Journal of Integrative Neuroscience

J. Integr. Neurosci. **2026**; 25(6): 48660
https://doi.org/10.31083/JIN48660

Review

Exploring the Microbiome-Kynurenine Axis in Mild Cognitive Impairment: From Gut to Brain

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Academic Editor: Gernot Riedel
Submitted: 29 November 2025 Revised: 12 February 2026 Accepted: 24 February 2026 Published: 15 June 2026

Abstract

Mild cognitive impairment (MCI) represents a critical prodromal stage of Alzheimer's disease. This review synthesizes current evidence to present a coherent pathological cascade driving MCI progression: gut microbiota dysbiosis (e.g., enrichment of *Prevotella* and depletion of *Akkermansia*) triggers a butyrate deficit and compromise of intestinal integrity, leading to systemic inflammation. This inflammatory milieu upregulates indoleamine 2,3-dioxygenase 1 (IDO1), shifting tryptophan metabolism toward the kynurenine pathway and resulting in the dominance of neurotoxic branches (3-hydroxykynurenine [3-HK], quinolinic acid [QUIN]) over neuroprotective kynurenic acid (KYNA). This metabolic imbalance promotes N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity, oxidative stress, and neuroinflammation, which collectively precipitate synaptic dysfunction and cognitive decline. We explicitly highlight this "gut-immune-metabolic" vicious cycle as the core framework of MCI pathology. Targeting this cycle through a dual strategy—restoring microbial diversity and pharmacologically inhibiting the IDO1/kynurenine 3-monooxygenase (KMO) enzymes—represents a promising therapeutic approach to delay the transition from MCI to dementia.

Keywords: kynurenine; mild cognitive impairment; gut-brain axis; gut microbiota; review

1. Introduction

Mild cognitive impairment (MCI) represents a critical clinical window between normal ageing and dementia and is associated with a rapidly increasing global burden. A 2025 systematic review involving more than 280,000 participants estimated the global prevalence of MCI in the older population to be 23.7% [1]. The principal challenge underlying this high prevalence is the instability of its clinical prognosis. A large longitudinal cohort study of 3553 individuals with MCI reported an annual progression rate to dementia of 15.7%, with 92.8% of patients eventually converting to dementia over a 17-year follow-up period [2]. Although epidemiological evidence highlights the urgency of early intervention, the core molecular mechanisms driving this transition—particularly the specific cascade linking peripheral metabolism to central pathology—remain incompletely understood. The aetiology of MCI is multifactorial; however, accumulating evidence indicates a strong association between gut microbiota and cognitive [3,4]. Through the gut-brain axis, intestinal microorganisms are proposed to modulate brain structure and physiological function, thereby influencing host immunity and metabolism that are essential for neurological homeostasis [4]. Multiple studies have demonstrated significant differences in bacterial composition between individuals with MCI and healthy controls [5–7]. Taxa such as Prevotella, Akkermansia, and members of the Enterobacteriaceae family have been significantly associated with cognitive decline [6,7]. In addition, microbial metabolites, including short-chain fatty acids (SCFAs) and kynurenine derivatives, have been implicated in the regulation of brain health and cognitive function [8,9]. This study explores the interplay between gut microbiota and kynurenine metabolism in MCI, examining how microbial dysbiosis may contribute to disease progression through alterations in metabolic pathways.

2. The Association Between Gut Microbiota and MCI

2.1 Gut Microbiome Strains and Their Impact on MCI

Recent research has increasingly highlighted a strong association between the gut microbiome and MCI. Multiple microbial strains have been identified that show significant correlations with cognitive function, suggesting a potential role in the onset and progression of cognitive decline and the development of neurodegenerative diseases. As summarised in Table 1 (Ref. [10–15]), these findings underscore the critical importance of specific microbial compositions in modulating cognitive outcomes in individuals with MCI. This section provides a comprehensive overview of current studies examining the gut microbiome and its mechanistic involvement in MCI, based on evidence synthesised from multiple research sources.

Table 1. Gut microbiome strains and their impact on mild cognitive impairment.

Reference	Sample	Bacteria strain	Taxonomic level	Strain abundance direction	Impact on MCI/AD
Fan *et al*., 2023 [10]	MCI vs healthy controls	*Flavonifractor*	Genus	Increased	Associated with executive function decline and inflammation
Fan *et al*., 2023 [10]	MCI vs healthy controls	*Lactococcus*	Genus	Increased	Potentially compensatory; involved in neurotransmitter synthesis
Pan *et al*., 2021 [11]	MCI vs healthy controls	*Staphylococcus intermedius*	Species	Increased	Enriched in MCI; possibly neurotoxic oral-derived strain
Pan *et al*., 2021 [11]	MCI vs healthy controls	*Leptotrichia buccalis*	Species	Decreased	Reduced abundance may reflect mucosal immune dysfunction
Gallo *et al*., 2024 [12]	MCI vs healthy controls	*Faecalibacterium prausnitzii*	Species	Decreased	Cited from multiple sources; SCFA producer; anti-inflammatory
Lu *et al*., 2025 [13]	MCI vs healthy controls	*Allisonella*	Genus	Increased	Histamine-related metabolism linked with cognitive dysfunction
Lu *et al*., 2025 [13]	MCI vs healthy controls	*Oscillibacter*	Genus	Decreased	Potential anti-inflammatory effect; less abundant in MCI
Vogt *et al*., 2017 [14]	AD vs Control	*Bacteroidetes*	Phylum	Decreased	Associated with increased inflammation and metabolic disruption in AD
Vogt *et al*., 2017 [14]	AD vs Control	*Firmicutes*	Phylum	Increased	Increased Firmicutes/Bacteroidetes ratio, indicating gut dysbiosis
Zhuang *et al*., 2018 [15]	AD vs Control	*Enterococcaceae*	Family	Increased	A potential pathobiont may influence inflammation

MCI, mild cognitive impairment; AD, Alzheimer's disease; SCFA, short-chain fatty acid.

Zhu and colleagues [16] reported that faecal 16S rRNA gene sequencing revealed significant differences in gut microbiota composition among individuals with MCI, Alzheimer's disease (AD), and normal controls (NC). The relative abundance of taxa from the Erysipelatoclostridiaceae family, as well as Erysipelotrichales and Saccharimonadales, was significantly increased in patients with MCI, and these taxa were significantly associated with poorer cognitive performance. In addition, patients with MCI exhibited higher levels of Prevotella, which showed a negative correlation with cognitive scores on the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) [16].

Similarly, Khedr *et al*. [17] demonstrated significant differences between the gut microbiota of patients with MCI and that of healthy individuals. Patients with MCI showed increased abundances of Prevotella, Akkermansia, and Enterobacteria compared with healthy controls. In contrast, levels of beneficial probiotic microorganisms, including Bifidobacterium and Firmicutes, were reduced in MCI. Notably, elevated Prevotella abundance was significantly negatively correlated with cognitive performance (e.g., MoCA scores), suggesting that a high relative abundance of Prevotella may serve as a potential biomarker for identifying cognitive deterioration in MCI [17]. Evidence from animal models further supports the involvement of gut microbiota in cognitive impairment. Harach and colleagues [18] investigated gut microbial alterations in amyloid precursor protein/presenilin 1 (APPPS1) transgenic mice and demonstrated marked disruptions in microbial composition compared with non-transgenic controls. Significant changes were observed in the abundance of Bacteroidetes, Firmicutes, and Akkermansia. These microbial alterations were directly correlated with amyloid-β (Aβ) plaque deposition in the brain. Importantly, depletion of the gut microbiota through antibiotic treatment resulted in a substantial reduction in cerebral Aβ accumulation, supporting a pathogenic role of gut microbiota in Aβ pathology progression [18]. Additional studies using the ageing senescence-accelerated mouse prone 8 (SAMP8) mouse model have suggested that gut microbiota dysbiosis contributes to memory impairment. Intervention with ProBiotic-4 was shown

to improve memory performance while modulating gut microbiota composition. Following probiotic treatment, a marked alteration in the Firmicutes-to-Bacteroidetes ratio was observed in the intestines of SAMP8 mice, which was associated with improved cognitive function in a negative trend [19].

Collectively, these findings indicate a robust association between alterations in gut microbiota composition and the cognitive deficits observed in MCI. Experimental studies in MCI animal models further demonstrate that modulation or reduction of gut microbiota, through antibiotic treatment or probiotic intervention, can substantially influence cognitive function and neuropathological outcomes.

2.2 Changes in the Metabolic Function of Gut Microbiota

SCFAs are fatty acids with fewer than six carbon atoms that are primarily produced through the colonic bacterial fermentation of dietary fibre; acetate (C2), propionate (C3), and butyrate (C4) constitute the majority of SCFAs [20]. Butyrate serves as the principal energy source for colonocytes and, together with other SCFAs, exerts biological effects via G-protein-coupled receptors (e.g., free fatty acid receptor 2 [FFAR2], free fatty acid receptor 3 [FFAR3], and G protein-coupled receptor 109A [GPR109A]) and histone deacetylase inhibition, thereby reinforcing epithelial tight junctions and modulating mucosal and systemic immune responses [20,21]. Through the microbiota–gut–brain axis, microbial metabolites such as SCFAs and tryptophan derivatives influence vagal, endocrine, and immune pathways, regulate blood-brain barrier (BBB) integrity and microglial activity, and affect neurotransmitter systems relevant to cognitive function [21]. Structural alterations in the gut microbiota are accompanied by marked changes in its metabolic activity in patients with MCI. SCFA production is essential for maintaining host immune function, preserving intestinal barrier integrity, and supporting normal nervous system health. Research by Putignani *et al*. [22] demonstrated that patients with MCI exhibit pronounced alterations in gut microbiota metabolite profiles, particularly in SCFA production. In these patients, overall SCFA metabolism was reduced, with butyric acid showing the most substantial decline compared with healthy controls. Reduced butyrate production may impair intestinal barrier integrity, a condition frequently associated with increased systemic inflammation [22]. Dietary patterns also play a critical role in shaping SCFA production. Studies by Maciejewska *et al*. [23] indicated that diets high in fat and cholesterol induce marked alterations in gut bacterial metabolic activity. In MCI mouse models, a high-fat and high-cholesterol diet led to abnormal SCFA profiles, characterised by decreased butyric acid levels and increased propionic acid levels [23]. These findings suggest that gut microbial dysbiosis and associated metabolic disturbances may contribute to the progression of MCI pathology.

Further evidence indicates that gut microbial metabolites, including SCFAs, tryptophan derivatives, and lipopolysaccharides (LPS), influence MCI pathogenesis through their effects on neural and immune functions. Research by Kelly *et al*. [24] showed that the metabolic activity of the gut microbiota differs between individuals with MCI and healthy controls. These microbial metabolites may affect MCI progression by modulating neurotransmitter synthesis and inflammatory responses [24].

Peredo-Lovillo *et al*. [25] investigated the effects of dietary fibre and prebiotics on the metabolic function of intestinal microbiota. Their findings demonstrated that dietary fibre intake promotes the growth of beneficial intestinal bacteria, enhances microbial metabolic activity, and increases SCFA production. These changes are associated with improved intestinal barrier function and immune responses. Modulation of dietary components may therefore help restore gut microbiota balance and alleviate metabolic dysfunction in patients with MCI [25].

In summary, the metabolic signature of MCI is characterised by a “butyrate gap”, reflecting a critical deficiency in energy substrates for colonocytes that precedes the barrier dysfunction described in the following section.

2.3 Gut Microbiota-Associated Early Biomarkers in MCI

Metabolic dysfunction and structural imbalance of the gut microbiota not only compromise intestinal barrier integrity but also profoundly affect key signalling pathways of the gut–brain axis. Evidence indicates that, when intestinal barrier function is impaired, pro-inflammatory molecules such as LPS can translocate into the circulation and activate systemic immune responses [26]. These pro-inflammatory factors may subsequently access the central nervous system (CNS) via a compromised BBB, leading to microglial activation. Activated microglia transition from a resting to a reactive state, releasing substantial quantities of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α), along with reactive oxygen species (ROS), thereby amplifying neuroinflammation [27]. Concurrently, astrocytes adopt a reactive (A1) phenotype. At this early stage, glial activation does not establish a full neurodegenerative cycle but serves to ‘prime’ the CNS immune environment, lowering the threshold for subsequent metabolic insults described in Section 2.2 This primes a hypersensitive state in which minor fluctuations in peripheral metabolites can provoke exaggerated neuroinflammatory responses [28,29].

The vagus nerve acts as a two-way bridge between the gut and the brain. Microbial products like SCFAs normally activate this nerve to send healthy signals to the brain. In MCI patients, a lack of SCFAs means the vagus nerve receives fewer triggers. This drop in signalling leads to lower levels of protective chemicals like acetylcholine. As a result, the brain loses its stability and memory gets worse [30]. This disruption impairs central ner-

vous system stability and may accelerate cognitive decline [26]. The impairment of this signalling pathway leads to CNS instability, resulting in further cognitive deterioration [31]. At a molecular level, these disruptions involve endothelial junctional components that maintain BBB integrity. Tight-junction proteins—including claudin-5, occludin, and junctional adhesion molecules (JAM-A/B), scaffolded by zonula occludens-1 and -2 (ZO-1/ZO-2)—and adherens-junction proteins such as vascular endothelial cadherin (VE-cadherin) with β-catenin and p120 catenin, together with perivascular basement membrane elements (laminins, collagen IV, nidogen, perlecan) and astrocytic end-foot proteins (AQP4, dystroglycan), collectively preserve barrier function [32–36]. Perturbation of these proteins increases BBB permeability, allowing potentially harmful substances to enter the CNS and exacerbate neuroinflammation and cognitive dysfunction. Experimental animal studies indicate that SCFA supplementation can stabilise the BBB and attenuate microglia-mediated inflammatory responses. Yu and colleagues [37] demonstrated that SCFAs promote BBB repair while inhibiting excessive microglial activation, thereby reducing neuroinflammation and improving cognitive function. Taken together, gut barrier disruption, dysregulation of BBB junctional proteins, and reduced SCFA levels constitute an early signature of gut–brain axis imbalance in MCI. These alterations suggest a set of quantifiable candidate biomarkers, including peripheral LPS and inflammatory profiles, faecal or plasma SCFA concentrations, and junctional proteins indicative of BBB integrity.

3. The Relationship Between Kynurenine Metabolism Pathway and MCI

3.1 The Roles of Key Kynurenine Pathway Metabolites in the Central Nervous System and Their Implications in MCI/AD Progression

The kynurenine pathway (KP) is the principal route for tryptophan catabolism, generating a series of neuroactive metabolites, among which kynurenic acid (KYNA), quinolinic acid (QUIN), and 3-hydroxykynurenine (3-HK) are of particular research interest. These metabolites exert distinct effects on the CNS and contribute to the progression from MCI to AD by modulating neuronal and glial cell functions as well as synaptic plasticity.

3.1.1 Kynurenic Acid (KYNA)

KYNA is a neuroprotective metabolite of the KP, primarily synthesised by astrocytes via kynurenine aminotransferases. Its mechanisms of action in the CNS are largely defined by its broad antagonism of ionotropic glutamate receptors [38]. KYNA blocks the glutamate/glycine co-agonist site on N-methyl-D-aspartate (NMDA) receptors, thereby reducing glutamate-mediated excitotoxicity [8]. At elevated concentrations, KYNA is also reported to antagonise α7 nicotinic acetylcholine receptors (α7-nAChRs), although this effect remains debated. Through these actions, KYNA limits excessive excitatory neurotransmission and protects neurons from glutamate-induced injury. However, excessive KYNA may impair normal synaptic plasticity, including long-term potentiation (LTP), and disrupt cholinergic and glutamatergic signalling required for cognitive function [39]. Thus, KYNA may exert a dual role in AD, providing neuroprotection while potentially compromising memory-related neural circuits when present in excess. Alterations in KYNA levels observed in MCI and AD patients support its involvement in disease progression [40]. Cerebrospinal fluid (CSF) studies indicate that KYNA concentrations are significantly elevated in AD patients compared with cognitively normal individuals, with a similar upward trend observed in MCI [41]. A longitudinal study by Knapskog *et al*. [41] further reported that higher CSF KYNA levels in AD patients were associated with a slower rate of cognitive decline. Under conditions of increased inflammation and excitotoxic stress, KYNA (along with another protective metabolite, picolinic acid) may be elevated to counteract excessive NMDA receptor activation and reduce neuronal damage. Mechanistically, KYNA antagonism of NMDA receptors alleviates calcium overload and excitotoxicity, while modulation of α7-nAChRs may influence synaptic plasticity and neurotransmitter release, processes that are linked to early cognitive dysfunction in AD [42]. Notably, recent animal studies have shown that transient increases in central KYNA levels can upregulate the expression of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (TrkB) [8]. These findings suggest that KYNA may exert neuroprotective effects through neurotrophic support, partially counterbalancing its inhibitory actions on synaptic signalling [43]. In summary, the role of KYNA in MCI is concentration-dependent. Moderate increases in KYNA are beneficial, inhibiting calcium overload and promoting neurotrophic support via BDNF expression. In contrast, supraphysiological KYNA levels indiscriminately block NMDA and α7-nAChR receptors, reducing LTP and impairing cholinergic signalling necessary for memory consolidation. Therefore, the observed rise in CSF KYNA in patients likely reflects an initial neuroprotective response that, when excessive, contributes to cognitive impairment through receptor over-inhibition.

3.1.2 3-Hydroxykynurenine (3-HK)

3-HK is an intermediate metabolite of the KP, synthesised from kynurenine via kynurenine 3-monooxygenase (KMO) in microglia [44]. It does not act as a conventional receptor ligand but functions as a redox-active prooxidant capable of spontaneously generating free radicals, such as superoxide anion and hydrogen peroxide, earning it the designation of a “radical donor”. In the presence of transition metals, 3-HK participates in Fenton-like reactions to produce hydroxyl radicals, which can damage pro-

teins and DNA. Its downstream metabolites, including 3-hydroxyanthranilic acid and QUIN, further propagate oxidative chain reactions. By inducing oxidative stress, 3-HK damages mitochondria and cell membranes, triggers cytochrome c release, and promotes apoptosis, establishing it as a major driver of KP-related neurodegeneration. Beyond direct neuronal injury, 3-HK indirectly affects glial cells and synaptic plasticity. Oxidative environments can activate microglia into inflammatory phenotypes and suppress astrocytic support for synapses, ultimately leading to synaptic degradation and decreased levels of neurotrophic factors, such as BDNF. *In vitro* studies have shown that IL-1β upregulates indoleamine 2,3-dioxygenase 1 (IDO1) and KMO, increasing 3-HK synthesis while reducing the survival and differentiation of human hippocampal neural progenitor cells [45]. These findings suggest that, under inflammatory conditions, elevated 3-HK may suppress hippocampal neurogenesis and synaptic remodelling, negatively affecting learning and memory [46]. In AD and MCI, 3-HK levels reflect disease-associated metabolic reprogramming. Chronic inflammation in AD is predicted to enhance KMO activity and 3-HK production. However, similar to QUIN, large clinical studies do not consistently report elevated 3-HK. This lack of consistency suggests that 3-HK elevation might be a stage-specific phenomenon rather than a constant feature of MCI. The discrepancy across studies may also reflect the dynamic nature of the kynurenine pathway, where 3-HK levels fluctuate depending on the immediate inflammatory status of the patient, rather than following a simple, linear increase. A meta-analysis of 27 studies found that CSF 3-HK levels were significantly lower in AD patients than in controls, with no significant differences observed in plasma or serum [47]. This discrepancy may result from 3-HK's high reactivity and rapid metabolism or from a shift in metabolic flux toward downstream metabolites, such as QUIN. A study has reported elevated peripheral 3-HK, which may distinguish AD patients from controls and indicate increased peripheral KMO activity in specific subgroups [48]. Data on 3-HK in MCI remain limited; observed trends suggest similar KP shifts to those in AD, although differences are smaller and not statistically significant. Mechanistically, chronic low-grade inflammation in early MCI may enhance KMO activity, elevating 3-HK and QUIN production, counteracting KYNA-mediated neuroprotection, and subtly promoting neurodegeneration [49].

In summary, KP metabolites exert differential effects within the CNS and collectively influence the progression from MCI to AD. KYNA is neuroprotective, antagonising NMDA receptors and buffering excitotoxicity and inflammation, particularly in early AD. QUIN promotes neurotoxicity, tau hyperphosphorylation, and inflammatory amplification, often in regions adjacent to amyloid plaques. 3-HK induces oxidative stress and suppresses neurogenesis. These mechanisms indicate that KP dysregulation is not merely a late-stage consequence of AD but contributes throughout the disease course [48]. In conclusion, chronic inflammation in MCI triggers a "metabolic switch" that tends to upregulate the neurotoxic branch (3-HK and QUIN). However, this switch is not absolute across all clinical contexts. The observed variability in 3-HK and QUIN levels underscores the need for a more integrated framework that accounts for individual metabolic differences and disease stages, rather than relying on a simplified model of constant neurotoxic dominance. Concurrently, this toxic shift suppresses hippocampal neurogenesis and downregulates BDNF signalling. The disruption of the neuroprotective balance (e.g., KYNA/QUIN ratio) represents a critical potential mechanism accelerating the transition from MCI to AD. However, future frameworks must integrate the divergent findings reported in systemic vs. central compartments, ensuring that the 'gut-immune-metabolic' axis is interpreted as a complex regulatory network rather than a unidirectional pathological pathway.

3.1.3 Quinolinic Acid (QUIN)

QUIN is a neurotoxic end-product of the KP, formed downstream of 3-hydroxykynurenine and produced predominantly by activated microglia and infiltrating macrophages during inflammatory states [39,50,51]. Functionally, QUIN acts as an NMDA-receptor agonist and, at elevated concentrations, overactivates N-methyl-D-aspartate receptors (NMDARs), provoking excessive Ca^{2+} influx, mitochondrial dysfunction, ROS generation, and apoptotic neuronal death (excitotoxicity) [39,50]. QUIN also promotes oxidative stress and lipid peroxidation; formation of Fe(II)-QUIN complexes can catalyse hydroxyl-radical production, amplifying damage to membranes and proteins [50]. Beyond direct neurotoxicity, QUIN exerts pro-inflammatory actions, activating and recruiting microglia and astrocytes. Experimentally, QUIN can impair BBB integrity via nitric-oxide–dependent cytoskeletal perturbations, thereby increasing BBB permeability [50,52]. In Alzheimer-related contexts, KP dysregulation with excess QUIN and upregulated IDO1 has been repeatedly reported. Aβ1-42 can induce IDO1/KP activation and enhance QUIN formation in neural and myeloid cells, while pharmacological IDO1 inhibition mitigates Aβ-associated neuroinflammation in cellular and transgenic mouse models [51]. Collectively, post-2019 evidence supports QUIN as a key excitotoxic and pro-inflammatory effector linking KP activation to neuronal injury and barrier dysfunction in neurodegeneration [39]. The accumulation of QUIN in senile plaque regions indicates its local release by activated microglia, which may induce excitotoxic death of nearby neurons and is strongly associated with plaque burden and chronic local inflammation [53]. Moreover, QUIN may directly interfere with tau metabolism; cellular studies have shown that QUIN induces abnormal hyperphosphorylation of tau protein, potentially accelerating neurofib-

rillary tangle formation and exacerbating AD neuropathology. Despite its well-established toxicity, clinical studies on QUIN levels in AD patients have produced inconsistent results. Early small-sample studies reported increased peripheral QUIN associated with cognitive decline [40]. However, recent large-sample systematic reviews and meta-analyses have not confirmed widespread QUIN elevation [54]. These findings indicate that QUIN's role in MCI may be more subtle than previously assumed. It is possible that localized concentrations of QUIN in specific brain regions, rather than systemic levels, are the true drivers of neurotoxicity, suggesting that future research should move beyond simple plasma measurements. For example, some studies found no significant differences in CSF or plasma QUIN levels between AD patients and cognitively normal individuals, while Liang *et al*. [51] reported slightly lower CSF QUIN concentrations in AD patients compared to controls. These findings challenge the traditional hypothesis of persistently elevated QUIN in AD. One explanation is that QUIN's role may be region- and stage-specific: microglial QUIN production may transiently increase in specific brain regions during early or acute inflammation, causing neuronal injury not reflected in global CSF or plasma levels. Furthermore, surviving neurons and glia may metabolise or utilise QUIN (e.g., converting it to nicotinamide adenine dinucleotide [NAD+]), preventing overall elevation in body fluids. Interestingly, some prospective studies have observed that individuals with lower plasma QUIN and lower QUIN/KYNA ratios are more likely to progress to MCI or AD [54]. This finding suggests that inadequate activation of the protective KYNA branch, combined with relatively low QUIN production, may reflect a dysfunctional response that fails to counteract excitotoxicity and inflammation, ultimately promoting disease progression.

Although endogenous KYNA levels rise in a compensatory attempt to protect neurons, this elevation is often insufficient to counteract the toxic burden and may inadvertently inhibit memory-related synaptic plasticity. Ultimately, the imbalance between escalating neurotoxicity and failing neuroprotection precipitates synaptic loss and cognitive decline, as illustrated in Fig. 1.

Pharmacological interventions targeting key KP enzymes have progressed from preclinical studies to clinical translation, highlighting their considerable potential as disease-modifying therapies (DMTs) for neurodegenerative diseases. Regarding IDO1 inhibition, a breakthrough study by Minhas *et al*. [55] in 2024 demonstrated that the highly selective IDO1 inhibitor PF-06840003 penetrates the BBB and significantly reverses memory deficits in AD models by alleviating astrocytic metabolic inhibition and restoring neuronal lactate supply. Furthermore, the IDO pathway modulator Indoximod has exhibited favourable CNS tolerability in clinical trials for paediatric brain tumours, thereby providing a safety rationale for metabolic reprogramming therapies in AD [56].

In the domain of KMO inhibitors, the novel compound KNS366 recently completed its first-in-human Phase I trial in healthy volunteers, successfully validating its ability to reduce levels of the neurotoxic metabolite 3-HK *in vivo* [57]. This achievement represents a pivotal step toward the clinical application of specific KMO inhibitors. Concurrently, drug repurposing strategies have demonstrated promise; the anti-inflammatory agent Diclofenac, identified as possessing KMO inhibitory activity, is currently undergoing clinical evaluation (NCT06636227) to assess its efficacy in modulating kynurenine metabolism [58]. These clinical advances underscore the therapeutic significance of targeting KP enzymes: precise inhibition of IDO1 or KMO not only halts the production of neurotoxic species but also restores cerebral immune-metabolic homeostasis. This dual mechanistic benefit—simultaneously mitigating neuroinflammation and reinstating energy metabolism—provides robust theoretical support for clinical translation and offers a promising avenue to disrupt the vicious cycle of AD pathology.

3.2 The Impact of Kynurenine and Its Metabolites on MCI

This is evidenced by a notable increase in QUIN levels and a decrease in KYNA, an imbalance that is hypothesised to further exacerbate nervous system compromise. Clinical data have demonstrated that higher plasma QUIN and lower KYNA levels in patients with MCI correlate with reduced cognitive function scores. Furthermore, blood levels of kynurenine, rather than tryptophan (1/6), associated with higher kynurenine-to-tryptophan ratios (1/3), are considered early biomarkers of MCI [59,60]. These metabolic alterations are closely related to the pathological progression of MCI.

As detailed in Section 3.2, the dysregulation of KYNA and QUIN disrupts synaptic homeostasis and NMDA receptor signalling, leading to the following pathological consequences in MCI. Crucially, QUIN amplifies the microglial activation cascade initiated by LPS (as detailed in Section 2.3). Unlike the initial immune response, QUIN-induced microglial activation is self-perpetuating, locking microglia in a neurotoxic phenotype that further impairs synaptic transmission [61].

This mechanism has been validated in animal models. IDO1 induction by inflammatory factors in mice increased QUIN levels, leading to cognitive impairment and hippocampal neuronal damage [39]. However, significant amelioration of kynurenine metabolic dysregulation, attenuation of neuroinflammation, neuronal protection, and substantial enhancement of cognitive function can be achieved through probiotic and short-chain fatty acid supplementation, which suppresses IDO1 overexpression [62]. These experimental results have enhanced our understanding of the role of kynurenine metabolism in the transition from MCI.

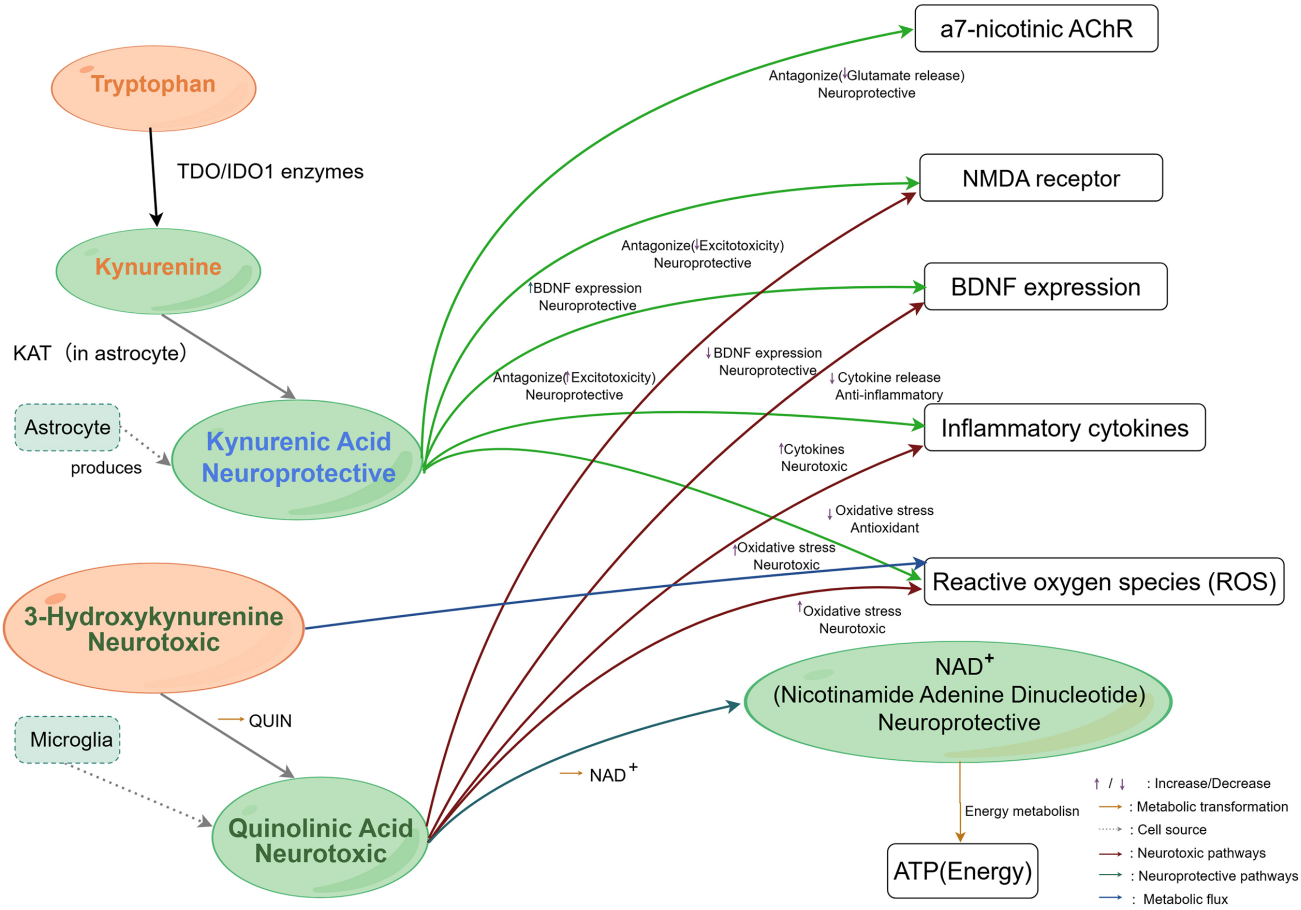

Fig. 1. Illustrates the role of the kynurenine pathway in regulating the nervous system, immune response, and cellular metabolic homeostasis. Schematic representation of the kynurenine pathway (KP) metabolism and its downstream targets in the CNS. Tryptophan is metabolized into kynurenine by IDO/TDO enzymes. Kynurenine is further metabolized into two distinct branches: The formation of kynurenic acid (KYNA) in astrocytes, which targets NMDA receptors, α7 nicotinic acetylcholine receptors (α7-nAChRs), and BDNF expression. The formation of 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN) in microglia. Arrows indicate the modulatory effects of these metabolites on oxidative stress (reactive oxygen species, ROS), inflammatory cytokines, and glutamate receptors. Green lines indicate neuroprotective pathways; red lines indicate neurotoxic pathways; blue lines indicate metabolic flux. IDO1, indoleamine 2,3-dioxygenase 1; TDO, tryptophan 2,3-dioxygenase; CNS, central nervous system; NMDA, N-methyl-D-aspartate; BDNF, brain-derived neurotrophic factor; KAT, kynurenine aminotransferase; ATP, adenosine triphosphate; NAD^+, nicotinamide adenine dinucleotide. Created with Figdraw (https://www.figdraw.com/).

Together, decreased KYNA and increased QUIN are hypothesised to promote a self-perpetuating pathological cycle. The loss of KYNA's protective effects, combined with QUIN's neurotoxicity, disrupts neurotransmitter balance, calcium ion homeostasis, and synaptic function, resulting in further cognitive decline [63]. Clinical and experimental evidence indicates that dysregulation of the kynurenine pathway contributes substantially to the pathological basis of MCI and that excessive metabolic abnormalities accelerate cognitive deterioration [64].

In conclusion, the balance of the kynurenine metabolism pathway can be considered a core feature of the pathological progression in patients with MCI. This imbalance is characterised by decreased KYNA levels, which weaken neuroprotective functions, and increased QUIN levels, which exacerbate neurotoxicity and inflammatory responses. As illustrated in Fig. 2.

4. The Regulation of the Gut Microbiota on the Kynurenine Metabolism Pathway

4.1 The Regulatory Mechanism of Gut Microbiota on the Tryptophan Metabolism Pathway

Building on the KP biochemistry described in Section 3.1, the metabolic fate of tryptophan is further governed by the composition of the intestinal microbiota. Under healthy conditions, beneficial bacteria expressing tryptophanase (TnaA), such as certain Lactobacillus and Bacteroides strains, metabolise a proportion of tryptophan into indole and indolepropionic acid (IPA). These metabo-

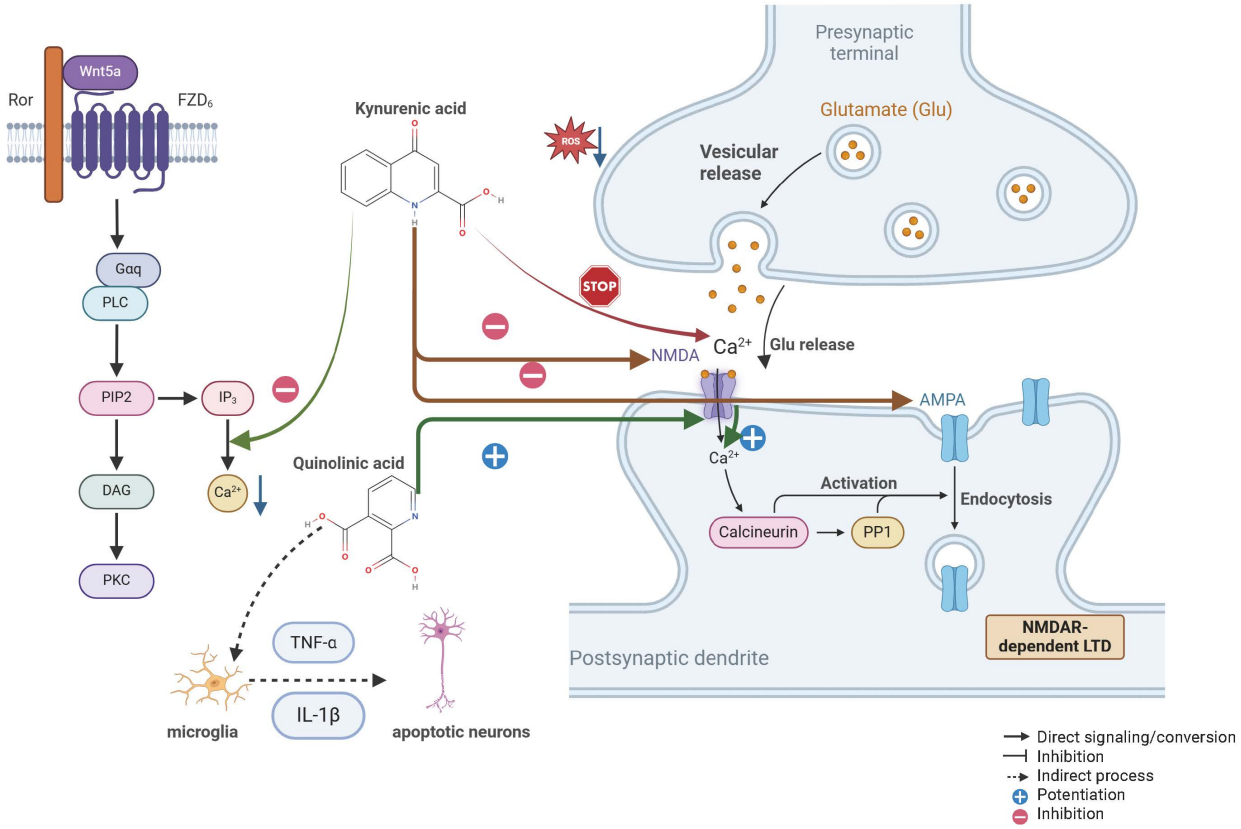

Fig. 2. Mechanisms of kynurenine metabolites in the nervous system: neuroprotective and neurotoxic effects. KYNA functions as a crucial maintainer of synaptic homeostasis. Mechanistically, it acts as a broad-spectrum antagonist at ionotropic glutamate receptors, specifically blocking the glycine site of NMDA receptors and antagonizing AMPA receptors. This blockade effectively inhibits excessive calcium influx (Ca^{2+}) and attenuates glutamate-mediated excitotoxicity. Furthermore, as depicted in the signalling pathway on the left side of Fig. 2, the Wnt5a-FZD_6-Ror (Wnt5a stands for Wingless-type MMTV integration site family, member 5A. FZD_6 stands for Frizzled Class Receptor 6. Ror refers to Receptor Tyrosine Kinase Like Orphan Receptor) axis plays a regulatory role in stabilizing intracellular calcium levels and maintaining synaptic plasticity (LTD). Under normal conditions, these pathways collectively suppress ROS generation and protect neurons from oxidative stress. Gaq, G protein subunit alpha q; PLC, Phospholipase C; PIP2, Phosphatidylinositol 4,5-bisphosphate; IP_3, Inositol trisphosphate; DAG, Diacylglycerol; PKC, Protein Kinase C; TNF-α, tumour necrosis factor-α; IL-1β, interleukin-1β; PP1, Protein Phosphatase 1; LTD, Long-term depression; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. Created with Biorender (https://www.biorender.com/).

lites exhibit antioxidant and anti-inflammatory properties, which reduce the entry of tryptophan into the kynurenine pathway, thereby decreasing QUIN production and mitigating its neurotoxicity [65]. However, under conditions of intestinal dysbiosis, the abundance of pro-inflammatory bacteria, such as Escherichia coli, increases. This shift promotes IDO1 expression, driving a greater influx of tryptophan into the kynurenine pathway [66]. Consequently, QUIN levels rise substantially, while KYNA levels decline markedly, further disrupting the dynamic equilibrium of tryptophan metabolism [67].

In addition to direct metabolic effects, intestinal dysbiosis indirectly regulates tryptophan pathway selection through inflammatory signalling. When intestinal barrier integrity is compromised, inflammatory mediators such as LPS enter the circulation and induce the release of pro-inflammatory cytokines, including IL-6 and Interferon-gamma (IFN-γ). These signals further upregulate IDO1 expression, promoting a metabolic shift towards the kynurenine pathway and expanding the production of neurotoxic metabolites [68,69].

4.2 The Protective Effect of Gut Microbiota Metabolites, Specifically SCFAs, on the Kynurenine Pathway

Building on the metabolic deficits described in Section 2.3, depletion of SCFAs leads to a specific loss of regulatory control over the kynurenine pathway. Beyond their general anti-inflammatory effects, SCFAs act as histone deacetylase (HDAC) inhibitors that directly suppress the transcriptional activation of IDO1. SCFAs do more than just fight inflammation directly. They also help the brain control the gut through the vagus nerve. This process

is called the "cholinergic anti-inflammatory reflex". The brain sends signals back down the vagus nerve to stop gut cells from making too many inflammatory toxins. This reflex keeps the gut wall strong and prevents leaks. When this system fails in MCI patients, gut inflammation gets out of control and harms the brain further [70]. Mechanistically, SCFAs, particularly butyrate, function as potent HDAC inhibitors. By modulating the epigenetic landscape of immune cells, they suppress the signal transducer and activator of transcription 1 (STAT1) signalling cascade required for IDO1 transcription. Consequently, SCFAs not only attenuate inflammation but also directly inhibit the genomic mechanisms that drive excessive tryptophan flux into the kynurenine pathway, maintaining IDO1 in a downregulated state. In addition, butyric acid reduces the expression of inflammatory genes by inhibiting the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway, thereby preventing inflammation-induced overactivation of the kynurenine pathway [67].

SCFAs also regulate peripheral immune responses and directly influence the central nervous system by crossing the BBB. Through these mechanisms, BDNF activation, neuronal repair, and synaptic plasticity are promoted, while QUIN production is reduced and neurotoxicity is alleviated [71]. Furthermore, SCFAs enhance KYNA synthesis, restoring its antagonistic effects on NMDA receptors, reducing excitotoxic neuronal damage, and preserving synaptic function [39]. Through these combined actions, SCFAs mediate communication between the gastrointestinal tract and the central nervous system. Ultimately, their coordinated roles in suppressing immune activation and protecting neuronal survival support the maintenance of kynurenine metabolic homeostasis [61].

4.3 The Impact of Intestinal Barrier Dysfunction on the Kynurenine Metabolic Pathway

The systemic LPS burden resulting from intestinal barrier dysfunction (as established in Section 2.3) acts as a potent upstream regulator of tryptophan metabolism. Specifically, circulating LPS stimulates extrahepatic IDO1 expression [62]. Consistently, in 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis, acupuncture and moxibustion restored colonic architecture and reduced mucosal inflammatory infiltration while rebalancing gut microbiota and associated metabolites, suggesting a protective effect on the intestinal barrier [72]. Furthermore, LPS translocation is capable of stimulating IDO1 expression, shifting tryptophan catabolism towards the kynurenine pathway and markedly increasing QUIN production [73]. Evidence indicates that intestinal barrier dysfunction is widespread in individuals with MCI, where it both exacerbates systemic inflammation and further amplifies inflammatory responses within the central nervous system [71].

Under this pathological condition, beneficial bacteria such as Akkermansia can restore intestinal epithelial integrity by producing mucin, thereby reducing inflammatory infiltration and excessive IDO1 activation [74]. In addition, improvement of intestinal barrier function may decrease the release of LPS-induced pro-inflammatory factors, thereby fundamentally alleviating metabolic disturbances associated with the kynurenine pathway [61].

4.4 The Neurotransmitter Balance and Kynurenine Metabolic Pathway Under the Regulation of Gut Microbiota

A dynamic competitive relationship exists between the kynurenine metabolic pathway and neurotransmitter balance, with the gut microbiota playing a critical regulatory role. When kynurenine pathway activity is excessively elevated, a substantial proportion of tryptophan is diverted towards the production of QUIN and KYNA, leading to a marked reduction in 5-hydroxytryptamine (5-HT) synthesis [75]. Reduced 5-HT levels directly affect emotional regulation, sleep quality, and cognitive function, which are characteristic features of MCI [76].

Indole metabolites and SCFAs generated by intestinal microbial metabolism promote serotonin (5-HT) synthesis by stimulating enterochromaffin cells, thereby alleviating excessive tryptophan consumption by the kynurenine pathway [77]. Serum metabolomics from an electroacupuncture clinical study further indicate normalisation of amino acid metabolism with rebalancing of glutamatergic and γ-aminobutyric acid (GABAergic) signalling, consistent with the restoration of synaptic homeostasis [78]. KYNA, acting as an antagonist of QUIN, inhibits excitotoxicity through competitive binding to NMDA receptors [79]. However, gut microbiota imbalance reduces KYNA production, thereby weakening its protective effects against QUIN-mediated neurotoxicity and exacerbating disruption of neurotransmitter balance [80].

This dynamic competitive interaction indicates that gut microbiota regulation of tryptophan metabolism not only influences kynurenine pathway activity but also substantially affects central nervous system function by altering neurotransmitter synthesis and metabolism [81]. The gut microbiota appears to modulate the activity and branch selection of the kynurenine metabolic pathway by influencing tryptophan metabolism, inflammatory signalling, SCFA production, and intestinal barrier integrity [82]. Under physiological conditions, these regulatory mechanisms maintain a balance between KYNA and QUIN, thereby preserving nervous system function. However, gut microbiota dysbiosis may contribute to excessive activation of the kynurenine pathway, disrupt neurotransmitter balance, and exacerbate neurotoxicity and inflammatory responses, ultimately promoting the pathological progression of MCI [83].

5. Intestinal Flora, Kynurenine Metabolism and MCI: A Panoramic Analysis From the Gut-Brain Axis to Neuropathological Mechanisms

The gut microbiota, as a core regulator of host metabolism and immunity, interacts with the central nervous system through the gut–brain axis and plays a crucial role in cognitive impairment disorders. In recent years, accumulating evidence has demonstrated that gut microbiota imbalance can significantly influence the pathological progression of MCI through the regulation of tryptophan metabolism, inflammatory responses, neurotransmitter synthesis, and related pathways. The following analysis focuses on three aspects: the molecular mechanisms by which gut microbiota imbalance drives MCI, the dynamic balance of endogenous regulatory networks, and the potential for clinical translation.

5.1 The Imbalance of Gut Microbiota and the Pathological Mechanism of MCI: The Cascade Effect of the Gut-Brain Interaction Network

MCI pathology emerges not as a localized brain event but as a systemic failure of regulatory containment, where the KP serves as a transductive hub converting peripheral microbial signals into central neurotoxic cascades [84]. This systemic integration is highly dependent on clinical subtypes: Amnestic MCI (aMCI) exhibits a more severe microbial and metabolic dysregulation profile than non-amnestic MCI (naMCI), with aMCI specifically linked to the enrichment of Alistipes indistinctus and the depletion of protective Bacteroides eggerthii [85]. These aMCI-specific taxonomic shifts correlate directly with neurovascular dysfunction, including decreased cerebral blood flow (CBF) and arterial transit time (ATT) [86]. At the molecular level, the resulting accumulation of QUIN acts as a potent NMDA receptor agonist, triggering excessive intracellular calcium Ca^{2+} influx and activating the protein kinase glycogen synthase kinase-3 beta (GSK-3β) [87]. This GSK-3β activation represents a critical nexus, as it directly drives the hyperphosphorylation of tau protein and the subsequent formation of neurofibrillary tangles (NFTs), particularly in hippocampal regions where IDO1 is co-localized with pathological tau [53]. From a systems perspective, this dysregulated KP flux not only promotes proteopathy but also impairs bioenergetics by diverting substrates away from NAD^+ synthesis, leading to mitochondrial failure [88]. Simultaneously, the "butyrate gap" observed in these patients compromises the glymphatic system's clearance capacity, driven by astrocytic AQP4 polarization failure, which prevents the effective removal of Aβ and tau aggregates and creates a self-perpetuating cycle of neurotoxicity [89].

5.1.1 The Repair Mechanism of Intestinal Flora Imbalance and the Regulation of Inflammatory Response

Intestinal flora imbalance is a prominent feature observed in the early stages of MCI and frequently represents the initiation point of a detrimental pathological cycle. External factors can alter the relative abundance of symbiotic and pathogenic bacteria within the intestinal microbiota, thereby predisposing individuals to pathological states. Endogenous regulatory mechanisms may mitigate the adverse effects of dysbiosis and limit the amplification of inflammatory cascades, potentially slowing the pathological progression of MCI.

Evidence indicates that symbiotic bacteria actively inhibit the proliferation of conditionally pathogenic bacteria and enhance intestinal microenvironmental stability through metabolic by-products and competitive metabolic mechanisms [90]. SCFAs enhance the competitive advantage of probiotics within their ecological niche by lowering intestinal pH, thereby promoting restoration of microbiota diversity and reducing intestinal inflammation [91]. In addition, SCFAs directly inhibit NF-κB signalling activity. Through binding to G protein-coupled receptors (GPCRs), this effect further enhances host immune tolerance, thereby establishing a foundation for the recovery of intestinal flora diversity [92].

Concurrently, the host immune system plays a pivotal role in this regulatory process. Protective immune regulation mediated by gut-associated lymphoid tissue (GALT), including the secretion of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) by regulatory T cells, effectively suppresses the dissemination of pro-inflammatory mediators, including TNF-α and IL-6, thereby reducing the overall intensity of the inflammatory response [93]. More importantly, intestinal epithelial cells restore barrier integrity by activating regenerative programmes for tight junction proteins. This process reduces the translocation of LPS and other pro-inflammatory factors into the circulation, thereby limiting the development of systemic inflammation [94].

At this stage, recovery of intestinal microbiota diversity and local suppression of inflammatory responses form a mutually reinforcing virtuous cycle. Restoration of SCFA production enhances anti-inflammatory immune responses, which further restrict systemic inflammatory dissemination and provide a stable microenvironment conducive to intestinal flora recovery [95].

5.1.2 The Endogenous Regulation of Tryptophan Metabolism and the Recovery of Gut-Brain Axis Function

As inflammatory responses progressively subside, the body further restricts the expansion of the vicious cycle through coordinated metabolic and neuroprotective mechanisms. Within the kynurenine metabolic pathway, although IDO1 activation promotes increased quinolinic acid production, KYNA is concurrently generated. As a neuro-

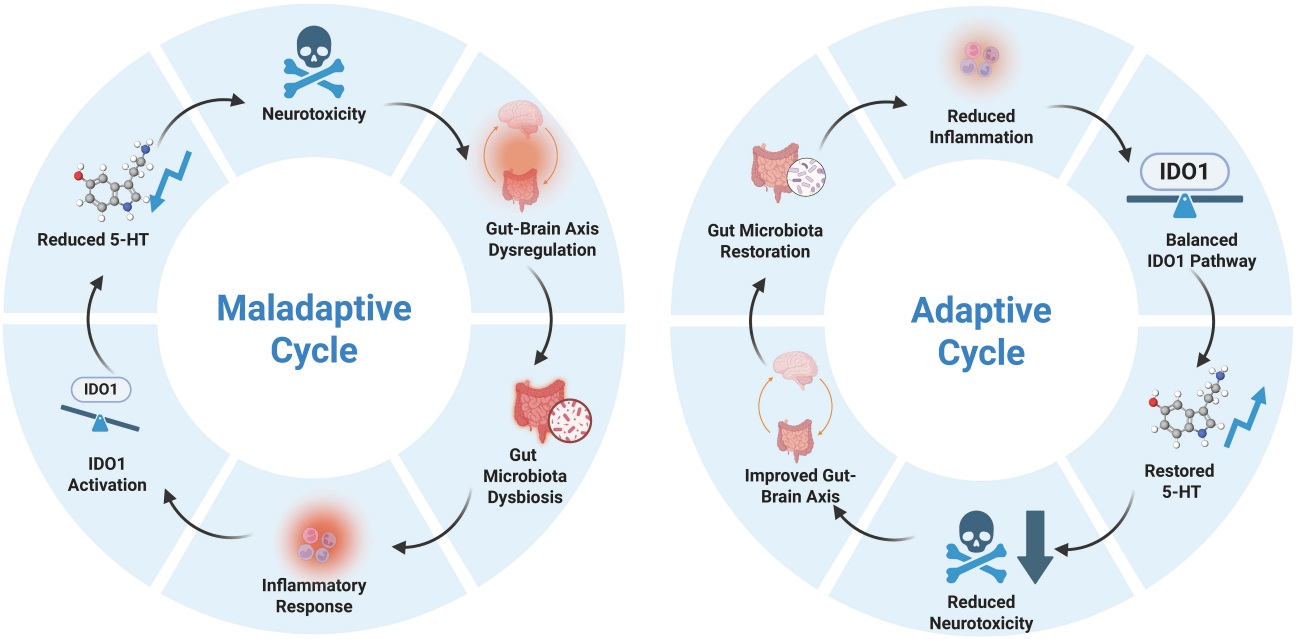

Fig. 3. Self-regulatory mechanisms of the gut-brain axis.Transition from vicious to beneficial cycles and their impact on MCI pathology. The arrows in the figure illustrate the causal progression and dynamic feedback loops within the gut-brain axis. Specifically, the clockwise arrows represent a self-perpetuating cycle where each pathological or physiological component reinforces the next, ultimately maintaining either a maladaptive (left) or adaptive (right) state. 5-HT, 5-hydroxytryptamine. Created with Biorender (https://www.biorender.com/).

protective metabolite, KYNA effectively mitigates neurotoxicity through antagonism of NMDA receptor activation [96,97]. In addition, KYNA suppresses excessive activation of microglia and astrocytes, thereby attenuating cumulative neuroinflammatory effects [98].

With declining levels of pro-inflammatory mediators, tryptophan metabolism gradually shifts from the kynurenine pathway towards serotonin (5-HT) synthesis. Restoration of 5-HT not only alleviates emotional disturbances and sleep disorders in patients with MCI but also directly enhances cognitive function by improving synaptic plasticity and neural network connectivity [61]. This metabolic rebalancing signifies a transition from a vicious pathological cycle to a beneficial regulatory cycle.

At the level of the gut-brain axis, BBB integrity begins to recover. Following attenuation of systemic inflammation, epithelial and endothelial cells reactivate tight junction protein synthesis, thereby reducing the translocation of toxic metabolites and pro-inflammatory factors across the blood–brain barrier [99,100].

In summary, the pathological cascade of "intestinal flora imbalance → enhanced inflammatory response → activation of the IDO1 pathway → increased quinolinic acid and decreased 5-HT → aggravated neurotoxicity and neuroinflammation → gut-brain axis dysfunction → intestinal flora imbalance" may gradually transform into a beneficial cycle of "intestinal flora recovery → reduced inflammatory response → balanced IDO1 pathway → increased KYNA levels and restored 5-HT → alleviated neurotoxicity and balanced neurotransmission → improved gut-brain axis function → intestinal flora recovery" through endogenous regulatory mechanisms. Refer to Fig. 3 for details. This dynamic system comprising intestinal flora, inflammatory responses, the kynurenine metabolic pathway, and the gut-brain axis illustrates the endogenous potential for transformation from a vicious cycle to a beneficial regulatory state. Through self-regulation of intestinal flora, gradual attenuation of inflammation, and activation of neuroprotective mechanisms, the organism can re-establish microbial balance, restore metabolic homeostasis, and repair neural function under adverse conditions. By elucidating this multilevel linkage within the gut-microbe-brain axis, the complexity of the microenvironment as a system governed by endogenous self-regulation is clarified, while simultaneously defining a complex yet modifiable framework for pathological improvement in MCI.

6. Conclusions and Future Prospects

This review highlights the significant association between gut microbiota and MCI, particularly the link between gut microbiota alterations and cognitive deterioration mediated through kynurenine metabolism. First, a distinct structural signature of gut microbiota alteration is evident in patients with MCI, characterised by an increased abundance of pro-inflammatory bacteria (Prevotella, Enterobacteriaceae) and a reduction in beneficial probiotics (Bi-

Table 2. Summary of key therapeutic targets, underlying pathological mechanisms, and future research recommendations for MCI intervention.

Therapeutic target	Mechanistic basis	Key recommendations for future research
Gut Microbiota	Dysbiosis (*Prevotella*, *Akkermansia*) leads to barrier impairment.	Develop next-generation probiotics targeting *Akkermansia* and *Faecalibacterium*; explore precision FMT donor screening based on metabolic phenotypes.
SCFAs	"Butyrate Gap" leads to insufficient HDAC inhibition and IDO1 upregulation.	Validate epigenetic inhibition mechanisms of butyrate on IDO1/KMO; develop colon-targeted SCFA formulations to repair the blood-brain barrier.
IDO1 Enzyme	Inflammation (LPS/Cytokines) induces overexpression, hijacking tryptophan metabolism.	Develop peripheral/gut-restricted IDO1 modulators; investigate synergistic effects of tryptophan dietary intervention and enzyme inhibitors.
KMO Enzyme	Key "switch" directing metabolic flow to the toxic branch (QUIN).	Develop BBB-permeable KMO inhibitors to reshape the QUIN/KYNA ratio and enhance endogenous neuroprotection.
Comprehensive Intervention	Multi-link interactions of the gut-brain axis.	Conduct clinical trials for "Microbiota Regulation + Enzyme Inhibition" combination therapy; establish MCI early warning and efficacy evaluation systems based on metabolomics.

KMO, kynurenine 3-monooxygenase; LPS, lipopolysaccharides; FMT, fecal microbiota transplantation; BBB, blood-brain barrier; HDAC, histone deacetylase.

fidobacterium). Concurrently, the metabolic functions of the gut microbiota undergo substantial changes, most notably in the production of SCFAs. These metabolites play a critical role in maintaining intestinal barrier integrity, immune homeostasis, and nervous system health.

Patients with MCI exhibit marked metabolic disturbances in kynurenine metabolism. In particular, a functional imbalance characterised by an increased QUIN/KYNA ratio—reflecting a shift towards neurotoxicity irrespective of absolute metabolite fluctuations—may exacerbate nervous system damage. QUIN excessively activates NMDA receptors, thereby inducing neuroinflammation and oxidative stress, which further accelerates cognitive decline. Conversely, reduced KYNA levels weaken neuroprotective mechanisms and diminish the nervous system's capacity to counteract excitotoxicity.

Accordingly, our perspective on future therapeutic strategies extends beyond single-agent interventions and instead proposes the establishment of a multi-level, multi-target "virtuous cycle" intervention model. Central to this approach is the restoration of gut microbiota diversity and SCFA production capacity (e.g., through supplementation with Akkermansia and Faecalibacterium) to repair the intestinal barrier and suppress upstream inflammatory drivers. In parallel, pharmacological interventions are applied to precisely modulate key KP enzymes (specifically targeting IDO1 and KMO), thereby correcting downstream metabolic imbalances and re-establishing a neuroprotective KYNA/QUIN ratio.

To inform future experimental design and facilitate clinical translation, this review systematically synthesises key therapeutic targets, their underlying pathological mechanisms, and specific recommendations for future research priorities. Table 2 comprehensively outlines a spectrum of potential intervention strategies, ranging from ecological remodelling of the gut microbiota to the precise modulation of metabolic enzymes. This integrated summary aims to provide a clear operational framework for addressing the pathological imbalances of MCI through synergistic multi-target interventions, thereby delaying or reversing disease progression and ultimately establishing a neuroprotection-centred "virtuous cycle".

Step 1: Restoring Gut Homeostasis. Intervention must begin at the source in the gut. By supplementing probiotics and dietary fiber, we can fill the "butyrate gap". Butyrate does more than just repair the intestinal barrier. It also acts as a key regulator to inhibit IDO1 enzyme activity at the genetic level. This reduces the production of harmful metabolites from the start.

Step 2: Maintaining Blood-Brain Barrier Function. SCFAs produced by gut bacteria are vital for brain health. These metabolites strengthen the integrity of the blood-brain barrier. This protection effectively blocks peripheral inflammatory factors from entering the central nervous system. It keeps neurons safe from external disturbances.

Step 3: Correcting Cerebral Metabolic Pathways. Inside the brain, we need to precisely downregulate IDO1 or KMO enzymes. Doing this redistributes the tryptophan metabolic flux. This not only reduces the buildup of neurotoxins (QUIN) but also boosts levels of protective substances (KYNA). This keeps the normal functions of neural synapses stable.

Author Contributions

Formulation: JZ, HX, SX, ML, QL, and WL; Literature management: JZ, HX, and YO; Supervision: HX, ML, and SX; Drawing Figures: JZ, HX, and TZ; Initial draft: JZ, YO, WL and HX; Revision and proofreading: JZ, HX,

QL, WL, ML, and YO. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We sincerely thank BioRender and FigDraw, two powerful graphic design software programs, for their important support in creating the illustrations and charts for my thesis.

Funding

This work was supported by the projects of the science and technology innovation Program of Hunan Province (No. 2024JK2132, No. 2024RC1061), the Scientific Research Project of Hunan Provincial Health Commission (No. 20257637), the State Administration of Traditional Chinese Medicine 2022 Youth Qihuang Scholars Training Program (National Letter of Traditional Chinese Medicine Education [2022] 256), the Hunan Provincial Graduate Joint Cultivation Base for Acupuncture-Moxibustion and Tuina of Hunan University of Chinese Medicine (No. [2022] 357, Hunan Provincial Department of Education Notice), the Acupuncture Bioinformation and Smart Wellness Innovation and Entrepreneurship Education Center of Hunan University of Chinese Medicine (No. [2021] 356, Hunan Provincial Department of Education Notice), and the Innovative Graduate Cultivation Base for Chinese Medicine Sub-health of Hunan University of Chinese Medicine (No. [2020] 19, University Administrative Research Document).

Conflicts of Interest

The authors declare no conflicts of interest.

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