Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

From gut to brain: pioneering microbial strategies against Alzheimer's disease

Jia Wu[a,1], Jinrong He[a,1], Rong Liu[b], Haiming Zhang[c,*], Lei Liu[d,e,*], Caixia Peng[a,e,*]

[a] Key Laboratory for Molecular Diagnosis of Hubei Province, Central Laboratory, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China
[b] Department of Pathophysiology, Key Laboratory of Ministry of Education for Neurological Disorders, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[c] Department of Oncology, Integrated Traditional Chinese and Western Medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China
[d] Department of Gastrointestinal Surgery, Intestinal Microenvironment Treatment Center, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China
[e] Hubei Provincial Engineering Research Center of Intestinal Microecological Diagnostics, Therapeutics, and Clinical Translation, Wuhan 430014, China

ARTICLE INFO

Article history:
Received 17 March 2025
Received in revised form 15 May 2025
Accepted 22 October 2025

Keywords:
Microbial-gut-brain axis
Alzheimer's disease
Probiotics
Gut microbes
Treatment strategy

ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a gradual decline in cognitive abilities and memory loss. Recent studies have indicated that the microbiota-gut-brain axis (MGBA) may be involved in the development of this condition. This research aimed to clarify the composition and function of the MGBA, particularly focusing on the diversity of gut microbiota, and its connection to gut barrier integrity and the nervous system. Herein, we conducted a narrative review of existing literature to investigate how microbial metabolites affect neural function, neuroinflammation, and metabolic issues related to AD. The results of this study indicate that changes in the diversity of the gut microbiota can worsen neuroinflammation, thereby accelerating the progression of AD. Additionally, we discovered that neurotransmitters, which are influenced by the gut microbiota, play a regulatory role, pointing to potential targets for therapy. In exploring treatment options, we assessed the effectiveness of probiotics, dietary changes, and fecal microbiota transplantation (FMT) in managing AD. Clinical trials have demonstrated that specific probiotic strains can improve cognitive function, while dietary approaches, such as the Mediterranean diet, are associated with a reduced risk of developing AD. Moreover, FMT appears to be a promising new treatment strategy, although there are still challenges to its implementation. In summary, our research highlights the significant role of the MGBA in the pathogenesis and treatment of AD, suggesting that modifying gut microbiota could provide new opportunities for therapeutic intervention in AD.

1. Introduction

The microbiota-gut-brain axis (MGBA) is a complex communication network that connects the gut microbiota, the gastrointestinal tract, and the central nervous system (CNS). This two-way pathway plays a crucial role in maintaining balance within the body and affects various physiological processes, such as mood regulation, cognitive function, and immune responses. Recent studies emphasize the significance of the MGBA in neurodegenerative diseases, particularly Alzheimer's disease (AD), which is characterized by a gradual decline in cognitive abilities and memory loss. Gaining insights into the MGBA's role could help clarify the underlying mechanisms of AD and pave the way for new treatment options[1-2].

[1] These authors contributed equally to this work.
[*] Corresponding authors.
E-mail address: pengcaixia@zxhospital.com (C.X. Peng); anwar_welsh@163.com (L. Liu); zxhospitalzhm@163.com (H.M. Zhang)
Peer review under responsibility of Beijing Academy of Food Sciences.

Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2025.9250864

AD is a pressing global health issue, with a prevalence rising concurrent with population aging. Currently, approximately 50 million individuals worldwide are living with dementia, and AD accounts for 60%–70% of these cases[3]. AD is associated with the buildup of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, leading to synaptic dysfunction and the loss of neurons. Epidemiological studies have identified modifiable risk factors, such as obesity, diabetes, and cardiovascular diseases, that increase the likelihood of developing AD[4-5].

Recent findings have revealed that the gut microbiota significantly influences the nervous system, indicating that alterations in the gut microbiome can impact neuroinflammation, neurotransmitter production, and overall brain function. Specific microbial metabolites, such as short-chain fatty acids (SCFAs), have shown neuroprotective effects and play a role in neuroinflammatory processes[6]. This relationship highlights the potential for microbiome-targeted therapies to reduce the risk or slow the progression of AD. Consequently, focusing on the gut microbiome may provide a novel therapeutic strategy for addressing this challenging condition[7]. To this end, this review aimed to clarify the composition and function of the MGBA, particularly focusing on gut microbiota diversity, and its connection to gut barrier integrity and the nervous system.

Methods, an extensive literature search of articles and reviews was conducted using the PubMed, Web of Science, and Scopus databases, which covered the period from 2014 to 2025. The search focused on keywords such as "microbiota-gut-brain axis"; "Alzheimer's disease"; "probiotics"; "fecal microbiota transplantation"; and "dietary interventions". Inclusion criteria comprised clinical trials, animal studies, and mechanistic reviews. Articles published in languages other than English, and those not directly related to the pathogenesis of AD, were excluded from the review. The data extraction process emphasized the microbial mechanisms involved, therapeutic outcomes, and specific limitations encountered in study design, sample size, and methodology[8-9].

2. MGBA composition and function

The gut microbiota, a complex and diverse community of microorganisms, plays a crucial role in human health, particularly in relation to the MGBA. Research has indicated that a diverse gut microbiota is essential for maintaining homeostasis and ensuring optimal physiological functions. A varied microbiome can bolster the resilience of the gut ecosystem, which in turn supports various metabolic and immune functions. Furthermore, studies have indicated a significant link between the diversity of gut microbiota and neurological health, with a richer microbiota associated with better cognitive function and emotional regulation[10]. Conversely, alterations in gut microbiota diversity have been connected to neurodegenerative disorders, highlighting the importance of a balanced microbial community for brain health. Factors such as diet, environment, and lifestyle can significantly influence the composition of gut microbiota, underscoring the necessity for personalized strategies aimed at enhancing microbiome diversity as a potential therapeutic approach for neuropsychiatric conditions[11-13].

2.1 Relationship between gut barrier function and AD

Maintaining the integrity of the gut barrier is essential for preventing harmful substances from entering the bloodstream, which in turn protects the nervous system from neurotoxic effects. Damage to the intestinal barrier causes "leaky gut", which promotes AD development[14]. The MGBA plays a vital role in facilitating communication between the gut and the CNS through various pathways, including the vagus nerve, immune signals, and microbial metabolites. Research indicates that a weakened gut barrier can lead to elevated levels of pro-inflammatory cytokines in the circulation, which may contribute to neuroinflammation and subsequent neuronal damage[15-16]. Therefore, it is crucial to understand the mechanisms regulating gut barrier integrity, as this knowledge could inform the development of interventions aimed at improving gut health and preventing AD[17].

2.2 Impact of microbial metabolites on neural function in AD

Recent studies show that gut microbiota significantly affect the host's physiological functions through their metabolites. Microbial metabolites, especially SCFAs, amino acids and their derivatives, and other metabolites such as biogenic amines and phenolic compounds, are closely related to the function of the nervous system.

SCFAs play a crucial role in modulating neural function and behavior. SCFAs are produced when gut bacteria ferment dietary fibers, and they significantly influence brain health by acting as energy sources for colonic epithelial cells, while also exerting anti-inflammatory effects[18]. Notably, SCFAs can cross the blood-brain barrier (BBB), which allows them to impact the production of neurotransmitters that are vital for maintaining mood and cognitive functions[19]. SCFAs traverse the BBB through mechanisms including passive diffusion, transport proteins, and modulation of intercellular junctions. The passive diffusion mechanism is a fundamental process by which SCFAs can cross the BBB. SCFAs are small molecules that can diffuse through lipid membranes without requiring energy or specific transport proteins. SCFAs influence BBB permeability by modulating tight junction proteins. These proteins are crucial for maintaining the barrier's integrity. Transport proteins assist SCFAs in crossing the BBB[20-21]. Dysbiosis can alter metabolite levels, which significantly affects brain health. This alteration may contribute to psychiatric conditions, including AD symptoms like depression and anxiety[22-23].

Amino acids and their derivatives exhibit considerable potential in neuroprotection, making it essential to maintain a proper balance of these compounds for the health of the nervous system. Disturbances in amino acid metabolism can contribute to the development of neurological disorders, including AD and depression[24]. Derivatives of amino acids, such as *D*-serine, enhance NMDA receptor functionality, promote neuronal survival and synaptic plasticity. Furthermore, gut microbiota produces biogenic amines and phenolic compounds through fermentation. An imbalance in biogenic amines is significantly linked to various neurological conditions. Additionally, histamine's role in neurodegenerative diseases, especially AD, is increasingly recognized, as it may influence pathological processes by modulating neuroinflammation and apoptosis[25]. The connection between phenolic compounds and neurodegenerative disorders has also attracted more focus, with studies indicating that diets rich in phenolic compounds could potentially lower the risk of developing neurodegenerative diseases like AD and Parkinson's disease (PD)[26]. Collectively, these findings suggest that the regulation of biogenic amines and phenolic compounds holds considerable potential for improving neurological health and preventing disorders.

This intricate relationship between microbial metabolites and the host immune system underscores the important connection between gut microbiota and brain function (Fig. 1). Consequently, modifying the composition of gut microbiota may offer promising therapeutic strategies for addressing neuropsychiatric disorders[11,27-28].

2.3 *Bidirectional MGBA influences*

The MGBA is a bidirectional communication system linking the gut microbiota and CNS *via* neural, endocrine, immune, and metabolic pathways[29-30]. The gut microbiota influences BBB permeability, neurogenesis, and synaptic plasticity through metabolic products like SCFAs, while the CNS affects intestinal motility, mucus secretion, and microbiota composition *via* the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis[30-31]. Aging impacts MGBA function, reducing gut microbiota diversity and SCFAs production, which leads to systemic inflammation and neurodegeneration[32]. In neurodegenerative diseases like AD and PD, MGBA disruption worsens BBB damage and neuroinflammation, accelerating disease progression[30,33]. Current literature does not explicitly address gender, but studies indicate that social psychological stress (like loss of status) can trigger depressive behaviors *via* the MGBA, with individual differences suggesting gender might influence MGBA through hormone-immune interactions[34]. More research is needed to confirm this. Future studies should aim to create personalized MGBA regulation strategies considering factors like age and gender[35-36].

3. MGBA plays a significant role in the development of AD

Neuroinflammation is a key factor in AD development, and recent studies have highlighted how the gut microbiota can influence this inflammatory response. The gut microbiome plays a significant role in regulating the immune system, which can either protect or harm neuronal health. The presence of dysbiosis—an imbalance in the gut bacteria—is associated with increased systemic- and neuro-inflammation, which can accelerate AD progression. For example, some gut bacteria are known to produce SCFAs that have anti-inflammatory effects, potentially reducing neuroinflammation and helping to slow cognitive decline in individuals with AD[2,37-38]. Furthermore, the gut microbiota can affect the integrity of the BBB, which in turn influences neuroinflammatory responses and overall CNS health[39]. This relationship between gut microbiota and neuroinflammation highlights the importance of maintaining a healthy microbiome as a preventative or mitigative strategy against neurodegenerative processes associated with AD.

3.1 *Association between metabolic dysregulation and AD*

Metabolic dysregulation is a significant factor in the development of AD, with the gut microbiome playing a crucial role in this connection. The gut microbiota can affect various metabolic pathways, particularly those related to lipid and glucose metabolism, which are essential for maintaining cognitive function. For example, changes in the composition of the gut microbiome can result in insulin resistance and higher levels of pro-inflammatory cytokines, both of which are linked to the onset of AD[40-42]. Furthermore, research has indicated that certain dietary patterns that influence the gut microbiome can either worsen or improve metabolic disorders and their related cognitive impairments[43-44]. One promising dietary approach is the ketogenic diet, which may enhance metabolic health and cognitive function in patients with AD by increasing the production of ketone bodies, offering an alternative energy source for the brain[45-46]. Apolipoprotein E (*APOE*) alleles are key genetic risk factors for AD, with APOE4 increasing risk compared to the neutral APOE3 and protective APOE2. APOE4 may worsen neuroinflammation and interact with gut microbiota, affecting SCFAs production and gut barrier integrity, thus accelerating AD. Studies suggest *APOE* alleles influence gut microbiome structure, as seen in the 5 Familial Alzheimer's Disease mutations (5XFAD) model[47-48]. Further research in humans and mice is needed to explore if changes in the gut microbiome are a novel mechanism by which *APOE* genotype affects AD. Gaining a deeper understanding of how the microbiome contributes to metabolic dysregulation could pave the way for innovative therapeutic strategies for AD.

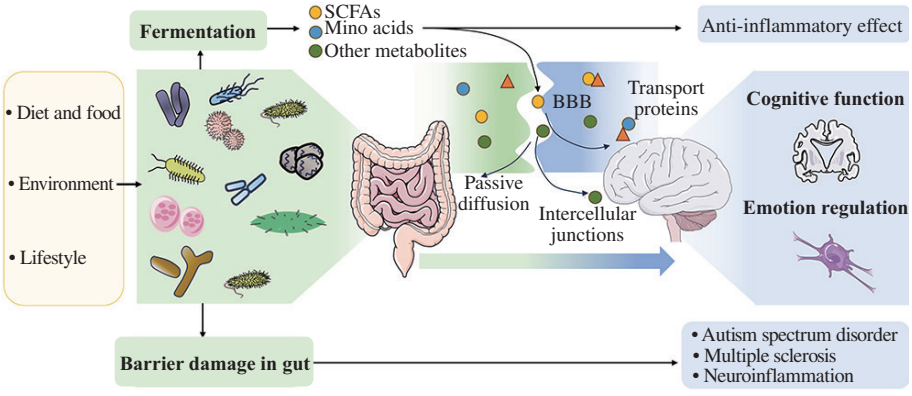

Fig. 1 MGBA encompasses the interactions between the gut microbiota, the gastrointestinal tract, and the CNS, influencing physiological and psychological processes. Factors such as dietary habits, living environment, and lifestyle jointly affect the gut microbiome system and can influence related metabolism and immune functions in multiple ways. Gut bacteria ferment dietary fibers to produce SCFAs, amino acids and their derivatives, and other metabolites. The mechanisms by which SCFAs cross the BBB include passive diffusion, transport proteins, and regulation of intercellular connections, and they have anti-inflammatory properties, which can affect brain health. Damaged intestinal barrier function is associated with neurological and mental disorders, leading to increased pro-inflammatory factors, which may trigger neuroinflammation and neuronal damage, indicating a connection between microbial diversity and neural health.

3.2 Regulatory role of neurotransmitters

Neurotransmitters play a crucial role in communication within the brain, and recent research has highlighted the significant influence of gut microbiota on their production and regulation. The microbiome affects the levels of important neurotransmitters, such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), all of which are vital for cognitive function and emotional health[39,49]. For example, the gut bacteria are responsible for producing precursors to serotonin, and any changes in the composition of gut microbiota can disrupt serotonin signaling. This disruption may contribute to mood disorders and cognitive decline, particularly in patients with AD[50]. Furthermore, the MGBA allows for two-way communication, meaning that fluctuations in neurotransmitter levels can also alter the composition of gut microbiota. This creates a feedback loop that could influence the progression of neurodegenerative diseases[37-38,51]. The intricate relationship between the microbiome and neurotransmitter regulation indicates that targeting gut microbiota might serve as a therapeutic strategy to adjust neurotransmitter levels and improve cognitive outcomes in individuals with AD (Fig. 2).

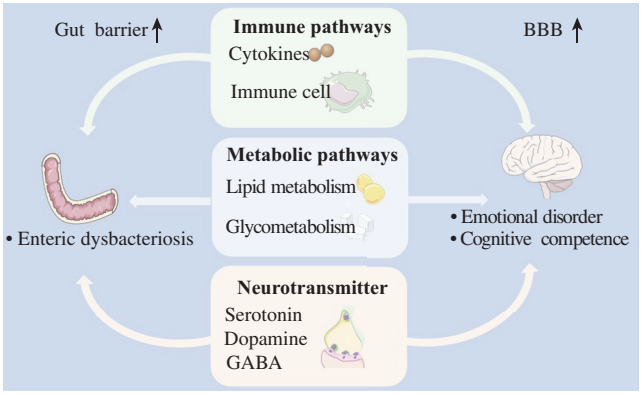

Fig. 2 MGBA plays a significant role in the development of AD. Within the MGBA, the gut microbiota influences the immune response, metabolism, neurotransmitter synthesis, and other pathways *via* the gut barrier and BBB. Imbalance in the gut microbiota can heighten neuroinflammation, contributing to mood disorders and cognitive decline, thereby potentially accelerating AD progression. SCFAs may alleviate neuroinflammation and cognitive decline in AD patients. The ketogenic diet can improve the metabolic health and cognitive function of AD patients by promoting the production of ketogenic bodies. Diminished secretion of neurotransmitters like serotonin, dopamine, and GABA may be linked to mood disorders and cognitive decline in AD patients.

4. Treatment and application of MGBA in AD

4.1 Probiotics in AD treatment

Probiotics are defined as live microorganisms that can offer health benefits to the host when taken in adequate amounts. Many probiotic strains have been researched for their potential to protect against neurodegeneration in AD[52]. Among the most commonly studied strains are those from the Lactobacillaceae and Bifidobacteriaceae families, which help to regulate the gut microbiota and create a balanced intestinal environment. These probiotics play a significant role in the MGBA, a bidirectional communication system linking the gastrointestinal tract with the CNS, thereby influencing cognitive functions and behaviors[53]. Probiotics contribute to health by producing SCFAs, modulating inflammatory responses, and enhancing intestinal barrier integrity. SCFAs, particularly butyrate, possess anti-inflammatory properties and can cross the BBB, potentially impacting neuroinflammation and cognitive decline associated with AD[54-55]. Furthermore, probiotics may aid in lowering Aβ levels, which are a key feature of AD pathology, through various biochemical mechanisms, indicating a complex and promising role for probiotics in the management of AD[56-57].

4.2 Clinical trial results and efficacy assessment

Clinical trials assessing the effectiveness of probiotics in AD have shown encouraging outcomes, indicating that these supplements may serve as valuable adjunctive therapies. For example, one systematic review and meta-analysis revealed that probiotic supplementation led to notable improvements in cognitive function and a reduction in symptoms among patients with mild-to-moderate AD[58]. Additionally, another study found that certain probiotic strains were able to slow the progression of cognitive decline, indicating a potential protective effect against neurodegeneration[57]. Moreover, research on combination therapy, which includes probiotic and vitamin co-supplementation, has indicated promise in preventing and delaying the onset of AD, emphasizing the importance of a comprehensive treatment approach[59-60]. However, despite these positive results, the variability in study designs, different probiotic strains used, and various assessment methods highlight the need for further, standardized research. This additional work is essential to establish standardized protocols, and to confirm the long-term efficacy and safety of probiotics in the treatment of AD[52,61]. Summarize key literature and create a clinical trials summary table (Table 1).

Table 1
Clinical trials summary.

Intervention	Sample size	Key outcomes	Limitations	Reference
Probiotics (*Lactobacillus/ Bifidobacterium*)	$n = 60$ (AD patients)	Improved mini-mental state examination (MMSE) scores by 15%	Small cohort; short duration	[58,61]
Mediterranean diet	$n = 200$ (at-risk)	Reduced Aβ plasma levels; 30% lower AD incidence	Self-reported dietary adherence	[74,90]
FMT (AD mouse model)	$n = 20$	Aβ plaques↓; cognitive function↑	Translational gap to humans	[17,101]

4.3 Potential of probiotics in combination with other treatments

The integration of probiotics with various therapeutic approaches offers a promising path to improve treatment outcomes in AD. Research has shown that probiotics can enhance the effectiveness of pharmacological treatments, such as cholinesterase inhibitors, which may lead to better cognitive function and an improved quality of life for patients[62]. Moreover, combining probiotics with dietary strategies, including prebiotics or synbiotics could further optimize gut health and cognitive performance by promoting a healthier gut microbiome[63-64]. Prebiotics and synbiotics, as adjuncts to probiotics, play a crucial role in regulating the intestinal microbiota and promoting host health[65]. Common prebiotics, like fructooligosaccharides (FOS), galactooligosaccharides (GOS), xylooligosaccharides (XOS), and inulin, promote beneficial bacteria

growth by providing nutrients. They improve probiotic survival and colonization, produce SCFA, and reduce intestinal permeability and endotoxin levels, thus reducing inflammation and oxidative stress[66]. Synbiotics, a blend of probiotics and prebiotics, enhance intestinal health more effectively than using either alone by providing live bacteria and necessary nutrients. They target multiple mechanisms, offering stronger immune support and disease risk reduction[67]. Synbiotics improve probiotic survival and function, benefiting intestinal health, metabolic diseases, and immune regulation. Future research should prioritize personalized methods and a deeper understanding of mechanisms[67-68]. Recent studies have also explored the combined use of probiotics and traditional Chinese medicines, highlighting their role in managing inflammation and oxidative stress, which are critical factors in the pathology of AD[69-71]. This multifaceted approach not only targets the symptoms of AD but also addresses its underlying mechanisms, offering a comprehensive strategy for disease management. Ongoing research into these combinations is crucial to fully realize the therapeutic potential of probiotics in the context of AD and to develop effective treatment protocols[52,72-73].

4.4 Dietary interventions play a crucial role in modulating MGBA

The Mediterranean diet, which is rich in fruits, vegetables, whole grains, legumes, nuts, and olive oil, has been associated with a reduced risk of AD. Research indicates that this diet positively influences the MGBA, which plays a crucial role in neuroinflammation and cognitive function. The diet's high polyphenol content promotes a diverse gut microbiome, which is vital for preserving cognitive health. A systematic review has shown that adherence to the Mediterranean diet correlates with lower levels of Aβ and Tau proteins, which are significant markers of AD pathology[74-76]. Additionally, the anti-inflammatory properties of this diet may help mitigate oxidative stress and inflammation, both of which are involved in the development of AD[77]. Dietary patterns that alter gut microbiota composition, particularly by increasing beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, lend support to the idea that diet can influence cognitive decline[78-79]. Overall, the Mediterranean diet emerges as a promising nonpharmacological strategy for lowering the risk of AD by impacting MGBA.

4.5 Impact of food components on gut microbiota

Food components significantly influence the gut microbiome, affecting both composition and functionality. Dietary fibers, polyphenols, and fatty acids are particularly important as they promote the growth of beneficial gut bacteria while inhibiting harmful strains. For example, dietary fibers are fermented by gut microbes, resulting in the production of SCFAs, including butyrate, which are known for their anti-inflammatory properties and ability to strengthen the gut barrier[80-81]. Additionally, polyphenols, which are plentiful in fruits and vegetables, can enhance the diversity of gut microbiota, leading to better metabolic health and lower levels of inflammation[82-84]. The balance between omega-3 and omega-6 fatty acids also plays a role in how the gut microbiome responds to inflammation, potentially impacting neuroinflammatory processes linked to neurodegenerative diseases[85]. This intricate relationship between diet and gut microbiota highlights the critical role of dietary composition in promoting gut health and preventing cognitive decline, suggesting a promising therapeutic approach for conditions such as AD.

4.6 Clinical studies on dietary interventions

Recent clinical research has largely focused on dietary interventions aimed at the MGBA to help reduce cognitive decline. One systematic review of clinical trials has revealed that dietary modifications, such as following the modified ketogenic diet (MIND) (a combination of the Mediterranean and Dietary Approaches to Stop Hypertension diets), may lead to slight improvements in cognitive function among older adults who are at high risk for AD[86]. Dietary intervention, for example, a diet rich in prebiotics and probiotics, can promote the diversity of the intestinal microbiota. It also helps maintain the integrity of the intestinal barrier. The metabolites of these microbiota, SCFAs can improve cognitive function through the MGBA by inhibiting microglial activation and reducing inflammatory factor release[87]. Studies have shown that the antioxidant components and unsaturated fatty acids in the Mediterranean diet can simultaneously reduce Aβ deposition and regulate Tau protein phosphorylation[88-89]. Participants who followed the MIND diet demonstrated slower rates of cognitive decline compared to those adhering to typical Western dietary patterns[90]. Furthermore, pilot studies exploring modified ketogenic diets have indicated positive changes in cerebrospinal fluid biomarkers linked to AD, suggesting that certain dietary interventions can influence the progression of the disease[46,91]. These findings underscore the need for larger trials to assess the effectiveness and underlying mechanisms of dietary interventions in impacting the MGBA, which could play a crucial role in preventing and managing cognitive impairment.

4.7 Future of fecal microbiota transplantation

Fecal microbiota transplantation (FMT) involves transferring fecal microbiota from a healthy donor to a recipient to restore the recipient's microbiota to a healthier state. This procedure is based on the understanding that gut microbiota plays a crucial role in influencing host health by impacting metabolism, immunity, and neurological functions. The primary goal of FMT is to address dysbiosis, which is linked to various diseases, including gastrointestinal disorders, obesity, and neurodegenerative conditions. Recent studies have shown that FMT can effectively restore microbial diversity and function, leading to improved health outcomes in conditions such as *Clostridium difficile* infection and inflammatory bowel disease[92-93]. Furthermore, gut microbiota modulation is being explored as a therapeutic strategy for a range of conditions, including metabolic and neurological disorders, highlighting the extensive potential of this approach[94-95].

The application of FMT in AD is an emerging area of research that has recently gained traction. Recent studies have indicated that an imbalance in the gut bacteria may play a role in the development of AD by affecting neuroinflammation, the buildup of Aβ, and overall cognitive function[50,96-97]. For example, research has shown that fecal microbiota from individuals with AD can lead to cognitive deficits and hinder the growth of new neurons in the hippocampus when tested in animal models, highlighting a potential connection between gut health and cognitive decline[98]. Additionally, interventions designed to modify gut microbiota have shown encouraging results in preclinical studies, pointing to FMT as a promising new treatment

strategy for AD[99-100]. For example, frequent fecal microbiota transplants from wild-type mice to AD mice have been found to improve the formation of Aβ plaques, reduce neurofibrillary tangles, decrease glial reactivity, and alleviate cognitive impairments[17]. Furthermore, FMT has been shown to enhance cognitive abilities and reduce Aβ accumulation in AD mouse models[101]. In another study involving APP/PS1 mice, dietary supplementation with SCFAs was found to restore balance in gut microbiota and Lessen cognitive deficits by reducing Aβ deposition and Tau hyperphosphorylation[102]. Diets such as the ketogenic or Mediterranean diet may also help manage AD by influencing gut microbiota and regulating neurotransmitters, including serotonin and GABA[45]. Moreover, leveraging dominant gut microbiota presents a potential alternative to FMT for treating AD[99]. FMT has shown neuroprotective potential in preclinical studies of AD, improving the cognitive function of model mice, reducing Aβ deposition and Tau protein phosphorylation in the brain, enhancing synaptic plasticity (such as increased expression of PSD-95 and synapsin I), and inhibiting neuroinflammation. The mechanism may involve regulating The TLR4/IKKβ/NF-κB pathway and the MGBA, as well as exerting indirect effects through metabolites such as SCFAs[103-104]. However, the efficacy of FMT is highly condition-dependent: factors such as administration frequency (for example, low frequency where it is ineffective), donor source, and individual differences significantly influence the outcome[103,105-106]. Currently, clinical evidence is limited to small-scale clinical studies or case reports[107]. Moreover, the long-term safety of FMT remains to be established, and standardized protocols, such as microbiota screening and transplantation processes, still need to be developed[99,104,108]. Therefore, FMT can be regarded as an exploratory adjunctive treatment strategy for AD, but its applicability and risk control measures require further clarification through randomized controlled trials. To effectively translate these promising findings into clinical practice, it is crucial to conduct thorough investigations into the safety and efficacy of FMT in patients with AD, as well as to establish optimal protocols, suitable donor profiles, and criteria for selecting recipients[109-110] (Fig. 3). In summary, we have created a milestone timeline (Fig. 4) and a comparison table of key research findings (Table 2) for the application of FMT in AD.

Furthermore, current research should also show the ethical considerations of FMT and the comparative analysis of emerging methods. Ethically, the widespread use of FMT faces significant regulatory challenges and moral questions, particularly concerning the standardization of donor screening processes, the need for informed consent, and uncertainties about long-term safety[111]. Given the complex nature of FMT preparations and the possibility of unidentified microorganisms or pathogens, it is essential that safety management follows strict ethical guidelines and operational protocols[111-112]. Regarding the comparison of FMT techniques, recent studies highlight a growing interest in capsule-encapsulated FMT (caFMT) due to its convenience and better patient compliance. Research shows similar success rates for locally produced and externally sourced caFMT in treating recurrent *Clostridioides difficile* infection (rCDI), with 65% and 72% success, respectively, compared to 79% with colonoscopy-delivered FMT[113]. Another study on freeze-dried fecal capsules reported an 82.14% success rate, increasing to 93.75% with higher bacterial counts, emphasizing the importance of formulation optimization[114]. Traditional methods like colonoscopic infusion remain effective, particularly for single treatments. Future research should assess the pros and cons of various administration routes and utilize multi-omics techniques like metagenomics and metabolomics to thoroughly evaluate the mechanisms and durability of microbial implantation[111,115]. It is essential for the ethical framework to evolve alongside technological advancements to ensure FMT is applied safely and fairly in clinical settings.

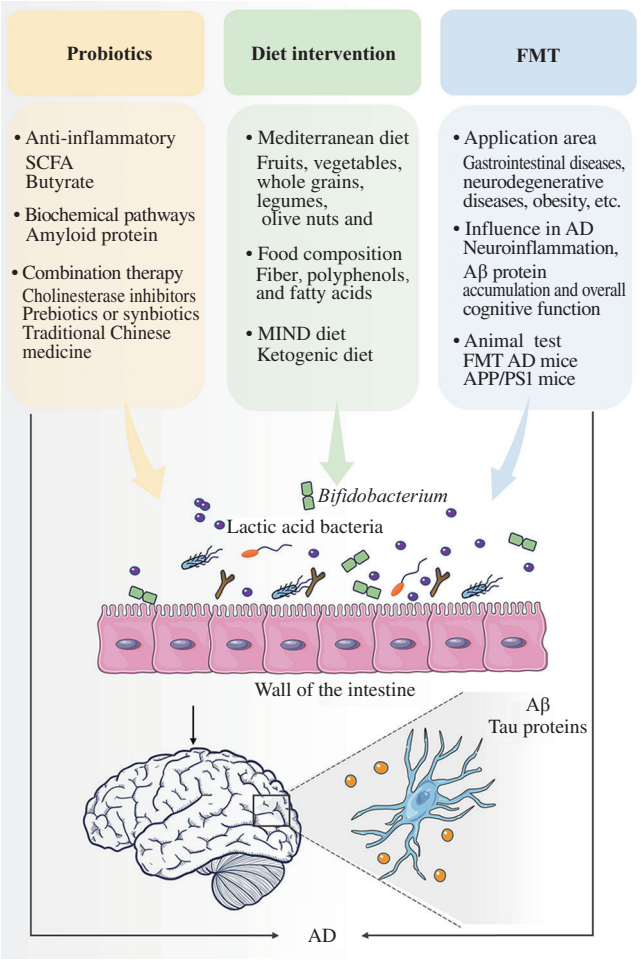

Fig. 3 Treatment and application of MGBA in AD are gaining attention. Currently, effective strategies for treating AD mainly include probiotic therapy, dietary intervention, and intestinal microbiota transplantation. When probiotics are combined with cholinesterase inhibitors, they can enhance the cognitive function and quality of life in patients with AD. In conjunction with traditional Chinese medicine, probiotic therapy contributes to the regulation of inflammation and oxidative stress. Dietary interventions, such as the Mediterranean diet that consists of fruits, vegetables, whole grains, legumes, nuts, and olive oil, may lower the risk of AD and the levels of Aβ and Tau by alleviating oxidative stress and inflammation. The MIND significantly improves cognitive function in older adults at high risk of developing AD. The fecal microbiota of AD patients can cause cognitive deficits in animal models. FMT represents a novel strategy for managing microbiota dysbiosis-associated diseases, encompassing gastrointestinal disorders, obesity, and neurodegenerative diseases. Clinical investigations show that FMT is an innovative therapy for AD by modulating gut microbiota dysregulation, which affects neuroinflammation, Aβ aggregation, and cognitive function. Moreover, FMT treatment has been shown to decrease brain Aβ deposition and ameliorate cognitive deficits in AD mouse models. SCFAs might decelerate cognitive decline in AD patients by fortifying the intestinal barrier; modulating neuroinflammation; and influencing neurotransmitter production at the BBB. Research on AD model mice and APP/PS1 mice has revealed that FMT can mitigate cognitive impairment through the reduction of Aβ deposition.

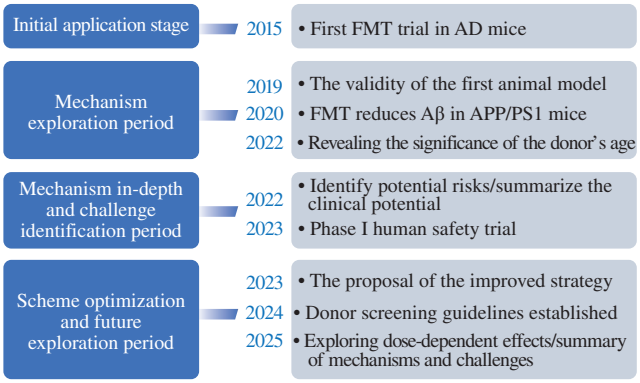

Fig. 4 A milestone timeline for the application of FMT in AD. Based on the analysis of over 20 articles from 2015 to 2025, the figure summarizes the research progress of FMT in the treatment of AD. The development process can be divided into 4 stages: the initial application stage, the mechanism exploration period, mechanism in-depth and challenge identification period, and the scheme optimization and future exploration period. It also systematically presents the treatment effects and application development at each time point.

4.8 Future research directions and challenges

Despite the promising potential of FMT, several challenges and future research directions need to be addressed. Future studies should clarify how gut microbiota affects host physiology, especially in the context of neurodegenerative diseases such as AD. It is also essential to standardize FMT protocols, which include thorough donor screening and microbiota characterization, to ensure consistency and safety in clinical applications[116]. A major area of research should focus on examining the long-term effects of FMT on the recipient's microbiome and overall health, including the potential for adverse effects or complications[117]. Furthermore, integrating advanced technologies, such as metagenomics and metabolomics, can enhance our understanding of the MGBA and the therapeutic possibilities of FMT[118-119]. By tackling these challenges, we can fully leverage the therapeutic potential of FMT for AD and other neurodegenerative conditions.

4.9 Emerging technologies and future directions

According to recent literature, a comparative analysis of shotgun sequencing and 16S rRNA sequencing methods in microbial community studies is feasible. The Kraken tool was initially developed for shotgun metagenomic sequencing, offering rapid and precise classification, and has demonstrated high performance in such projects. With the advent of Kraken 2, the tool now extends its support to the 16S rRNA database, enabling direct comparisons with tools like QIIME 2, which specialize in 16S rRNA analysis. In the context of 16S rRNA analysis, Kraken 2 and Bracken exhibit significantly enhanced performance, being 100 and 300 times faster, respectively, than QIIME 2 in terms of database generation and classification speed. They also utilize fewer memory resources while delivering more accurate results. This advancement indicates that innovative technologies such as Kraken 2 are effectively bridging the gap between shotgun sequencing and 16S rRNA methodologies by offering efficient analytical tools that optimize microbial community analysis. Future research directions may involve further integration of these tools, combining the comprehensive nature of shotgun sequencing with the specificity of 16S rRNA targeting, to enhance the speed and accuracy of microbial community analyses. The literature concludes that Kraken 2 and Bracken provide fast and efficient solutions for microbial group analysis[120].

5. Conclusion

In conclusion, the MGBA is vital for understanding the pathophysiology of AD. Recent studies have suggested that alterations in the gut microbiota composition can influence neuroinflammation, Aβ accumulation, and neurodegeneration, highlighting its significant role in the onset and progression of AD. This perspective paves the way for new research opportunities and underscores the importance of a comprehensive approach to managing AD. Therapeutic strategies targeting the microbiota offer a promising new direction for treating AD. By adjusting the gut microbiome through dietary changes, probiotics, or prebiotics, we may alleviate symptoms or slow the

Table 2
Comparison table of key research results on FMT for AD treatment[99,101,103,105-108].

Research model	FMT solution	Main positive results	Main negative/restrictive results
APP/PS1 transgenic mice	Colon perfusion	Improve cognition; reduce Aβ deposition and Tau phosphorylation; enhance synaptic plasticity; reduce neuroinflammation	Preclinical study
5xFAD transgenic mice	Once a week *vs*. once every 2 days	Once every 2 days; restore the microbiota; reduce Aβ; inhibit the TLR4/NF-κB pathway; improve cognition	Once a week is invalid. The therapeutic effect weakens over time (timeliness)
5xFAD transgenic mice	7-day short-term treatment	Significantly reduce plaques and improve behavior; prove the effectiveness of short-term treatment	The therapeutic effect is highly dependent on the donor's age (younger donors are key)
Wild-type mice (received TBI)	Transplant the microbiota from AD mice	Not applicable	Adverse microbiota worsens outcomes: AD source FMT can increase neuroinflammation and impair function post-brain trauma
APP/PS1 transgenic mice	Transplantation of "dominant microbiota" (not full FMT)	Restore the balance of the microflora; reduce Aβ deposition and inflammation in the brain; offer potential alternatives to FMT	Animal research; the "dominant bacterial flora" formula requires standardization
Arsenic exposure induces AD rats	FMT intervention	Partial improvements: reduce Tau phosphorylation and increase beneficial bacteria	Neurobehavioral deficits and neurotoxicity cannot be completely reversed
Systematic review (including human cases)	Pooled analysis	Improvement in MMSE score; there is a potential improvement in cognition	Low evidence level: only case reports and small-scale trials, lacking strict randomized controlled clinical trials

Notes: TBI, traumatic brain injury.

disease's advancement. In recent years, dietary intervention has gained extensive attention as an important way to regulate the MGBA in AD research. Existing studies have shown that different dietary patterns can not only significantly alter the composition of the gut microbiota, but also profoundly impact the onset and progression of AD by regulating neuroinflammation, metabolic pathways, and neuroprotective mechanisms. There is preliminary evidence supporting the potential value of dietary intervention in the prevention and treatment of AD, current research still has certain limitations. First of all, some dietary patterns, such as the Mediterranean diet and the ketogenic diet, have shown positive effects on patients with AD, the viewpoints and findings among different studies are still inconsistent. The inconsistent findings may stem from various factors such as research design, sample selection, the duration of dietary intervention, and individual differences. Secondly, the current research on the mechanism of dietary intervention is still insufficient. Although it is known that diet can affect the nervous system by regulating the gut microbiota, the specific biological mechanisms remain to be explored in depth. Future research should focus on revealing how dietary intervention influences physiological and pathological processes related to AD through the MGBA, thereby providing a stronger theoretical basis for clinical applications.

However, it is worth noting that contradictory results have emerged in probiotic research. The analysis reveals several reasons. First, probiotic effects are highly strain-specific. Individual probiotics or their components exhibit heterogeneous impacts on different diseases or health conditions. This inherent variability contributes significantly to the mixed results observed in human trials. For example, different gene modules present on the same probiotic can have distinct effects on various diseases. Host microbiome composition and individual variability: the composition of an individual's resident gut microbiota and their specific health status significantly influence probiotic responses. This variability makes it difficult to replicate consistent outcomes across different human populations based solely on animal studies. Diseased individuals often exhibit disruptions or lacks in beneficial probiotic-associated gene modules compared to healthy individuals. Furthermore, maintaining the integrity of probiotic community gene functions is more important than merely increasing the abundance of specific probiotic genes[121-122]. The application of animal models in the research of this problem also has certain limitations. While valuable, animal models cannot fully replicate the complexity and heterogeneity of the human gut environment and microbiome. Translational challenges arise due to: 1) dose discrepancy, effective doses in animals do not always scale predictably to humans; 2) microbiome differences, the baseline and induced changes in gut microbiota composition and function often differ substantially between animal models and humans[123]. Therefore, conflicting evidence in probiotic trials arises from several factors, including strain specificity, individual host-microbiome variability, and viability or delivery challenges. Additionally, limitations exist in translating complex animal data to diverse human populations. Addressing these issues requires innovative delivery technologies (especially nanoencapsulation), precise strain identification tools, probiotic engineering, and possibly a transition to defined functional metabolites derived from probiotics[124-125]. While initial studies show promising outcomes, it is essential to consider the variability in research findings. Differences in study designs, microbiome assessment techniques, and patient demographics make it challenging to interpret results consistently. Therefore, it is crucial to standardize microbiome analysis methods and conduct larger, well-controlled clinical trials to validate these therapeutic strategies.

Of course, there are also potential risks in regulating the microbiota. FMT may disrupt the microbiota balance, posing a risk of dysbiosis. On the one hand, the transplanted donor microbiota may disrupt the recipient's intestinal microbiota composition. This disruption can lead to excessive growth of pathogenic bacteria or a reduction in symbiotic bacteria. On the other hand, dysbiosis may increase intestinal permeability, promote the release of inflammatory factors, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta, thereby activating systemic inflammatory responses and even affecting the progression of CNS diseases[126-127]. Although the ketogenic diet regulates the microbiota and improves metabolism, its prolonged use carries risks. It may reduce intestinal flora diversity, decrease SCFA-producing bacteria, impair intestinal barrier function and energy metabolism, and lacks verification of long-term efficacy[128-129]. In conclusion, the core risk of microbial regulatory therapy lies in the possibility of disrupting the homeostasis balance between the host and microorganisms. If FMT is performed improperly or donor screening is insufficient, it may lead to colonization by pathogenic bacteria or trigger inflammatory cascade reactions. However, long-term use of the ketogenic diet may lead to a decrease in microbiota diversity and abnormal metabolic functions due to a single nutritional structure. In the future, standardized operation procedures and long-term follow-up studies are needed to clarify the safety boundaries.

Future research is crucial to enhance our understanding of the relationship between the microbiota and AD. It is essential to conduct longitudinal studies that investigate the causal connections between specific changes in microbial populations and the pathology of AD. Furthermore, uncovering the mechanisms through which the gut microbiota affects neurobiological processes will offer important insights that could lead to the development of targeted interventions. As we delve deeper into the extensive field of the microbiome, it is vital to incorporate these findings into clinical practice to ensure that new therapies are based on solid evidence and customized to meet the unique needs of each patient.

Ultimately, the MGBA holds significant potential for deepening our understanding of AD and introducing innovative treatment options that could transform patient care. Interdisciplinary collaboration is key to bridging basic research with clinical applications, which will enhance the quality of life for those affected by this challenging condition.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgement

This work was supported, in whole or in part, by grants from the National Natural Science Foundation of China (81301084 and 82105009), Natural Science Foundation of Hubei Province (2024AFB884 and 2025AFB647), the Medical Scientific Research Foundation of Wuhan Municipal Health Commission (WZ22C47 and WZ21Q14).

References

[1] B. Kim, M.I. Kanai, Y. Oh, et al., Response of the microbiome-gut-brain axis in *Drosophila* to amino acid deficit, Nature 593 (2021) 570-574. https://doi.org/10.1038/s41586-021-03522-2.

[2] J.S. Loh, W.Q. Mak, L.K.S. Tan, et al., Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases, Signal Transduct. Target. Ther. 9 (2024) 37. https://doi.org/10.1038/s41392-024-01743-1.

[3] P. Scheltens, B. De Strooper, M. Kivipelto, et al., Alzheimer's disease, Lancet 397 (2021) 1577-1590. https://doi.org/10.1016/S0140-6736(20)32205-4.

[4] J. Graff-Radford, K.X.X. Yong, L.G. Apostolova, et al., New insights into atypical Alzheimer's disease in the era of biomarkers, Lancet Neurol. 20 (2021) 222-234. https://doi.org/10.1016/S1474-4422(20)30440-3.

[5] M. Ishii, C. Iadecola, Risk factor for Alzheimer's disease breaks the blood-brain barrier, Nature 581 (2020) 31-32. https://doi.org/10.1038/d41586-020-01152-8.

[6] C. Chen, J. Liao, Y. Xia, et al., Gut microbiota regulate Alzheimer's disease pathologies and cognitive disorders *via* PUFA-associated neuroinflammation, Gut 71 (2022) 2233-2252. https://doi.org/10.1136/gutjnl-2021-326269.

[7] A.L. Ferreiro, J. Choi, J. Ryou, et al., Gut microbiome composition may be an indicator of preclinical Alzheimer's disease, Sci. Transl. Med. 15 (2023) eabo2984. https://doi.org/10.1126/scitranslmed.abo2984.

[8] M. Ballard, P. Montgomery, Risk of bias in overviews of reviews: a scoping review of methodological guidance and four-item checklist, Res. Synth. Methods 8 (2017) 1229. https://doi.org/10.1002/jrsm.1229.

[9] M.D.J. Peters, C. Marnie, A.C. Tricco, et al., Updated methodological guidance for the conduct of scoping reviews, JBI Evid. Synth. 18 (2020) 2119-2126. https://doi.org/10.11124/JBIES-20-00167.

[10] H. Zhang, Y. Chen, Z. Wang, et al., Implications of gut microbiota in neurodegenerative diseases, Front. Immunol. 13 (2022) 785644. https://doi.org/10.3389/fimmu.2022.785644.

[11] Y.K. Kim, C. Shin, The microbiota-gut-brain axis in neuropsychiatric disorders: pathophysiological mechanisms and novel treatments, Curr. Neuropharmacol. 16 (2018) 559-573. https://doi.org/10.2174/1570159X15666170915141036.

[12] E. Schneider, K.J. O'Riordan, G. Clarke, et al., Feeding gut microbes to nourish the brain: unravelling the diet-microbiota-gut-brain axis, Nat. Metab. 6 (2024) 1454-1478. https://doi.org/10.1038/s42255-024-01108-6.

[13] Y.F. Hou, C. Shan, S.Y. Zhuang, et al., Gut microbiota-derived propionate mediates the neuroprotective effect of osteocalcin in a mouse model of Parkinson's disease, Microbiome 9 (2021) 34. https://doi.org/10.1186/s40168-020-00988-6.

[14] C. Sun, S. Dong, W. Chen, et al., Berberine alleviates Alzheimer's disease by regulating the gut microenvironment, restoring the gut barrier and brain-gut axis balance, Phytomedicine 129 (2024) 155624. https://doi.org/10.1016/j.phymed.2024.155624.

[15] K.A. Conn, E.M. Borsom, E.K. Cope, Implications of microbe-derived γ-aminobutyric acid (GABA) in gut and brain barrier integrity and GABAergic signaling in Alzheimer's disease, Gut Microbes 16 (2024) 2371950. https://doi.org/10.1080/19490976.2024.2371950.

[16] J. Yang, J. Liang, N. Hu, et al., The gut microbiota modulates neuroinflammation in Alzheimer's disease: elucidating crucial factors and mechanistic underpinnings, CNS. Neurosci. Ther. 30 (2024) e70091. https://doi.org/10.1111/cns.70091.

[17] M.S. Kim, Y. Kim, H. Choi, et al., Transfer of a healthy microbiota reduces amyloid and Tau pathology in an Alzheimer's disease animal model, Gut 69 (2020) 283-294. https://doi.org/10.1136/gutjnl-2018-317431.

[18] W. Xiao, J. Su, X. Gao, et al., The microbiota-gut-brain axis participates in chronic cerebral hypoperfusion by disrupting the metabolism of short-chain fatty acids, Microbiome 10 (2022) 62. https://doi.org/10.1186/s40168-022-01255-6.

[19] Z. Liu, X. Dai, H. Zhang, et al., Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment, Nat. Commun. 11 (2020) 855. https://doi.org/10.1038/s41467-020-14676-4.

[20] E. Fock, R. Parnova, Mechanisms of blood-brain barrier protection by microbiota-derived short-chain fatty acids, Cells 12 (2023) 657. https://doi.org/10.3390/cells12040657.

[21] R. Yan, L. Zhang, Y. Chen, et al., Therapeutic potential of gut microbiota modulation in epilepsy: a focus on short-chain fatty acids, Neurobiol. Dis. 209 (2025) 106880. https://doi.org/10.1016/j.nbd.2025.106880.

[22] M. Valles-Colomer, G. Falony, Y. Darzi, et al., The neuroactive potential of the human gut microbiota in quality of life and depression, Nat. Microbiol. 4 (2019) 623-632. https://doi.org/10.1038/s41564-018-0337-x.

[23] Z. Zhuang, R. Yang, W. Wang, et al., Associations between gut microbiota and Alzheimer's disease, major depressive disorder, and schizophrenia, J. Neuroinflammation. 17 (2020) 288. https://doi.org/10.1186/s12974-020-01961-8.

[24] N. Saji, Y. Saito, T. Yamashita, et al., Relationship between plasma lipopolysaccharides, gut microbiota, and dementia: a cross-sectional study, J. Alzheimers. Dis. 86 (2022) 1947-1957. https://doi.org/10.3233/JAD-215653.

[25] C.E. Santana-Gómez, D. Pérez-Pérez, D. Fonseca-Barriendos, et al., Transcranial focal electrical stimulation modifies biogenic amines' alterations induced by 6-hydroxydopamine in rat brain, Pharmaceuticals 14 (2021) 706. https://doi.org/10.3390/ph14080706.

[26] A.E. Alkhalifa, N.F. Al-Ghraiybah, A. Kaddoumi, Extra-virgin olive oil in Alzheimer's disease: a comprehensive review of cellular, animal, and clinical studies, Int. J. Mol. Sci. 25 (2024) 1914. https://doi.org/10.3390/ijms25031914.

[27] X. Wang, Z. Wang, J. Cao, et al., Gut microbiota-derived metabolites mediate the neuroprotective effect of melatonin in cognitive impairment induced by sleep deprivation, Microbiome 11 (2023) 17. https://doi.org/10.1186/s40168-022-01452-3.

[28] D. Ji, W.Z. Chen, L. Zhang, et al., Gut microbiota, circulating cytokines and dementia: a Mendelian randomization study, J. Neuroinflamm. 21 (2024) 2. https://doi.org/10.1186/s12974-023-02999-0.

[29] L.K. Yassin, M.M. Nakhal, A. Alderei, et al., Exploring the microbiota-gut-brain axis: impact on brain structure and function, Front. Neuroanat. 19 (2025) 1504065. https://doi.org/10.3389/fnana.2025.1504065.

[30] M.M. Nakhal, L.K. Yassin, R. Alyaqoubi, et al., The microbiota-gut-brain axis and neurological disorders: a comprehensive review, Life 14 (2024) 1234. https://doi.org/10.3390/life14101234.

[31] M. Jiang, L. Kang, Y.L. Wang, et al., Mechanisms of microbiota-gut-brain axis communication in anxiety disorders, Front. Neurosci. 18 (2024) 1501134. https://doi.org/10.3389/fnins.2024.1501134.

[32] Y. Jing, Q. Wang, F. Bai, et al., Role of microbiota-gut-brain axis in natural aging-related alterations in behavior, Front. Neurosci. 18 (2024) 1362239. https://doi.org/10.3389/fnins.2024.1362239.

[33] T. Nie, L. You, F. Tang, et al., Microbiota-gut-brain axis in age-related neurodegenerative diseases, Curr. Neuropharmacol. 23 (2025) 524-546. https://doi.org/10.2174/1570159x23666241101093436.

[34] R. Yang, X. Wang, J. Yang, et al., Perturbations in the microbiota-gut-brain axis shaped by social status loss, Commun. Biol. 8 (2025) 401. https://doi.org/10.1038/s42003-025-07850-1.

[35] S. Binda, A. Tremblay, U.H. Iqbal, et al., Psychobiotics and the microbiota-gut-brain axis: where do we go from here? Microorganisms 12 (2024) 634. https://doi.org/10.3390/microorganisms12040634.

[36] T. Ba, R. Niu, J. Gao, et al., Microbiota-gut-brain-axis: a new target of acupuncture therapy for post-stroke cognitive impairment, Front. Microbiol. 16 (2025) 1425054. https://doi.org/10.3389/fmicb.2025.1425054.

[37] X. Wang, G. Sun, T. Feng, et al., Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression, Cell Res. 29 (2019) 787-803. https://doi.org/10.1038/s41422-019-0216-x.

[38] P. Liu, Z. Liu, J. Wang, et al., Immunoregulatory role of the gut microbiota in inflammatory depression, Nat. Commun. 15 (2024) 3003. https://doi.org/10.1038/s41467-024-47273-w.

[39] V. Braniste, M. Al-Asmakh, C. Kowal, et al., The gut microbiota influences blood-brain barrier permeability in mice, Sci. Transl. Med. 6 (2014) 263ra158. https://doi.org/10.1126/scitranslmed.3009759.

[40] F.I. Pinheiro, I. Araújo-Filho, A.C.M. do Rego, et al., Hepatopancreatic metabolic disorders and their implications in the development of Alzheimer's disease and vascular dementia, Ageing Res. Rev. 96 (2024) 102250. https://doi.org/10.1016/j.arr.2024.102250.

[41] A. Nogal, A.M. Valdes, C. Menni, The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health, Gut

Microbes 13 (2021) 7212. https://doi.org/10.1080/19490976.2021.1897212.
[42] Y. Chen, Y. Li, Y. Fan, et al., Gut microbiota-driven metabolic alterations reveal gut-brain communication in Alzheimer's disease model mice, Gut Microbes 16 (2024) 2302310. https://doi.org/10.1080/19490976.2024.2302310.
[43] H. Shi, Y. Yu, D. Lin, et al., *β*-Glucan attenuates cognitive impairment *via* the gut-brain axis in diet-induced obese mice, Microbiome 8 (2020) 143. https://doi.org/10.1186/s40168-020-00920-y.
[44] H. Shi, Q. Wang, M. Zheng, et al., Supplement of microbiota-accessible carbohydrates prevents neuroinflammation and cognitive decline by improving the gut microbiota-brain axis in diet-induced obese mice, J. Neuroinflamm. 17 (2020) 77. https://doi.org/10.1186/s12974-020-01760-1.
[45] A.H. Dilmore, C. Martino, B.J. Neth, et al., Effects of a ketogenic and low-fat diet on the human metabolome, microbiome, and foodome in adults at risk for Alzheimer's disease, Alzheimers Dement. 19 (2023) 4805-4816. https://doi.org/10.1002/alz.13007.
[46] M.C.L. Phillips, L.M. Deprez, G.M.N. Mortimer, et al., Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease, Alzheimers Res. Ther. 13 (2021) 51. https://doi.org/10.1186/s13195-021-00783-x.
[47] T.T.T. Tran, S. Corsini, L. Kellingray, et al., APOE genotype influences the gut microbiome structure and function in humans and mice: relevance for Alzheimer's disease pathophysiology, FASEB J. 33 (2019) 8221-8231. https://doi.org/10.1096/fj.201900071R.
[48] I.J. Parikh, J.L. Estus, D.J. Zajac, et al., Murine gut microbiome association with *APOE* alleles, Front. Immunol. 11 (2020) 200. https://doi.org/10.3389/fimmu.2020.00200.
[49] J.P. Wei, W. Wen, Y. Dai, et al., Drinking water temperature affects cognitive function and progression of Alzheimer's disease in a mouse model, Acta Pharmacol. Sin. 42 (2021) 45-54. https://doi.org/10.1038/s41401-020-0407-5.
[50] E.J. Kang, M.G. Cha, G.H. Kwon, et al., *Akkermansia muciniphila* improve cognitive dysfunction by regulating BDNF and serotonin pathway in gut-liver-brain axis, Microbiome 12 (2024) 181. https://doi.org/10.1186/s40168-024-01924-8.
[51] J. Li, Y. Liu, L. Yuan, et al., A tissue-like neurotransmitter sensor for the brain and gut, Nature 606 (2022) 2. https://doi.org/10.1038/s41586-022-04615-2.
[52] X. Yang, D. Yu, L. Xue, et al., Probiotics modulate the microbiota-gut-brain axis and improve memory deficits in aged SAMP8 mice, Acta Pharm. Sin. B 10 (2020) 475-487. https://doi.org/10.1016/j.apsb.2019.07.001.
[53] D. Erny, N. Dokalis, C. Mezö, et al., Microbiota-derived acetate enables the metabolic fitness of the brain innate immune system during health and disease, Cell Metab. 33 (2021) 10. https://doi.org/10.1016/j.cmet.2021.10.010.
[54] Q. Liu, Y. Xi, Q. Wang, et al., Mannan oligosaccharide attenuates cognitive and behavioral disorders in the 5xFAD Alzheimer's disease mouse model via regulating the gut microbiota-brain axis, Brain Behav. Immun. 95 (2021) 330-343. https://doi.org/10.1016/j.bbi.2021.04.005.
[55] X. Ge, M. Zheng, M. Hu, et al., Butyrate ameliorates quinolinic acid-induced cognitive decline in obesity models, J. Clin. Invest. 133 (2023) 154612. https://doi.org/10.1172/JCI154612.
[56] C. Zhao, R. Kuraji, C. Ye, et al., Nisin a probiotic bacteriocin mitigates brain microbiome dysbiosis and Alzheimer's disease-like neuroinflammation triggered by periodontal disease, J. Neuroinflamm. 20 (2023) 228. https://doi.org/10.1186/s12974-023-02915-6.
[57] X.H. Qian, S.Y. Chen, H.D. Tang, Multi-strain probiotics ameliorate Alzheimer's-like cognitive impairment and pathological changes through the AKT/GSK-3β pathway in senescence-accelerated mouse prone 8 mice, Brain Behav. Immun. 119 (2024) 14-27. https://doi.org/10.1016/j.bbi.2024.03.031.
[58] T. Zhang, G. Gao, L.Y. Kwok, et al., Gut microbiome-targeted therapies for Alzheimer's disease, Gut Microbes 15 (2023) 2271613. https://doi.org/10.1080/19490976.2023.2271613.
[59] O.F. Sultana, R.A. Hia, P.H. Reddy, A combinational therapy for preventing and delaying the onset of Alzheimer's disease: a focus on probiotic and vitamin co-supplementation, Antioxidants 13 (2024) 202. https://doi.org/10.3390/antiox13020202.
[60] V. Andrews, G. Zammit, F. O'Leary, Dietary pattern, food, and nutritional supplement effects on cognitive outcomes in mild cognitive impairment: a systematic review of previous reviews, Nutr. Rev. 81 (2023) 1462-1489. https://doi.org/10.1093/nutrit/nuad013.
[61] C.S. Kim, L. Cha, M. Sim, et al., Probiotic supplementation improves cognitive function and mood with changes in gut microbiota in community-dwelling older adults: a randomized, double-blind, placebo-controlled, multicenter trial, J. Gerontol. A Biol. Sci. Med. Sci. 76 (2021) 32-40. https://doi.org/10.1093/gerona/glaa090.
[62] D.Y. Lee, J.K. Kim, S.W. Yun, et al., DW2009 elevates the efficacy of donepezil against cognitive impairment in mice, Nutrients 13 (2021) 3273. https://doi.org/10.3390/nu13093273.
[63] L. Redondo-Cuevas, L. Belloch, V. Martín-Carbonell, et al., Do herbal supplements and probiotics complement antibiotics and diet in the management of SIBO? A randomized clinical trial, Nutrients 16 (2024) 1083. https://doi.org/10.3390/nu16071083.
[64] T. Chunchai, W. Thunapong, S. Yasom, et al., Decreased microglial activation through gut-brain axis by prebiotics, probiotics, or synbiotics effectively restored cognitive function in obese-insulin resistant rats, J. Neuroinflamm. 15 (2018) 11. https://doi.org/10.1186/s12974-018-1055-2.
[65] M.K. Yadav, I. Kumari, B. Singh, et al., Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics, Appl. Microbiol. Biotechnol. 106 (2022) 505-521. https://doi.org/10.1007/s00253-021-11646-8.
[66] Y.A. Kim, J.B. Keogh, P.M. Clifton, Probiotics, prebiotics, synbiotics and insulin sensitivity, Nutr. Res. Rev. 31 (2018) 35-51. https://doi.org/10.1017/S095442241700018X.
[67] N. Vallianou, T. Stratigou, G.S. Christodoulatos, et al., Probiotics, prebiotics, synbiotics, postbiotics, and obesity: current evidence, controversies, and perspectives, Curr. Obes. Rep. 9 (2020) 179-192. https://doi.org/10.1007/s13679-020-00379-w.
[68] K. Akutko, A. Stawarski, Probiotics, prebiotics and synbiotics in inflammatory bowel diseases, J. Clin. Med. 10 (2021) 2466. https://doi.org/10.3390/jcm10112466.
[69] J. He, Y. Jin, C. He, et al., Danggui Shaoyao San: comprehensive modulation of the microbiota-gut-brain axis for attenuating Alzheimer's disease-related pathology, Front. Pharmacol. 14 (2023) 1338804. https://doi.org/10.3389/fphar.2023.1338804.
[70] Y. Liu, X. Zhong, S. Lin, et al., *Limosilactobacillus reuteri* and caffeoylquinic acid synergistically promote adipose browning and ameliorate obesity-associated disorders, Microbiome 10 (2022) 226. https://doi.org/10.1186/s40168-022-01430-9.
[71] Y. Liu, H. Li, X. Wang, et al., Anti-Alzheimers molecular mechanism of icariin: insights from gut microbiota, metabolomics, and network pharmacology, J. Transl. Med. 21 (2023) 277. https://doi.org/10.1186/s12967-023-04137-z.
[72] S. Yuan, J. Yang, Y. Jian, et al., Treadmill exercise modulates intestinal microbes and suppresses LPS displacement to alleviate neuroinflammation in the brains of APP/PS1 mice, Nutrients 14 (2022) 4134. https://doi.org/10.3390/nu14194134.
[73] L. Bonfili, M. Cuccioloni, C. Gong, et al., Gut microbiota modulation in Alzheimer's disease: focus on lipid metabolism, Clin. Nutr. 41 (2022) 698-708. https://doi.org/10.1016/j.clnu.2022.01.025.
[74] R. Nagpal, B.J. Neth, S. Wang, et al., Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment, EBioMedicine 47 (2019) 529-542. https://doi.org/10.1016/j.ebiom.2019.08.032.
[75] S. Hoscheidt, A.H. Sanderlin, L.D. Baker, et al., Mediterranean and Western diet effects on Alzheimer's disease biomarkers, cerebral perfusion, and cognition in mid-life: a randomized trial, Alzheimers Dement. 18 (2022) 457-468. https://doi.org/10.1002/alz.12421.
[76] P. Agarwal, S.E. Leurgans, S. Agrawal, et al., Association of Mediterranean-DASH intervention for neurodegenerative delay and mediterranean diets with Alzheimer disease pathology, Neurology 100 (2023) e2259-e2268. https://doi.org/10.1212/WNL.0000000000207176.
[77] T.S. Ghosh, S. Rampelli, I.B. Jeffery, et al., Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries, Gut 69 (2020) 1218-1228. https://doi.org/10.1136/gutjnl-2019-319654.
[78] M.P. Cardelo, A. Corina, A. Leon-Acuña, et al., Effect of the Mediterranean diet and probiotic supplementation in the management of mild cognitive

impairment: rationale, methods, and baseline characteristics, Front. Nutr. 9 (2022) 1037842. https://doi.org/10.3389/fnut.2022.1037842.

[79] J.S. Baek, Y.J. Shin, X. Ma, et al., *Bifidobacterium bifidum* and *Lactobacillus paracasei* alleviate sarcopenia and cognitive impairment in aged mice by regulating gut microbiota-mediated AKT, NF-κB, and FOXO3a signaling pathways, Immun. Ageing 20 (2023) 56. https://doi.org/10.1186/s12979-023-00381-5.

[80] C. Tanes, K. Bittinger, Y. Gao, et al., Role of dietary fiber in the recovery of the human gut microbiome and its metabolome, Cell Host Microbe 29 (2021) 12. https://doi.org/10.1016/j.chom.2020.12.012.

[81] W. Wei, C.C. Wong, Z. Jia, et al., Parabacteroides distasonis uses dietary inulin to suppress NASH *via* its metabolite pentadecanoic acid, Nat. Microbiol. 8 (2023) 1534-1548. https://doi.org/10.1038/s41564-023-01418-7.

[82] J. Li, C. Chen, H. Yang, et al., Tea polyphenols regulate gut microbiota dysbiosis induced by antibiotic in mice, Food Res. Int. 141 (2021) 110153. https://doi.org/10.1016/j.foodres.2021.110153.

[83] D.P. Cladis, A.M.R. Simpson, K.J. Cooper, et al., Blueberry polyphenols alter gut microbiota & phenolic metabolism in rats, Food Funct. 12 (2021) 2442-2456. https://doi.org/10.1039/d0fo03457f.

[84] M. van der Merwe, D. Moore, J.L. Hill, et al., The impact of a dried fruit and vegetable supplement and fiber rich shake on gut and health parameters in female healthcare workers: a placebo-controlled, double-blind, randomized clinical trial, Microorganisms 9 (2021) 843. https://doi.org/10.3390/microorganisms9040843.

[85] C. Sanchez, C. Colson, N. Gautier, et al., Dietary fatty acid composition drives neuroinflammation and impaired behavior in obesity, Brain Behav. Immun. 117 (2024) 330-346. https://doi.org/10.1016/j.bbi.2024.01.216.

[86] L.L. Barnes, K. Dhana, X. Liu, et al., Trial of the MIND diet for prevention of cognitive decline in older persons, N. Engl. J. Med. 389 (2023) 602-611. https://doi.org/10.1056/NEJMoa2302368.

[87] S.N.A. Bukhari, Dietary polyphenols as therapeutic intervention for Alzheimer's disease: a mechanistic insight, Antioxidants 11 (2022) 554. https://doi.org/10.3390/antiox11030554.

[88] D. Ornish, C. Madison, M. Kivipelto, et al., Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial, Alzheimers Res. Ther. 16 (2024) 122. https://doi.org/10.1186/s13195-024-01482-z.

[89] J. Viña, C. Borrás, C. Mas-Bargues, Genistein, a phytoestrogen, delays the transition to dementia in prodromal Alzheimer's disease patients, J. Alzheimer's Dis. 101 (2024) S275-S283. https://doi.org/10.3233/JAD-240308.

[90] C. Papandreou, C. Papagiannopoulos, M. Koutsonida, et al., Mediterranean diet related metabolite profiles and cognitive performance, Clin. Nutr. 42 (2023) 173-181. https://doi.org/10.1016/j.clnu.2022.12.012.

[91] B.J. Neth, A. Mintz, C. Whitlow, et al., Modified ketogenic diet is associated with improved cerebrospinal fluid biomarker profile, cerebral perfusion, and cerebral ketone body uptake in older adults at risk for Alzheimer's disease: a pilot study, Neurobiol. Aging 86 (2020) 54-63. https://doi.org/10.1016/j.neurobiolaging.2019.09.015.

[92] H. Sokol, C. Landman, P. Seksik, et al., Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study, Microbiome 8 (2020) 12. https://doi.org/10.1186/s40168-020-0792-5.

[93] Y. Zhong, J. Cao, Y. Ma, et al., Fecal microbiota transplantation donor and dietary fiber intervention collectively contribute to gut health in a mouse model, Front. Immunol. 13 (2022) 842669. https://doi.org/10.3389/fimmu.2022.842669.

[94] J. Xie, A. Bruggeman, C. De Nolf, et al., Gut microbiota regulates blood-cerebrospinal fluid barrier function and Aβ pathology, EMBO J. 42 (2023) e111515. https://doi.org/10.15252/embj.2022111515.

[95] F. Scheperjans, R. Levo, B. Bosch, et al., Fecal microbiota transplantation for treatment of parkinson disease: a randomized clinical trial, JAMA Neurol. 81 (2024) 925-938. https://doi.org/10.1001/jamaneurol.2024.2305.

[96] B.J.H. Verhaar, H.M.A. Hendriksen, F.A. de Leeuw, et al., Gut microbiota composition is related to AD pathology, Front. Immunol. 12 (2021) 794519. https://doi.org/10.3389/fimmu.2021.794519.

[97] S. Grabrucker, M. Marizzoni, E. Silajdžić, et al., Microbiota from Alzheimer's patients induce deficits in cognition and hippocampal neurogenesis, Brain 146 (2023) 4916-4934. https://doi.org/10.1093/brain/awad303.

[98] N. Kim, S.H. Jeon, I.G. Ju, et al., Transplantation of gut microbiota derived from Alzheimer's disease mouse model impairs memory function and neurogenesis in C57BL/6 mice, Brain Behav. Immun. 98 (2021) 357-365. https://doi.org/10.1016/j.bbi.2021.09.002.

[99] M. Li, H. Yang, C. Shao, et al., Application of dominant gut microbiota promises to replace fecal microbiota transplantation as a new treatment for Alzheimer's disease, Microorganisms 11 (2023) 2854. https://doi.org/10.3390/microorganisms11122854.

[100] X. Chen, W. Zhang, Z. Lin, et al., Preliminary evidence for developing safe and efficient fecal microbiota transplantation as potential treatment for aged related cognitive impairments, Front. Cell Infect. Microbiol. 13 (2023) 1103189. https://doi.org/10.3389/fcimb.2023.1103189.

[101] J. Sun, J. Xu, Y. Ling, et al., Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice, Translational Psychiatry 9 (2019) 189. https://doi.org/10.1038/s41398-019-0525-3.

[102] Y. Sun, H. Zhang, X. Zhang, et al., Promotion of astrocyte-neuron glutamate-glutamine shuttle by SCFA contributes to the alleviation of Alzheimer's disease, Redox Biology 62 (2023) 102690. https://doi.org/10.1016/j.redox. 2023.102690.

[103] X. Jiang, Y. Zheng, H. Sun, et al., Fecal microbiota transplantation improves cognitive function of a mouse model of Alzheimer's disease, CNS. Neurosci. Ther. 31 (2025) e70259. https://doi.org/10.1111/cns.70259.

[104] J. Ren, Q. Wang, H. Hong, et al., Fecal microbiota transplantation in Alzheimer's disease: mechanistic insights through the microbiota-gut-brain axis and therapeutic prospects, Microorganisms 13 (2025) 1956. https://doi.org/10.3390/microorganisms13081956.

[105] S. Soriano, K. Curry, Q. Wang, et al., Fecal microbiota transplantation derived from Alzheimer's disease mice worsens brain trauma outcomes in wild-type controls, Int. J. Mol. Sci. 23 (2022) 4476. https://doi.org/10.3390/ijms23094476.

[106] S. Li, J. Li, K. Chen, et al., Chronic arsenic exposure causes Alzheimer's disease characteristic effects and the intervention of fecal microbiota transplantation in rats, J. Appl. Toxicol. 45 (2025) 1476-1486. https://doi.org/10.1002/jat.4782.

[107] S.T. Nassar, T. Tasha, A. Desai, et al., Fecal microbiota transplantation role in the treatment of Alzheimer's disease: a systematic review, Cureus 14 (2022) e29968. https://doi.org/10.7759/cureus.29968.

[108] S. Elangovan, T.J. Borody, R.M.D. Holsinger, Fecal microbiota transplantation reduces pathology and improves cognition in a mouse model of Alzheimer's disease, Cells 12 (2022) 119. https://doi.org/10.3390/cells12010119.

[109] R. Chen, Y. Xu, P. Wu, et al., Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota, Pharmacol. Res. 148 (2019) 104403. https://doi.org/10.1016/j.phrs.2019.104403.

[110] J.S. Kim, H. Park, J.H. Lee, et al., Effect of altered gene expression in lipid metabolism on cognitive improvement in patients with Alzheimer's dementia following fecal microbiota transplantation: a preliminary study, Ther. Adv. Neurol. Disord. 17 (2024) 17562864231218181. https://doi.org/10.1177/17562864231218181.

[111] A. Yadegar, H. Bar-Yoseph, T.M. Monaghan, et al., Fecal microbiota transplantation: current challenges and future landscapes, Clin. Microbiol. Rev. 37 (2024) e0006022. https://doi.org/10.1128/cmr.00060-22.

[112] J.Y. Lee, Y. Kim, J. Kim, et al., Fecal microbiota transplantation: indications, methods, and challenges, J. Microbiol. 62 (2024) 1057-1074. https://doi.org/10.1007/s12275-024-00184-3.

[113] E.A. Jochumsen, M.S. Kragsnaes, A.C. Nilsson, et al., 'Does this fecal microbiota transplant work?' quality assurance of capsule based fecal microbiota transplant production, Scand. J. Gastroenterol. 59 (2024) 1234-1239. https://doi.org/10.1080/00365521.2024.2401460.

[114] D. Sipos, A. Varga, Á. Kappéter, et al., Encapsulation protocol for fecal microbiota transplantation, Front. Cell Infect. Microbiol. 14 (2024) 1424376. https://doi.org/10.3389/fcimb.2024.1424376.

[115] C. Herman, E. Bolyen, A. Simard, et al., Assessing microbiome engraftment extent following fecal microbiota transplant with q2-fmt, PLoS Comput.

Biol. 21 (2025) e1013299. https://doi.org/10.1371/journal.pcbi.1013299.
[116] G. Cammarota, G. Ianiro, H. Tilg, et al., European consensus conference on faecal microbiota transplantation in clinical practice, Gut 66 (2017) 569-580. https://doi.org/10.1136/gutjnl-2016-313017.
[117] N. Pai, J. Popov, Protocol for a randomised, placebo-controlled pilot study for assessing feasibility and efficacy of faecal microbiota transplantation in a paediatric ulcerative colitis population: PediFETCh trial, BMJ Open 7 (2017) e016698. https://doi.org/10.1136/bmjopen-2017-016698.
[118] J.T. Morton, D.M. Jin, R.H. Mills, et al., Multi-level analysis of the gut-brain axis shows autism spectrum disorder-associated molecular and microbial profiles, Nat. Neurosci. 26 (2023) 1208-1217. https://doi.org/10.1038/s41593-023-01361-0.
[119] M. Zhou, Y. Fan, L. Xu, et al., Microbiome and tryptophan metabolomics analysis in adolescent depression: roles of the gut microbiota in the regulation of tryptophan-derived neurotransmitters and behaviors in human and mice, Microbiome 11 (2023) 145. https://doi.org/10.1186/s40168-023-01589-9.
[120] J. Lu, S.L. Salzberg, Ultrafast and accurate 16S rRNA microbial community analysis using Kraken 2, Microbiome 8 (2020) 124. https://doi.org/10.1186/s40168-020-00900-2.
[121] T. Vatanen, D.R. Plichta, J. Somani, et al., Genomic variation and strain-specific functional adaptation in the human gut microbiome during early life, Nat. Microbiol. 4 (2019) 470-479. https://doi.org/10.1038/s41564-018-0321-5.
[122] A. Kurilshikov, C. Medina-Gomez, R. Bacigalupe, et al., Large-scale association analyses identify host factors influencing human gut microbiome composition, Nat. Genet. 53 (2021) 156-165. https://doi.org/10.1038/s41588-020-00763-1.
[123] L.H. Morais, H.L. Schreiber, S.K. Mazmanian, The gut microbiota-brain axis in behaviour and brain disorders, Nat. Rev. Microbiol. 19 (2021) 241-255. https://doi.org/10.1038/s41579-020-00460-0.
[124] S. Wu, T. Feng, W. Tang, et al., metaProbiotics: a tool for mining probiotic from metagenomic binning data based on a language model, Brief. Bioinform. 25 (2024) 85. https://doi.org/10.1093/bib/bbae085.
[125] D.X. Ma, H.J. Cheng, H. Zhang, et al., Harnessing the polysaccharide production potential to optimize and expand the application of probiotics, Carbohydr. Polym. 349 (2025) 122951. https://doi.org/10.1016/j.carbpol.2024.122951.
[126] A. Yarahmadi, H. Afkhami, A. Javadi, et al., Understanding the complex function of gut microbiota: its impact on the pathogenesis of obesity and beyond: a comprehensive review, Diabetol. Metab. Syndr. 16 (2024) 308. https://doi.org/10.1186/s13098-024-01561-z.
[127] M. Alam, K. Abbas, M. Mustafa, et al., Microbiome-based therapies for Parkinson's disease, Front. Nutr. 11 (2024) 1496616. https://doi.org/10.3389/fnut.2024.1496616.
[128] L. Crosby, B. Davis, S. Joshi, et al., Ketogenic diets and Chronic disease: weighing the benefits against the risks, Front. Nutr. 8 (2021) 702802. https://doi.org/10.3389/fnut.2021.702802.
[129] C.G.P. Roberts, S.J. Athinarayanan, R.E. Ratner, et al., Illnesses associated with ketosis including diabetic ketoacidosis during very low carbohydrate and ketogenic diets, Diabetes Obes. Metab. 27 (2025) 2531-2539. https://doi.org/10.1111/dom.16252.