production is modulated by microbial, nutritional, and hormonal signals [277]. Microbiome and metabolomic

studies reveal that reduced abundance of specific tryptophan-metabolizing bacteria correlates with depressive symptoms in adolescents [278]. Through the Kyn pathway, indoleamine 2,3-dioxygenase (IDO) converts tryptophan to metabolites such as 3-hydroxy-L-kynurenine (3-HK) and kynurenic acid (Kyna), which exert opposing effects, 3-HK enhances neuroinflammation via N-methyl-D-aspartate receptor activation. In contrast, Kyna suppresses microglial activity and cytokine release, reducing excitotoxicity [279, 280]. Additionally, microbiota-derived indole and its derivatives, including indole-3-acetic acid (IAA) and indole-3-propionic acid (IPA), act through the aryl hydrocarbon receptor (AhR) to regulate immune balance, attenuate neuroinflammation, and confer neuroprotection within the gut–brain axis [278, 281].

Bile acids, synthesized in the liver and subsequently transformed by gut microbiota into secondary forms such as deoxycholic and lithocholic acids, act as signaling molecules primarily through the farnesoid X receptor (FXR) and the G-protein-coupled bile acid receptor 5 (TGR5) [282]. Within the central nervous system, FXR is predominantly expressed in neurons of the hippocampus, cortex, and cerebellum, whereas TGR5 is more widely distributed in microglia and astrocytes [283, 284]. This spatial distinction implies that FXR primarily regulates neuronal excitability, synaptic plasticity, and neurotransmitter balance, while TGR5 modulates neuroimmune and neurovascular responses to bile acid-derived signals. FXR activation also influences neurotransmitter systems, including serotonin (5-HT) and γ-aminobutyric acid (GABA). Furthermore, bile acid synthesis and microbial biotransformation exhibit marked sex-dependent differences, as sex hormones shape hepatic bile acid composition and the abundance of bile acid-converting gut taxa, resulting in distinct bile acid pools and receptor activation patterns between male and female APP/PS1 transgenic Alzheimer's disease mice models [285].

The gut microbiota produces several key neurotransmitters and their precursors, such as serotonin (5-HT), dopamine (DA), GABA, and glutamate (Glu) that play crucial roles in gut–brain axis communication, influencing both peripheral and central neural activity [286]. GABA, synthesized by microbial taxa including *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*, supports intestinal integrity by regulating mucin production and tight-junction proteins, and by transmitting neural signals to the brain via vagal nerve pathways [287]. Supplementation with GABA-producing *Lactobacillus* strains enhances gut barrier function and elevates brain GABA concentrations, thereby reducing neuroinflammation and oxidative stress. These neuroprotective effects have been demonstrated in experimental models of essential tremor, autism spectrum disorder (ASD), and anxiety/depression [288–290].

GABA is crucial in psychiatric conditions due to its role in inhibitory tuning [291], since a reduced GABAergic activity is considered a depression hallmark [292]. Microbial-derived GABA influences systemic GABA levels and brain function, affecting behavior and connectivity [293]. Higher GABA degradation correlates with greater depression severity. Depressed individuals exhibit elevated GABA degradation and diminished biosynthesis [294], which affects both depression and cognitive aging [295]. Greater GABA degradation correlates with increased severity of current depressive symptoms [210]. Functional associations of GABA suggest that lower glutamate degrading potential may reflect increased glutamate excitotoxicity, contributing to neurodegeneration [296], and a higher histamine synthesizing potential supports the role of neuroinflammation in the pathogenesis of dementia [297].

Conversely, harmful metabolites can arise from an imbalanced gut. Lipopolysaccharide from certain enterobacteria can leak into the bloodstream, triggering inflammation associated with depression [298]. Trimethylamine (TMA), a metabolite derived from choline metabolism by gut microbiota, crosses the intestinal epithelial barrier into the bloodstream and is transported to the liver. There, it is oxidized to TMAO by flavin-containing monooxygenases (FMO1 and FMO3) [299]. Initially regarded as a biologically inert waste product, TMAO is now recognized as a key metabolite influencing human health. Elevated plasma TMAO levels are strongly associated with cardiovascular diseases [300] and have been shown to enhance platelet reactivity [301]. Although early research primarily focused on its role in cardiovascular diseases, emerging evidence links TMAO to cancer, neurodegenerative disorders, and type 2 diabetes mellitus. While part of the circulating TMAO is excreted renally, residual amounts can persist in the bloodstream, inducing systemic inflammation, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and impaired physiological homeostasis. As a prominent gut microbiota–derived metabolite, TMAO holds substantial potential as a biomarker for disease prediction and progression monitoring, as well as for the development of personalized therapeutic strategies [299]. Similarly, when microbes produce choline from animal products, they convert it into trimethylamine, which is then converted into TMAO, a compound that promotes atherosclerosis [300]. This process becomes more pronounced with age, as the microbial pathways for TMAO production become more prevalent [302].

According to Kolobaric et al. [210], an individual's susceptibility to future cognitive decline can be predicted by several factors. These include lower initial cognitive scores, reduced levels of the gut bacterium of *Intestinibacter*, impaired glutamate degradation, and elevated histamine production. The likelihood of worsening depressive

symptoms is associated with higher initial levels of depression and anxiety, poor cognitive performance, a diagnosis of diabetes, a lower abundance of *Bacteroidota*, and reduced glutamate degradation [210].

Probiotics: Pathways to Improve Health

The FAO/WHO defines probiotics as live microorganisms that provide health benefits when consumed in adequate amounts (~ 1×10^9 CFU/day) [303]. An ideal probiotic must meet stringent criteria, including safety, survival in the GI tract, adhesion to the epithelium, and beneficial immunomodulation without toxicity [304, 305].

A primary pathway for their effect is the microbiota-gut-brain axis. Probiotics influence the CNS by modulating metabolic, immune, and neural pathways [306, 307]. Specific psychobiotics exert antidepressant and anxiolytic effects by modulating neurotransmitter activity [308, 309]. Dysbiosis, notably reduced levels of *Bifidobacterium* and *Lactobacillus*, is linked to depression [310] and other cognitive disorders [211]. Beyond mental health, probiotics, prebiotics, synbiotics, and postbiotics (their metabolites such as SCFAs) have potential for managing conditions ranging from constipation to cardiovascular disease. Diet plays a crucial role, as various foods [223] and spices can enrich beneficial microbiota through mechanisms such as vagus nerve signalling and neuroimmune regulation [311, 312].

The gut microbiota directly synthesizes neurotransmitters [313], and specific beneficial microbes (e.g., *Faecalibacterium prausnitzii*) support cognitive health by producing SCFAs and regulating metabolism [314]. Dysbiosis, marked by reduced SCFA producers and a rise in pathogens, is associated with a range of psychiatric and physical disorders. Interventions with probiotics (especially *Lactobacillus* and *Bifidobacterium*), postbiotics (e.g., heat-inactivated *Akkermansia*), and fecal transplantation are recognized treatments for conditions like *C. difficile* infection [315, 316] and show promise for IBD, metabolic disorders, and cancer [317–319].

Lactobacillus species that have been granted GRAS/QPS status, are among the most extensively studied probiotics [320]. Effects are strain-specific, although some, such as *L. rhamnosus* GG show broad efficacy [321]. Current research is pivoting towards postbiotics, isolated bioactive components such as bacteriocins, SCFAs, and cell fragments, to develop more targeted, effective, and stable therapies than live microbes [322].

The historical focus on live bacteria is shifting. Research is increasingly focused on postbiotics, the specific bioactive compounds (e.g., SCFAs, enzymes, cell fragments) produced by probiotics. This represents a significant advancement, as the use of defined postbiotics could offer more targeted, consistent, and safer therapeutic options without the challenges of maintaining bacterial viability during storage and digestion. This strategy, from whole microbes to their functional components, represents the future of precision microbiome therapy.

Epithelial Cell Barrier Integrity Maintenance

Stress alters intestinal permeability, allowing bacterial antigens, such as LPS, to enter the circulation and cause systemic adverse effects [323]. Acute stress disrupts colonocyte differentiation and reduces the expression of tight junction (TJ) proteins [324]. This "leaky gut" is implicated in a wide range of GI, inflammatory, metabolic, and neurological disorders [325, 326], including specific IBS and allergic subtypes [327]. The GI mucosal barrier is a multi-layered system comprising: (a) commensal microbiota, (b) a mucus layer with secretory immunoglobulin A (sIgA) and antimicrobial peptides, (c) an intestinal epithelial cell (IEC) monolayer, and (d) the gut-associated lymphoid tissue (GALT) [328]. This barrier is vital for nutrient absorption and immune surveillance while blocking pathogens [329].

TJ integrity, maintained by proteins such as claudin, occludin, and ZO-1, which is connected to the actin cytoskeleton, is crucial [241]. Many enteric pathogens (e.g., *Listeria monocytogenes*, *C. difficile*, *E. coli*, *Salmonella*) disrupt TJs to breach the barrier [241, 330, 331]. Probiotics, particularly *Lactobacillus* strains, help maintain TJ integrity [191]. Their mechanisms include enhancing mucus and antimicrobial peptide secretion, stimulating sIgA production, directly strengthening TJ integrity, and competing with pathogens for adhesion sites [304, 331–334].

Specific strains demonstrate efficacy, like *Lactiplantibacillus plantarum*, which upregulates ZO-1 and occludin expression via TLR-2 activation [335] and enhances TJ gene expression in human biopsies [336]. *Lacticaseibacillus rhamnosus* GG (LGG) upregulates ZO-1, claudin, and occludin [337], protects against *E. coli* O157:H7 [338] and promotes TJ formation via NLRP3 inflammasome inhibition [339]. LGG expresses adhesive pili, facilitating strong mucosal adhesion and biofilm formation, thereby aiding persistence [340]. It also reduces intestinal permeability, supports the blood-brain barrier, and shows superior adhesion [246, 288, 341].

Lactobacilli use surface structures (e.g., LPXTG-motif proteins, S-layer proteins, pili, moonlighting proteins) for adhesion and competition with other microbes. For example, S-layer proteins in *L. acidophilus* exhibit antiviral activity [342] and SpaC pili in LGG outcompete *Enterococcus faecium* for sites [343]. Some moonlighting proteins

perform dual roles, including serving as surface adhesion proteins [344, 345].

An intact gut barrier is paramount, and its compromise ("leaky gut") is a plausible root cause for a stunningly diverse array of diseases far beyond the GI tract. This systems-level view moves away from treating isolated symptoms and towards addressing a common underlying dysfunction. The detailed mechanistic evidence for specific probiotic strains is the most compelling aspect. It moves the field beyond vague claims to a molecular understanding of how they work. The fact that *L. plantarum* and LGG act through distinct receptors (TLR-2 vs. NLRP3) yet converge on the same outcome, enhanced TJ integrity, is a crucial insight. It suggests a multi-pronged therapeutic strategy, which could be most effective. This research validates a targeted, strain-specific approach to probiotics. The future lies not in generic "lactobacilli" supplements but in clinically validated strains, such as LGG, selected for their proven mechanisms.

Mucus Production

The intestinal lining is protected by a mucus layer, a gel-like shield produced by Goblet cells. This mucus, primarily composed of the glycoprotein MUC2, forms a vital barrier that protects delicate gut tissues from digestive juices and harmful pathogens while aiding digestion [329].

Beneficial *Lactobacillus* species play a key role in fortifying this barrier. Research shows that they stimulate the production of protective mucus by upregulating the MUC2 gene, even when pathogens like *C. difficile* challenge the gut [346]. They also help maintain and restore Goblet cell numbers and mucus thickness during inflammation [347]. For instance, specific strains of *Limosilactobacillus reuteri* have been shown to reduce the severity of colitis in mice, an effect linked to their ability to increase mucus production [348]. Similarly, the multi-strain probiotic formula VSL#3 has been demonstrated to enhance the mucus layer in laboratory and animal models by increasing the expression of key mucin genes [349].

Antimicrobial Peptides/Factors

Lactic acid-producing bacteria (LAB), common in probiotics, defend the gut through a multi-pronged strategy. They outcompete harmful microbes for nutrients and space while producing a potent arsenal of antimicrobial compounds. This arsenal includes organic acids (such as lactic and acetic acid) that lower the gut pH, as well as specialized antimicrobials, including bacteriocins, hydrogen peroxide, and antifungal peptides [350, 351]. Certain LAB, known as heterofermentative strains, generate an even wider range of inhibitory metabolites, including various acids, gases, and aromatic compounds [352]. Such activities are crucial for maintaining a balanced gut ecosystem. Major bacterial phyla in a healthy gut work together to crowd out pathogens and produce their own antimicrobials, creating a stable environment that resists invasion [329]. For older adults with a declining immune system, this probiotic-mediated protection against enteric pathogens can be a significant factor in preserving quality of life.

The gut lining produces its own natural antibiotics known as antimicrobial peptides, with cathelicidins and defensins being key players in frontline immunity [329]. Cathelicidins are constantly present in the gut and can be enhanced by butyrate, a beneficial metabolite produced by gut bacteria. However, the influence of probiotics on cathelicidin levels remains understudied. Defensins, another primary class, are small peptides that attack a broad spectrum of microbes, including bacteria, fungi, and viruses. Interestingly, specific probiotics, such as *L. acidophilus* and *L. fermentum*, have been shown to enhance this defense by triggering the production of human β-defensin-2 in gut cells, albeit through pro-inflammatory signaling pathways [353].

Probiotics play a crucial role in maintaining a healthy gut ecosystem, which is essential for overall well-being. Certain bacteria, such as *Bacteroides* species, are emerging as next-generation probiotics because they can directly communicate with our immune system and regulate metabolic processes [354]. Beyond well-known genera, specific strains produce potent, targeted antimicrobials. For example, some *Lactobacillus crispatus* strains secrete phenyl-lactic acid, a compound effective even against multidrug-resistant pathogens [355]. Other lactobacilli produce specialized proteins, such as psoriasin, to combat uropathogens, or bacteriocins like Abp118 from *L. salivarius*, which has been shown to protect mice from lethal infections [356, 357]. A cutting-edge area of research involves bacterial extracellular vesicles (EVs)—nanoscale particles that can carry diverse cargos. Pathogens like *Streptococcus pneumoniae* use EVs to deliver toxins [358]. Beneficial bacteria also produce them; for example, EVs from *Streptococcus thermophilus* show promise as "postbiotics" that can beneficially modulate the host's immune response [359].

Secretory Immunoglobulins

Secretory IgA (sIgA) acts as a primary guardian in the gut, providing robust immune defense without triggering significant inflammation [360]. This antibody is produced locally in the gut lining, transported across the epithelial cells, and released into the intestinal lumen where it interacts directly with the microbial environment [361]. Its functions are essential for maintaining harmony. sIgA helps manage the

gut ecosystem by neutralizing pathogens and dietary antigens while preventing commensal bacteria from expressing pro-inflammatory signals [362]. It also blocks microbes from adhering to the gut wall and helps remove any that breach the epithelial barrier [363]. Probiotics, particularly lactobacilli, can enhance this protective system. Studies have shown that they increase intestinal sIgA levels [364, 365]. For instance, a clinical trial in children found that *L. plantarum* supplementation increased fecal sIgA, likely by promoting TGF-β1 activity, an immunoregulatory cytokine [366]. Furthermore, lactobacilli help regulate gut immunity by calming pro-inflammatory pathways, such as those involving Th17 cells and TNF-α, which may contribute to their broader role in supporting metabolic and bone health [367–369].

Neuroendocrine Homeostasis

The gut microbiome acts as a key interpreter in the gut-brain axis, significantly influencing our body's response to stress and even our eating behavior. It does so partly by regulating the hypothalamic-pituitary-adrenal axis, the body's central stress-response system. Studies in germ-free mice with a hyperactive hypothalamic-pituitary-adrenal axis and elevated stress hormones highlight the essential role of gut bacteria in maintaining balance [370]. Importantly, this imbalance can be corrected. Specific probiotic strains from the *Lactobacillus* family (such as *L. rhamnosus* and *L. plantarum*) have been shown to calm this overactive stress response, reducing circulating levels of stress hormones and promoting psychoneuroendocrine homeostasis [371, 372]. Beyond stress, the gut is now recognized to possess a "neurobiotic sense", a gut-based sensory modality whereby specialized epithelial and neuropod cells decode microbial-derived signals (e.g., SCFAs, peptide ligands, 5-HT, and microbial-associated molecular patterns) and rapidly relay them via vagal and spinal afferents to brain regions involved in appetite regulation, stress responsivity, and cognitive circuits. This concept integrates emerging evidence that gut microbes and their metabolites modulate hypothalamic and brainstem pathways in real time, shaping feeding behavior, emotional state, and possibly cognitive resilience in aging [250, 373]. This suggests that modulating our gut microbiota through probiotics could be a powerful strategy for sending beneficial signals to the brain, potentially helping to guide healthier food choices and manage cravings [373].

Modulating the GI Tract and Other Infections

Probiotics help maintain intestinal health and mitigate various risk factors [374]. Lactobacilli prevent pathogen adhesion by competing for epithelial binding sites, thereby collectively reducing the risk of intestinal damage during bacterial infections [329]. Lactobacilli have demonstrated inhibitory effects against a variety of pathobionts, including *Clostridioides difficile* and *Clostridium perfringens* [375], *Salmonella enterica* [376], *Campylobacter jejuni* [377], *Staphylococcus aureus* [378], *Escherichia coli* [379], and *Yersinia* spp [380]. Clinically, *Lactobacillus* species have demonstrated therapeutic potential in mitigating symptoms of several gastrointestinal disorders, including acute infectious diarrhea, *C. difficile*-associated diarrhea, antibiotic-associated diarrhea, and inflammatory conditions such as ulcerative colitis and IBS [381]. Specific species such as *L. jensenii* and *L. gasseri* have demonstrated potent antimicrobial activity [382, 383], while *L. crispatus*, prevalent in healthy genitourinary tracts, is considered to have strong protective ability among lactobacilli [384–386]. Scientific evidence supports the benefits of specific probiotics in managing various GI tract diseases, including IBS, IBD, *H. pylori* infection, and other digestive disorders.

Additionally, probiotics have shown potential to address allergic conditions, such as atopic dermatitis, as well as metabolic and systemic diseases, including insulin resistance syndrome, type 2 diabetes, obesity, and non-alcoholic fatty liver disease, and in promoting immune, metabolic, and brain health [248]. The potential of probiotics is also being examined as an adjunctive therapy for the treatment and inhibition of COVID-19 [387]. Among infection-related gastrointestinal disorders, *H. pylori* infection and antibiotic-associated diarrhea appear to be exceptionally responsive to therapeutic interventions involving *Lactobacillus* species. IBS, a functional gastrointestinal disorder, is characterized by dysregulation of the gut-brain-microbiota axis. The estimated prevalence of IBS ranges from 4% to 10%, depending on the geographical location and analytical standards used [388, 389]. Clinical evidence suggests that an eight-week course of *Bifidobacterium longum* 35,624® resulted in a significant and clinically meaningful improvement in symptoms in a representative adult IBS population [390].

H. pylori infection is considered one of the most prevalent bacterial infections globally, affecting over 50% of the world population, with prevalence ranging from 24% in Oceania to 70% in Africa [380]. *H. pylori* colonizes the gastric epithelium lining, leading to various GI tract conditions, including chronic gastritis, peptic ulcer disease, and gastric cancer. However, many individuals remain asymptomatic [391]. Standard treatment typically includes multiple antibiotics and a proton pump inhibitor; however, its efficacy is declining due to increasing antibiotic resistance among *H. pylori* strains. Several randomized controlled trials have reported that supplementation with *L. casei* Shirota, *L. casei* DN-114 001 (OAC-LC), and *L. acidophilus* LB can increase

the effectiveness of treatments [392]. However, the results are mixed, with some studies reporting minimal or no benefit from probiotic supplementation [393, 394].

Antibiotic-associated diarrhea (AAD) results from disruption of the normal gut microbiota due to antibiotic use. It presents with signs ranging from mild diarrhea to severe conditions such as pseudomembranous colitis (PMC) [395]. AAD happens in about 5–30% of patients during or up to two months after antibiotic treatment. *C. difficile* is the primary pathogen linked to AAD [396], accountable for 10–30% of distinctive AAD cases and 90–100% of critical cases, such as PMC. Other associated but less common pathogens include *Staphylococcus aureus*, *C. perfringens*, and *Klebsiella oxytoca*.

With increasing concerns about antimicrobial resistance, recent therapeutic strategies have emphasized fecal microbiota transplantation (FMT) and the use of probiotics to reestablish microbial equilibrium [397]. Although the mechanisms underlying probiotic effects in AAD remain unclear, proposed benefits include microbiota stabilization, pathogen inhibition, preservation of barrier integrity, and immune modulation. Several *Lactobacillus* species, including *L. gasseri* and *L. rhamnosus* GG (ATCC 53103), have shown preventive efficacy against AAD [398]. A structured review of 51 randomized controlled trials found *L. rhamnosus* GG to be remarkably more potent than other probiotics. *L. casei* strains were found to be most efficacious specifically against *C. difficile* infection [399]. A separate review focusing on children confirmed the safety and effectiveness of *L. rhamnosus* GG in both preventing AAD and managing acute gastroenteritis symptoms [400]. Furthermore, probiotics show promise for reducing antibiotic use; thus, they can be used as a substitute for antibiotic therapy or to promote growth performance in animal health [401].

Stable colonization and adhesion to the mucosa, accompanied by subsequent immunomodulatory and anti-inflammatory activities, are critical for probiotic-mediated health benefits in aging populations [402–404]. Probiotic effects are often strain-dependent or host-specific; thus, a bioengineering approach may be necessary to improve probiotic functionality, especially in a dysbiotic gut. Next-generation probiotics (NGP) have been developed by expressing desirable traits, including adhesion molecules, enzymes, cytokines such as IL-27 and IL-10, and growth factors, thereby enhancing immunomodulatory responses and anti-infective properties [405, 406]. *Lacticaseibacillus casei* strains expressing the invasion protein, InlAB, reduced *L. monocytogenes* infection in an in vitro cell culture model [407, 408]. Likewise, the cloning and expression of *Listeria* adhesion protein (LAP), also known as acetaldehyde alcohol dehydrogenase (AdhE) in *L. paracasei* and *L. casei* prevented *L. monocytogenes* interaction with the human intestinal epithelial cells in vitro [409] and in a mouse model by competitive exclusion, tightening the epithelial cell junction barrier, and immunomodulation [333, 410]. This NGP also prevented the fetoplacental transmission of *L. monocytogenes* infection in the laboratory animal model (pregnant guinea pig) [411]. The application of such bioengineered strains should increase stable colonization, biofilm formation, and improved gut barrier function, thereby preventing enteric diseases in the aging population as their immune systems become weaker.

Psoriasis is a chronic, immune-mediated inflammatory skin disease characterized by well-demarcated, erythematous, and scaly plaques, with a global prevalence of approximately 2–4% [412]. Probiotics modulate the gut microbiome, helping to stabilize immune responses and reduce generalized inflammation, which supports their therapeutic role in conditions like psoriasis, where inflammation is already present [413]. By regulating the microbiome, probiotics support the gut-skin axis, thereby mitigating symptom severity in inflammatory skin conditions [414–416]. However, they are less effective in addressing the genetic and environmental factors that trigger disease onset. Research findings indicate no significant relationship between probiotic consumption and the risk of developing psoriasis in the general population. However, probiotic supplementation has been shown to reduce psoriasis symptoms, supporting its use as a potential management strategy for the condition [416, 417].

Current research on probiotics focuses on identifying disease- and strain-specific probiotics to enhance the therapeutic effectiveness. Most promising probiotic outcomes have been demonstrated in pre-clinical models across various medical fields, including gastrointestinal, psychiatric, cardio-metabolic, dermatological, gynecological, neurological, and oncological domains [418, 419].

Controlling Intestinal Inflammation

The human immune system comprises innate and adaptive pathways. Innate immunity provides immediate, non-specific defense via phagocytic cells (macrophages, monocytes, neutrophils, eosinophils) and antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, which bridge to adaptive immunity. Adaptive immunity relies on the activation of B and T cells, with B cells mediating humoral immunity by secreting antibodies [329]. Lactobacilli in the GI tract strengthen the intestinal barrier and shield against pathogenic microorganisms by modulating both innate and adaptive immune responses. This immunomodulatory effect is mediated through microbial-associated molecular patterns (MAMPs), which engage pattern recognition receptors, including Toll-like receptors (TLRs),

nucleotide-binding oligomerization domain (NOD) receptors, and C-type lectins, expressed on intestinal epithelial and immune cells [420]. Dempsey and Corr [329] reported that the immunomodulatory effects of lactobacilli are mediated by cytokines [interleukins (IL), interferons (IFN), TNF, transforming growth factor (TGF)], and chemokines, influencing the balance of pro- and anti-inflammatory responses. Immunoregulatory probiotics promote the Treg cell population and IL-10 production, thereby mitigating inflammatory conditions like autoimmune diseases, IBD, and allergies. IL-10, produced by various immune cells, inhibits pro-inflammatory signaling, protecting against intestinal inflammation.

Probiotics are widely used as adjunctive therapies for the management of AAD, IBS, and pediatric allergic diseases. The most frequently administered probiotic strains include *Weizmannia coagulans* (formerly *Bacillus coagulans*), *Lacticaseibacillus rhamnosus*, *Alkalihalobacillus clausii* (formerly *Bacillus clausii*), *Limosilactobacillus reuteri*, and *Saccharomyces boulardii* [421]. Specifically, peptidoglycans from *L. casei* Shirota, *L. johnsonii* JCM 2012, and *L. plantarum* ATCC 14,917 down-regulate IL-12 via TLR2 [422]. *L. rhamnosus* CRL1505 peptidoglycan enhances innate and adaptive responses, ameliorating Th2 responses [423]. *L. plantarum* LTA elicits anti-inflammatory effects in intestinal epithelial cells by inhibiting IL-8 [424, 425]. *L. rhamnosus* GG SpaCBA pili, crucial for adhesion, also modulate IL-8, suggesting an immunomodulatory role [426]. *L. delbrueckii* subsp. *bulgaricus* OLL1073R-1 EPS stimulates NK cells and IFN-γ production [427]. Furthermore, *Lactobacillus* metabolites, particularly SCFAs (propionate, acetate, butyrate), inhibit pro-inflammatory activity and Treg suppression by binding to epithelial cell receptors [428, 429].

Probiotics and, more recently, postbiotics, which are metabolic products of probiotic fermentation, have been shown to modulate signaling biomolecules involved in immunity, inflammation, metabolism, and oxidative stress [430]. In line with the International Scientific Association of Probiotics and Prebiotics (ISAPP), postbiotics, defined as preparations of inanimate microorganisms and/or their components, non-viable bacterial harvests or metabolic byproducts such as cell lysates (CLs), enzymes, and cell wall remnants derived from probiotic bacteria, are emerging as promising replacements to live probiotics due to their stability and health-promoting effects [322, 431]. A recent in vitro study evaluated the anti-inflammatory potential of cell lysates derived from *L. plantarum* (LP CL) and *L. rhamnosus* GG (LR CL) in the human intestinal epithelial cell line HT-29 [432], focusing on their ability to inhibit virus-induced inflammatory responses. Disruptions in gut microbiota homeostasis can overstimulate inflammatory responses, contributing to chronic disease by downregulating anti-inflammatory signaling [433]. Postbiotics have shown potential to mitigate pro-inflammatory signalling and reduce cytokine storm, making them a promising adjuvant therapeutic protocol for conditions such as SARS-CoV-2 [434]. Postbiotics derived from *B. longum* CECT7347- demonstrated notable anti-inflammatory effects and alleviated GI tract disturbances via targeted immune responses [435]. In contrast, *Lactococcus lactis*-derived bacteriocins increased IL-6 and IL-1β production in porcine immunocytes, promoting differentiation and proliferation of T- and B-cells [436]. Bacteriocins, extracellular peptides produced by LAB, have been associated with substantial anti-inflammatory activities [437, 438] and have been reported to suppress inflammation caused by intestinal and urogenital infections [439].

Lactobacillus species in the gut interact with the gut epithelium to preserve gut barrier integrity, mucosal defense, and modulate host immune responses [347, 440]. Inflammatory diseases affecting the gut, heart, lungs, bones, and neural tissues, are common in humans. Increasing evidence indicates that *Lactobacillus* spp. and their components (e.g., metabolites, peptidoglycans, surface proteins) modulate the immune system through immunological signaling between the gastrointestinal tract and distant organs. The bidirectional (gut-brain) crosstalk of *Lactobacillus* species promotes anti-inflammatory responses, aiding in the management of conditions such as asthma, chronic obstructive pulmonary disease (COPD), neuroinflammatory diseases (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis), cardiovascular diseases, IBD, and other chronic infections in humans. Metabolic syndromes such as obesity and diabetes, characterized by low-grade inflammation, are alleviated by *Lactobacillus* species through the regulation of oxidative stress and inflammatory mechanisms [440]. Osteoporosis involves bone inflammation and resorption [441]. *Lactobacillus*, along with its metabolites, acts as a potent regulator of immune cells, aiding in the control of bone resorption and formation, thereby promoting bone health [367, 440].

Probiotics: Modulating Microbiota Gut-brain Axis

Gut microbiota dysbiosis can modify brain structure, vascular physiology, and blood-brain barrier permeability, potentially leading to neurological ailments and cognitive decline [13]. Gut microbiota modulation may influence hippocampal function, with bacterial toxins such as lipopolysaccharides and amyloid beta (Aβ) impacting the vagus nerve, immune (cytokine-related), and systemic (hormonal/neurotransmitter-related) pathways, thereby increasing permeability of the blood-brain and intestinal barriers, and impairing hippocampal function [17]. Disruption of gut microbiota can

contribute to adverse effects on mental health; therefore, restoring gut microbiota is a potential strategy to enhance mental well-being [18]. The gut microbiota is a promising target for preventing and treating cognitive deficits [14, 15]. The gut microbiota influences brain development and functions, including microglia and astrocyte polarization, neurotransmission, neurogenesis, and myelination [16]. Probiotic supplementation can alter the structure and diversity of the gut microbiota, restore gut ecosystem balance, and serve as a potential intervention for cognitive impairments [23, 24]. Gut microbiota dysbiosis, frequently associated with diarrhea, should be evaluated in conjunction with symptoms such as abdominal distension and pain, as well as underlying conditions and patient-specific risk factors.

The production of antioxidants (such as butyrate, glutathione, and folate), antioxidant enzymes (including catalase and superoxide dismutase), and metal ion chelators by probiotics helps reduce oxidative stress. They may also suppress inflammatory responses by inhibiting TLR activation, thereby improving BBB integrity and neurological function [26, 442]. Probiotics can increase cognitive function in individuals with depression by reducing HPA axis dysfunction, enhancing monoamine levels, and promoting neuroplasticity [26]. They are linked to increased brain-derived neurotrophic factor (BDNF) expression, which is associated with improved cognitive performance [443]. Long-term probiotic supplementation increases peripheral tryptophan levels, supporting mental health, and enhances serotonin synthesis by upregulating enzymes involved in its synthesis [444]. Probiotics also modulate 5-HT receptors, dopamine levels, and c-Fos protein, thereby affecting central nervous system biochemistry [445]. Probiotics positively influence neurotransmitters and neuromodulators, including GABA, serotonin, dopamine, acetylcholine, norepinephrine, N-acetylaspartate, and glutamate, thereby modulating brain function through various metabolic pathways [446, 447].

The gut microbiota generates numerous metabolites and reactive molecules by metabolising dietary components and xenobiotics, influencing both intestinal and systemic physiology [448]. Key microbial metabolites, including SCFAs, tryptophan derivatives, serotonin, indole, GABA, and bile acids, which serve as essential signaling molecules in host–microbe interactions, regulating host metabolism and health. Increasing evidence shows that probiotics can modulate the secretion of these bioactive compounds, facilitating bidirectional communication along the gut–brain, gut–lung, gut–liver, and gut–heart axes [449], thereby contributing to disease prevention and health improvement. SCFA-producing probiotics play a critical role in maintaining metabolic homeostasis and intestinal integrity. Several strains have shown efficacy in alleviating metabolic disorders, IBD, and cancer [450]. For instance, *Lactococcus lactis* G15 and Q14 improved epithelial barrier function, repaired glucose intolerance, and lowered lipid levels in type 2 diabetic mice by activating the SCFA-producing bacteria-related GPR43 pathway and modulating tight junction proteins [451]. Similarly, *Bifidobacterium animalis* ssp. *lactis* GCL2505 reduced visceral fat, improved glucose tolerance, and elevated acetate and GLP-1 levels, suggesting that increased acetate production mediates metabolic benefits [452]. SCFAs also exert neuroprotective effects. *Roseburia hominis*, a candidate psychobiotic, mitigated neuroinflammation by producing butyrate and propionate, which inhibit histone deacetylases [453]. Moreover, probiotics such as *Lactobacillus acidophilus* increased SCFA levels and activated G protein–coupled receptors to suppress NLRP3 inflammasome activity and promote autophagy in ulcerative colitis models [454].

Dysregulation of the tryptophan–kynurenine (Trp–KYN) pathway, which is linked to neurodegenerative and autoimmune diseases, can also be modulated by probiotics. *Lactobacillus* species reduce stress-induced increases in kynurenine by inhibiting intestinal indoleamine 2,3-dioxygenase (IDO1) activity [455]. In clinical studies, *Lactobacillus plantarum* 299v improved cognitive performance and enhanced SSRI (selective serotonin reuptake inhibitors) therapy in patients with major depressive disorder by reducing kynurenine levels [456]. Similarly, supplementation with *L. helveticus* and *Bifidobacterium longum* for 8 weeks improved depression scores and reduced the serum KYN/Trp ratio [457]. An imbalance in GABA metabolism is implicated in neurological conditions such as Alzheimer's disease and bipolar disorder [458]. Probiotics like *Lactobacillus reuteri* can modulate GABAergic transmission, restoring fear memory and ameliorating autism-like behaviors in mice [459]. In humans, *Lactobacillus plantarum* P-8 increased the levels of neuroactive metabolites, including SCFAs and GABA, enhancing stress resilience and reducing anxiety symptoms [460]. Probiotics also influence bile acid metabolism and liver health. *Lactobacillus rhamnosus* GG (LGG) reduced hepatic bile acid synthesis via the intestinal FXR–FGF15 pathway, preventing liver injury [461]. *Bacteroides thetaiotaomicron* improve intestinal barrier integrity and lipid metabolism by modulating mucus production and bile acid-regulating genes [462]. Additionally, probiotics affect TMA/TMAO metabolism, a pathway linked to atherosclerosis. *Lactobacillus plantarum* ZDY04 decreased serum TMAO and cecal TMA by altering the gut microbial composition [463], while *L. reuteri* CCFM8631 reduced plasma cholesterol, LDL, and TMAO, increased SCFA levels and alleviated hypercholesterolemia [464]. *Bifidobacterium* strains contribute to human health through several mechanisms, including the regulation of GI tract microbial homeostasis [465], the production of

essential vitamins [466], modulation of both local and systemic immune responses [467], and the hydrolysis of bile salts [468].

Imbalances in *Bacteroidota* are linked with several health issues, including IBD and metabolic disorders. It plays a crucial role in contributing to gut homeostasis, making it a potential target for therapeutic interventions [469, 470]. A diverse population of *Bacteroidota* contributes to gut microbial homeostasis by suppressing the overgrowth of pathogenic microorganisms and promoting a stable, functionally resilient microbial ecosystem [471]. *Bacteroides* spp. have shown promise in treating various conditions, including GI tract inflammation, immune dysfunction, metabolic disorders, and cancer prevention [354]. *Bacteroides fragilis* LTBF12, isolated from a healthy individual in a long-lived population in China, was transferred to naturally aging C57BL/6J mice, which exhibited reduced anxiety and hippocampal neuronal cell necrosis, enhanced antioxidant capacity, and decreased inflammation levels [472]. In vitro analysis demonstrated that *B. breve* DSM 32,583 possesses several key traits characteristic of beneficial bacteria, including survival under conditions that mimic the human digestive tract, the ability to adhere to human epithelial cell lines, and the reduction of the growth of potential pathogens [473]. In summary, probiotic modulation of gut microbial metabolites, such as SCFAs, tryptophan derivatives, GABA, bile acids, and TMAO, plays a pivotal role in maintaining host metabolic, neurological, and cardiovascular health. These findings highlight probiotics as promising therapeutic agents for metabolic, inflammatory, and neurodegenerative diseases through microbiota-mediated metabolic regulation.

Probiotics Modulate Cognition during Aging

Given the gut microbiota's effect on brain function, modifying it through probiotic supplementation may help protect against cognitive function decline. Mental disorders have been increasingly associated with gut microbiota imbalances, prompting interest in probiotics, especially *Lactobacillus*, for their therapeutic potential in mental health [211]. A particularly promising probiotic strain is *L. rhamnosus* GG, recognized for its rapid growth, strong adhesive properties, and bile resistance, which enables it to persist longer in the GI tract and exert better effects, including protection of the gut lining [340]. Along the gut-brain-microbiome axis, *Lactobacillus* strains have been linked to reductions in inflammatory cytokines [474], increased hippocampal levels of cAMP response element-binding protein (CREB), and BDNF in rats [474], and decreased kynurenine metabolites [456]. Combined therapies of probiotic and synbiotic reduced oxidative stress and inflammation, restored neurotransmitter balance, and alleviated energy deficits in rats fed a high-fat diet (HFD).

Additionally, the administration of *L. plantarum* and *Asparagus officinalis* significantly altered gut microbiota composition by increasing *Lactobacillus* species and decreasing populations of coliform, *Staphylococci*, and fungi. These results indicate that oral intake of *A. officinalis* prebiotics and/or *L. plantarum* probiotics can counteract HFD-induced cognitive impairments and neurodegeneration by modulating the gut-brain axis, with synbiotic treatment demonstrating the most pronounced restorative effects [25]. *Lactobacillus murine* and *L. reuteri* increased hippocampal GABA levels and alleviated depression-like behaviors in Dcf1 knockout mice [475]. *L. rhamnosus zz-1* reduced depression-like behaviors in chronic unpredictable mild stress-induced mice, regulated the HPA axis, increased monoamine neurotransmitters, BDNF, and tyrosine kinase receptor B (Trk B) by restoring gut microbiota, including *Lachnospiraceae* NK4A136, *Bacteroides*, and *Muribaculum* [476]. Sgritta et al. [477] found that *L. reuteri* reversed social deficits in mice via the vagus nerve.

Bifidobacterium [478] and *Lactobacillus* produce GABA, an inhibitory neurotransmitter that regulates neural pathways [479]. Breastmilk enhances immune and microbial health by increasing IgA and *Bifidobacterium* populations while reducing IL-6 levels and inflammation, thereby lowering the risk of age-related gastroenteritis in children [480]. In adulthood, the microbiome becomes dominated by the *Bacteroidetes* and *Firmicutes*, replacing the early dominance of *Lactobacillus* and *Bifidobacterium* genera [481]. Smaller populations of *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, *Fusobacteria*, and the *Cyanobacteria* are also present [480]. The study revealed that poor cognitive function is connected with a reduced comparative abundance of *Bifidobacterium* [210]. *Rouxiella badensis* subsp. *acadiensis* increases hippocampal expression of mRNA for serotonin (5-HT) 2 C and serotonin-1 A (5-HT1A) receptors, potentially enhancing cognitive function [482]. *Pediococcus acidilactici* CCFM6432 relieved anxiety-like behaviors in stressed mice by suppressing *Escherichia* and *Shigella*, and encouraging *Bifidobacterium* growth in C57BL/6 mice [483]. *Akkermansia muciniphila* decreased depressive-like behavior by correcting gut microbial imbalances in a mouse model [484].

In a study of 423 postpartum women in New Zealand, *L. rhamnosus* HN001 significantly reduced anxiety and depression scores [485]. A study reported that *L. rhamnosus* Probio-M9 increased physiological and psychological well-being in stressed adults by increasing beneficial gut bacteria [486]. A mixed strain of *L. reuteri* NK33 and *Bifidobacterium adolescentis* NK98 enhanced psychological health and sleep quality in adults with subclinical symptoms

[487]. Another multi-strain probiotic, combined with biotin, improved depressive symptoms, beta-diversity, and levels of *Ruminococcus gauvreauii* and *Coprococcus* [488]. A multi-strain probiotics mixture reversed stress-induced reductions in *Actinobacteria* and *Cyanobacteria*, and decreased depressive-like behaviors in mice [489]. LGG elevates neurotransmitters (like dopamine, serotonin, noradrenaline, and GABA levels) that play imperative roles in depression, and are beneficial in depression treatment [490]. It also mitigates neuroinflammation and promotes neuron survival [491]. At 1.5×10^9 cfu/ml, LGG prevents HPA axis hyperactivity and demonstrates anti-stress effects [492]. *L. rhamnosus* GG (ATCC 53103) exhibits more potent anti-depressant effects than bupropion and venlafaxine in rats, supporting its role as a psychobiotic for the treatment of mental disorders [493]. Overall, some strains of *Bifidobacterium*, *Lactobacillus*, *Akkermansia muciniphila*, and *Pediococcus acidilactici* demonstrated notable protective and therapeutic effects against anxiety and depression. These probiotics influenced neurotransmitter production, modulated the HPA axis, and increased BDNF and Trk B expression by altering gut microbiota composition. Multi-strain formulations may be more beneficial for managing mental health than a single-strain probiotic. Understanding bacterial interactions and metabolite pathways is crucial for optimizing therapeutic effects [211].

A probiotic mixture consisting of *L. rhamnosus*, *L. acidophilus*, and *B. longum* was administered continuously for three months, which enhanced levels of bifidobacteria and lactobacilli, and alleviated autism symptoms as measured by the Autism Treatment Evaluation Checklist [494]. *B. breve* strain A1 improved hippocampus learning and memory function in a Parkinson's disease model in mice by upregulating synaptophysin and postsynaptic density protein-95 (PSD95), crucial for synaptic function [495]. A multi-strain probiotic mix (*B. longum*, *B. bifidum*, *L. rhamnosus* GG, *L. rhamnosus*, *L. plantarum* LP28, and *L. lactis*) improved motor neuronal function in Parkinson's disease in a mouse model [496]. Combined *B. animalis* subsp. *lactis* and arginine supplementation enhanced cognitive flexibility in C57BL/6 mice, supporting the use of functional foods for cognitive enhancement [497]. Eight-week supplementation with *B. bifidum* and *L. plantarum* also increased hippocampal choline acetyltransferase and BDNF levels in Wistar rats [449]. *L. plantarum* DP189 modulated the PI3K/AKT/GSK-3β signaling pathway, improving gut dysbiosis and preventing tau hyperphosphorylation in Alzheimer's disease-affected mice [498]. *L. plantarum* PS128 regulated glycogen synthase kinase 3β activity, ameliorating cognitive dysfunction in streptozotocin-induced mouse models [499].

Gut microbiota can modulate multiple aspects of brain development and function, including the polarization and maturation of microglia and astrocytes, as well as the regulation of neurotransmission, neurogenesis, and myelination [16]. The consumption of probiotics (*Bifidobacterium* and *Lactobacillus*) has been associated with improved overall cognitive function, reduced inflammation, and increased brain neurotrophin levels in patients with Alzheimer's disease [500, 501]. Improvements in memory cognitive function have also been reported following administration of *B. breve* A1 [172], while enhanced verbal fluency and learning have been observed after consuming *Limosilactobacillus fermentum* and *L. plantarum* C29 [171, 188, 502, 503]. In patients with notable anxiety and depressive disorder, a probiotic combination of *L. helveticus* R0052 and *B. longum* R0175 led to reduced free cortisol levels, decreased symptoms, and increased problem-solving skills [504]. Gut microbiota modulation via probiotic supplementation also influences cortisol synthesis by regulating the HPA axis, with several studies showing reduced cortisol levels in saliva and urine in stressed individuals and those with major depressive disorders (MDD) after *Lactobacillus* administration [29, 30]. Probiotic intake has been associated with improved sleep quality, as estimated by the Pittsburgh Sleep Quality Index, suggesting potential benefits for sleep and the prevention of neurodegenerative and psychological health syndromes [31, 505].

A study involving 33 participants who consumed a multispecies probiotic (*L. rhamnosus* and *B. lactis*) showed significant improvements in cognitive and memory function, as well as depressive symptoms. Enhancements in executive functions were also noted in planning, problem-solving, cognitive flexibility, selective attention, impulse control, and inhibition, indicating an overall improvement in mental and emotional functioning among older adults due to probiotics supplementation [31]. The capability of probiotics to produce beneficial effects despite gut microbiota diversity and potential epigenetic influences is a particularly intriguing aspect of human probiotic interventions [506]. Symptoms of depression, such as melancholy, malaise, insomnia, diminished interest, and neuroses, have been linked to improvement with *Lactobacillus* formulations [32, 507]. Biological factors in depression, including a dysregulated HPA axis, neuroinflammation, and altered neurochemistry, suggest a central role of gut microbes in the disorder [20–22, 418]. Conventional pharmacological treatments for MDD target brain neurotransmitters; similarly, *Lactobacillus* and *Bifidobacterium* strains influence neurotransmitter activity, showing antidepressant-like effects [418, 447, 508]. Studies show that *L. paracasei* PS23, *L. helveticus* NS8, *L. rhamnosus*, and *B. longum* increase hippocampal 5-HT levels in preclinical depression models [509–511], while *L. plantarum* PS128 boosts 5-HT and depressive disorder levels in the striatum [306]. Despite limited clinical evidence for MDD,

probiotics hold significant potential, especially as precision psychiatry advances. Probiotics may be considered adjunctive treatments in general MDD and as stand-alone therapies in mild MDD, where conventional pharmacological interventions might not be necessary [512].

In a clinical trial, 45 adult participants received a probiotic blend (*Bifidobacterium longum*, *Lacticaseibacillus casei*, *Levilactobacillus brevis*, *Lacticaseibacillus rhamnosus*, *Lactobacillus delbrueckii*, *Lactobacillus helveticus*, *Lactococcus lactis*, and *Streptococcus thermophilus* (1 capsule, 10^8 CFU/capsule/day), together with lifestyle modifications (including guidance on physical activity, sleep hygiene, healthy dietary practices, and anxiety management) for 60 days, which led to significant improvements in multiple clinical and health-related parameters [513]. These positive changes were associated with enhanced gut microbiota composition, healthier eating behaviors, increased physical activity, reduced anxiety, and improved sleep quality among adult individuals with obesity [513]. High-resolution imaging has revealed anatomical and functional variations in brain regions involved in the pathophysiology of emotional disorders after probiotic consumption [514]. However, owing to the heterogeneous physiological properties of probiotic strains, it remains challenging to delineate the relative efficacy of "strong" versus "weak" probiotics in mitigating gut microbial dysbiosis and cognitive decline in older adults.

Next-generation probiotics, such as *Akkermansia muciniphila*, have shown promise through the activity of the Amuc-1100 protein and extracellular vesicles, which contribute to metabolic regulation, preservation of gut barrier integrity, and reduction of lipopolysaccharide leakage and inflammation [18]. Nonetheless, further research involving detailed microbiome characterization is necessary to elucidate individual responses and optimize probiotic-based strategies for the prevention and management of cognitive impairment. Additional clinical trials are essential to assess the effects of specific strains, dosages, and intervention durations on cognitive outcomes among elderly subjects. The effects of probiotics on cognitive function in elderly people are summarized in Table 2. The impact of unhealthy aging and probiotics supplementation on the Microbiota-Gut-Brain-axis has been highlighted in Fig. 4. Despite existing evidence on the mechanisms of probiotics in cognitive enhancement, more research is needed to advance probiotic-based therapies for cognitive decline [18].

Probiotics, prebiotics, and synbiotics modulate the gut–brain axis by shaping microbial composition, metabolic activity, immune regulation, and neurochemical signaling, potentially alleviating neurological and psychiatric symptoms, enhancing cognition, and boosting immunity [526]. Next-generation probiotics, engineered via synthetic biology and bioinformatics, offer improved stability, viability, and targeted therapeutic effects [527]. High-throughput sequencing and bioinformatics have accelerated the identification of novel strains, including *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Bacteroides fragilis*, *Eubacterium hallii*, *Bacteroides thetaiotaomicron*, and *Christensenella minuta*, with promising roles in the management of dysbiosis-related disorders [528, 529]. The optimal use of single strains versus microbial consortia remains uncertain; however, NGPs show promise for personalized medicine and chronic disease management, pending further long-term clinical validation [530]. Postbiotics, comprising microbial metabolites and soluble factors, exert bacteriostatic, immunomodulatory, antioxidant, hepatoprotective, antihypertensive, and gut-regulatory effects, offering a safer and more predictable alternative to probiotics [531–534].

Depression, a multifactorial disorder, is increasingly addressed with adjunctive strategies targeting the gut–brain axis. Probiotics, such as MH-Pro (*Lacticaseibacillus rhamnosus* CBT LR5 and skim milk), may enhance cognitive function in older adults by modulating gut–brain communication [535]. However, methodological variability necessitates large-scale, standardized trials to confirm efficacy and clarify mechanisms [536]. Dairy products, rich in protein, calcium, magnesium, zinc, and vitamins, also support neurological health and may protect against depression, osteoporosis, diabetes, and cardiovascular diseases [537].

Investigating the impact of probiotics on cognitive enhancement in older adults is a relatively novel area of research. Existing studies have explored various probiotic species and strains, typically using fixed doses and intervention durations. However, no available reports have systematically examined the impact of different dosages of a single probiotic strain across variable study periods on cognitive function in older adults. Long-term probiotic administration appears essential for sustaining gut microbiota balance and mitigating age-associated dysbiosis. Moreover, as summarized in Table 2, several probiotic strains have demonstrated potential to improve cognitive performance among elderly populations, underscoring the need for further longitudinal and dose–response studies to clarify their therapeutic efficacy and optimal intervention parameters.

Biomarkers of MGBA Modulation and Cognitive Benefit

Several biomarker classes show promise for validating functional improvements after probiotic supplementation in older adults. Metabolic markers include fecal and plasma SCFAs (especially butyrate and propionate), tryptophan and

Table 2 The representative studies on the influences of probiotic intervention on cognitive impairment in older adults

Subjects	Interventions	Findings	References
Old persons (60–95 years old) with Alzheimer's disease (AD)	*Lactobacillus acidophilus*, *L. casei*, *L. fermentum*, and *Bifidobacterium bifidum* (2×10^9 CFU/g for each) supplementation for 12 weeks	Positively influences cognitive function and certain metabolic functions in patients with AD. No substantial effects on other biomarkers of oxidative stress and inflammation, fasting plasma glucose, and other lipid profiles	Akbari et al. [515]
Patients (55 to 100 years of age) with a diagnosis of AD	Selenium (200 μg/day) plus probiotics containing *L. acidophilus*, *B. bifidum*, and *B. longum* (2×10^9 CFU/day each) supplementation for 12 weeks	Patients with AD showed improvements in cognitive function and certain metabolic profiles.	Tamtaji et al. [501]
Adults with active physical activity (avg. age ~ 64.3 years)	*L. rhamnosus* GG	No significant improvement in cognitive function.	Sanborn et al. [516]
Patients (50 to 90 years old) having mild to moderate dementia	Multi-strain probiotics supplementation with *B. longum* subsp. *Infantis* BLI-02, *B. animalis* subsp. *Lactis* CP-9, *B. breve* Bv-889, *B. bifidum* VDD088, and *L. plantarum* PL-02 (1×10^{10} CFU/ day/patient) for 12 weeks	Demonstrated a 36% rise in BDNF, a decrease in IL-1β, and an increase in antioxidant SOD. A trend toward reduced cognitive decline was observed; however, it was not statistically significant.	Hsu et al. [500]
Older adults (age > 60 years) with mild cognitive impairment	Mixed probiotics of *Lactococcus lactis* BioF-224, *L. lactis* LY-66, *B. animalis* BB-115, *B. lactis* CP-9, *B. infantis* BLI-02, *B. lactis* HNO19, *L. plantarum* CN2018, *L. rhamnosus* Bv-77, *L. plantarum* BioF-228, *L. rhamnosus* HNO01, *L. paracasei* MP137, *L. johnsonii* MH 68, *L. paracasei* GL 156, *L. salivarius* AP-32, *L. casei* CS-773, *L. acidophilus* TYCA06, *L. reuteri* TSR332, and *L. fermentum* TSF331 (> 2×10^{10} CFU/g); 2 g/day for 12 weeks	The relative abundances of *Anaerostipes*, *Blautia*, *Coprococcus*, *Erysipelotrichaceae*, *Haemophilus*, *Pantoea*, *Prevotellaceae*, *Ruminococcus*, *Lachnospiraceae*, and *Muribaculaceae* were observed. Cognitive function and sleep quality were also improved.	Fei et al. [517]
Elderly patients (66 years) following the non-cardiac surgical procedure	Capsule containing the probiotics of *L. acidophilus*, *B. longum*, and *Enterococcus faecalis* (≥ 10^7 CFU of each strain/capsule); two capsules/day provided during their hospital stay	Decreased the plasma IL-6 and cortisol levels in the elderly patients. Probiotic supplementation relieved postoperative cognitive decline after the non-cardiac surgery.	Wang et al. [518]
Healthy adults (aged 50–79 years) with mild cognitive impairment (MCI)	*B. breve* MCC1274 (1×10^{10} CFU/ capsule); Two capsules per day for continuous 16 weeks	Enhanced anti-inflammatory responses and reduced the mild cognitive damage symptoms.	Bernier et al. [519]
Older adults (aged 50–79 years) with MCI	*B. breve* A1, 2×10^{10} CFU per person for 16 weeks	Significant enhancements in the domain scores of immediate memory, visuospatial/constructional, and delayed memory were observed in both the intention-to-treat and per-protocol (PP) analyses.	Xiao et al. [172]
Elderly with memory impairment	*Limosilactobacillus fermentum* A2.8 (10^7 or 10^8 CFU) for 12 weeks	The supplemented group with 10^7 CFU displayed enhancements in memory, visuospatial function, learning, and verbal fluency.	Handajani et al. [502]
Men and women with good physical health with MCI	Soybean (DW2009) fermented with *Lactobacillus plantarum* C29 (800 mg/day/person)	Elevated serum BDNF levels, offering preliminary evidence for its cognitive benefits and highlighting the potential role of the gut-brain axis in alleviating cognitive impairments in MCI patients.	Hwang et al. [520]
Patients (age ≥ 60 years) undergoing hip or knee arthroplasty	Mixed probiotics of *L. acidophilus*, *Enterococcus faecalis*, *B. longum* and (> 10^7 CFU each strain in one capsule); Four capsules, twice/day given during the hospitalization period	Perioperative use of probiotics may help prevent postoperative cognitive dysfunction and enhance verbal memory.	Hu et al. [521]
Elderly patients with MCI	24-week supplementation of *B. breve* A1 (two capsules containing approximately 2.0×10^{10} CFU	Improved cognitive function by preserving the standard of living of the aged persons	Kobayashi et al. [171]
Healthy elderly persons (age ≥ 65 years)	*B. longum* BORI and *B. bifidum* BGN4 (1×10^9 CFU each strain/capsule); Four capsules per day for 12 weeks	Enhanced the cognitive flexibility test and stress score. Decreased stress and inflammation.	Kim & Park [22]

Table 2 (continued)

Subjects	Interventions	Findings	References
Healthy older adults (60–75 years old) without cognitive function decline	*B. longum* BB68S (5×10^{10} CFU/sachet); One sachet per day for continuous 8 weeks	Augmented the comparative abundances of *Cellulosilyticum*, *Lachnospira*, *Dorea*, and *Bifidobacterium*. Reduced the relative abundances of *Porphyromonas*, *Parabacteroides*, *Bilophila*, *Tyzzerella*, *Collinsella*, *Granulicatella*, *Epulopiscium*, and unclassified_c_ Negativicutes. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score was significantly increased.	Shi et al. [522]
Old-aged adults (65–88 years) with MCI	*B. breve* MCC1274 (2×10^9 CFU) fed for 24 weeks	Alzheimer's Disease Assessment Scale (ADAS) subscales "orientation in time" and "writing" were substantially augmented. Repressed brain atrophy development	Asaoka et al. [523]
Men and women volunteers aged 30–55 years old	One stick of 1·5 g/d of PF (Probio'Stick®: batch no. 6533308; Institut Rosell-Lallemand, Blagnac, France) comprising *B. longum* R0175 and *L. helveticus* R0052 and (3×10^9 CFU/stick)	Alleviation of psychological distress.	Messaoudi et al. [504]
Adults of middle age (52–59 years) and old age (60–75 years) with MCI	Probiotic *L. rhamnosus* GG (10^9 CFU/day/person) and Prebiotic inulin from chicory root extract (200 mg)/capsule. Two capsules/day for a continuous 12 weeks	Abridged the abundances of *Dehalobacterium* and *Prevotella*. Enhanced the cognitive function score of MCI patients	Aljumaah et al. [524]
Old Participants (age ≥ 55 years old)	A capsule comprising a multispecies probiotic (3.3 billion CFU *L. rhamnosus* and *B. lactis*) fed for 10 weeks	Probiotic administration led to significant improvements in planning, attention, problem-solving, impulse control, selective cognitive flexibility, and inhibitory control, thereby improving both emotional and cognitive functions.	Ruiz-Gonzalez et al. [31]
Community-dwelling adult person aged 52–75 years (mean age, 64.3 years)	Culturelle Vegetarian Capsules containing a 10^9 CFU blend of *L. rhamnosus* GG (manufactured by iHealth, Inc., Cromwell, CT, USA) for a 3-month intervention	Increased cognitive functions in middle-aged and older adults with cognitive function deficiency.	Sanborn et al. [525]

kynurenine pathway metabolites, and circulating TMAO, which reflect changes in microbial fermentation and host–microbe co-metabolism. Immunological markers such as CRP, IL-6, TNF-α, and cortisol, together with neurotrophins like BDNF, can index modulation of low-grade inflammation and HPA-axis activity; some RCTs have reported shifts in these markers in parallel with modest cognitive or affective improvements [188, 189]. Neuroimaging endpoints, including resting-state and task-based fMRI, can capture changes in activity and connectivity within networks involved in emotion regulation, memory, and default-mode function following probiotic or synbiotic interventions. Diffusion tensor imaging and PET tracers of amyloid or neuroinflammation are emerging as tools to test whether MGBA-targeted interventions influence white-matter microstructure or neuroinflammatory burden in elderly populations; however, data are still limited [188, 538].

Inconsistent Findings, Unresolved Questions, and Limitations

Despite encouraging results from several RCTs in MCI and Alzheimer's disease, probiotic and synbiotic trials show substantial heterogeneity in effect sizes, with some studies reporting no significant improvement in global cognition or domain-specific outcomes. Differences in strain composition, dose, duration, baseline microbiome, diet, comorbidities, and cognitive assessment tools likely contribute to inconsistent findings and limit generalizability [50, 188].

The meta-analyses suggest modest improvements in selected cognitive domains but emphasize that most trials are small, at risk of bias, and often underpowered to detect clinically meaningful changes, particularly in advanced neurodegenerative diseases. Null or weak effects in several well-designed trials, together with publication bias toward positive results, underscore that probiotics should currently be viewed as adjunctive rather than stand-alone disease-modifying interventions for cognitive decline [31, 50, 188].

This systematic review has some limitations. First, although we applied predefined inclusion and exclusion criteria, our approach remains partly narrative, and it may be susceptible to selection bias, particularly regarding emerging psychobiotics trials and negative or unpublished studies. Second, most clinical evidence comes from small, short-term RCTs in selected populations; heterogeneity in strains, formulations, dosing regimens, and cognitive endpoints complicates synthesis and risks oversimplifying causal links between microbial modulation and complex

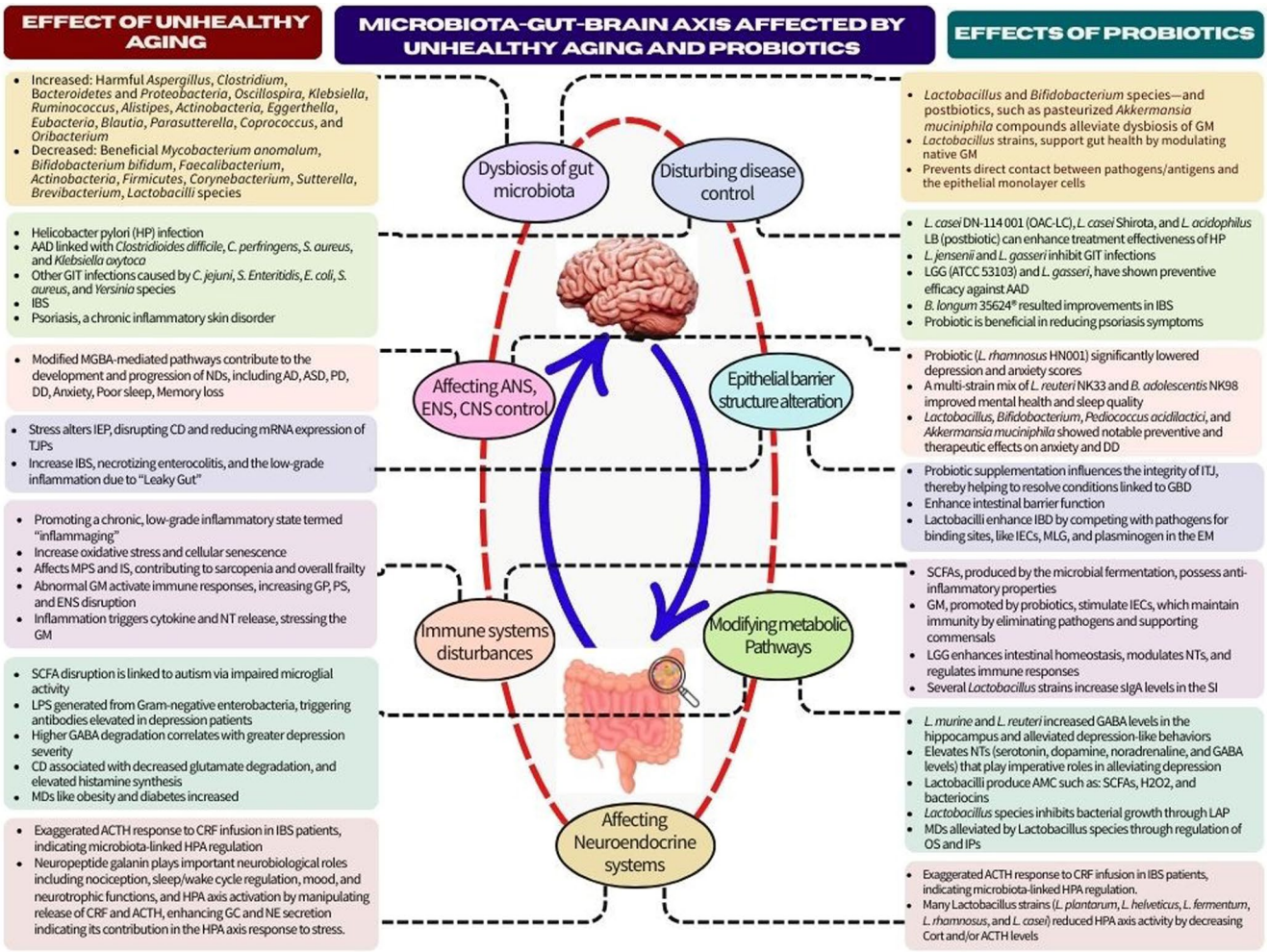


Fig. 4 Microbiota-Gut-Brain-Axis is affected by unhealthy aging and probiotics. GM = gut microbiota, AAD = Antibody-Associated Autoimmune Disease, GIT = Gastrointestinal tract, ANS = Autonomic nervous system, ENS = Enteric neural system, CNS = Central nervous system, NDs = Neurodegenerative diseases, MGBA = Microbiota-gut-brain axis, AD = Alzheimer's disease, ASD = Autism spectrum disorders, PD = Parkinson's disease, DD = Depressive disorder, MPS = Muscle protein synthesis, and IS = Insulin sensitivity, GP = Gut permeability, PS = Pain sensitivity, NT = neurotransmitter, SCFAs = Short-chain fatty acids, IESs = Intestinal epithelial cells, LGG = *Lactobacillus rhamnosus* GG, sIgA = secretory immunoglobulin A, SI = Small intestine, GF = Germ free, HPA = Hypothalamic-pituitary-adrenal, CRF = Corticotropin-releasing factor, ACTH = Adrenocorticotropic hormone), Cort = corticosterone, GC = Glucocorticoid, NE = Norepinephrine, ECs = Enteroendocrine cells, BDNF = Brain-derived neurotrophic factor, Trk B = Tropomyosin receptor kinase B, GABA = Gamma-aminobutyric acid, LPS = Lipopolysaccharide, CD = Cognitive decline, MDs = Metabolic disorders, AMC = antimicrobial compounds, H_2O_2 = Hydrogen peroxide, LAP = Lactic acid production, OS = Oxidative stress, IPs = Inflammatory pathways, IEP = Intestinal epithelial permeability, CD = colonocyte differentiation, TJPs = tight junction proteins, ITJ = Intestinal tight junctions, GBD = Gut barrier dysfunction, IBD = Intestinal barrier defense, MLG = Mucus layer glycoproteins, EM = extracellular matrix, IBS = Irritable bowel syndrome, IECs = Intestinal epithelial cells, AAD = Antibiotic-associated diarrhea

cognitive outcomes [188, 539]. Third, mechanistic insights are extrapolated largely from rodent and in vitro models that may not capture the complexity of human aging, multimorbidity, polypharmacy, and diverse lifestyles, which can blunt or modify probiotic effects. Finally, our proposed 'neurobiotic sense' framework is conceptual and awaits further validation; future large-scale longitudinal and multi-omics studies incorporating neuroimaging and robust clinical endpoints are needed to test its translational relevance [188, 189, 538].

Conclusion and Future Perspectives

The growing body of evidence solidifies a fundamental shift in our understanding of brain health: we can no longer view the brain as an isolated organ. Its function and resilience are deeply entwined with the state of the gut microbiome, forming a dynamic, bidirectional communication system, the gut-brain axis. While aging and genetics set the stage, the modifiable factors of diet, physical activity, and environmental exposures have the greater power in maintaining

a state of eubiosis. This grants us significant agency, transforming daily lifestyle choices into preventive medicine for the brain.

The implications for neurodegenerative and neuropsychiatric disorders are profound. Dysbiosis acts as a slow-burning fuse, contributing to the pathogenesis of age-related diseases by compromising the very barriers meant to protect the brain and by priming glial cells for a harmful inflammatory response. The promise of targeting this axis is immense, as it moves us beyond merely managing symptoms to the potential of slowing disease progression. The potential use of specific microbial signatures as early diagnostic biomarkers could revolutionize our approach, allowing for interventions decades before clinical symptoms manifest.

Currently, the most immediate application is in the realm of mental health, where specific probiotic strains have earned their place as adjunctive or even stand-alone therapies for mild-to-moderate depression. This represents a critical step towards destigmatizing mental healthcare and integrating holistic, multi-system approaches.

However, the path forward is fraught with complexity. The stark gap between compelling preclinical models and inconsistent human trials highlights a critical limitation: the human microbiome is a complex ecosystem, not a simple machine. Introducing a single probiotic strain is akin to introducing one new plant into a vast, established forest; the outcome depends on a multitude of pre-existing conditions. Therefore, future research must abandon a one-size-fits-all approach. The mantra must be strain-specific, condition-specific, and host-specific. We must move from simply asking *"Do probiotics work?"* to meticulously answering *"Which specific bacterial strain*, *at what dose*, *in which formulation (including prebiotics)*, *works for which individual*, *with which specific condition?"* This necessitates a new generation of rigorous, large-scale clinical trials that embrace this complexity.

Furthermore, we must look beyond live probiotics. Future research on perspectives must invest more seriously in the exploration of postbiotics, the inanimate microorganisms and their beneficial components. These defined, stable, and safe compounds could overcome the challenges of live culture delivery, shelf life, and variability, offering a more pharmacological-like approach as a "neurobiotic sense" to modulating the gut-brain axis, particularly in vulnerable populations.

Future MGBA research in aging will benefit from integrating multi-omics layers, shotgun metagenomics, metatranscriptomics, metabolomics, and, where feasible, host transcriptomics and proteomics, to move beyond taxonomic shifts and delineate causal pathways. Such approaches can link specific probiotic or synbiotic interventions to functional outputs such as SCFA profiles, bile acid transformation, tryptophan–kynurenine metabolism, and neurotrophin or cytokine signaling relevant to cognitive decline [189, 210]. In parallel, machine-learning models applied to baseline microbiome and metabolome profiles, together with clinical variables (e.g., age, diet, apolipoprotein E (APOE) status, comorbidities), are beginning to stratify 'responders' versus 'non-responders' to probiotic interventions. Adapting these predictive frameworks to older adults could enable precision 'neurobiotic' prescriptions, matching specific strains or synbiotic formulations to those most likely to derive cognitive benefit [50, 139, 539].

Ultimately, the future of brain health lies in a synergistic strategy: leveraging personalized lifestyle interventions to cultivate a resilient native microbiome, complemented by precisely targeted, evidence-based biotics (pro-, pre-, and post) when necessary. By nurturing the brain's internal ecosystem, we directly invest in the long-term health of the brain it serves. Future research should prioritize understanding host–microbiota interactions, variability among microbial strains and substrates, and the impact of individual genetic and environmental factors. Standardized, large-scale randomized trials that integrate multi-omics approaches are essential to elucidate the functional effects of interventions. Personalized strategies that account for microbiota composition, genetics, diet, and lifestyle are key to enhancing efficacy and reducing risks. Optimizing microbial formulations and defining precise therapeutic windows for various diseases remains crucial for the aged population. Emerging technologies, such as machine learning and systems biology, will enable the prediction of host responses and design of tailored microbial therapies, including next-generation probiotics and designer synbiotics targeting neuroinflammation and immune modulation.

Abbreviations

AAD	Antibiotic-associated diarrhea
Actinobacteria	New name - *Actinomycetota*
AhR	Aryl hydrocarbon receptor
APOE	Apolipoprotein E
ASD	Autism spectrum disorder
Bacteroidetes	New name - *Bacteroidota*
BDNF	Brain-derived neurotrophic factor
COPD	Chronic obstructive pulmonary disease
CRD	Complex Reactionmeter Drenovac
CREB	cAMP response element-binding protein
DALYs	Disability-adjusted life years
FMO	Flavin-containing monooxygenase
Firmicutes	New name - *Bacillota*
FMT	Fecal microbiota transplantation
FSH	Follicle-stimulating hormone
FXR	Farnesoid X receptor
GABA	Gamma-Aminobutyric Acid

GLP-1	Glucagon-like peptide-1
γ-GT	Gamma-glutamyl transferase
GRAS	Generally Recognized As Safe
HbA1C	Hemoglobin A1C
HDL	High-density lipoproteins
HFD	High-fat diet
HGC	High gene count
3-HK	3-hydroxy-L-kynurenine
HPA	Hypothalamic-pituitary-adrenal axis
5-HT	5-hydroxytryptamine
HPG	Hypothalamic-pituitary-gonadal
IBD	Inflammatory Bowel Disease
IBS	Irritable bowel syndrome
IECs	Intestinal epithelial cells
IAA	Indole-3-acetic acid
IDO1	indoleamine 2,3-dioxygenase
IPA	Indole-3-propionic acid
ISAPP	International Scientific Association of Probiotics and Prebiotics
LMICs	Low- and middle-income countries
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LPS	Lipopolysaccharide
LH	Luteinizing hormone
MAMPs	Microbial-associated molecular patterns
MDD	Major depressive disorder
MCI	Mild cognitive impairment
MCP-1	Monocyte chemoattractant protein
NCBI	National Center for Biotechnology Information
NCDs	Non-communicable diseases
NGP	Next-generation probiotics
NLRP3	Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3
NOD	Nucleotide-binding oligomerization domain
PAF	Population attributable fraction
PMC	Pseudomembranous colitis
Proteobacteria	New name - Pseudomonadota
PSD95	Postsynaptic density protein-95
PSQI	Pittsburgh Sleep Quality Index
QPS	Qualified Presumption of Safety
RCTs	Randomized Control Trials
ROS	Reactive oxygen species
SCFA	Short-chain fatty acids
SPF	Specific pathogen-free
SSRI	Selective serotonin reuptake inhibitors
SYP	Synaptophysin
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
TGR5	The G-protein-coupled bile acid receptor 5
TLR	Toll-like receptor
Trk B	Tyrosine kinase receptor B

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests A.K.B. discloses the ownership of a patent titled "bioengineered Lactobacillus probiotics and the uses thereof". Patent No US20210386819A1 (Issue date Dec 16, 2021).

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