Molecular Neurodegeneration

REVIEW

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# Gut microbiota-host lipid crosstalk in Alzheimer's disease: implications for disease progression and therapeutics

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**Abstract**

Trillions of intestinal bacteria in the human body undergo dynamic transformations in response to physiological and pathological changes. Alterations in their composition and metabolites collectively contribute to the progression of Alzheimer's disease. The role of gut microbiota in Alzheimer's disease is diverse and complex, evidence suggests lipid metabolism may be one of the potential pathways. However, the mechanisms that gut microbiota mediate lipid metabolism in Alzheimer's disease pathology remain unclear, necessitating further investigation for clarification. This review highlights the current understanding of how gut microbiota disrupts lipid metabolism and discusses the implications of these discoveries in guiding strategies for the prevention or treatment of Alzheimer's disease based on existing data.

**Keywords** Gut microbiota, Lipid metabolism, Alzheimer's disease, Cholesterol, SCFAs, LPS, APOE, Neuroinflammation, Probiotics, Lifestyle, Exercise

## Background

Alzheimer's disease (AD), constituting 60-70% of dementia cases, is the most prevalent cause of dementia, with global estimates surpassing 50 million patients, thereby imposing a substantial societal and familial burden [1]. Clinically, AD manifests with progressive memory loss, cognitive impairment, and behavioral changes. Neuropathologically, β-amyloid (Aβ) deposits extracellularly, forming neuroinflammatory plaques, while intracellularly, excessive phosphorylation of tau leading to the formation of neurofibrillary tangles (NFTs), accompanied by synaptic loss and neurodegeneration [2–4]. Moreover, abnormalities in lipid metabolism have been identified as the third pathological feature of AD, associated with disease onset and progression [5]. Lipids, constituting 50% of the brain's weight, encompassing fatty acids, cholesterol, phospholipids, and sphingolipids, play a pivotal role in brain function [6]. For instance, fatty acid oxidation contributes 20% of the brain's energy supply [7], and cholesterol and sphingolipids are major components of lipid rafts [8, 9], playing crucial roles in neurotransmitter transmission, signal transduction, and neural synaptic plasticity. Alterations in lipid homeostasis manifest in the early stages of AD [10], with studies indicating abnormal lipid deposition in the brains of AD patients and 3×Tg AD mice, signifying disrupted lipid metabolism [11–14]. Concurrently, a systematic review also encapsulated the prevalent occurrence of lipid

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dysregulation in AD mouse models such as 5×FAD, APP/PS1, among others [15]. Metabolic analysis of serum, plasma, and cerebrospinal fluid from AD patients reveals the dysregulation of lipid metabolism is closely linked to cognitive decline and neuronal dysfunction [16, 17].

The gut microbiota, populating the human gastrointestinal tract, consists of approximately 100 trillion bacteria, archaea, and eukaryotes, collectively encoding over 3 million genes and generating a diverse array of metabolites [18]. Through the bidirectional "gut-brain axis" [19, 20], the gut microbiota actively modulates host metabolic processes [21–24]. During pathological conditions, dynamic alterations in the gut microbiota have been observed in tandem with the progression of the host's disease [25–27]. 16S rRNA gene sequencing of gut microbiota in AD patients reveals a reduction in both abundance and diversity [28–30], such as, the significant correlation between the increased abundance of *Enterobacteriaceae* and the severity and progression of AD has been observed [30]. The alterations in the composition of the gut microbiota have also been associated with Aβ and tau pathological biomarkers [31]. Our study establishes *Helicobacter pylori* (H. pylori) infection as a risk factor for AD [32, 33], 5×FAD mice [34], and Tauopathy mouse model [25] has been provided. Chandra S and colleagues have extensively summarized these findings [35]. Mezö et al. found that Germ-free (GF) 5×FAD mice enhance the uptake of Aβ deposits by hippocampal microglia, mitigating plaque burden and neuronal loss, and improving memory function [36]. Antibiotic treatment in APP/PS1 mice also led to a reduction in Aβ deposition [37]. Harach et al. reached the same conclusion in GF APP/PS1 mice [38], providing compelling evidence for the role of gut microbiota in AD. Transplanting gut microbiota from AD mice into wild-type C57BL/6 mice results in impaired memory function and neurogenesis [39]. Conversely, fecal microbiota transplantation from healthy mice effectively mitigates Aβ plaque deposition and neurofibrillary tangle formation in AD mice, thereby ameliorating cognitive impairment [40]. These findings underscore the complex involvement of gut microbiota in AD pathology and suggest its potential as a therapeutic avenue for AD.

Emerging evidence suggests a significant interaction between gut microbiota and lipid metabolism in AD [41]. Such as correlations were observed between gut microbiota and fatty acids as well as glycerophospholipids in APP/PS1 mice [42]. A recent multi-omics study has unveiled the intricate connection between gut microbiota and host glycerophospholipid metabolism, as well as neuroinflammation in APP/PS1 mice [43, 44]. Additionally, gut microbiota from 3×Tg mice induced increased pro-inflammatory signal transduction through polyunsaturated fatty acid metabolism [45]. Multi-strain probiotic formulation resulted in reduced total cholesterol levels, improved lipid metabolism, and enhanced cognitive function [46]. These findings present compelling evidence for the involvement of gut microbiota in the lipid metabolism of AD.

Given the pivotal roles of lipid metabolism and gut microbiota in AD, this review systematically explores the dysregulation of lipid metabolism in the context of AD. Subsequently, it emphasizes the intricate interplay between gut microbiota and lipid metabolism during AD pathology, with a specific focus on gut microbiota metabolites, key genes, and molecular mechanisms. Lastly, the paper provides a comprehensive summary and analysis of current research pertaining to strategies aimed at modulating gut microbiota and lipid metabolism, to improve the pathological progression of AD.

## Lipids dysregulation in Alzheimer's disease

Decades of research have unveiled the involvement of lipid metabolism in the pathological processes of AD. This section primarily elucidates the changes and roles of lipids dysregulation in AD pathology from the perspectives of fatty acids, cholesterol, phospholipids, and sphingolipids.

### Fatty acids

Fatty acids, characterized by long hydrocarbon chains, are categorized into saturated fatty acids (SFAs) and unsaturated fatty acids (UFA), which encompass both monounsaturated and polyunsaturated fatty acids (PUFAs) [47]. ω-3 polyunsaturated fatty acids (ω-3 PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), as well as ω-6 polyunsaturated fatty acids (ω-6 PUFAs) like arachidonic acid (AA), have been identified to play a significant role in AD [48]. Metabolomic analysis of post-mortem samples from the Baltimore Longitudinal Study of Aging (BLSA) cohort revealed the strongest correlation between PUFAs and AD [49]. Current research suggests that ω-3 PUFAs, such as EPA and DHA, exert anti-inflammatory effects, mitigating Aβ deposition and improving cognition in AD mice [50]. DHA as the most abundant PUFAs in the brain, reduces amyloid production and inhibits the aggregation and formation of amyloidogenic fibrils by decreasing the activity of γ- and β-secretase enzymes, and its levels are significantly reduced in the brains and plasma of AD patients [49, 51, 52]. In contrast to ω-3 PUFAs, ω-6 PUFAs are recognized as pro-inflammatory precursors, contributing to the synthesis of leukotrienes, prostaglandins, and thromboxane [53]. ω-6 PUFAs activate GPR40 activation, which is implicated in neuronal degeneration and death; thus, the excessive intake of ω-6 PUFAs is considered a risk factor for AD [54]. AA, a plentiful ω-6 PUFA found in the gray matter of the brain,

exhibits heightened levels in individuals with AD, thereby fostering the generation and accumulation of Aβ through a series of inflammatory cascades. Despite the prevailing perception of ω-3 PUFAs as protective elements for AD patients, it is crucial to recognize that both ω-3 and ω-6 PUFAs are integral to brain physiology. Therefore, it is imperative to uphold a judicious balance in the intake of ω-6/ω-3 PUFAs for optimal individual well-being [55].

SFAs are generally considered to increase the risk of AD [56]. Such as palmitic acid (PA), the most common SFAs in the brain, has been found to have elevated levels in the temporal and frontal cortices of AD patients [57, 58] PA induces SIRT1 dysfunction and activates the NF-κB pathway [59]. Through SIRT1 inhibition, PA indirectly upregulates SREBP1 transcription and expression, leading to β-site amyloid precursor protein-cleaving enzyme 1(BACE1) promoter transactivation. This cascade results in increased BACE1 expression, heightened enzymatic activity, and elevated amyloid-beta generation. Additionally, PA induces tau hyperphosphorylation and neuroinflammation [60].

#### Cholesterol

In the presence of the blood-brain barrier, cerebral cholesterol primarily originates from endogenous synthesis. In brief, astrocyte-synthesized cholesterol, coupled with apolipoprotein E and J, is secreted through ATP-binding cassette transporters, followed by neuronal uptake. Excessive intracellular free cholesterol is enzymatically converted into cholesterol ester (CE) by cholesterol acyltransferase, leading to intracellular accumulation or plasma membrane efflux [5]. Increased brain cholesterol concentrations are regarded as a risk factor for AD due to the robust association with synaptic dysfunction and impaired neurotransmission, as evidenced in brain tissue from both AD patients and mouse models [61]. Post-mortem examinations of AD patients revealed an association between hypercholesterolemia and increased accumulation of Aβ in the brain [62]. The observed association could stem from blood-brain barrier impairment, resulting in an augmented cholesterol influx into the brain and exacerbating the cerebral cholesterol burden. Subsequently, this mechanism accelerates Aβ aggregation within neurons and synaptic loss, thereby aggravating the pathological progression of AD [63].

A cholesterol-binding domain has been reported within the transmembrane domain of amyloid precursor protein (APP), suggesting a direct interaction between cholesterol and APP. Cholesterol upregulates the activity of γ-secretase, promoting the colocalization of APP with γ and β-secretases, thereby stimulating the generation of Aβ [64, 65]. A reduction in cholesterol may enhance non-pathogenic cleavage by α-secretase, consequently reducing Aβ production [66]. In addition, CE can bind to the cholesterol-binding domain on APP, affecting APP processing and Aβ production. In contrast to the Aβ regulation, CE regulate the phosphorylation of tau in neurons through a proteinase-pTau axis. The reduction in CE generation leads to a decrease in the expression levels of phosphorylated tau at multiple sites [67].

#### Phospholipid

Phospholipids form the lipid bilayer of cell membranes, acting as a safeguarding barrier for cellular and subcellular structures. They also participate in maintaining homeostasis, managing immune responses, oxidative stress and neuroinflammation in the brain. The main brain phospholipids are phosphatidylcholine (PC) and phosphatidylethanolamine (PE) [68]. There have been reports that the lyso-PC to PC ratio decreases, and water-soluble PC metabolites increase in individuals with AD [69]. Indeed, increased levels of glycerophosphocholine and decreased levels of lysoPC(18:1(11Z)), PC (16:0/16:0) and phosphatidylcholine were observed in the brains of APP/PS1 transgenic mice [43]. This suggests that there is more hydrolysis of phospholipids during the course of AD. The degradation of PC and PE is considered as a significant metabolic anomaly in AD, with the decreased concentrations being closely associated with the severity of amyloid protein and neurofibrillary pathology [70–72]. Moreover, there is a substantial 70% decrease in ethanolamine plasmalogens (PlsEtns) in AD patients, which exert neuroprotective effects by activating G-protein coupled receptors (GPCRs), increasing AKT and ERK pathway phosphorylation, preventing neuronal death, reducing γ-secretase activity, and decreasing Aβ production [73, 74]. Additionally, mice deficient in PlsEtns have increased activity of the tau phosphorylating kinase glycogen synthase kinase 3 beta (GSK3β), possibly leading to excessive tau phosphorylation [75].

Another noteworthy phospholipid is Phosphatidylserine (PtdSer), constituting 13–15% of phospholipids in the human cerebral cortex [76]. PtdSer serves as an indispensable participant in signal transduction, asymmetrically distributed on the leaflet of the lipid bilayer [77]. PtdSer on the inner leaflet of the membrane facilitates the activation of signaling proteins and receptors crucial for neuronal survival, differentiation, and synaptic neurotransmission [78]. Externalized phosphatidylserine (ePtdSer) serves as one of the ligands for The Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) [79]. ePtdSer exposed on synaptic surfaces acts as an "eat-me" signal, facilitating microglia-mediated synapse pruning [80] and phagocytic activity [81]. In Nondemented individuals with AD neuropathology (NDAN), microglia induced by ePtdSer-TREM2 exhibit enhanced efficiency in clearing damaged synapses, which may underlie the synaptic structural and functional integrity in NDAN

individuals, thus preventing cognitive impairment [82]. Under oxidative stress conditions of AD, the asymmetry of PtdSer is disrupted, evidenced by increased exposure of PtdSer in the outer leaflets of the frontal cortex in individuals with Mild Cognitive Impairment (MCI) and AD, initiating early apoptosis and ultimately leading to increased neuronal damage [77]. Another study suggests that in the early stages of AD, the release of ePtdSer serves as an "eat-me" signal, prompting microglia to preferentially eliminate ePtdSer$^+$ damaged synapses through TREM2, thereby maintaining neural and synaptic homeostasis. However, microglia expressing dysfunctional R47H TREM2 fail to phagocytose ePtdSer$^+$ synapses, resulting in increased apoptotic-like synaptic burden in the hippocampus [83].

#### Sphingolipids

Sphingolipids, which are essential components of neuronal cell membranes, include bioactive lipids such as ceramide (Cer), sphingosine-1-phosphate (S1P) and sphingosine, and are involved in the regulation of neuronal stress, proliferation, differentiation and maturation [84]. Metabolomic analysis of brain and blood in preclinical and prodromal stages of AD shows a correlation between decreased sphingolipid levels and the severity of AD pathology [71, 85, 86]. Blood sphingolipid concentrations correlate with cerebrospinal fluid Aβ levels, brain atrophy and cognitive decline, suggesting the potential of sphingolipids as early biomarkers of AD [71].

Ceramides which increased in the brain tissue of AD patients [87] contribute to the stability of BACE1 and facilitate the excessive generation of Aβ [88]. Neurons accelerate Aβ aggregation by releasing extracellular vesicles rich in ceramides, while inhibition or silencing of neutral sphingomyelinase-2 (nSMase2), which is responsible for vesicle secretion, has been shown to improve Aβ plaque formation, slow the pathological progression of AD and improve cognitive function [89]. In addition, S1P, recognized for its neuroprotective effects, exhibits decreased levels in the brain tissues of both AD patients and 5×FAD mice, potentially accelerating neuronal degeneration [87, 89].

## Gut microbial metabolites regulate AD lipids and pathology

Gut microbiota generate diverse metabolites, including short-chain fatty acids, bile acids, lipopolysaccharides, trimethylamine, tryptophan metabolites, and more. These metabolites serve as signaling molecules and substrates within the host, thereby regulating host physiological functions [90]. Fluctuations in gut microbiota coincide with alterations in metabolite levels throughout the progression of AD. Several studies have elucidated the regulatory role of bacterial metabolites in lipid metabolism, shedding light on their involvement in the progression of AD pathology (Fig. 1). This section provides a comprehensive summary of studies in the literature investigating the impact of bacterial metabolites on lipid metabolism and pathological progression in AD.

#### Short chain fatty acids

Gut microbiota enzymatically degrades carbohydrates and plant polysaccharides to produce SCFAs, particularly acetate, propionic acid, and butyrate, which collectively constitute about 95% of the total SCFAs in the human body. *Bacteroidetes* and *Firmicutes* preferentially generate propionate, *Firmicutes* (*Eubacterium*, *Anaerostipes*, *Roseburia*, and *Faecalibacterium prausnitzii*) are well-defined as the predominant producers of butyrate. *Akkermansia muciniphila* has the unique ability to utilize intestinal mucin as its sole carbon and nitrogen source for proliferation, with propionate as a central metabolite. These SCFAs have the capacity to traverse the blood-brain barrier or the gut-brain axis, exerting regulatory effects on neurotransmitter synthesis, mitochondrial function, lipid metabolism, and gene expression [44].

Targeted metabolomics analysis of feces from AD patients indicates a reduction in the levels of SCFAs-producing phyla such as *Firmicutes*, *Clostridia*, and *Ruminococcus*, resulting in decreased SCFAs levels [91]. SCFAs play a pivotal role in AD pathology through Ligands for G protein-coupled receptors (GPRs) signaling [92]. Specifically, SCFAs bind to GPR43 and GPR109A receptors, modulate cholesterol and lipid metabolism, activate MAPK pathway, and suppress NF-κB pathway [93]. In addition, studies have explored the functions and roles of individual SCFA in AD, such as, acetate up-regulates GPR41 expression, inhibits the ERK/JNK/NF-κB pathway, alleviates neuroinflammation, and improves cognition in APP/PS1 mice [94]. Additionally, propionic acid binds to GPR41 in brain endothelial cells, hinders low-density lipoprotein receptor-related protein 1(LRP-1) expression through a CD14-dependent mechanism, and shields the blood-brain barrier from oxidative stress via NRF2 signaling [95]. Furthermore, epigenetics represents one of the mechanisms by which SCFAs impact AD. Butyrate, acting as a histone deacetylase inhibitor, has demonstrated the ability to elevate the expression of genes associated with

learning, restore histone acetylation, and markedly enhance learning and memory ability in AD mice [96], acetate also enhances cognition by facilitating histone H3K18 acetylation [97].

Furthermore, Colombo et al. observed a significant reduction in Aβ plaque burden in the brains of GF APP/PS1 mice compared to specific pathogen-free (SPF) APP/PS1 mice, with improved cognitive performance in spatial memory tasks. Subsequent investigations revealed

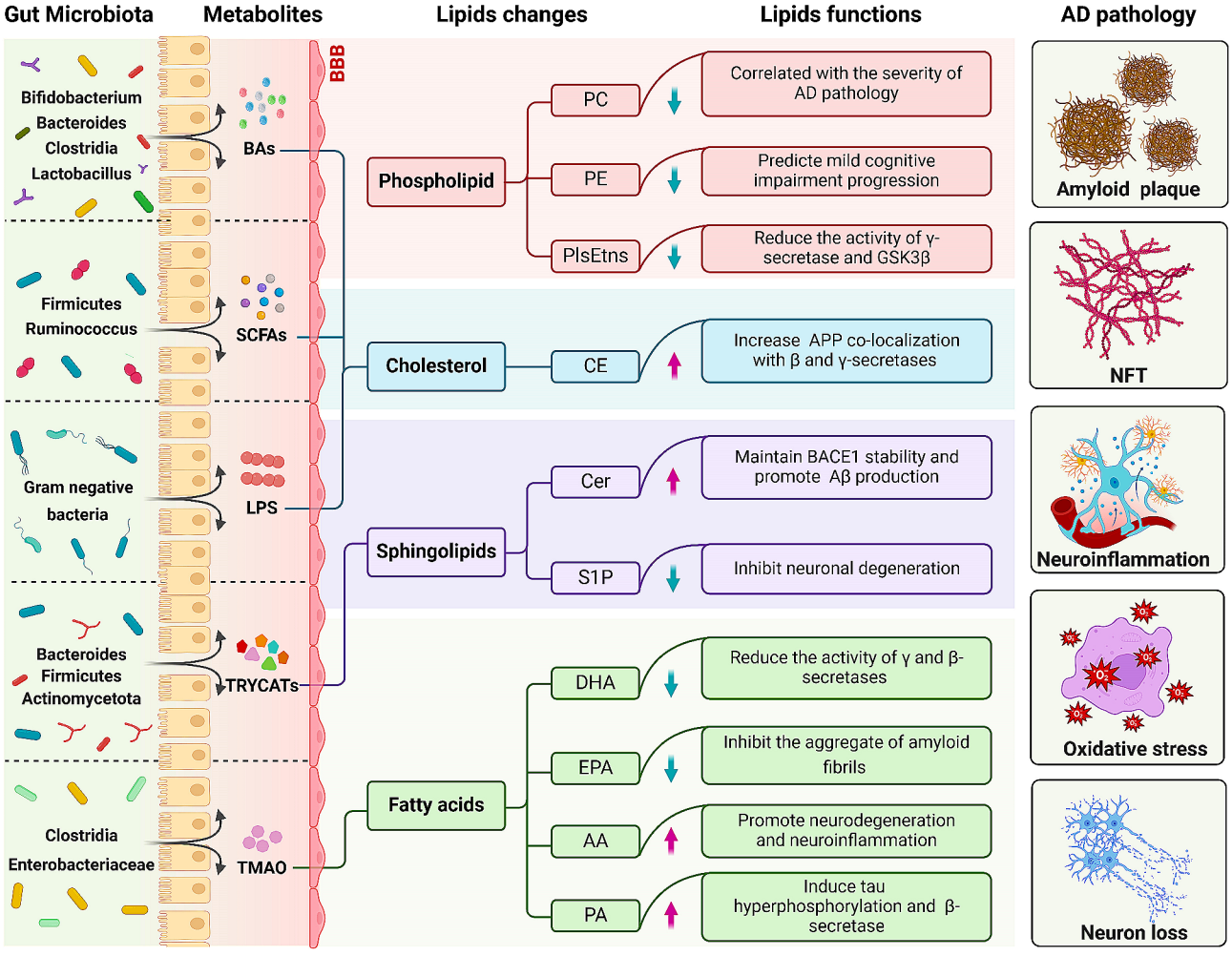


**Fig. 1** The potential association between gut microbiota and their metabolites with lipid dysregulation in AD. Throughout the progression of Alzheimer's disease (AD), there is a reduction in phosphatidylcholine (PC) and phosphatidylethanolamine (PE). PC exhibits a negative correlation with the severity of AD pathology, while PE serves as a prognostic indicator for patients with mild cognitive impairment. Plasmalogens (PlsEtns) mitigate tau phosphorylation and experience downregulation in AD. Cholesterol, a pivotal lipid in AD, notably increases in the brain, accompanied by a significant elevation in cholesterol esters (CE). Cholesterol and CE play pivotal roles in AD, contributing to Aβ pathology, tau hyperphosphorylation, and neuroinflammation. Gut microbiota metabolites such as BAs, SCFAs, and LPS interact with cholesterol, thereby modulating AD pathology. Ceramide (Cer) levels escalate in AD, stabilizing BACE1 and fostering Aβ production, whereas sphingosine-1-phosphate (S1P) exhibits neuroprotective effects, and its decrease facilitates neurodegeneration. Tryptophan metabolites (TRYCATs) are intricately associated with sphingolipids through the AhR receptor. Fatty acids like docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) decrease in AD, playing a role in inhibiting Aβ generation. Arachidonic acid (AA) is a prominent participant in neuroinflammation, instigating neuronal degeneration. Palmitic acid (PA), a representative saturated fatty acid, fosters AD through heightened β-secretase activity and tau hyperphosphorylation. Trimethylamine N-oxide (TMAO) exacerbates AD progression by promoting fatty acid oxidation and oxidative stress

that the increased concentration of SCFAs in the plasma of SPF mice was the primary cause of this outcome, contrary to prior findings; supplementation of SCFAs simulated the role of the microbiota and increased Aβ plaque burden [98]. Erny and colleagues also demonstrated that acetate treatment exacerbated Aβ plaque deposition and neuroinflammation in GF 5×FAD mice [99]. In addition, recent investigation demonstrated that SCFAs act as mediators in the neuroinflammation-neurodegeneration axis, intensifying reactivity in neural glial cells and exacerbating p-tau pathology in TE4 P301S tau transgenic mice [100]. Nevertheless, the experimental findings reported by Zhou et al. indicate that dietary supplementation with high acetate and butyrate (HAMSAB) may attenuate cognitive decline in 5×FAD mice [101], highlighting a potential protective role of endogenous SCFA. These findings suggest the paradoxical roles and functions of SCFAs in AD under different circumstances. Further studies are essential to gain a deeper understanding of the effects of SCFAs on AD. While the role of SCFAs remains controversial, their significance as key molecular mediators in the gut-brain axis of AD is undeniable.

Modulation of SCFAs and their related pathways may represent promising therapeutic targets in the early peripheral circulation of AD.

#### Bile acids

Bile acids (BAs) can be further subdivided into primary Bas and secondary Bas; the primary Bas consist of cholic acid (CA) and chenodeoxycholic acid (CDCA) [102, 103]. The bile salt hydrolase, which are produced in the intestine by *Bacteroides*, *lostridium cluster VIA, Lactobacillus*, and *Bifidobacterium*, transform primary bile acids into secondary bile acids, which include deoxycholic acid (DCA), lithocholic acid (LCA), and cholic ursodeoxycholic acid (UDCA) [102, 104]. Primary bile acids are responsible for lipid absorption and maintaining cholesterol homeostasis, as they can penetrate the blood-brain barrier (BBB) and bind to nuclear receptors to regulate brain physiological functions. A multicenter metabolomic study involving 1464 participants found that in the serum metabolome of AD patients, DCA and its conjugated forms with glycine and taurine increased, and deoxycholic acid was associated with decreased cognitive abilities [104]. Another metabolomic analysis revealed that the alternative synthesis pathway of bile acids is more active in individuals with AD, and increased serum concentrations of cytotoxic bile acids [103, 105], indicating that dysregulation of bile acid metabolism caused by gut microbiota imbalance is involved in the pathological process of AD.

In addition, some BAs have been reported to exhibit neuroprotective effects. A recent systematic review summarized that UDCA reduces the levels of ROS, tumor necrosis factor alpha (TNFα), and interleukin-1 beta (IL-1β), exerting anti-apoptotic, oxidative stress and inflammatory effects in AD [106]. In addition, tauroursodeoxycholic acid (TUDCA) reduces Aβ deposition, inhibits the progression of amyloid pathology and suppresses GSK3β activity, thereby reducing tau hyperphosphorylation and microglial cell activation [107]. Further research has confirmed that TUDCA can bind to the G protein-coupled bile acid receptor 1/Takeda G protein-coupled receptor 5 (GPBAR1/TGR5) in microglial cells, increasing cAMP levels, inducing an anti-inflammatory phenotype of microglial cells, and attenuating inflammatory responses [108]. These findings indicate the potential therapeutic effects of TUDCA in AD [109, 110].

#### Lipopolysaccharides

Lipopolysaccharides (LPS), endotoxins produced by intestinal gram-negative bacteria such as *Escherichia coli*, *Bacteroides fragilis*, and *Salmonella enterica*, were found to coexist with *E. coli* fragments in amyloid plaques in postmortem brain tissues of AD patients [111]. Furthermore, the blood levels of LPS were significantly increased in AD patients, and the presence of LPS was also detected in the neocortex and hippocampus of AD patients at levels more than seven times higher than control subjects [112]. These findings indicate that LPS is widely present in the brains of AD patients and may represent a risk factor for cognitive impairment and the progression of AD [113].

The role of LPS in the pathophysiology of AD has been extensively documented [113]. LPS can disrupt the intestinal and blood-brain barriers, triggering a robust inflammatory response in the brain, promoting Aβ deposition, and inducing excessive phosphorylation of tau [111, 114]. Furthermore, it upregulates the activity of APP cleaving enzyme BACE-1 and γ-secretase while reducing the activity of α-secretase, thus promoting Aβ generation. It also induces neuroinflammation in microglia cells and impairs cognitive function of AD mice in a CatB-dependent manner [115]. Meanwhile, LPS downregulates the expression of LRP-1, impairs P-glycoprotein function, and disrupts Aβ clearance through multiple pathways. LRP-1 is the primary metabolic receptor for APOE in the brain and involved in APOE-mediated lipid transport processes [116], indicating that LPS may indirectly regulate the function of APOE. Additionally, LPS induces oxidative stress and mitochondrial dysfunction through NOX2, leading to neuronal damage and synaptic loss [113].

Furthermore, an important point not to be overlooked regarding LPS is its close association with microglial activation and neuroinflammation [117, 118]. LPS serves as a receptor agonist for Toll-like receptor 4 (TLR4), which is considered one of the key receptors involved in the innate immune system of microglia [119], promoting the production of pro-inflammatory cytokines and increasing Aβ accumulation [120]. Additionally, LPS can interact with TREM2 to modulate microglial phenotype transition from anti-inflammatory to pro-inflammatory [121]. Therefore, LPS-induced neuroinflammation is also a crucial factor in promoting neurodegeneration and cognitive impairment in AD.

From the perspective of lipid metabolism, research has shown that LPS can induce the expression of microglial Cholesterol 25-hydroxylase (CH25H) [122]. CH25H is an enzyme responsible for hydroxylating cholesterol to produce oxysterol 25-hydroxycholesterol (25-HC), which is upregulated in brain tissues of AD patients, as well as in APP/PS1 and PS19 mouse brain tissues [123]. Regulation of CH25H by LPS results in increased synthesis and release of 25-HC, which in turn activates LXR gene expression and inhibits SREBP expression, enhancing cholesterol esterification and lipid droplet accumulation in astrocytes [124]. Further studies have found that LPS-mediated activation of 25-HC disrupts mouse hippocampal plasticity and memory learning function [122]. Given

the evidence that Gram-negative bacteria and LPS impact various AD pathologies, Gram-negative bacteria and LPS represent attractive novel targets for AD therapy.

#### Trimethylamine N-oxide

The anaerobic bacteria in the gut microbiota, such as *Clostridia* and *Enterobacteriaceae*, degrade carnitine, choline, and lecithin to produce trimethylamine (TMA), which is subsequently oxidized and reduced in the liver to generate Trimethylamine N-oxide (TMAO) [103, 125]. Elevated levels of TMAO have been found in the cerebrospinal fluid of patients with mild cognitive impairment and AD, and are associated with pathological markers of AD including tau phosphorylation, Aβ deposition, and neurodegeneration [126].

TMAO activates the NOD-like receptor protein 3 (NLRP3) inflammasome to induce inflammatory responses through SIRT3-SOD2-mtROS pathway [127]. TMAO also influences lipid and hormone homeostasis, regulates cholesterol and steroid metabolism, and reduces cholesterol reverse transport, thereby promoting the development of various diseases [128]. Furthermore, TMAO affects the tricarboxylic acid (TCA) cycle by decreasing ketone and fatty acid oxidation, thus lowering energy metabolism and inhibiting mitochondrial function. Researchers observed that TMAO promotes the downregulation of synaptic plasticity-related proteins and mTOR signaling pathway expression, leading to mitochondrial damage and superoxide production, impairing synapses, and causing a decline in mice cognitive function [129]. Decreasing plasma TMAO levels has been shown to reduce the expression of pro-inflammatory cytokines IL-2, IL-17, and TNF-α, alleviate the hippocampal inflammation in APP/PS1 mice, and improve the cognitive ability and pathological progression [130].

#### Tryptophan catabolites

Tryptophan (TRP), an indispensable aromatic amino acid obtained from dietary source [131], undergoes regulation by the intestinal microbiota [132]. Through liquid chromatography metabolomics analysis, significant differences were found in tryptophan catabolites (TRYCATs) between AD patients and healthy controls, indicating a link between cognitive impairment in AD patients and dysregulated tryptophan metabolism resulting from microbial imbalance [91]. TRYCATs have been shown to stimulate neurogenesis in mice through an aryl hydrocarbon receptor (AhR)-dependent manner [133, 134]. Furthermore, AhR is intricately linked to sphingolipid metabolism, as it upregulates sphingolipid and S1P levels, thereby contributing to the maintenance of axonal myelination [135, 136]. These findings suggest a potential connection between tryptophan metabolism and sphingolipid metabolism in AD.

Indole, the principal microbial metabolite originating from tryptophan degradation in adult organisms, assumes a crucial neuroprotective role in AD by modulating inflammatory responses, preserving gut barrier integrity, and regulating immune homeostasis [137]. Notably, a diminished abundance of indole-producing bacteria, including *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Lactobacilli*, was observed in AD patients [91], concomitant with a significant reduction in indole levels [138]. Indole-3-propionic acid (IPA), synthesized by *Clostridium sporogenes*, is capable of intestinal absorption and entry into the brain, where it serves to scavenge hydroxyl radicals, reduce DNA damage, and inhibit the formation of amyloid fibrils [137]. Indole compounds exhibit neuroprotective effects due to their antioxidant, anti-inflammatory, immunomodulatory, and anti-amyloidogenic properties, gradually emerging as candidate drugs for improving neurodegenerative diseases. Relevant drug development efforts are currently underway [139]. The indole compound NC009-1 has been shown to improve cognitive deficits of 3× Tg-AD mice by upregulating the expression of APOE and tropomyosin receptor kinase A and reducing the levels of Aβ and tau in the hippocampus and cortex [140].

Besides, metabolomic analyses, both untargeted and targeted, of cerebrospinal fluid (CSF) derived from individuals with AD unveiled a specific dysregulation in the tryptophan-kynurenic acid pathway within the central nervous system. Notably, tryptophan catabolic metabolites, namely kynurenic acid and quinolinic acid, exhibited elevated concentrations in the CSF of AD patients. Moreover, these metabolites demonstrated a robust correlation with the core pathological amyloid proteins Aβ42 and phosphorylated Tau181 [141].

### Gut microbiota metabolites interact with key genes of AD lipid metabolism

Genome-wide association studies (GWAS) have pinpointed risk genes for AD, including apolipoprotein E (APOE), clusterin (also referred to as apolipoprotein J, CLU), and ATP-binding cassette sub-family A, members 1 and 7 (ABCA1/7). These genes play a central role in lipid metabolism and their alterations contribute to the development of lipid metabolism disorders in AD [142–144]. Furthermore, SREBP-2 is also a key regulator of cholesterol metabolism and is genetically associated with an altered risk of AD [145]. Numerous studies indicates that the gut microbiota and its metabolites interact with these key lipids genes and participate in the pathological progression of AD (Fig. 2). Therefore, this section focuses on summarizing the above-mentioned content.

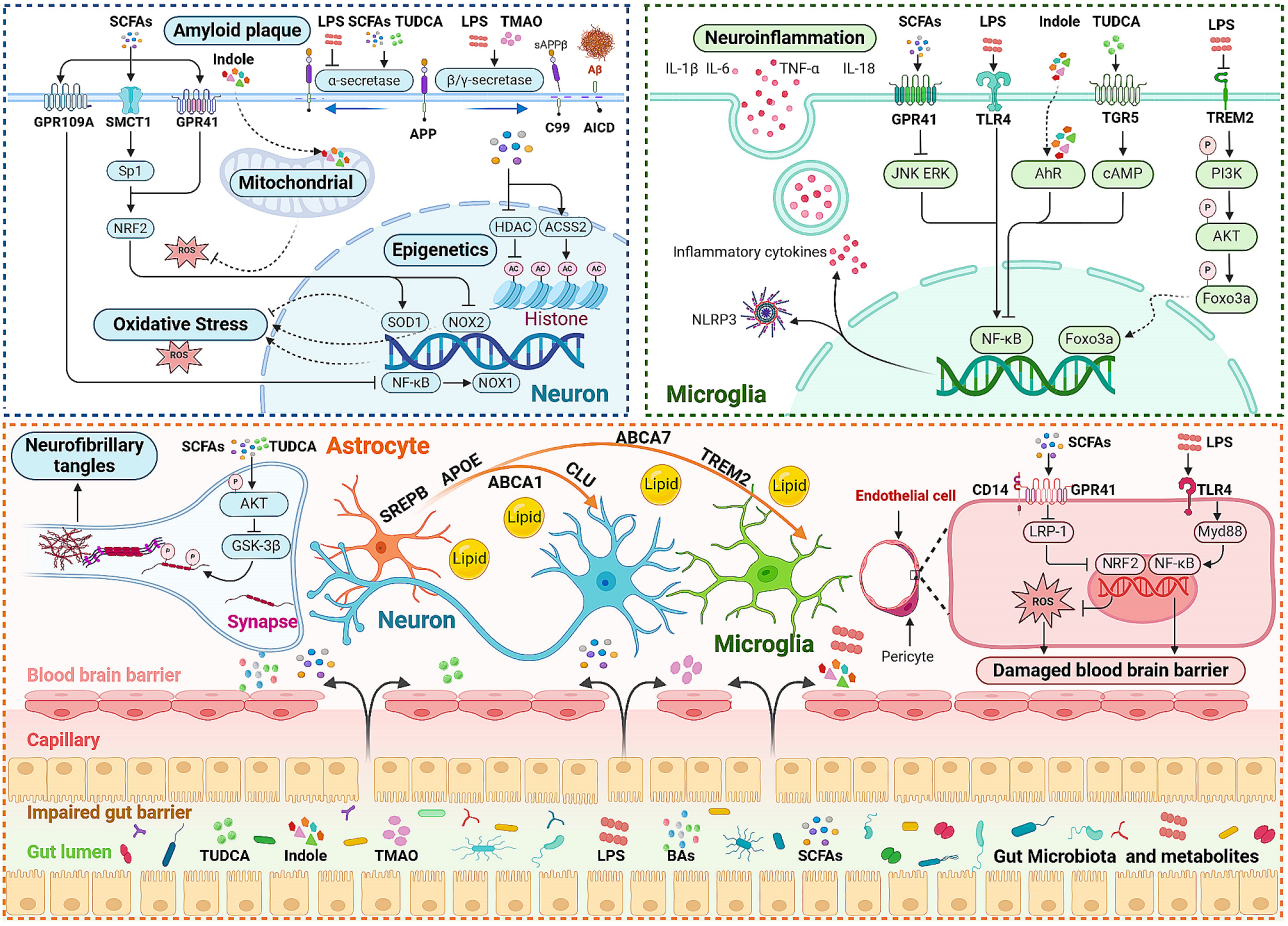


**Fig. 2** The connection mechanisms between gut microbiota and pathology of Alzheimer's disease. The dysregulation of gut microbiota compromises the integrity of the intestinal and blood-brain barriers, allowing gut microbiota metabolites to enter the central nervous system and participate in the pathological processes of Alzheimer's disease (AD). Astrocytes within the central nervous system synthesize lipids through key genes such as SREBP, APOE, ABCA1, CLU, ABCA7, TREM2, transferring them to neurons and microglial cells. Microbial metabolites can interact with these genes, influencing lipid homeostasis. Furthermore, gut microbiota metabolites primarily contribute to AD pathology through involvement in Aβ pathology, tau pathology, neuroinflammation, oxidative stress, mitochondrial dysfunction, and epigenetic regulation. SCFAs binding to GPR41, dependent on CD14 expression, inhibits NRF2 signaling, reducing oxidative stress in endothelial cells, maintaining the blood-brain barrier. In contrast, LPS binding to TLR4 promotes Myd88 expression, activating NF-κB transcription, releasing pro-inflammatory cytokines, damaging the blood-brain barrier. For Aβ Pathology: LPS reduces α-secretase activity, promoting APP production, while both LPS and TMAO upregulate BACE-1 and γ-secretase activities, enhancing Aβ production. SCFAs and TUDCA promote α-secretase activity and inhibit Aβ generation. Tau Pathology: SCFAs and TUDCA inhibit GSK-3β activity by promoting AKT phosphorylation, thereby suppressing tau phosphorylation, and reducing NFTs formation. Neuroinflammation: SCFAs upregulate GPR41 expression, inhibit the ERK/JNK/NF-κB pathway, reducing COX2 and IL-1β levels, alleviating neuroinflammation. TUDCA binds to the TGR5 receptor in microglial cells, increases cAMP levels, inhibits the NF-κB pathway, induces an anti-inflammatory phenotype, and mitigates inflammation. Indole reduces NLRP3 inflammasome expression through the AhR/NF-κB pathway, decreasing the release of inflammatory factors TNF-α, IL-6, IL-1β, and IL-18, inhibiting microglia-induced neuroinflammation. TREM2 activates the PI3K/AKT/Foxo3a pathway, suppressing the inflammatory response. Conversely, downregulation of TREM2 expression by LPS leads to an increased inflammatory response. LPS also activates TLR4 and NF-κB transcription, leading to the release of pro-inflammatory cytokines TNFα, IL-6, and IL-1β. Oxidative Stress and Mitochondrial Function: SCFAs binding to GPR109A blocks NF-κB signaling, reducing neuronal oxidative stress levels. SCFAs binding to sodium-coupled monocarboxylate transporter 1 (SMCT1) or activating GPR41 promotes NRF2, leading to increased SOD1 production and inhibition of NOX2, preventing excessive accumulation of neuronal ROS. Indole binds to respiratory chain complex enzymes, reducing mitochondrial electron leakage, neutralizing hydroxyl radicals, and inhibiting ROS production. Epigenetic Regulation: SCFAs inhibit HDAC activity, promoting excessive acetylation of histone H3K18, improving cognition. Alternatively, SCFAs promote histone acetylation, restoring synaptic plasticity and cognitive function in an ACSS2-dependent manner

## APOE

APOE functions as a lipid transport protein with a crucial role in the central nervous system, and its significance and functions in the context of Alzheimer's disease have been extensively documented in numerous research studies [146–149]. APOE facilitates the transport of cholesterol and lipids between astrocytes and neurons by interacting with the low-density lipoprotein receptor (LDLR) and LDLR-related protein 1 (LRP1). This mechanism is pivotal in synaptic formation and tissue repair

processes [147]. With its three main isoforms, APOE exhibits a range of effects. APOE2 exhibiting a protective effect, APOE3 playing a neutral role, while the APOE4 allele increases the risk of developing AD by approximately 12 times in homozygous individuals [150]. Consequently, APOE4 is considered the most potent risk factor for late-onset Alzheimer's disease (LOAD) [114, 151, 152].

In-depth analyses of the gut microbiota in AD mice with different APOE genotypes, utilizing 16S rRNA sequencing and fecal metabolomics, have revealed correlations between APOE genotypes and the abundance of gut microbiota. Specifically, APOE2 genotype mice displayed higher levels of *Ruminococcaceae* and *Prevotellaceae*, bacterial families involved in SCFAs production. This is thought to contribute to the protective effect of the APOE2 genotype against AD. In APOE4 genotype AD mice, an increase in *Lachnospiraceae* and *Deferribacteraceae*, and a decrease in *Bacteroidaceae* were observed, accompanied by reduced concentrations of SCFAs and their precursors [153]. These findings suggest that APOE genotypes influence the composition of the gut microbiota and the generation of metabolites in AD mice. Changes of microbiota and metabolites induced by different APOE genotypes may play an important role in the impact of APOE genes on AD. Carriers of the APOEε4 allele often experience disturbances in CNS cholesterol homeostasis, and APOE4 mice also exhibit abnormal cholesterol levels and lipid metabolism disruptions [153]. This suggests that the gut microbiota and SCFAs may influence CNS cholesterol levels by affecting APOE gene.

Moreover, the microbiota and its metabolites also influence APOE genes. For instance, the microbiota-produced secondary bile acid TUDCA reduce the expression of APOE in the hippocampus and frontal cortex, inhibiting the production and accumulation of Aβ [154]. In the presence of melatonin, APOE4's characteristics shift from promoting amyloid fibril formation to inhibiting it [137]. Additionally, the gut microbiota reduces neuroinflammation, tau pathology, and neurodegeneration in an APOE genotype-specific manner [100]. These findings highlight the significant interplay between the microbiota, its metabolites, and APOE genes in AD.

#### TREM2

TREM2 is a transmembrane receptor of the immunoglobulin superfamily specifically expressed in microglial cells of the central nervous system. It plays a role in microglial proliferation, transportation, phagocytic functions, and inflammatory responses [155, 156]. When functional loss mutations, such as R47N, R62H, and D87N, occur in TREM2, the risk of developing LOAD increases. These mutations result in reduced cholesterol clearance by microglial cells, decreased uptake of CLU, LDL, and Aβ, exacerbating cholesterol lipid accumulation, amyloid pathology, and neuronal damage [81, 157–159].

Research has reported a close association between bacterial anionic LPS and TREM2. LPS bind to TREM2 [160], promoting the transition of microglial cells from an anti-inflammatory phenotype to a pro-inflammatory phenotype [161]. A study in BV2 cells confirmed that LPS reduces TREM2 expression, promotes the translocation of Foxo3a from the cytoplasm to the nucleus, triggering an inflammatory response. Conversely, upregulation of TREM2 expression can activate the PI3K/AKT/Foxo3a axis, inhibiting pro-inflammatory factors and shifting microglial cells toward an M1 phenotype [162]. Moreover, TREM2 facilitates the expression of Sirtuin3, suppressing LPS-induced oxidative stress and neuroinflammation [163]. The deletion of TREM2 results in a substantial increase in inflammatory mediators, including Cxcl10, Rac2, and Casp1, upon exposure to LPS, thereby fostering the initiation of inflammatory responses [164].

#### ABCA1/7

ATP-binding cassette subfamily A (ABCA) belongs to the ATP-binding cassette transporter family, mediating the export of cholesterol and phospholipids in the brain. Notably, rare variants of ABCA1 and ABCA7 have been identified as risk genes for AD [64]. ABCA1 transports cholesterol, phospholipids, and other lipid molecules to lipoprotein carriers [165] and facilitates the distribution of cholesterol from astrocytes to neurons, protecting cells from the toxic effects of excessive free cholesterol [166]. Simultaneously, ABCA1 is responsible for lapidating the APOE protein in the brain. The deficiency of ABCA1 results in impaired APOE lipidation, leading to increased Aβ plaque load, while overexpression of ABCA1 can reduce Aβ deposition [167, 168]. Research indicates that the gut microbiota metabolite butyrate activates the expression of ABCA1, promoting cholesterol efflux, thereby improving lipid metabolism in APOE$^{-/-}$ mice [169]. TMAO has been demonstrated to downregulate the expression of ABCA1, promoting cholesterol accumulation [170, 171].

ABCA7, sharing 54% homology with ABCA1, is currently recognized for its involvement in facilitating lipid transport from neurons to glial cells, providing protection to neurons against oxidative lipid damage. Ongoing research suggests that ABCA7 also plays a crucial role in cholesterol transport and phagocytosis by microglial cells [172, 173]. Conversely, the absence or functional impairment of ABCA7 may intensify fatty acid consumption, disturb brain inflammatory responses, reduce microglial phagocytic function, and elevate Aβ levels [49, 174].

Furthermore, in the setting of LPS-induced brain inflammation, ABCA7 haplodeficiency enhances the production of EPA during the acute inflammatory phase, thereby facilitating the resolution of acute inflammation [175].

#### CLU

CLU, alternatively referred to as apolipoprotein J, demonstrates predominant expression within the central nervous system and holds a pivotal role in cholesterol and lipid transport. Genome-wide association studies have established a significant association between CLU allelic variations and the susceptibility to AD. In comparison to control counterparts, AD patients manifest notably increased CLU levels, and empirical evidence supports the direct interaction of CLU with Aβ, thereby facilitating the formation of Aβ fibrils [176].

Researchers have observed that the deletion of the CLU gene alters the abundance and composition of the gut microbiota, characterized by an increase in *Bacteroidetes* and a decrease in *Firmicutes*, indicating a close association between CLU and the gut microbiota [177]. Increased TMAO levels induce elevated CLU protein expression, consequently triggering neuroinflammation and the production of β-secretase and βCTF in the hippocampus, resulting in Aβ deposition. Conversely, the inhibitor 3,3-Dimethyl-1-butanol reduces TMAO levels, inhibits CLU protein expression, and improves hippocampal inflammation and cognition [130]. Treatment with *Lactobacillus plantarum* has been demonstrated to inhibit the production of gut microbiota-derived TMA and synthesis of TMAO, leading to reduced CLU expression, alleviation of cognitive impairment, and attenuation of neuropathology [178]. Currently, limited evidence supports the connection between CLU and the gut microbiota, necessitating further exploration of their relationship and the roles they play in the progression of AD. Considering the reduction of TMAO production via microbial modulation may offer a potential avenue for mitigating CLU-mediated lipid homeostasis in AD.

#### SREBP-1/2

Sterol regulatory element-binding proteins (SREBPs) function as transcription factors, modulating the expression of genes associated with lipid synthesis. There are three isoforms of SREBP in mammals: SREBP1a, contributing to overall lipid synthesis and growth; SREBP1c, associated with fatty acid synthesis and energy storage; and SREBP2, playing a role in cholesterol regulation [179, 180]. The overexpression of SREBP-2 in APP/PS1 mice has been reported to exacerbate amyloid pathology and neuronal death, accompanied by a decline in cognitive abilities, while the inhibition of SREBP-2 alleviates amyloid burden in AD mice [181, 182]. Additionally, another study validates that SCFAs can enhance the gene expression of SREBP2, consequently facilitating hepatic absorption of serum cholesterol and augmenting the excretion of fecal bile acids [183]. In 3×Tg-AD mice, elevated expression of SREBP1c results in increased cholesterol synthesis. Treatment with the probiotic SLAB51 reduces the protein expression of SREBP1c in the brain and liver, thereby improving the lipid profile and cognitive function [46].

## Molecular mechanisms of gut microbiota regulation of AD lipids and pathology

The mechanistic links between lipid metabolism dysregulation and AD include amyloid pathology, tau pathology, neuroinflammation, oxidative stress, and mitochondrial dysfunction. Additionally, the gut microbiota can directly or indirectly participate in the pathological mechanisms of AD by influencing lipid metabolism (Fig. 2). This section focuses on presenting evidence for the role of gut microbiota in the mechanisms of AD lipids and pathology.

#### Amyloid pathology

The abnormal deposition of amyloid is a central pathological feature of AD [184]. Aβ, a peptide with a length of 36–43 amino acid residues, is generated through consecutive cleavages of APP by β-secretase (mainly BACE1) and γ-secretase [185, 186], with Aβ40 and Aβ42 being the most common in AD. The activities of β-secretase and γ-secretase are highly dependent on the lipid levels in the membrane, emphasizing the close connection between Aβ pathology and lipids [186]. Certainly, the generation of Aβ takes place within specialized membrane microdomains called lipid rafts, which are enriched with cholesterol, phospholipids, and sphingolipids [186, 187]. Increased brain cholesterol levels boost the activity of β-secretases and γ-secretases within lipid rafts, suppress α-secretase activity, and stimulate the generation of harmful Aβ [185]. Aggregates of Aβ can directly engage with cell membrane lipids and cholesterol, disrupting membrane integrity and permeability, fostering $Ca^{2+}$ influx, ultimately resulting in neuronal death [188].

Research indicates that BAs produced by gut microbiota increase the permeability of both the intestinal and blood-brain barriers [189], facilitating the entry of peripheral cholesterol into the central nervous system. The elevated brain cholesterol directly binds with APP, promoting the insertion of APP into the lipid raft phospholipid layer and consequently increasing the production of Aβ. Moreover, BAs downregulate the expression of cholesterol-metabolizing enzyme CYP46A through the farnesoid X receptor (FXR), promoting cholesterol accumulation and increasing Aβ production [190]. LPS, similar to BAs, have been shown to enhance the expression of APP, reduce the activity of α-secretase,

upregulate the activity of APP-cleaving enzyme BACE-1 and γ-secretase, promoting Aβ generation [115]. Furthermore, the gut microbiota metabolite TMAO has been implicated in promoting Aβ accumulation in AD mice by increasing the activity of β-secretase through elevating CLU levels, leading to cognitive impairment [130].

#### Tau pathology

Tau pathology is initiated by the aggregation of phosphorylated tau into oligomers, protofibrils, and filamentous NFTs, leading to synaptic damage and neurodegeneration [191, 192]. Hence, tau pathology is also considered a major driving factor in the neurodegenerative changes associated with AD [1]. Evidence suggest that cholesterol and lipoprotein particles impact the excessive phosphorylation of tau in neurons [193]. Further investigations reveal that CE induce tau phosphorylation through the CE-proteasome-tau axis. Inhibiting cholesterol synthesis in astrocytes significantly reduces the neuronal tau burden [67, 193]. These studies confirm that disrupted cholesterol metabolism influences tau pathology of AD.

In a recent study, researchers subjected tau transgenic mice expressing different APOE isoforms to GF housing and antibiotic interventions. They found that modulation of gut microbiota reduced tau pathology, and neurodegeneration in an APOE genotype-dependent manner. Supplementation with SCFAs exacerbated tau pathology in GF-TE4 mice [100]. Additionally, increased abundance of the *Bacteroides fragilis* upregulates the PUFA metabolites PGE1 and 12-HHTrE, triggering C/EBPβ/AEP signaling activation, and exacerbating tau pathology [194]. *Lactobacillus plantarum* DP189 increases the presence of *Firmicutes* and, through the modulation of the PI3K/AKT/GSK3β pathway, decreases the levels of GSK3β, effectively suppressing tau hyperphosphorylation [195]. TUDCA inhibits the activation of AKT and suppresses GSK3β activity, reducing tau hyperphosphorylation and microglial activation, ultimately improving AD pathology [107].

#### Neuroinflammation

Neuroinflammation is recognized as a crucial characteristic of brain tissue in AD patients, orchestrated predominantly by microglial cells and astrocytes [196]. In this context, misfolded and aggregated proteins bind to pattern recognition receptors, such as Toll-like receptors (TLRs), located on the surfaces of microglial and astrocytic cells, initiating inflammatory responses. Acute inflammatory responses are believed to contribute to the clearance of Aβ, restoring tissue homeostasis. However, sustained inflammation induced by persistent Aβ stimulation and immune activation leads to the continuous release of pro-inflammatory factors and inflammatory mediators, increasing Aβ deposition and promoting the formation of neurofibrillary tangles, thereby exacerbating neuronal and synaptic damage and contributing to the progression of AD [197]. Indeed, the critical role of neuroinflammation in AD has been reported as early as the year 2000 [198].

Current research has elucidated the impact of the gut microbiota on neuroinflammation in AD. The potential connection between the microbiota and AD may involve an imbalance in gut homeostasis, characterized by an increase in inflammatory responses and a reduction in anti-inflammatory microbes [196, 199]. Microbiota analysis in AD patients reveals an increased abundance of pro-inflammatory bacterial groups and a decrease in butyrate-producing taxa such as *Butyrivibrio*, *Eubacterium*, *Clostridium sp. strain SY8519*, and *Faecalibacterium prausnitzii* [200]. In 3×Tg mice, similar phenomenon is observed, where beneficial anti-inflammatory bacterial groups, such as *Firmicutes* and *Cyanobacteria*, gradually decrease with age, while pro-inflammatory taxa, including *Bacteroidetes* and *Ruminococcus*, significantly increase [45]. Furthermore, there is a close association between gut microbiota and their metabolites with the activation of glial cells [201, 202]. Gut microbiota can stimulate glial cells to participate in the neuroinflammatory response in AD [203, 204]. For instance, antibiotic treatment in APP/PS1 mice has been shown to reduce neuroglial reactivity, thereby alleviating Aβ plaque deposition [37, 205]. Acetate has been shown to upregulate the expression of GPR41 in microglial cells, inhibit the ERK/JNK/NF-κB pathway, reduce the levels of COX2 and IL-1β, counteract neuroinflammation in APP/PS1 mice, and improve cognitive abilities [94]. LPS, by activating the microglial cell surface TLR4 receptor, triggers downstream NF-κB transcription, leading to the activation of numerous pro-inflammatory factors such as TNFα, IL-6, and pro-IL-1β [114]. Indole acts through the AhR-NF-κB pathway, decreasing the expression of NLRP3 inflammasomes, reducing the release of inflammatory cytokines TNF-α, IL-6, IL-1β, and IL-18, alleviating inflammation, and improving cognitive and behavioral abilities in APP/PS1 mice [138].

The gut microbiota may influence neuroinflammatory responses in AD by affecting lipid metabolism. In brief, activation of the C/EBPβ/AEP signaling pathway by the gut microbiota in the brains of 3×Tg mice upregulates mRNA transcription for inflammatory enzymes related to AA [206], resulting in increased release of AA metabolites such as prostaglandin E2 (PGE2), thromboxane B2, LKB4, and 12-HHT. This activation triggers microglial cell activation and intensifies neuroinflammation, ultimately worsening cognitive impairment. Further investigations revealed that specific gut bacteria, including *Bacteroides intestinalis*, *Bacteroides fragilis*,

and *Bacteroides xylanisolvens*, produce AA metabolites and contribute to AD neuroinflammatory responses. Conversely, a decrease in the abundance of anti-inflammatory SCFAs, due to reduced levels of *Butyrivibrio* and *Eubacterium*, exacerbates chronic neuroinflammation, elevates APP and tau expression levels, and contributes to AD pathogenesis [45]. In a recent study, the authors identified that *Bacteroides fragilis* and its metabolites, 12-hydroxy-17-carbon-triene acid and PGE2, mediate PUFA metabolism in the gut microbiota of AD. This activation leads to microglial cell induction of AD-like pathology and cognitive impairments [194], providing compelling evidence for the role of gut microbiota in regulating AD lipid metabolism and neuroinflammation.

#### Oxidative stress

Oxidative stress refers to the imbalance in cellular redox equilibrium caused by the accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS play a vital role in normal physiological conditions by participating in signaling pathways and transcriptional activation. Nevertheless, continuous accumulation of ROS, coupled with compromised cellular antioxidant capacity, can result in the assault on cellular macromolecules such as lipids, proteins, and DNA. This process leads to lipid peroxidation, protein oxidation, and nucleic acid damage [207, 208]. Concurrently, inflammation and mitochondrial dysfunction disturb redox balance, fostering the generation and release of ROS [209]. The elevation of ROS and oxidative stress is recognized as one of the hallmarks of AD.

The central event of oxidative stress is lipid peroxidation, and the brain, rich in polyunsaturated fatty acids, is susceptible to oxidative stress due to lipid peroxidation [210]. SCFAs play a crucial role in regulating lipid peroxidation. For example, butyrate enhances fatty acid oxidation, electron transport chain, and oxidative stress gene expression, while propionate interacts with fatty acid receptors, upregulating lipoprotein lipase to promote lipid synthesis [211, 212]. Acetate is involved in regulating cholesterol metabolism and adipogenesis [213]. Thus, existing evidence supports the role of gut microbiota in mediating oxidative stress alterations in AD [208]. Propionate bind to the free fatty acid receptor GPR41 in brain endothelial cells, inhibiting the expression of LRP-1 through a CD14-dependent mechanism, and protecting the blood-brain barrier from oxidative stress through NRF2 signaling [95]. Butyrate act as ligands for GPR109A, and by activating GPR109A, they block the NF-κB signaling pathway [212], a crucial pathway in oxidative stress in AD [214, 215]. Additionally, cells uptake butyrate through the sodium-coupled monocarboxylate transporter 1 (SMCT1), leading to the generation of Sp1. This activation of Sp1 stimulates NRF2, thereby promoting the production of SOD1 and suppressing NOX2, preventing the excessive accumulation of reactive ROS in neurons [216]. Indole derivative IPA, an effective scavenger of hydroxyl radicals, protects central neurons from oxidative damage by reducing DNA damage and lipid peroxidation [212].

#### Mitochondrial dysfunction

Various pieces of evidence indicate that mitochondrial dysfunction is an early event in the pathogenesis of AD, including alterations in mitochondrial structure, respiratory dysfunction, reduced ATP generation, impaired dynamics, and elevated mitochondrial-associated oxidative stress [192, 217, 218]. Mitochondrial dysfunction leads to the release of cytochrome c, which activates Caspase-9-dependent neuronal apoptosis, disrupting $Ca^{2+}$ homeostasis and triggering neuronal death. The association between the gut microbiota and mitochondria has been extensively documented over an extended period [219, 220]. Microbial metabolite N6-carboxymethyllysine (CML) mediates ROS burst, damaging mitochondrial activity and ATP storage in microglial cells [221]. Butyrate enhances mitochondrial biogenesis in astrocytes by upregulating the expression of PGC-1A, contributing to improved mitochondrial function and enhanced cognitive abilities in AD mice [222]. IPA and indole-3-propionamide (IPAM) exert neuroprotective effects by mitigating mitochondrial electron leakage and neutralizing hydroxyl radicals. Moreover, indole compounds, including IPA and IPAM, permeate the mitochondrial membrane, binding to the rate-limiting phosphorylation site on respiratory chain complex I. This action serves as an energy metabolism stabilizer, leading to a reduction in ROS production and contributing to neuroprotection [137].

#### Epigenetic regulation

Epigenetic regulation encompasses processes such as histone modification, DNA methylation, chromatin remodeling, and non-coding RNA regulation, all of which have been demonstrated to play a crucial role in neurodegenerative diseases [92, 93]. It is well-established that the expression levels of key proteins implicated in AD, including APP, BACE1, PS1, and APOE, are subject to epigenetic regulation. Therefore, the imbalance in epigenetic regulation may underlie the aberrant expression of genes associated with synaptic plasticity and memory in AD [223]. Histone modification is a common form of epigenetic regulation in AD, influencing the stability of nucleosomes, chromatin-mediated processes to participate in the regulation of gene expression. Histone modification encompasses acetylation, methylation, ubiquitination, among others, with acetylation playing a crucial role in AD [224]. Research has revealed a reduction in H4K12 histone acetylation levels in aged

mice, leading to defects in the expression of learning and memory-related genes [225]. Histone acetylation is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). In AD mice and patients, the expression of HDAC2 increases with age [226]. HDAC2 overexpression reduces dendritic spine density, impairs neural plasticity and memory function, and suppressing or downregulating HDAC expression effectively restores cognitive function in AD animals [227].

Butyrate is described as a HDAC inhibitor, improving memory function in APP/PS1 mice by enhancing hippocampal histone acetylation [96]. Acetate enhances histone H3K18 over-acetylation and epigenetic regulation of BDNFPII and PIV promoter regions, leading to increased expression of BDNF and improvement in cognition [97]. Furthermore, acetate supplementation, as demonstrated in 5×FAD mice, enhances histone acetylation, restoring synaptic plasticity and cognitive function in an ACSS2-dependent manner [228]. Studies have reported that the immature phenotype of microglia in GF mice arises from epigenetic markings of key mitochondrial genes by H3K4me3 and H3K9ac, accompanied by intracellular fatty acid and lipid depletion. Acetate, driving microglial maturation and metabolic homeostasis, can rescue the impaired microglial function in GF mice. In the pathological context of AD, acetate exhibits inhibitory effects on microglial phagocytic function, leading to increased Aβ burden in 5×FAD mice [99].

## Targeting gut microbiota and lipids for the treatment of AD

Given the evidence supporting the role of gut microbiota and lipid metabolism in the pathological progression of AD, it becomes crucial to understand how modulating the levels of microbiota and metabolites to improve AD pathology. Therefore, this section summarizes the primary preventive and therapeutic interventions aimed at regulating gut microbiota and lipid metabolism (Fig. 3).

### Gut microbiota-based therapy

#### *Probiotics*

Probiotics, as live microbial supplements, have been shown to effectively improve gut microbiota balance and provide therapeutic benefits for patients with AD [229]. Studies have demonstrated the therapeutic effects of SLAB51 on AD, it improves glucose homeostasis, reduces tau phosphorylation [230], increases SCFAs such as acetate, propionate, and butyrate, while decreasing inflammation and Aβ deposition [231]. It activates a SIRT1-dependent mechanism, reducing oxidative stress in the brains of AD mice [232]. Another study found that SLAB51 inhibits cholesterol biosynthesis, lowers the ω-6/ω-3 fatty acid ratio, improves neuroinflammation and oxidative stress, ultimately reducing Aβ and tau aggregation, and slowing down AD progression [46]. Candida rugosa lipase (CRL) has been reported to increase the abundance of *Acetatifactor* and *Clostridiales vadin BB60* in the gut, enhancing lipid hydrolysis and maintaining unsaturated fatty acid homeostasis, leading to reduced neuroinflammation and cognitive deficits in APP/PS1 mic [233]. *Lactobacillus plantarum* DP189 regulates gut microbiota dysbiosis and inhibits tau hyperphosphorylation, as reported [195]. Additionally, it suppresses TMA production and TMAO synthesis, thereby reducing CLU expression and alleviating neuroinflammation and neuropathological defects in APP/PS1 mice [233]. The probiotic VSL#3 efficiently reduces serum prostaglandin and deoxycholic acid levels, ameliorating intestinal inflammation and permeability. Nonetheless, its influence on brain plaque deposition, cytokine levels, and gliosis appears to be relatively limited [234]. Synthesizing this evidence with findings from other studies implies that combining probiotics with exercise could represent a more promising therapeutic strategy for enhancing cognitive function [235, 236]. In summary, probiotics modulate gut microbiota composition and lipid metabolism homeostasis, exerting positive effects on brain inflammation, oxidative stress, Aβ pathology, and tau pathology. Therefore, by regulating the microbial composition through probiotics, new preventive and therapeutic options for AD are proposed.

#### *Prebiotics*

Prebiotics, composed of nondigestible oligosaccharides, human milk oligosaccharides, and soluble, fermentable fibers, serve as an alternative to probiotic supplements. They effectively enhance beneficial bacteria such as *Bifidobacteria* and *Lactobacilli*, improving cognitive impairment in APP/PS1 mice through the gut-brain axis [237, 238]. The neuroprotective effects of prebiotics make them a potential oral formulation for the prevention and treatment of AD [239]. Fructooligosaccharides (FOS) demonstrate beneficial effects in APP/PS1 mice [190], and prebiotic mannan oligosaccharide (MOS) reshapes the gut microbiota, maintains intestinal barrier integrity, increases SCFAs production, inhibits neuroinflammation and oxidative stress, effectively alleviating cognitive and behavioral deficits in 5×FAD mice [240]. In conclusion, supplementing prebiotics to modulate microbial composition and function holds promise for improving AD; however, further research is needed to explore the applicability of prebiotics in AD treatment.

#### *Fecal microbiota transplantation*

Fecal microbiota transplantation (FMT) involves transferring a sample of healthy donor fecal microbiota into the gut of a patient or diseased animal to restore gut microbial health and improve disease treatment. Studies

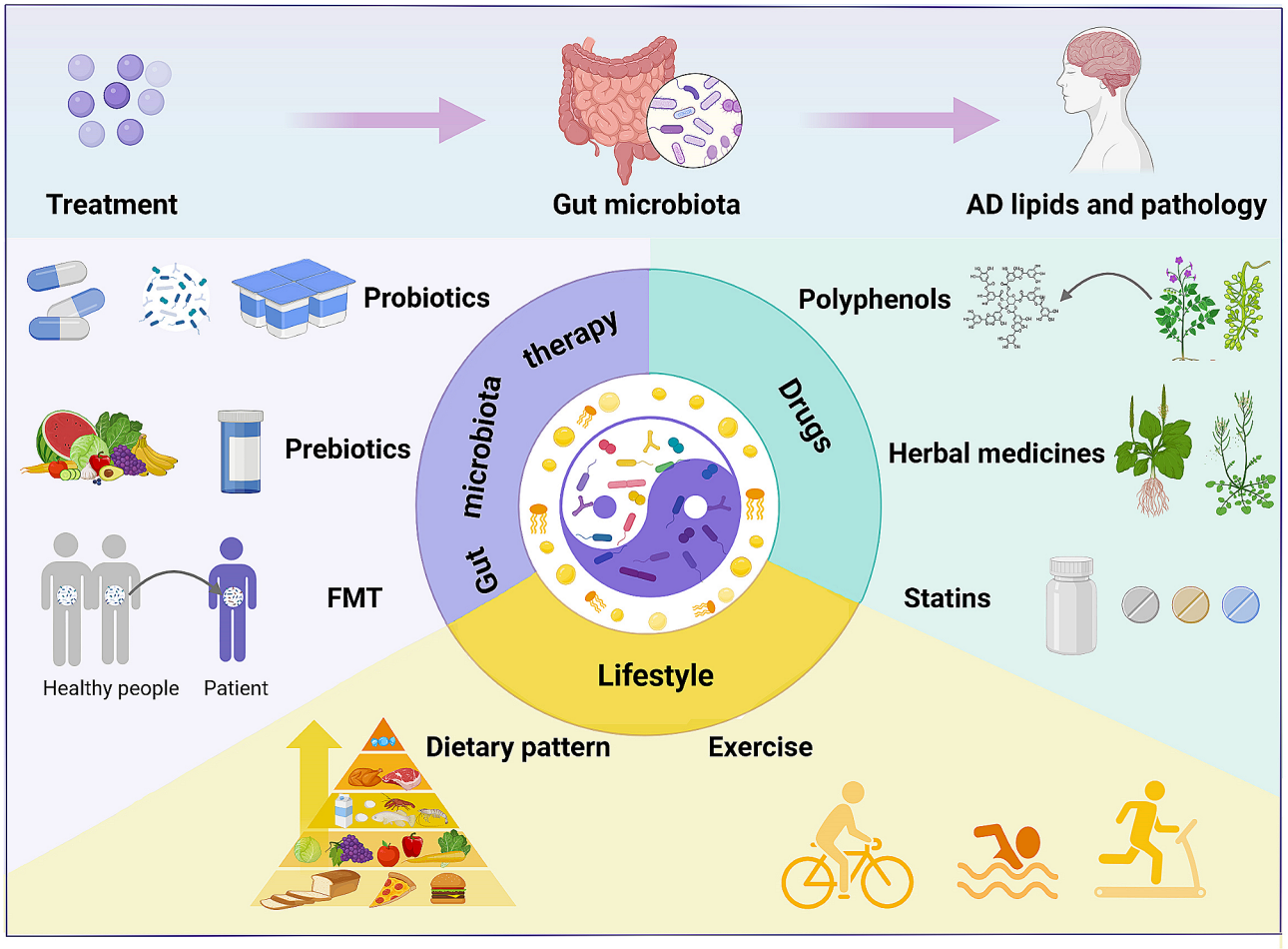


**Fig. 3** Potential interventions in the gut microbiota to regulate lipid balance and mitigate pathological progression in Alzheimer's disease. Current evidence suggests that interventions such as gut microbiota-based therapies (probiotics, prebiotics, fecal microbiota transplantation), pharmacological treatments (polyphenols, herbal remedies, statins), and lifestyle modifications (dietary patterns, exercise) can target the gut microbiome. These interventions promote gut microbiota and lipid homeostasis, ultimately enhancing cognitive function. These measures hold promise as potential strategies for preventing and treating the progression of Alzheimer's disease

have shown that transplanting fecal microbiota from wild-type mice to ADLP$^{APT}$ mice effectively ameliorated Aβ plaques, neurofibrillary tangles, glial reactivity, and cognitive impairment, suggesting that restoring gut microbial homeostasis through FMT may have beneficial effects on AD treatment [40]. Another study confirmed that fecal transplantation from WT mice increased the abundance of *Bacteroidetes*, reduced *Proteobacteria* and *Verrucomicrobia* in the gut of APP/PS1 mice, increased butyrate levels, and significantly improved pathological features such as Aβ accumulation, synaptic dysfunction, neuroinflammation, and cognitive deficits [241]. Intervention with FMT from WT mice modulate glycerophospholipid metabolism in APP/PS1 mice, leading to an amelioration of Aβ pathology and neuroinflammation [43]. Conversely, transplanting gut microbiota from AD mice impaired memory function and neurogenesis in wild-type mice [242, 243]. Although the specific functions of the gut microbiota in these contexts are not yet fully elucidated, based on these results, healthy gut microbiota transplantation appears to exhibit a positive role in AD pathology. Table 1 summarizes current research on the gut microbiota-based therapy in improving AD lipid metabolism and pathological features.

## Pharmaceutical formulation

### Polyphenols

Polyphenols, natural compounds found in fruits and vegetables, possess antioxidant and anti-inflammatory properties. It has been demonstrated that they improve the pathological processes of AD by modulating microbiota homeostasis, mitochondrial function, oxidative stress, and inflammatory responses [250]. Oral administration of 200 mg/kg hawthorn flavonoid (HF) increased the proportion of *Dubosiella* and *Alloprevotella*, reversing gut

**Table 1** Current research on the gut microbiota-based therapy in improving AD lipid metabolism and pathological features

| Intervention | Model | Alterations of GM | Alterations of lipids | Main effects | Reference |
|---|---|---|---|---|---|
| VSL#3 | APP NL-GF mice | *Verrucomicrobia*↑, *Actinobacteria*↑, Taurodeoxycholic acid↓ | PGE2↓, 6-keto PGF1α↓, PGF2α↓, AA↑ | Regulate inflammation response | [234] |
| *L. plantarum* | APP/PS1 mice | TMA↓, TMAO↓ | CLU↓ | Alleviate neuroinflammation, reduce hippocampal Aβ levels, improve cognitive | [178] |
| SLAB51 | 3×Tg-AD mice | *Bifidobacterium spp.*↑, *Campylobacterales*↓, Acetic acid↑, Propionic acid↑, Butyric acid↑ | High-density lipoprotein cholesterol↑, stearic acid↑, heptadecanoic acid↑, low-density lipoprotein cholesterol↓, oxysterol 27-hydroxycholesterol↓, total cholesterol↓, ω-6/ ω-3 PUFAs ratio↓ | Improve glucose metabolism, ameliorate lipid metabolism disorders, alleviate inflammatory responses, reduce cerebral oxidative stress, decrease Aβ deposition, and enhance cognition | [46, 230–232] |
| *Bifidobacterium breve* strain A1 | Aβ injection mice | *phylum Actinobacteria*↑, *family Bifidobacteriaceae*↑, *family doribacteraceae*↓, *Lachnospiraceae*↓, acetate↑ | SCFAs↑ | Suppress inflammation and immune response, enhance cognitive, | [244] |
| NK46 | 5×FAD-Tg mice | *Prevotellaceae*↑, *Ruminococacea*↓, *Lachnospiraceae*↓, *Helicobacteriaceae*↓, *Pseudomonadaceae*↓, LPS↓ | SCFAs↑ | Inhibit inflammatory responses, reduce Aβ production and accumulation, alleviate memory and cognitive decline | [245] |
| Human *Lactobacillaceae* | APP/PS1 mice | *Bacteroidetes*↑, *Staphylococcus*↑, *Acinetobacter*↑, *Weissella*↑, *Butyricicoccus*↑, *Sphingobacterium*↑, *Proteobacteria*↓, *Desulfobacterota*↓, *Patescibacteria*↓, *Eisenbergiella*↓ | Malondialdehyde↓ | Reduce oxidative stress, attenuate microglia activation, improved the cognitive deficiencies | [246] |
| *Bifidobacterium Lactis* Probio-M8 | APP/PS1 mice | *Desulfovibrionaceae*↑, *Oscillospira*↑, *Coprococcus*↑, *Clostridiales*↑, *acidifaciens*↑, *Adlercreutzia*↓, *Lactobacillus*↓,*Streptococcus*↓ | fatty acid biosynthesis↑, SCFAs↑ | Reduced Aβ plaque burden, protected against gut microbiota dysbiosis, alleviate cognitive impairment | [247] |
| *Clostridium butyricum* | APP/PS1 mice | *Alloprevotella*↑, *Deferribacteres*↓, *Helicobacteraceae*↓, *Helicobacter*↓, butyrate↑ | SCFAs↑ | Ameliorated microglia activation, neurodegeneration, Aβ deposition and cognitive deficits | [248] |
| Mannan oligosaccharide | 5×FAD-Tg mice | *Prevotella*↑, *Oscillospira*↑, *Lactobacillus*↑, *Helicobacter*↓, butyrate↑,LPS↓ | SCFAs↑ | Ameliorated microglia activation, neurodegeneration, Aβ deposition and cognitive deficits | [240] |
| Morinda officinalis | APP/PS1 mice | *Arthrobacter*↑, *Phycicoccus*↑, *Streptococcus*↑, *Akkermansia*↑, *Blautia*↑, *Ruminococcus*↑, *Coprococcus*↑, *Allobaculum*↑, *Dehalobacterium*↑, *Methanolinea*↑, *Candidatus Methanoregula Lactobacillus*↑, *Allobaculum*↑, *Lactobacillaceae*↑, *Lachnospiraceae*↑, *Mucispirillum*↓, *Odoribacter*↓, *Rikenella*↓, *Faecalibacterium*↓, *Alistipes*↓, *Parabacteroides*↓, *Anaerotruncus*↓ | linolelaidic acid↑, LysoPC↑, LysoPE↑, 15(S)-hydroxyeicosatrienoic acid↓ | Reduce neuronal apoptosis, improve memory | [249] |

**Table 1** (continued)

| Intervention | Model | Alterations of GM | Alterations of lipids | Main effects | Reference |
|---|---|---|---|---|---|
| FMT | APP/PS1 mice | *Bacteroidetes*↑, *Proteobacteria*↓, *Verrucomicrobia*↓, butyrate↑ | SCFAs↑ | Relieved cognitive deficits, Aβ accumulation, synaptic dysfunction and neuroinflammation | [241] |
| FMT | APP/PS1 mice | / | 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine↓, PC (16:0/16:0) ↓ | Decreased Aβ plaque, proliferation and activation of astrocyte and microglia | [43] |

**Abbreviations**: AA=Arachidonic acid; AD=Alzheimer's disease; Aβ=amyloid β; CLU=Clusterin; FMT=Fecal microbiota transplantation; LPS=Lipopolysaccharides; PC=Phosphatidyl choline; PGE2=Prostaglandin E2; PGF1α=Prostaglandin f1alpha; PGF2α=Prostaglandin F2alpha; SCFAs=Short-chain fatty acids; TMA=Trimethylamine; TMAO=Trimethylamine N-oxide

microbiota and metabolic disturbances in AD mice. This led to elevated levels of docosapentaenoic acid (DPA), sphingolipids, and PC, significantly ameliorating cognitive deficits, Aβ accumulation, and abnormal activation of hippocampal astrocytes in AD mice [251]. Curcumin reduced the abundance of *Prevotellaceae*, *Bacteroides*, and *Escherichia/Shigella* in the gut of APP/PS1 mice. In BV2 microglial cells, it upregulated the expression of TREM2, alleviating neuroinflammation and amyloid plaque burden, thereby enhancing cognition [252, 253]. Bilberry anthocyanins (BA) lowered serum and brain LPS levels, increased SCFAs in feces, induced microglial phagocytosis of Aβ through the CD33/TREM2/TYROBP signaling pathway, alleviated hippocampal neuroinflammation, and reversed cognitive impairments in APP/PS1 mice [254]. In conclusion, the interaction of polyphenols with the gut-brain axis enables them to influence the central nervous system and exert neuroprotective activity. Further development of their therapeutic potential in AD is warranted.

#### *Herbal medicines*

Herbal medicines (HMs), also known as botanical medicines or phytomedicines, refer to plant-derived materials or preparations with therapeutic or other human health benefits. Studies have reported that the chemical substances in herbal medicines can be transformed by gut microbiota into metabolites, thereby improving the composition, functional impairments, and associated pathological progress of the gut microbiota. The regulatory effects of herbal medicines on the gut microbiota have also been applied in AD [255]. Patchouli alcohol (PA) has been demonstrated to effectively inhibit pro-inflammatory microbial groups such as *Bacteroides*, *Klebsiella*, *Bilophila*, *Proteobacteria*, and *Enterobacteriaceae*. It enhances the abundance of anti-inflammatory microbial groups, such as *Firmicutes* and *Lactobacillus*, suppresses the activation of the C/EBPβ/AEP pathway, alleviates Aβ plaque deposition, tau hyperphosphorylation, and neuroinflammation, ultimately improving cognitive deficits in TgCRND8 mice [256]. Schisandra chinensis (S. chinensis) improves learning and memory abilities in AD rats by increasing SCFAs levels and alleviating neuroinflammation [257]. Alpinae Oxyphyllae Fructus (AOF) has been proven to regulate TREM2 and mitigate LPS-induced neuroinflammation, promoting a beneficial M2 phenotype in microglial cells and ameliorating cognitive impairments in mice [258, 259]. Epimedii Folium and Curculiginis Rhizoma, extracts of Horny Goat Weed and Xianmao, enhance TREM2 protein expression in the hippocampus by reducing TNF-α and IL-1β, regulating the transformation and activation of microglial cells, thus improving LPS-induced cognitive impairments [260]. In addition, Pyrolae herba (PH) regulates TREM2 expression, inhibits LPS-induced neuroinflammation, and alleviates cognitive impairments [261]. The therapeutic effects of herbal medicine on AD are highly complex, involving multiple aspects, with gut microbiota and lipid metabolism being just one facet. The precise therapeutic mechanisms remain to be elucidated.

#### *Statins*

Statins inhibit HMG CoA reductase in the cholesterol biosynthetic pathway, affecting intracellular cholesterol distribution, gene expression, and proteasome activity. This leads to a reduction in Aβ production, lowering the risk of AD and demonstrating positive effects on cognitive function. Beyond their well-known lipid-lowering effects, statins may also influence AD cognitive function through mechanisms involving the gut microbiota. For instance, atorvastatin has been shown to effectively increase the abundance of intestinal *Lactobacillus* while reducing *Blautia* and *Ruminococcaceae*. This modulation of the gut-brain axis alleviates neuroinflammation and improves cognition. Both atorvastatin and rosuvastatin increase the abundance of butyrate-producing bacteria, such as *Butyricimonas*, *Bacteroides*, and *Mucispirillum*, leading to reduced IL-1β levels and improved inflammation [262]. Oral administration of simvastatin has been demonstrated to enhance gut microbial activity, increase

SCFAs levels in feces, strengthen intestinal cell connections, and reduce cell death and amyloid plaque deposition in the hippocampal tissue [263]. As showed in Table 2. Furthermore, the effects and influences of statins on AD are still under ongoing exploration, with the interaction with gut microbiota being a potential mechanism.

## Lifestyle

### *Dietary patterns*

Dietary patterns have been shown to play a role in AD pathology. The Western diet, characterized by high fat, high protein, and low fiber intake, has been associated with a reduced abundance of beneficial microbial strains, including *Lactobacillus*, *Ruminococcaceae*, *Lachnospiraceae*, and SCFA-producing bacteria such as *Ruminococcus bromii*, *Faecalibacterium prausnitzii, Eubacterium rectale*, *Eubacterium hallii*, and *Anaerostipes coli SS2/1*, correlating with an increased risk of AD [266]. In contrast, the Mediterranean diet (MeDi), representing a balanced nutritional pattern rich in unsaturated fatty acids, vegetables, fruits, and lean meat proteins, has demonstrated the ability to effectively modulate the abundance of beneficial bacteria, including *Bifidobacterium* and *Lactobacillus*, in the gut, thereby reducing the risk of AD onset [267]. The ketogenic diet emphasizes very low carbohydrate intake and high-fat foods, exhibiting therapeutic effects in AD patients by modulating gut homeostasis, reducing neuronal overexcitation, enhancing mitochondrial metabolism, and decreasing oxidative stress [268]. In a randomized, double-blind, single-center

**Table 2** Relevant studies on the current oral drug formulations affecting the gut microbiota and lipids in AD

| Category | Compound | Model | Alterations of GM | Alterations of lipids | Main effects | Reference |
|---|---|---|---|---|---|---|
| **Polyphenols** | Hawthorn flavonoid | D-galactose and aluminum chloride induced AD mice | *Dubosiella*↑, *Allopre-votella*↑, *Bifidobacterium*↑, *Acinetobacter*↓, | Docosapentaenoic acid↑, sphingo-lipid↑, PC↑ | Ameliorated Aβ accumulation and abnormal activation of hippocampal microglia, improved cognitive deficits | [251] |
| | Curcumin | APP/PS1 mice, BV2 Microglial Cells | *Prevotellaceae*,↓ *Bacteroides*↓, *Escherichia/Shigella*↓ | TREM2 expression↑ | Inhibits neuroinflammation, reduce the amyloid plaque burden, improve the spatial learning and memory abilities | [252, 253] |
| | Bilberry anthocyanins | APP/PS1 mice | Serum and brain LPS levels↓, | SCFAs↑ | Decreases hippocampal neuroinflammatory responses, Aβ plaques, reverse cognitive disfunction | [254] |
| | Luteolin | / | Butyrate↑, Neurotoxin cytokines↓, LPS↓,TMAO↓ | SCFAs↑ | Reduce neuroinflammation, intracellular tau-related neurofibrillary tangles and extracellular Aβ deposition | [264] |
| **Herbal medicines** | Schisandra chinensis | Aβ injection SD rats | *Lactobacillus*↑, *Firmicutes*↑, *Bacteroidetes*↑, *Pseudomonadaceae_ Pseudomonas*↓,butyrate↑, propionate↑, | SCFAs↑ | Improved learning and memory capacity, reduced neuroinflammation, and restoration of the integrity of the intestinal barrier | [257] |
| | Epimedii Folium and Curculiginis Rhizoma | LPS-induced neuro-inflammatory mouse model | LPS↓ | TREM2 expression↑,APOE expression↓ | Inhibited neuroinflammation, ameliorated cognitive impairment | [260] |
| | Pyrolae herba | LPS injection C57BL6/J mice | LPS↓ | TREM2 expression↓ | Reduce pro-inflammatory factors, improve cognitive function | [261] |
| **Statin** | Atorvastatin | SD rats | *Lactobacillus*↑, *Blautia*↓, *Ruminococcaceae*↓ | RA metabolism↑ | Inhibit neuroinflammation, improve cognitive decline | [265] |
| | Simvastatin | Ovariectomized/D-galactose AD rat | Propionic acid↑, acetic acid↑, butyric acid↑, tight junctions of intestinal cells↑ | SCFAs↑ | Decreased cell death and Aβ plaques, reducted neuronal inflammation, protected learning and memory function | [263] |

**Abbreviations**: AD = Alzheimer's disease; APOE = Apolipoprotein E; APP = Amyloid precursor protein; Aβ = amyloid β; GM = Gut microbiota; LPS = Lipopolysaccharides; RA = Retinoic acid; SCFAs = Short-chain fatty acids; TMAO = Trimethylamine N-oxide; TREM2 = Triggering Receptor Expressed on Myeloid Cells 2

clinical study, the Modified Mediterranean-Ketogenic Diet (MMKD), which allows increased carbohydrate consumption compared to the ketogenic diet, involves higher intake of vegetables, fruits, olive oil, as well as fats and proteins from fish sources. The results demonstrated that MMKD increased the abundance of the *Phylum Tenericutes* and the *family Enterobacteriaceae*, both negatively correlated with the expression levels of Aβ42 in the cerebrospinal fluid. This dietary approach also increased butyrate levels, restricted LPS diffusion, promoted gut barrier stability, effectively restored gut microbiota composition, enhanced steroid biosynthesis, and improved AD pathology [267]. Therefore, the modulation of gut microbiota and lipid metabolism by dietary patterns holds significant importance in the prevention of AD and the attenuation of disease progression.

#### *Exercise*

Exercise can stimulate the proliferation of "beneficial" microbial communities, maintaining gut microbiota balance and subsequently improving health conditions [269]. Consequently, exercise is regarded as an effective and readily available therapeutic approach, possibly the single most important and accessible lifestyle component offering protection against a broad range of diseases [270, 271]. There is a close association between exercise and the gut-brain axis. Studies have found a negative correlation between physical activity and the risk of AD, indicating that regular exercise in the elderly can prevent AD and slow cognitive decline. Therefore, exercise serves as both a preventive strategy and an intervention measure in the treatment of AD [272, 273].

A 16-week running wheel exercise regimen has been demonstrated to increase the abundance of *Firmicutes* while decreasing the abundance of *Bacteroidetes* and *Tenericutes*, effectively improving gut microbiota composition and memory [274]. Running exercise has also been shown to increase the microbial content of *Eubacteria*, *Roseburia*, and *Clostridia* in the intestines of APP/PS1 mice, while decreasing the abundance of *Prevotella*, *Bacteroides*, *Bacteroides fragilis*, and *L. johnsonii*. This alteration inhibits the transfer of LPS to the brain, thereby alleviating LPS-induced neuroinflammation and improving cognitive function and pathological markers in AD mice [273, 275]. Moreover, voluntary wheel running (VWR) exercise has been found to upregulate the abundance of phylum *Bacteroidetes* and genus *Prevotella* while reducing the abundance of phylum *Actinobacteria* and *TM7*, as well as genus *Oscillospira* and *Ruminococcus*. This modulation mitigates cognitive dysfunction induced by TMAO [276]. These studies collectively indicate that exercise serves as an effective measure in regulating gut microbiota to improve the pathological progression of AD, presenting substantial potential in both the treatment and prevention of AD. However, it is imperative to recognize that as an intervention for AD, further research is needed to explore the specifics of exercise protocols, modes, and intensities.

## Conclusions and perspectives

As emphasized in this review, the intricate interplay between gut microbiota and lipid metabolism in the pathogenesis of AD is a noteworthy research area. We summarize the current research evidence, highlighting the central role of gut microbiota-derived metabolites such as SCFAs, LPS, TMAO, BAs, and tryptophan indole derivatives in the lipid metabolism disruption of AD pathology. As the ultimate products of gut microbiota, microbial metabolites not only interact with key lipid metabolism genes such as APOE, TREM2, ABCA1, ABCA7, SREBP1, SREBP2, and CLU but also participate in AD lipid metabolism and pathological processes by regulating Aβ and tau pathologies, neuroinflammation, oxidative stress, mitochondrial dysfunction, and epigenetic regulation. These mechanisms are interconnected and mutually influential, and while we have only begun to elucidate their complex pathological associations, the exact underlying mechanisms warrant further in-depth exploration. In future research, the application of omics techniques such as metagenomics, meta transcriptomics, and metabolomics will aid in uncovering the intricate mechanisms governing the relationship between lipids, gut microbiota, and AD, providing a deeper understanding of their interconnections. Moreover, current therapeutic strategies and drugs for AD remain limited, and the close connection between gut microbiota and lipid metabolism provides new insights into treatment approaches. Supplementation with potential beneficial bacteria through probiotics, prebiotics, and fecal microbiota transplantation may impede or slow the pathological progression of AD. Additionally, the direct impact of diet on the production of microbial metabolites should not be overlooked, emphasizing the importance of dietary regulation. Exercise, as a beneficial lifestyle factor, also holds importance in the prevention of Alzheimer's disease. Polyphenols, herbal medicines, and statin drugs demonstrate neuroprotective effects in the gut microbiota and lipid metabolism of AD, potentially holding translational value.

**Abbreviations**

| | |
|---|---|
| 25HC | 25-hydroxycholesterol |
| AOF | Alpinae Oxyphyllae Fructus |
| AD | Alzheimer's disease |
| Aβ | Amyloid beta |
| APP | Amyloid precursor protein |
| APOE | polipoprotein E |
| AA | Arachidonic acid |
| AhR | Aryl hydrocarbon receptor |
| ABCA1 | ATP-binding cassette A1 |
| ABCA7 | ATP-binding cassette A7 |
| ABCA | ATP-binding cassette subfamily A |

| | |
|---|---|
| BAs | Bile acids |
| BBB | Blood-brain barrier |
| CRL | Candida rugosa lipase |
| Cer | Ceramide |
| CSF | Cerebrospinal fluid |
| CDCA | Chenodeoxycholic acid |
| CHOL | Cholesterol |
| ACAT | Cholesterol acyltransferase |
| CE | Cholesterol ester |
| CH25H | Cholesterol-25-hydroxylase |
| CA | Cholic acid |
| UDCA | Cholic ursodeoxycholic acid |
| CLU | Clusterin |
| DCA | Deoxycholic acid |
| DHA | Docosahexaenoic acid |
| EPA | Eicosapentaenoic acid |
| PlsEtns | Ethanolamine plasmalogens |
| ePtdSer | Externalized phosphatidylserine |
| FXR | Farnesoid X receptor |
| FAs | Fatty acids |
| FMT | Fecal microbiota transplantation |
| FFA | Free fatty acid |
| GPBAR1/TGR5 | G protein-coupled bile acid receptor 1/Takeda G protein-coupled receptor 5 |
| GPRs | G protein-coupled receptors |
| GWAS | Genome-wide association studies |
| GSK3β | Glycogen synthase kinase 3 beta |
| GM | Gut microbiota |
| GPCRs | G-protein coupled receptors |
| GF | Germ-free |
| HF | Hawthorn flavonoid |
| HATs | Histone acetyltransferases |
| HDACs | Histone deacetylases |
| IPAM | Indole-3-propionamide |
| IPA | Indole-3-propionic acid |
| IL-1β | Interleukin-1 beta |
| LOAD | Late-onset Alzheimer's disease |
| LRP1 | LDLR-related protein 1 |
| LPS | Lipopolysaccharides |
| LCA | Lithocholic acid |
| LDLR | Low-density lipoprotein receptor |
| LRP-1 | Low-density lipoprotein receptor-related protein 1 |
| MCI | Mild Cognitive Impairment |
| MMKD | Modified Mediterranean-Ketogenic Diet |
| CML | N6-carboxymethyllysine |
| NDAN | Nondemented individuals with AD neuropathology |
| NFTs | Neurofibrillary tangles |
| NLRP3 | NOD-like receptor protein 3 |
| NF-κB | Nuclear factor kappa B |
| PA | Palmitic acid |
| PGE2 | Prostaglandin E2 |
| PGF1α | Prostaglandin f1alpha |
| PGF2α | Prostaglandin F2alpha |
| PC | Phosphatidylcholine |
| PE | Phosphatidylethanolamine |
| PUFAs | Polyunsaturated fatty acids |
| PtdSer | Phosphatidylserine |
| RA | Retinoic acid |
| RNS | Reactive nitrogen species |
| ROS | Reactive oxygen species |
| SFAs | Saturated fatty acids |
| SCFAs | Short-chain fatty acids |
| S1P | Sphingosine-1-phosphate |
| SPF | Specific pathogen-free |
| SREBPs | Sterol regulatory-element binding proteins |
| TUDCA | Tauroursodeoxycholic acid |
| TLRs | Toll-like receptors |
| TLR4 | Toll-like receptor 4 |
| TCA | Tricarboxylic acid |
| TREM2 | Triggering Receptor Expressed on Myeloid Cells 2 |
| TMA | Trimethylamine |
| TMAO | Trimethylamine N-oxide |
| TRP | Tryptophan |
| TRYCATs | Tryptophan catabolites |
| TNFα | Tumor necrosis factor alpha |
| UFAs | Unsaturated fatty acids |
| BACE1 | β-site amyloid precursor protein-cleaving enzyme 1 |
| ω-3 PUFAs | ω-3 polyunsaturated fatty acids |
| ω-6 PUFAs | ω-6 polyunsaturated fatty acids |

## Supplementary Information

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Supplementary Material 1

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## Declarations

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