

Review

Microbial Influences on Amyotrophic Lateral Sclerosis: The Gut–Brain Axis and Therapeutic Potential of Microbiota Modulation

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Abstract: Background/Objectives: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive degeneration of motor neurons. The gut microbiota, a community of microorganisms in the digestive tract, has recently been implicated in ALS pathogenesis through its influence on neuroinflammation and metabolic pathways. This review explores the potential role of digestive microbiota and its metabolites in ALS progression and investigates therapeutic approaches targeting gut microbiota. Methods: A comprehensive review of the current literature was conducted to assess the relationship between gut microbiota composition, microbial metabolites, and ALS progression in patients. We searched for published reports on microbiota composition, microbial metabolites, and ALS, emphasizing the complex interplay between dysbiosis, neuroinflammation, and systemic metabolism. Special emphasis was placed on studies exploring short-chain fatty acids (SCFAs), bacterial amyloids (curli-like factors), and neurotoxins such as β -methylamino-L-alanine (BMAA). The role of the liver–gut axis was evaluated as well. The potential changes in microbiota would sustain the rationale for therapeutic strategies such as probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary interventions. Results: ALS patients exhibit gut dysbiosis, characterized by reduced SCFA-producing bacteria and an increase in potentially pathogenic genera. Of note, different studies do not agree on common patterns of microbiota being linked to ALS, supporting the need for further, more extensive studies. Dysbiosis sometimes correlates with systemic inflammation and disrupted liver function, amplifying neuroinflammatory responses. Key microbial metabolites, including SCFAs, bacterial amyloids, and BMAA, may exacerbate motor neuron degeneration by promoting protein misfolding, oxidative stress, and neuroinflammation. Emerging therapeutic strategies, including probiotics and FMT, show potential in restoring microbial balance, although clinical data in ALS patients remain limited. Conclusions: The gut microbiota could modulate neuroinflammation and systemic metabolism in ALS. Microbiota-targeted therapies, such as probiotics and dietary interventions, represent promising avenues for mitigating disease progression. Further research is required to validate these interventions through large-scale, longitudinal studies and to develop personalized microbiota-based treatments tailored to individual ALS phenotypes.

Keywords: probiotics; motor neuron disease; dysbiosis; neuroinflammation; heterogeneity; gut–brain axis; liver–brain axis



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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the progressive loss of motor neurons, leading to muscle weakness, atrophy, and eventual paralysis [1,2]. The disease can manifest in familial and sporadic forms, with genetic mutations accounting for approximately 10% of cases, while the remaining 90% are sporadic [3,4]. Despite extensive research, the exact mechanisms underlying ALS remain poorly understood, which has fueled the search for contributing factors beyond genetics, including environmental influences and microbial involvement [5–8]. Emerging evidence suggests that the gut microbiota—the vast community of microorganisms residing in the gastrointestinal tract—plays a critical role in maintaining health and regulating immune and neurological functions [9,10]. Recent studies have highlighted the intricate communication between the gut and the brain, often called the gut–brain axis. This bidirectional communication system involves neural, hormonal, and immune pathways, enabling the gut microbiota to potentially influence the central nervous system (CNS) [11,12]. The gut–brain axis has garnered significant attention in the context of neurodegenerative diseases, particularly ALS. Changes in gut microbiota composition, or dysbiosis, have been observed in ALS patients, suggesting that these microbial alterations may contribute to disease onset and progression [8,13–16]. While the precise mechanisms remain elucidated, several hypotheses propose that gut microbiota can modulate neuroinflammation, influence metabolic pathways, and produce neuroactive compounds that impact motor neuron function. Indeed, further complicating this relationship, recent reviews evidence the potential importance of the exposome in neurodegeneration [17].

This narrative review aims to explore the potential role of digestive microbiota in ALS pathogenesis, focusing on recent findings that highlight its impact on neuroinflammation, immune modulation, and disease progression. Furthermore, we examine the therapeutic potential of targeting the gut microbiota as a novel approach to modulating ALS outcomes [18,19].

2. Methods

The primary objective of this narrative review is to explore the relationship between gut microbiota composition, microbial metabolites, and ALS progression, emphasizing the complex interplay between dysbiosis, neuroinflammation, and systemic metabolism. In particular, we examine the role of short-chain fatty acids, bacterial amyloids, and microbial neurotoxins, such as β -methylamino-L-alanine, in shaping ALS pathophysiology. Additionally, we assess the influence of the gut–liver–brain axis on disease progression and discuss how microbiota-targeted strategies—ranging from probiotics and dietary interventions to fecal microbiota transplantation—may hold therapeutic potential in modifying disease outcomes. Understanding these mechanisms could contribute to developing microbiota-based interventions tailored to specific ALS phenotypes.

We undertook a review following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [20]. Still, given the observed heterogeneity (i.e., practically no common metabolite or common microbial aggrupation was found), we did not include quantitative outcomes.

The search strategy included searches from PubMed and Scopus databases. As inclusion criteria, we initially identified all papers containing combinations of the following search terms: “microbial*”, “amyotrophic*”, and “motor neuron”, with availability to the full text and written in English. No date restriction was applied to the search engines. We included in the identification the following types of contributions: Adaptive Clinical

Trial, Classical Article, Clinical Conference, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Clinical Trial Protocol, Collected Work, Comment, Introductory Journal Article, Lecture, Letter, Meta-Analysis, Multicenter Study, News, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Technical Report, Twin Study, and Validation Study.

As exclusion criteria, we discarded other types of studies, specifically those employing preclinical models and preprint-type contributions and discussing non-ALS conditions (i.e., neuralgic amyotrophy, spinal muscular atrophy, progressive multiple sclerosis, multiple sclerosis, Huntington's disease, Parkinson's disease, and Alzheimer's disease). Duplicate findings were removed by manual revision.

After screening and duplicate removals, 81 studies were identified and included in our review (Figure 1).

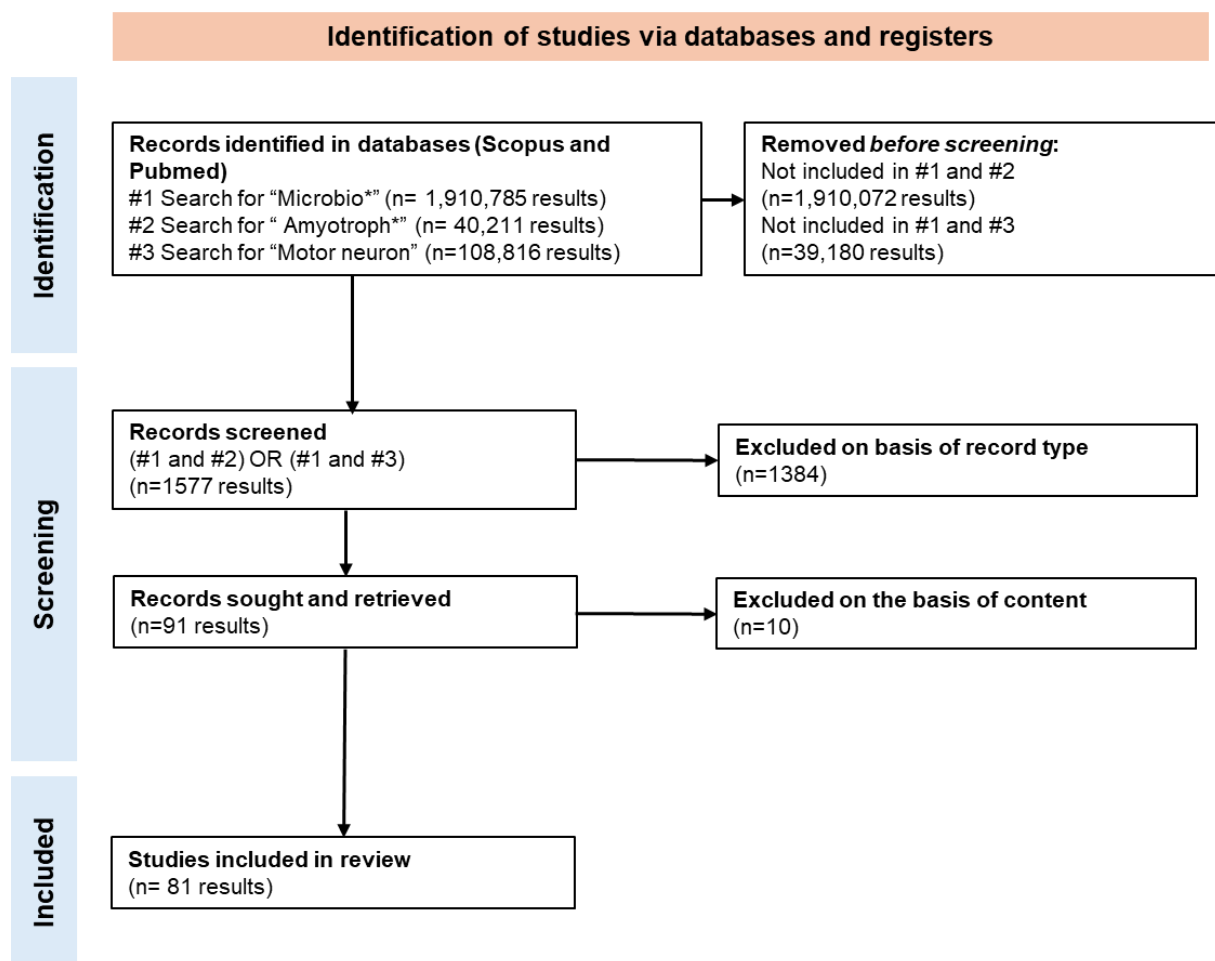


Figure 1. Flowchart of the selection of reviewed studies.

3. Results and Discussion

3.1. Gut Microbiota and ALS: Current Understanding

As confirmed by the bibliographical search, ALS, a complex neurodegenerative disease where genetic and environmental factors contribute to its etiology, does not escape from the potential influence of microbiota as a disease-modifying factor [15,18]. One emerging area of interest is the role of the gut microbiota in modulating neurodegenerative processes through the gut–brain axis. The gut microbiota consists of trillions of microorganisms, including bacteria, viruses, and fungi, which collectively influence the host's immune

system, metabolism, and neurological functions [21]. Dysbiosis, or an imbalance in the gut microbial composition, has been implicated in the development and progression of several neurodegenerative diseases, including ALS [22,23]. Given the intrinsic heterogeneity in a host–response relationship, differences in dysbiosis and its host’s response might contribute to explaining disease heterogeneity in patients. As shown in Figure 2, several factors could help explain the microbiota’s role in ALS pathophysiology.

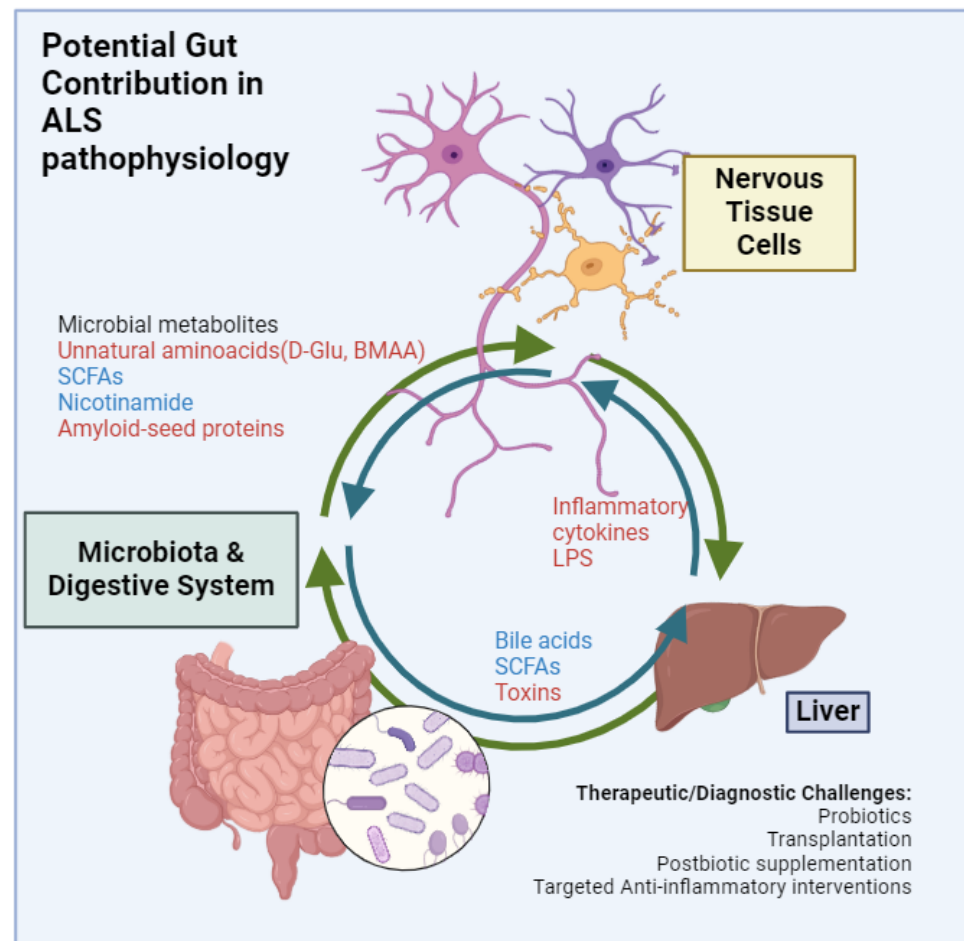


Figure 2. Potential gut contribution to ALS pathophysiology via the gut–liver–brain axis. Gut dysbiosis in ALS patients, characterized by a decrease in short-chain fatty acid (SCFA)-producing bacteria and an increase in potentially pathogenic bacteria, may contribute to neuroinflammation and disease progression. Microbial metabolites, including SCFAs (such as butyrate, with neuroprotective properties), lipopolysaccharides (LPS, with pro-inflammatory effects), and toxins (such as β -methylamino-L-alanine (BMAA) or D-glutamate, with neurotoxic potential), influence the central nervous system (CNS) through the gut–liver–brain axis. Anatomically connected to the intestine, the liver plays a crucial role in modulating the systemic inflammatory response. Liver dysfunction, common in ALS, can exacerbate neuroinflammation by allowing endotoxins, such as LPS, and other bacterial metabolites to enter the systemic circulation, activating immune cells in the CNS (microglia and astrocytes) and promoting the release of proinflammatory cytokines. Furthermore, alterations in bile acid production and metabolism, modulated by microbiota, can affect signaling through receptors such as FXR and TGR5, influencing inflammation and lipid metabolism. The interplay between gut dysbiosis, liver dysfunction, and neuroinflammation establishes a vicious cycle that may accelerate motor neuron degeneration in ALS. Microbiota-targeted therapeutic strategies, such as the use of probiotics, postbiotic supplementation (e.g., SCFAs), and fecal microbiota transplantation (FMT), represent promising approaches to restore intestinal homeostasis, reduce neuroinflammation, and potentially slow disease progression.

Recent studies have shown that ALS patients exhibit significant alterations in their gut microbiota compared to healthy individuals. For example, ALS patients show a decreased abundance of Firmicutes and Bacteroidetes, two major bacterial phyla essential for maintaining gut health and metabolic homeostasis [13,21]. Other studies have found an increased abundance of Bacteroidetes [24], confirming the need for further studies. Moreover, specific bacterial genera such as *Blautia*, *Ruminococcus*, and *Prevotella* are reduced in ALS patients, while *Escherichia* and other potentially pathogenic genera are increased [25]. Of note, the *Escherichia* population in ALS has not been found to consistently change compared to healthy controls [26]), again supporting the need for further studies before a conclusive statement. All in all, these microbial changes suggest that gut dysbiosis may promote neuroinflammation and alter the metabolic environment, at least in some patients, potentially contributing to the neurodegenerative processes observed in ALS [27]. In silico predictions found similar microbial dysbiosis patterns in Alzheimer's, Parkinson's, and multiple sclerosis, but ALS showed distinct differences [28]. In neurodegeneration, microbes increased in patients mainly belonging to *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Firmicutes*. Indeed, these in silico studies show a need for evaluating metabolic links, including reduced SCFA synthesis, increased L-glutamate production, and lower representation of tryptophan, histamine, and spermidine, highlighting their potential role in neurodegeneration [28].

The gut–brain axis is a key mediator of the interactions between gut microbiota and the CNS. This communication is facilitated by various pathways, including the production of microbial metabolites, such as short-chain fatty acids (SCFAs) and other microbial metabolites. The evidence, thus far, suggests that gut microbiota alterations could contribute to ALS by modulating inflammatory and immune responses, influencing the gut–brain axis. However, much remains unknown, and further studies are needed to understand better the causal relationship between gut dysbiosis and ALS pathogenesis [29].

In this sense, given the anatomical continuity between the intestine and the liver, not surprisingly, the interaction between the gut microbiota and the liver has recently gained attention as a critical component in modulating neuroinflammation and systemic metabolism. This interconnected relationship, the liver–gut axis, is essential in maintaining metabolic homeostasis, detoxifying harmful substances, and regulating immune responses [30,31]. In ALS, liver dysfunction and metabolic abnormalities have been proposed as contributing factors to disease progression. Recent studies have demonstrated a correlation between liver health and ALS progression. Zhu et al. (2024) highlighted that ALS patients often exhibit liver abnormalities, such as elevated liver stiffness and increased fat content, which may correlate with disease severity [32]. The liver's role in filtering gut-derived toxins, such as LPS, becomes compromised when dysbiosis is present, potentially allowing neurotoxic substances to enter circulation and contribute to neuroinflammation. Furthermore, liver-produced bile acids, modulated by the gut microbiota, play a key role in regulating inflammation and maintaining the integrity of the gut barrier [33].

In ALS, the liver's impaired ability to metabolize fatty acids and detoxify harmful substances can exacerbate systemic inflammation. This may be particularly relevant given the observed gut dysbiosis in ALS patients, where pathogenic bacteria increase the production of LPS and other endotoxins. Due to compromised gut permeability, commonly referred to as “leaky gut”, these endotoxins can escape into the systemic circulation and further activate inflammatory pathways in both the liver and the central nervous system [34,35].

The Gut Microbiota's Influence on Liver Health

The gut microbiota directly influences liver function by producing metabolites such as SCFAs and regulating bile acid metabolism. SCFAs, especially butyrate, have been shown

to have anti-inflammatory effects in both the gut and the liver. However, a reduction in SCFA-producing bacteria has been observed in ALS patients, potentially weakening these protective mechanisms (see Section 3.2.1).

Bile acids, synthesized in the liver and metabolized by gut bacteria, also affect immune regulation. In ALS, dysbiosis may disrupt bile acid homeostasis, leading to altered signaling through the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor (TGR5), both of which are involved in controlling inflammation and lipid metabolism [36]. This disruption could result in increased hepatic inflammation, contributing to a feedback loop where both the liver and the gut exacerbate neuroinflammation in ALS patients. The liver acts as a buffer in healthy individuals, filtering out gut-derived toxins before reaching systemic circulation. However, in ALS, liver dysfunction combined with gut dysbiosis may compromise this protective function [32]. This allows endotoxins such as LPS to circulate freely, triggering Toll-like receptor (TLR) pathways and activating pro-inflammatory cytokines in the liver and the central nervous system.

Moreover, hepatic inflammation can increase oxidative stress and release pro-inflammatory molecules, such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF- α), further exacerbating neurodegenerative processes. The liver's diminished capacity to handle oxidative stress may accelerate the motor neuron degeneration seen in ALS [32].

3.2. Key Microbial Metabolites and Factors and Their Influence on ALS

As a potential explanation of the microbiota influence in ALS, specific microbial metabolites have been highlighted as possible contributors to disease progression due to their effects on neuroinflammation, protein aggregation, and immune modulation (Table 1).

Table 1. Microbiota-related metabolites in case-control studies of ALS.

Metabolomic Change	Cases	Controls	Exclusion and Inclusion Criteria	Methodology	Geographical Background	Reference
ALS patients displayed a significantly higher serum load of Torque Tenoviurs-DNA compared to healthy controls, potentially suggesting enteral permeability changes; patients with ALS exhibited a higher total FFA level, while their SCFA level was generally lower; 10 out of 14 tested cytokines showed a lower expression in ALS patients compared to healthy controls and IL-8 (CXCL8) being more highly expressed in ALS patients.	100 diagnosed ALS patients (35 females)	34 controls among spouses (13 females)	Dementia or any other condition that compromised the ability to consent; known organic gastrointestinal disease; celiac disease and/or documented food intolerances; autoimmune disorders; severe comorbidities; history of complicated gastrointestinal surgery; and acute infections at the time of sampling	Torque Tenovirus load in serum determined by a real-time PCR assay; serum levels of fatty acids determined by GC/MS; serum cytokines by Milliplex MAP kits	Italy	Niccolai et al., 2024 [37]
The degree of upper motor neuron damage in the ALS group was inversely correlated with the plasma levels of carnitine, betaine, choline, and TMAO. ALS patients and their spouses exhibit disruptions in the gut microbiota's TMAO metabolic pathway, which may indicate that the alterations in the gut microbiota took place before the development of the disease.	160 patients with ALS (62 females)	148 healthy controls	Exclusion of pregnant or breastfeeding women. Also, abnormal findings on electrodiagnostic, neurophysiologic, neuroimaging, or clinical laboratory studies that could not be explained by ALS, the presence of dementia, or psychiatric disorders; the presence of gastrointestinal disorders or the performance of gastrointestinal surgery that might affect gastrointestinal absorption; severe diseases of the heart, liver, kidney, or other organs; and treatment with antibiotics, L-carnitine, or intestinal flora regulation within 3 months before enrollment	TMAO and its precursors were quantified using stable isotope dilution liquid chromatography-tandem mass spectrometry	China	Chen et al., 2020 [38]
The fecal metabolome showed increased levels of specific amino acids and their metabolic products in patients with ALS after FMT, particularly in the arginine biosynthesis pathway.	2 patients undergoing fecal microbial transplantation	1 healthy donor	No specified	Non-targeted liquid chromatography–mass spectrometry	Japan	Yan et al., 2024 [19]
Fecal metabolites suggested changes in retrograde endocannabinoid signaling, inflammatory mediator regulation of the transient receptor potential channels, sphingolipid, nicotinamide, and thiamine metabolism in ALS. Several fecal metabolites differed between patients with cognitive impairment, including lower cholic acid and chenodeoxycholic acid, besides other metabolites.	35 ALS patients (14 females)	35 healthy controls, age- and sex-matched (14 females)	Any possible evidence for familial amyotrophic lateral sclerosis (fALS) with other neurodegenerative diseases with definite gastrointestinal diseases, heart failure, acute infection, tumor, immunodeficiency, and autoimmune diseases; any use of antibiotics within the last month, regular drinking of commercial probiotics within the previous year, or any drinking of commercial probiotics within the last week; obvious symptoms of dysphagia or dyspnea	Liquid chromatography–mass spectrometry (untargeted metabolomics)	China	Gong et al., 2022 [39]

Table 1. Cont.

Metabolomic Change	Cases	Controls	Exclusion and Inclusion Criteria	Methodology	Geographical Background	Reference
Kynurenine metabolites related to ALS risk.	20,806 cases of ALS	59,804 controls (GWAS summary statistics from IALSC); 18,340 participants (GWAS summary statistics from MiBioGen); 7824 participants (GWAS summary statistics from TwinsUK and KORA)	Not specified	Not specified	Worldwide	Ning et al., 2022 [40]
Metabolomics in sera in ALS suggest alterations in the tryptophan–nicotinamide metabolism as indole acetate, kynurenine, serotonin, and circulating nicotinamide. Other changes included increased levels of riluzole creatine and 3-hydroxy-2-ethyl propionate and reduced levels of methyl indole 3-acetate and triethanolamine in ALS patients.	37 ALS patients (8 females)	29 healthy, BMI- and age-matched family members (20 females)	Pregnancy or fertility treatments; use of antibiotics or antifungals in the three previous months; consumption of probiotics 1 month before; active inflammatory or neoplastic disease three years before enrolment; chronic gastrointestinal disorder, myocardial infarction, or cerebrovascular accident in the six months before participation; coagulation disorders; chronic immunosuppressive medication usage; or pre-diagnosed type I or type II diabetes mellitus or treatment with anti-diabetic medication	Metabolon-based profiling	Israel	Blacher et al., 2019 [41]
Microbiome-related variables in plasma (human endotoxin, SCFA, NO ₂ -N/NO ₃ -N, and γ -aminobutyric acid) showed some tendencies in patients with ALS potentially compatible with dysbiosis.	8 ALS patients (4 females)	8 healthy controls (4 females) with no declared age, sex, or dietary regimes match	ALS-like illnesses, severe systemic disorders, and excessive eating or drinking throughout the previous two weeks	Non-targeted mass spectrometry for selected metabolites, according Yang et al. [42]	China	Zhai et al., 2019 [43]
Local (gut or oral) bacterial translocation was associated with more severe symptoms.	36 Patients with bulbar or spinal ALS (24 spinal onset with 15 females; 12 bulbar onset with 8 females)	20 healthy controls living with patients	Exposure to antibiotics/probiotics, immunocompromising illness/therapy, previous abdominal/anorectal surgery, GI-/respiratory-/gynecological-tract infection, food poisoning, or major epistaxis requiring treatment; active/persistent primary disease of the GI-/respiratory-/gynecological-tract, endocrinal disease, heart failure, severe renal-insufficiency, current pregnancy, drug/alcohol abuse, and active smoking within 6-months	Bacterial translocation to the blood was assessed by evaluating lipopolysaccharide binding protein (LBP) and 16S rRNA copies in the blood	USA	Kim et al., 2022 [44]

Table 1. Cont.

Metabolomic Change	Cases	Controls	Exclusion and Inclusion Criteria	Methodology	Geographical Background	Reference
ALS was linked to specific lipids related to fatty acid and acylcarnitine metabolism by mendelian randomization assay.	75 ALS patients (32 females)	110 controls (66 females), matched for sex and age	For controls, neurodegenerative condition or family history of ALS	Metabolon-based profiling of serum. Metabolite–gut microbiome associations using weighted gene co-expression network analysis and two-way orthogonal partial least square with discriminant analysis	USA	Guo et al., 2024 [45]
ALS was associated with increased plasma formaldehyde. Trimethylamine and trimethylamine oxide did not show differences, but patients with increased formaldehyde levels also showed increased concentrations of trimethylamine and its oxide.	50 ALS patients (19 females)	40 healthy controls (17 females)	Not specified	Plasma formaldehyde levels were quantified using a commercial kit. Trimethylamine and trimethylamine oxide in the plasma were quantified by multiple reactions monitoring mass spectrometry	Australia	Lee et al., 2019 [46]

3.2.1. SCFAs, LPS, and Other Lipids

SCFAs such as butyrate, acetate, and propionate are among the most well-studied metabolites produced by gut bacteria through the fermentation of dietary fibers [47,48]. SCFAs butyrate, propionate, and acetate regulate inflammation, maintain the integrity of the blood–brain barrier, and modulate the immune response [49,50]. Indeed, SCFAs have neuroprotective properties [51,52]. A reduction in SCFA-producing bacteria has been observed in ALS patients, potentially leading to an impaired anti-inflammatory response, further exacerbating neuroinflammation [53]. These SCFAs have been shown to exert anti-inflammatory effects and support the integrity of the intestinal barrier, which can indirectly influence the brain via immune modulation and the maintenance of the blood–brain barrier.

Butyrate, as indicated above, has garnered attention for its neuroprotective properties, including its role in promoting regulatory T-cell differentiation and inhibiting proinflammatory cytokines [54,55]. Additionally, SCFAs are known to stimulate the production of brain-derived neurotrophic factor (BDNF) [56], which supports neuronal survival and function, processes that are severely impaired in ALS [57]. Butyrate exerts neuroprotective effects through multiple mechanisms, including the inhibition of histone deacetylases (HDACs), which leads to increased acetylation of histones and promotes the expression of neuroprotective genes [58]. Of note, butyrate might be readily converted into acetyl-CoA to enter the tricarboxylic acid cycle in mitochondria, boosting ATP production [59,60]. Furthermore, butyrate can enhance the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, thereby reducing oxidative stress in neuronal cells [61]. It has also been demonstrated that butyrate can modulate autophagy, a crucial cellular process for the clearance of misfolded proteins and damaged organelles, which is often dysregulated in ALS [62–64]. In preclinical models of ALS, butyrate administration has been shown to improve motor function, prolong survival, and reduce motor neuron loss, further supporting its therapeutic potential [65]. Thus, the reduced presence of SCFA-producing bacteria in ALS patients may lead to diminished neuroprotection and increased neuroinflammation, exacerbating the disease's progression.

In addition to SCFAs, other microbial metabolites, such as lipopolysaccharides (LPSs), can have pro-inflammatory effects when released into circulation [66,67]. LPS, a component of the outer membrane of gram-negative bacteria, can activate the immune system through TLRs, leading to systemic inflammation and neuroinflammation, which are known contributors to ALS progression [68]. Specifically, LPS can activate microglia and astrocytes, the primary immune cells of the CNS, leading to the release of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) [43]. These cytokines can further exacerbate neuroinflammation and contribute to motor neuron damage. Moreover, LPS can disrupt the blood–brain barrier, allowing peripheral immune cells and inflammatory mediators to infiltrate the CNS, further promoting neurodegeneration [41]. To this extent, we should remember the important role of microbiota as a modulator of CNS-resident microglial cells, helping to explain the potential influence of microbiota in neuroinflammation [69,70].

Besides SCFAs and LPS, other lipids can be involved in the host–microbiota relationship. These include sphingolipids, endocannabinoid-like lipids, and bile acids. For example, gut bacteria produce sphingolipids [71], which can modulate inflammation and apoptosis. Dysregulated sphingolipid metabolism has been linked to neuroinflammatory processes in neurodegenerative diseases [72]. In the case of endocannabinoid-like lipids, certain microbiota-derived fatty acids influence the endocannabinoid system [73], affecting inflammation and immune responses and potentially playing a role in neuroinflammatory conditions. Indeed, recent data show that gut dysbiosis, reduced intestinal motility, and increased intestinal permeability, which allow bacterial products to circulate and pass

through the blood–brain barrier, could impact mast cells resident in the brain, thereby enhancing neuroinflammation [74]. Finally, microbial metabolism of bile acids affects immune signaling pathways [75] and may influence neuroinflammation. Studies on these lipids and SCFAs provide a broader understanding of how gut microbiota may influence the immune and neuroinflammatory response relevant to diseases like ALS.

3.2.2. Microbiota Influence on Protein Aggregation in ALS: Potential Parallels in Bacterial Systems

Gut microbiota might play a significant role in neurodegenerative diseases, including ALS, by different mechanisms, in addition to the entry of microbiota-derived metabolites. ALS is marked by the abnormal aggregation of proteins such as TDP-43, FUS, and SOD1, all containing intrinsically disordered regions (IDRs) [76,77]. These regions are prone to misfolding and aggregation, often contributing to pathological mechanisms. Intriguingly, bacterial systems, though vastly different from human cells, contain proteins that exhibit functional or structural characteristics reminiscent of these ALS-associated proteins. Such similarities provide a potential avenue for understanding how microbial influence may affect neurodegenerative processes like ALS. Therefore, the presence of these specific proteins might activate a prion-like response in specific genetic backgrounds invoked in ALS pathophysiology [78,79]. Indeed, preclinical models of motor neuron disease exhibit enhanced sensitivity towards curli-producing bacteria [35], accelerating the phenotype. This is not limited to ALS, as other aggregation-prone proteins, such as synuclein, can be aggregated in this bacterial amyloid [80]. Interestingly, curli amyloid fibril interacts with other factors relevant to ALS pathogenesis, such as lipopolysaccharide assembly and adenosylcobalamin synthesis [81]. In bacterial cells, other proteins such as Hfq, CsrA, and others are involved in stress responses, display RNA-binding properties, and participate in regulating post-transcriptional gene expression, much like the RNA metabolism functions of TDP-43 and FUS. While bacterial proteins lack extensive disordered regions like their eukaryotic counterparts, their functional analogy in controlling RNA stability and processing draws an interesting parallel. Hfq, for instance, is known to form ribonucleoprotein complexes that regulate RNA fate in bacteria [82,83], a concept that mirrors the RNA-binding and regulatory role of TDP-43 and FUS in neurons.

Moreover, the phenomenon of liquid–liquid phase separation (LLPS), which is central to the aggregation of ALS-related proteins like TDP-43 and FUS, has also been observed in bacterial proteins. For example, PopZ in *Caulobacter crescentus* undergoes phase separation to form spatially organized assemblies [84]. While the biological contexts differ, the principle of phase separation may reflect the evolutionary conservation of cellular organization mechanisms that, when dysregulated, lead to pathological aggregation in ALS.

Bacteria also respond to environmental stress by forming stress-induced protein aggregates, which bear resemblance to stress granules observed in human neurodegenerative conditions. In human cells, stress granules play a role in sequestering misfolded proteins, but in ALS, aberrant aggregation of TDP-43 and FUS within these granules contributes to disease progression [85,86]. Certain bacterial systems exhibit similar behaviors during stress, with ribosome-associated protein granules forming to protect cellular components—a process that may provide insights into how gut microbiota respond to and influence host stress responses, potentially affecting neurodegenerative outcomes.

Chaperone proteins in bacteria, such as DnaK and GroEL, are responsible for maintaining protein homeostasis by preventing misfolding and aggregation [87]. While these bacterial proteins do not directly correspond to human ALS-associated proteins, their functional role in protein maintenance could be analogous to cellular mechanisms that break down in ALS. Dysbiosis, or an imbalance in microbial populations, might influence

the host's ability to manage protein misfolding and stress responses, thereby contributing to neurodegeneration.

Finally, the discovery of prion-like domains in some bacterial proteins opens a fascinating area of exploration [88]. Prion-like domains, known for their propensity to aggregate and spread misfolded proteins, are found in many ALS-related proteins such as TDP-43 and FUS. Though rare in bacteria, certain bacterial proteins exhibit low-complexity regions with similar aggregation properties, suggesting that microbial proteins might influence or interact with host proteins in ways that impact ALS pathogenesis. For instance, bacterial amyloids, such as curli fibers produced by *Escherichia coli*, have been shown to interact with host proteins and promote their aggregation [24]. Curli fibers can act as a nidus for the misfolding and aggregation of proteins implicated in neurodegenerative diseases, including α -synuclein in Parkinson's disease and potentially TDP-43 and SOD1 in ALS. This interaction suggests a possible mechanism by which gut microbiota could influence the progression of ALS through the promotion of protein aggregation, a hallmark of the disease.

Thus, while direct homologs of ALS-associated proteins are not present in bacteria, the existence of functionally analogous proteins and mechanisms in bacterial systems raises the possibility that the gut microbiota may influence ALS progression. Understanding the crosstalk between microbial and host protein homeostasis, aggregation, and stress responses could provide valuable insights into the environmental and biological factors that contribute to ALS.

3.2.3. β -Methylamino-L-Alanine (BMAA) and Other Amines as Postbiotic Neurotoxic Factors

Another important microbial metabolite potentially involved in ALS is β -methylamino-L-alanine (BMAA), a neurotoxin cyanobacteria produce [58,59]. Recent data show that this toxin may be produced by all known groups of cyanobacteria, including cyanobacterial symbionts and free-living cyanobacteria [89]. The ubiquity of cyanobacteria in terrestrial, freshwater, brackish, and marine environments makes this agent potentially relevant. BMAA has been implicated in the development of neurodegenerative diseases [90], particularly in geographical regions where cyanobacterial contamination of food and water sources is prevalent [91,92]. For instance, the ten-fold increase in the incidence of ALS documented in New Hampshire regions around Lake Mascoma might be related to toxin exposure via inhalation of aerosolized toxins [93], consuming fish, or ingestion of lake water [94]. These studies confirm previous data in New England finding hot spots of increased ALS incidence [95]. These studies complement other data showing the potential influences of *Legionella* [96]. Similarly, other studies focused on *Mycobacterium avium* subspecies inhalation that could explain occupational and recreational-sports-related increases in ALS risk [97]. Studies suggest that BMAA induces excitotoxicity and oxidative stress, mechanisms that are closely linked to ALS pathology [98]. BMAA may function as a postbiotic factor, wherein dysbiosis or environmental exposure to cyanobacteria leads to the accumulation of neurotoxic compounds that exacerbate motor neuron damage. The association between BMAA exposure and increased ALS risk has been particularly noted in studies involving populations from the Kii Peninsula in Japan and the island of Guam, where there are higher rates of ALS [99]. This suggests that BMAA, whether directly ingested or produced endogenously by gut microbiota, might contribute to ALS pathogenesis through its neurotoxic effects. BMAA's neurotoxicity is mediated through several mechanisms, including activating glutamate receptors, leading to excitotoxicity, and the induction of oxidative stress by generating reactive oxygen species (ROS) [100]. Furthermore, BMAA can be misplaced into proteins in place of serine, potentially causing protein misfolding and aggregation, characteristic features of ALS pathology [101]. Recent studies have also suggested that certain gut microbiota compositions may enhance the

endogenous production of BMAA, further implicating dysbiosis in the neurotoxic effects associated with this compound [102]. Other microbial factors, such as trimethylamine N-oxide (TMAO), indoles, and polyamines, could also play a role in ALS (Table 1). TMAO, produced by gut microbiota from dietary precursors like choline and carnitine, has been linked to inflammation and oxidative stress, although its role in neurodegeneration is still under investigation. Indoles, derived from the microbial metabolism of tryptophan, can have both beneficial and detrimental effects depending on their concentration and the specific derivatives formed. Polyamines, such as putrescine, spermidine, and spermine, are involved in cell growth and differentiation, and their dysregulation has been implicated in neurodegenerative diseases. While these factors have not been extensively studied in the context of ALS, they represent additional avenues through which the gut microbiota could influence disease progression [103,104].

3.2.4. Microbiota Differences in Spinal vs. Bulbar ALS

Emerging research suggests that patients with bulbar ALS, due to the early onset of dysphagia and related difficulties in eating, are particularly susceptible to alterations in the gut microbiota [13,53]. Dysphagia limits oral intake, leading to malnutrition and affecting the diversity of gut microbiota by reducing the availability of dietary fibers that support beneficial bacterial populations. As a result, patients with bulbar ALS often show greater dysbiosis compared to those with spinal ALS [13].

It is known that patients with bulbar ALS exhibited lower levels of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, which are known for their anti-inflammatory and gut-protective properties [44,105]. In contrast, spinal ALS patients may have a more stable microbiota profile in the earlier stages of the disease, but as motor neuron degeneration progresses, dysbiosis becomes more prominent. This shift in microbiota composition may further exacerbate neuroinflammation, contributing to disease progression in both phenotypes.

3.2.5. Impact of Dysphagia on Oral and Gut Microbiota

Dysphagia, a common symptom in ALS, affects not only the nutritional status of patients but also the composition of the oral and gut microbiota [34]. The decreased ability to swallow and digest food can result in bacterial overgrowth, both in the oral cavity and the gut, leading to a dominance of pathogenic species such as *Escherichia coli* and *Klebsiella pneumoniae* [106]. These bacteria can produce LPS and other pro-inflammatory molecules that may enter systemic circulation, thereby promoting inflammation in the gut and the CNS.

Furthermore, enteral feeding in ALS patients with advanced dysphagia alters the normal process of digestion and absorption, potentially impacting the microbial ecosystem. Nutrient absorption is disrupted, leading to reduced fermentation of dietary fibers and lower production of beneficial SCFAs [107,108]. The resulting dysbiosis may increase gut permeability, allowing harmful bacterial metabolites and endotoxins to cross the gut barrier and contribute to neuroinflammation, a key driver of ALS progression.

3.2.6. The Role of Antibiotics and Dietary Changes in ALS Progression

In ALS patients, antibiotics are commonly used to prevent or treat infections that can arise due to impaired immune function and reduced mobility. However, frequent antibiotic use can profoundly impact the gut microbiota, reducing bacterial diversity and promoting the overgrowth of resistant or pathogenic bacteria [109,110]. This reduction in microbial diversity has been linked to worse outcomes in neurodegenerative diseases, including ALS, due to the disruption of protective bacterial functions and the amplification of inflammatory processes [26,109].

Additionally, dietary changes, whether due to dysphagia or nutritional interventions, can significantly influence microbiota composition in ALS patients. For example, high-protein diets that are sometimes recommended for ALS patients may inadvertently reduce the availability of fermentable fibers, thereby limiting SCFA production and contributing to gut dysbiosis [111]. Conversely, diets rich in fiber and prebiotics could help restore microbial balance and support anti-inflammatory pathways. Supporting this relationship, independent studies show that vegetable fiber intake could influence the disease progression rate and survival time [112]. However, more research is needed to confirm their therapeutic potential in ALS.

3.3. Therapeutic Potential of Microbiota Modulation

Given the growing evidence linking gut microbiota dysbiosis with ALS progression, microbiota modulation has emerged as a promising therapeutic avenue. Interventions aimed at restoring microbial balance could potentially mitigate the neuroinflammatory processes and metabolic disruptions associated with ALS. Here, we explore the potential of probiotics, prebiotics, and other microbiota-based therapies as tools to influence the disease course.

3.3.1. Probiotics and Prebiotics

Probiotics, defined as live microorganisms that confer health benefits when administered adequately, have shown potential in maintaining gut health and reducing inflammation [113,114]. The rationale behind their use in ALS lies in their ability to restore a healthy microbial balance, especially by increasing the populations of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, depleted in ALS patients in some studies. These bacteria have been shown to enhance the production of SCFAs, such as butyrate, which have neuroprotective properties and can modulate the immune response [52,115]. Indeed, the concept of neurobiotics has been coined to cover the potential boosting of neural regeneration via the modulation of microbiota, and it might be applicable to ALS assistance [116]. Indeed, a very exhaustive study suggests the potential possibility of boosting the levels of nicotinamide neuroprotective metabolites by modulating the levels of specific bacteria, such as *Akkermasia muciniphila* [41].

Prebiotics, non-digestible food ingredients that promote the growth of beneficial bacteria, can also play a role in ALS treatment by fostering an environment conducive to healthy gut microbiota. Dietary fibers, such as inulin and oligosaccharides, are among the most studied prebiotics for their ability to stimulate SCFA production and improve gut barrier function. In ALS, incorporating prebiotics might help counteract the reduced SCFA levels commonly observed, thereby supporting the maintenance of intestinal and blood–brain barrier integrity [117].

Although preliminary studies in other neurodegenerative diseases like Parkinson's and Alzheimer's have shown some benefit from probiotics and prebiotics, more research is needed to determine their efficacy, specifically in ALS. Small clinical trials are beginning to emerge, but larger, more robust studies are necessary to validate their therapeutic potential in this context [118].

3.3.2. Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT), which involves transferring fecal material from a healthy donor into the gastrointestinal tract of a recipient, is another therapeutic approach being explored for neurodegenerative diseases. By introducing a diverse and balanced microbial community, FMT aims to restore the gut microbiota to a healthier state, potentially reversing dysbiosis [19,119].

In ALS, FMT may help to replenish beneficial bacteria and reduce the dominance of pathogenic species, thereby improving gut permeability and reducing systemic inflammation. However, while promising results have been observed in animal models of neurodegeneration, clinical trials in ALS patients remain scarce. Early findings suggest that FMT could be a feasible treatment for mitigating improving respiratory symptoms and improving quality of life, but more data are needed to understand its impact on ALS progression [19] in a pathway involving branched chain amino-acid metabolites.

3.3.3. Dietary Interventions

Dietary interventions, particularly those aimed at modifying gut microbiota, have gained interest in ALS research. Diets rich in fibers, polyphenols, and prebiotics could help promote beneficial bacterial growth and SCFA production, potentially alleviating inflammation and oxidative stress in ALS. Conversely, as indicated above, high-protein or low-fiber diets, which are sometimes recommended for ALS patients due to their increased energy demands, may exacerbate dysbiosis by limiting the availability of fermentable substrates for gut bacteria.

Recent studies have proposed ketogenic diets as a potential therapeutic strategy for ALS. These diets have been shown to alter gut microbiota composition and increase the production of beneficial metabolites, such as ketone bodies, which may provide neuroprotective effects [120–122]. However, the long-term impact of such diets on gut health and ALS progression is not yet fully understood and requires further investigation.

3.3.4. Targeting Specific Bacterial Metabolites

An alternative approach to directly altering microbiota composition involves targeting the microbial metabolites. Therapeutic interventions that promote the production of neuroprotective metabolites, such as SCFAs, or inhibit harmful metabolites like LPS and bacterial amyloids (curli), may hold promise in mitigating ALS pathology. SCFA supplementation has already shown potential in animal models of neurodegenerative diseases, though its application in ALS remains under-explored [123]. In this line, a patent has been reported on the use of several blended metabolites for the treatment of neurodegenerative conditions [124]. These metabolites comprise a heterogeneous mixture of bile acids, SCFA, GABA, and kynurenine and arginine metabolite pathways. In this sense, butyrate-supplemented feeding has already been demonstrated to delay ALS symptom onset, ameliorate neuromuscular junction degeneration, and prolong the life span of hSOD1G93A mice [125,126].

Similarly, efforts to block the systemic effects of harmful bacterial amyloids or reduce the production of pro-inflammatory microbial metabolites may offer new therapeutic pathways. As our understanding of the microbial contributions to ALS grows, these metabolite-targeted therapies could complement traditional ALS treatments.

3.4. Current Gaps and Future Directions

Although significant strides have been made in understanding the role of gut microbiota in ALS, several gaps that limit the full comprehension of its impact on disease progression and therapeutic potential remain. Addressing these limitations through future research is crucial for unlocking microbiota-targeted strategies to manage ALS more effectively.

3.4.1. Need for Larger and Longitudinal Studies

Current studies investigating microbiota alterations in ALS often suffer from small sample sizes, limiting the generalizability of findings. Larger cohort studies are needed to establish definitive links between specific microbial changes and ALS phenotypes. Additionally, the cross-sectional nature of many studies does not account for how the microbiota might evolve throughout ALS progression. Longitudinal studies that track

microbiota changes from early diagnosis to late stages of the disease would provide critical insights into how microbial dysbiosis correlates with disease severity and progression.

3.4.2. Heterogeneity in ALS Phenotypes and Microbiota Response

ALS is a highly heterogeneous disease with significant variability in clinical presentation, progression, and response to treatment. Similarly, the gut microbiota composition can vary greatly between individuals due to genetics, diet, and geography. As a result, it is challenging to draw uniform conclusions about the role of microbiota in ALS across different populations [13]. Enriching the situation, recent data show that environmental clues interact with microbial determinants, inducing neuropathological risk [127]. Future studies should consider stratifying ALS patients based on factors such as phenotype (spinal vs. bulbar ALS), disease severity, geographical and contaminant traits, metabolome, and dietary habits to account for this variability. This approach may uncover specific microbial signatures or dysbiosis patterns associated with particular subtypes of ALS, leading to more personalized interventions. As recently reported, several limitations of existing studies [61] produce inconsistent findings (Table 2). While some studies suggest differences in microbial composition between ALS patients and healthy individuals, as well as potential alterations in microbe-derived metabolites like butyrate and nicotinamide (Table 1), the overall picture remains inconclusive. Several factors contribute to these discrepancies. The inherent rarity of ALS often leads to studies with small sample sizes, increasing the risk of random error and limiting statistical power, particularly given the complexity of microbiome research.

Table 2. Case-control studies of ALS-linked changes in microbiome.

Potential Microbiota Alterations in ALS	Cases	Controls	Exclusion Criteria	Methodology for Metagenome	Geographical Background	Reference
Decreased Firmicutes-to-Bacteroidetes ratio in ALS cases; increased <i>Dorea</i> ; decreased <i>Oscillibacter</i> , <i>Anaerostipes</i> , <i>Lachnospiraceae</i> at genus level for ALS cases.	6 ALS patients	5 healthy controls, with apparently no matching in BMI, sex, or age	FVC ¹ < 70%, mental illness or neurological disorders, or nocturnal hypoventilation	Bacterial 16S rRNA (V3–V4 region) sequencing for gut microbiome profiling	China	Fang et al., 2016 [62]
ALS cases showed decreased diversity, with 3 of 5 ALS patients having a low Firmicutes-to-Bacteroidetes ratio.	5 ALS patients (4 females)	96 healthy controls, with apparently no matching in BMI, sex, or age	Cases with concurrent intestinal diseases or abdominal symptoms	Bacterial 16S rRNA-based PCR with multiple primer design aimed at phylum- and class-level classification	USA	Rowin et al., 2017 [65]
A higher OTU number in cases, though indexes of neither alpha nor beta diversity differed significantly; only one OTU (<i>uncultured Ruminococcaceae</i>) at the genus level differed significantly. Authors concluded that ALS patients do not exhibit a substantial alteration of gut microbiota composition.	25 ALS patients (13 females)	32 healthy controls (16 females) matched for age and sex	Recent antibiotic use, neoplastic disease, autoimmune disease, gastrointestinal disorders, or active infections	Bacterial 16S rRNA sequencing (454 pyrosequencing)	Germany	Brenner et al., 2018 [26]
Increased Firmicutes-to-Bacteroidetes ratio in cases; ALS associated with increased <i>Methanobrevibacter</i> , and decreased <i>Faecalibacterium</i> and <i>Bacteroides</i> , at the genus level.	8 ALS patients (4 females)	8 healthy controls (4 females) with no declared age, sex, or dietary regimes match	ALS-like illnesses, severe systemic disorders, and excessive eating or drinking throughout the previous two weeks	Bacterial 16S rRNA (V4–V5 region) sequencing; unclear declaration of methods employed for statistical analyses	China	Zhai et al., 2019 [43]
Several microbiome differences between ALS cases and controls, with <i>Bifidobacterium pseudocatenulatum</i> being correlated with serum nicotinamide levels, with alterations in gene content for tryptophan and nicotinamide metabolism in cases.	37 ALS patients	29 healthy controls consisting of family members; matched for age and BMI	Pregnancy, fertility therapies, antibiotics, probiotics, and inflammatory or malignant diseases were among the exclusion criteria	Shotgun metagenomic sequencing	Israel	Blacher et al., 2019 [41]
Increased alpha diversity (evaluated by Shannon index) but not beta diversity in ALS; increased in Bacteroidetes; decreased in Firmicutes, at phylum level; Increased in <i>Kineothrix</i> , <i>Parabacteroides</i> , <i>Odoribacter</i> , <i>Sporobacter</i> , <i>Eisenbergiella</i> , <i>Mannheimia</i> , <i>Anaerotruncus</i> , and unclassified <i>Porphyromonadaceae</i> ; decreased in <i>Megamonas</i> at the genus level.	20 probable or definite ALS patients (8 females)	20 healthy controls (8 females) with overall similar living conditions and dietary structure; probable age and sex matching	Diseases and drugs of the gastrointestinal tract, gastrointestinal surgical history, and nutritional imbalances in the diet	Two methods: 16S rRNA (V4 region) sequencing for gut bacterial microbiome profiling, and shotgun metagenomic sequencing for gut microbiome profiling and functional measure	China	Zeng et al., 2020 [24]
Similar alpha and beta diversities; increased in <i>Escherichia</i> (unclassified) and <i>Streptococcus</i> ; decreased in <i>Bilophila</i> (unclassified) at the genus level; <i>Clostridiaceae bacterium</i> JC118, <i>Copro bacter fastidiosus</i> , <i>Eubacterium eligens</i> , and <i>Ruminococcus</i> sp 5 1 39 BF, with two butyrate-producing bacteria (<i>Eubacterium rectale</i> and <i>Roseburia intestinalis</i>) significantly lower in ALS; total relative abundance of the eight dominant butyrate producers significantly lower in ALS.	66 at least suspected ALS (26 females)	61 healthy controls (36 females) consisting of caregivers and other healthy individuals; 12 neurodegenerative controls (7 females)	Adults (older than 18 years), not employing probiotics for 14 days, no use of antibiotics or immune suppressants in the last three months, and no active inflammatory bowel disease, GI malignancy, irritable bowel syndrome, or other GI sickness needing treatment (apart from gastroesophageal reflux) for more than 18 years	Two methods: 16S rRNA (V4 region) sequencing for gut bacterial microbiome profiling, and shotgun metagenomic sequencing for gut microbiome profiling and functional measure	USA	Nicholson et al., 2020 [100]

Table 2. Cont.

Potential Microbiota Alterations in ALS	Cases	Controls	Exclusion Criteria	Methodology for Metagenome	Geographical Background	Reference
No difference in alpha and beta diversities.	49 Motor Neuron Disease patients (15 females)	51 healthy controls (21 females) consisting of spouses, friends, and family members; age, sex, and BMI matching	Individuals with a history of diabetes, gastrostomy use, antibiotic or probiotic use, or FVC < 60%	Bacterial 16S rRNA (V6–V8 region) sequencing for gut microbiome profiling	Australia	Ngo et al., 2020 [101]
Increased alpha diversity in cases (Chao1 index), also with changes in beta diversity; no changes in the Firmicutes-to-Bacteroidetes ratio; increased in <i>Cyanobacteria</i> at the phylum level; increased in <i>Lactobacillus</i> , <i>Citrobacter</i> , and <i>Coprococcus</i> at the genus level; the PCR-denaturing gradient gel electrophoresis analysis demonstrated a distinct cluster split between the bacterial profiles of ALS patients and healthy people. Compared to Eubacteria, the profiles of yeast were significantly simpler, and there was no clear correlation between the two that indicated the presence or absence of illness; lower DNA content in feces from ALS patients; lower amount of <i>Clostridium</i> cluster I and yeasts and a higher concentration of <i>E. coli</i> and <i>Enterobacteriaceae</i> were detected in ALS patients.	50 probable or defined ALS patients (22 females)	50 controls (22 females) of unrelated subjects, unrelated family members, or friends; matched for sex, age, origin, eating habits, and geographic region	Individuals with noninvasive ventilation, gastrostomy, illnesses, antibiotic or medication use during the last eight weeks, or FVC < 50%	Bacterial 16S rRNA (V3–V4 region) sequencing for gut microbiome profiling; PCR-Denaturing Gradient Gel Electrophoresis for the first 38 control and 38 diseased subjects recruited in order to have a preliminary investigation of total Eubacteria and yeast populations. DNA was amplified using primers targeting the V2–V3 region of 16S rDNA and the D1 region of 26S rDNA; absolute quantification of <i>Lactobacillus</i> spp., <i>Bifidobacterium</i> spp., <i>Clostridium</i> cluster I (including <i>C. baratii</i> , <i>C. histolyticum</i> , <i>C. butyricum</i> , <i>C. prefringens</i> , <i>C. botulinum</i> , and <i>C. tetani</i>), <i>Escherichia coli</i> , <i>Enterobacteriaceae</i> , and total yeasts was performed with qPCR	Italy	Di Gioia et al., 2020 [102]; Mazzini et al., 2018 [128]
ALS was associated with decreased <i>Succinivibrionaceae</i> and <i>Lachnospiraceae</i> family abundance, with dominance of <i>Streptococcaceae</i> and <i>Ruminococcaceae</i> in controls. LEfSE analyses showed that <i>Atopobiaceae</i> , <i>Actinomycetaceae</i> , <i>Erysipelatoclostridiaceae</i> , and <i>Peptococcaceae</i> families differed between ALS and controls.	6 ALS patients (1 female)	6 family members living in the same house (4 females); 8 unrelated individuals (3 females) were also chosen	Participants with a history of diarrhea or antimicrobial drug use in the past 3 weeks and with a history of inflammatory bowel disease or history of bowel operations were excluded	Bacterial primers selected from the 16S rRNA region (ITS1 and ITS4) and next-generation sequencing	Turkey	Özaydin Aksun et al., 2024 [129]
Patient microbiomes showed a higher diversity with a higher number of taxa. ALS patients were also deficient in <i>Prevotella</i> spp.	10 ALS patients (3 females)	30 healthy controls (20 females) with overall similar living conditions and dietary structure; probable age and sex matching	Patients receiving enteral nutrition as well as those with a history of bowel disease other than constipation, malignancy, dementia/other cognitive disorders, or Parkinson’s disease/other neurodegenerative diseases	16S rRNA (V4 region) gene sequencing	USA	Hertzberg et al., 2022 [130]
Nasal microbiome changes over ALS, with a lower alpha diversity. <i>Gaiella</i> , <i>Sphingomonas</i> , <i>Polaribacter_1</i> , <i>Lachnospiraceae_NK4A136_group</i> , <i>Klebsiella</i> , and <i>Alistipes</i> were higher in ALS cases at the genus level. No significant differences in nasal microbiota richness and evenness were detected in ALS patients.	66 ALS patients (29 females)	40 healthy controls, caregivers (the spouses of the ALS patients) who lived in close proximity with the patients, potentially matched for diet, daily schedule, pollution exposure, and other related factors.	Human immunodeficiency virus infection, primary immunodeficiency, systemic inflammatory disorder, or history of intranasal drug administration, including antibiotics, immune suppressants, or probiotics within the prior 3 years, and oral administration or infusion of antibiotics in the prior 2 months	16S rRNA (V3–V4 region) gene sequencing	China	Liu et al., 2024 [131]

Table 2. Cont.

Potential Microbiota Alterations in ALS	Cases	Controls	Exclusion Criteria	Methodology for Metagenome	Geographical Background	Reference
No changes in alpha diversity associated with ALS. Lower <i>Bifidobacterium</i> in ALS at the genus level	27 ALS patients (12 females)	15 healthy controls chosen as donors in a fecal microbiota transplantation procedure	FVC < 70%, having a first-degree relative or more than one relative with ALS, a diagnosis of major depression or psychosis acute infection or inflammatory conditions within the preceding 4 weeks, history of abdominal surgery, autoimmune or chronic inflammatory conditions, probiotic or antibiotic use in the past 3 months, active malignancy, pregnancy, and drug abuse	16S rRNA (V3–V4 region) gene sequencing	China	Feng et al., 2024 [132]
Decreased abundance of <i>Fusicatenibacter</i> and <i>Catenibacterium</i> ; increased abundance of <i>Lachnospira</i> .	20,806 cases with ALS	59,804 controls (GWAS summary statistics from IALSC); 18,340 participants (GWAS summary statistics from MiBioGen); 7824 participants (GWAS summary statistics from TwinsUK and KORA)	Not specified	Not specified	Worldwide	Ning et al., 2022 [40]
Increased abundance of the <i>Soutella</i> and <i>Lactobacillales</i> orders in ALS; interaction with genetically predicted increased susceptibility to ALS; increased risk for ALS linked to unclassified <i>Enterobacteriaceae</i> and unclassified <i>Acidaminococcaceae</i> .	20,806 cases with ALS	59,804 controls (GWAS summary statistics from IALSC); 1812 samples (GWAS summary statistics); 7824 adult individuals (GWAS summary statistics from 2 European cohorts)	Not specified	Not specified	Worldwide	Zhang et al., 2022 [133]
Lower alpha diversity in ALS patients, beta-diversity significantly different as well, and <i>Firmicutes</i> and <i>Cyanobacteria</i> differed in ALS patients, at the phylum level. Higher relative abundance in ALS cases of <i>Bacteroides</i> , <i>Parasutterella</i> , and <i>Lactococcus</i> and higher relative abundance in control of <i>Faecalibacterium</i> and <i>Bifidobacterium</i> at the genus level. Lower abundance of butyrate-producing species in ALS.	75 ALS patients (32 females)	110 controls (66 females), matched for sex and age	For controls, neurodegenerative condition or family history of ALS	16S rRNA gene sequencing (V4 region)	USA	Guo et al., 2024 [45]
No differences in Firmicutes-to-Bacteroidetes ratios. α diversity did not differ between ALS patients and healthy controls. β diversity differed between ALS patients and healthy controls. ALS patients had lower phylum <i>Proteobacteria</i> , and from genus <i>Escherichia</i> , <i>Shigella</i> , <i>Klebsiella</i> , <i>Lachnoclostridium</i> , <i>Sutterella</i> , and <i>Catenibacterium</i> ; and genus unclassified family <i>Enterobacteriaceae</i> with increased <i>Subdoligranulum</i> , order <i>Coriobacteriales</i> , <i>Olsenella</i> , <i>Pygmaibacter</i> , <i>Ralstonia</i> , <i>Gordonibacter</i> , <i>Ezakiella</i> , and families <i>Coriobacteriales</i> and <i>Atopobiaceae</i> . Cognitive impairment affected microbiome abundances.	35 ALS patients (14 females)	35 healthy controls, age- and sex-matched (14 females)	Any possible evidence for familial amyotrophic lateral sclerosis (fALS); with other neurodegenerative diseases; with definite gastrointestinal diseases, heart failure, acute infection, tumor, immunodeficiency and autoimmune diseases; any use of antibiotics within the last month; regular drinking of commercial probiotics within the last year or any drinking of commercial probiotics within the last week; obvious symptoms of dysphagia or dyspnea	16S rRNA gene sequencing; the cognitive function of the ALS patients was evaluated using the Edinburgh Cognitive and Behavioral ALS Screen	China	Gong et al., 2022 [39]

Table 2. Cont.

Potential Microbiota Alterations in ALS	Cases	Controls	Exclusion Criteria	Methodology for Metagenome	Geographical Background	Reference
Alpha and beta diversity varied between patients with ALS and healthy donors. <i>Firmicutes</i> was predominant in patients with ALS, resulting in an elevated F/B ratio. Some species with beneficial profiles (<i>B. stercoris</i> , <i>B. uniformis</i> , <i>B. vulgatus</i> , and <i>F. prausnitzii</i>) were lower in ALS patients.	2 patients undergoing fecal microbial transplantation	1 healthy donor	Not specified	Metagenomic sequencing	Japan	Yan et al., 2024 [19]
Any antibiotics use—especially two prescriptions of beta-lactamase-sensitive penicillin—was associated with a higher risk of ALS.	2484 ALS patients according to the Swedish national registers	12,420 healthy individuals matched by sex, birth year, and area of residence	Eligible controls were individuals who were alive and free of ALS diagnosis on the diagnosis date of their corresponding cases	Nested case-control study, conditional logistic regression model to calculate odds ratios	Sweden	Sun et al., 2019 [110]
Marginally significant difference in the abundances of specific bacterial species after FDR correction; <i>Anaerostipes hadrus</i> , <i>Bacteroidales bacterium ph8</i> , <i>Bifidobacterium pseudocatenulatum</i> (correlating with serum nicotinamide), <i>Clostridium leptum</i> , and <i>Escherichia coli</i> . Decreased content in several key genes participating in the metabolism of tryptophan and nicotinamide, focused on <i>Akkermasia muciniphila</i> .	37 ALS patients (8 females)	29 healthy, BMI- and age-matched family members (20 females)	Pregnancy or fertility treatments; use of antibiotics or antifungals in the 3 previous months; consumption of probiotics 1 month before; active inflammatory or neoplastic disease three years before enrolment; chronic gastrointestinal disorder, myocardial infarction, or cerebrovascular accident in the six months before participation; coagulation disorders; chronic immunosuppressive medication usage; or pre-diagnosed type I or type II diabetes mellitus or treatment with anti-diabetic medication	Shotgun metagenomics sequencing	Israel	Blacher et al., 2019 [41]
No changes in alpha or beta diversity in ALS, nor in the Firmicutes-to-Bacteroidetes ratio; ALS patients showed higher <i>Fusobacteria</i> and <i>Acidobacteria</i> at the phylum level.	16 diagnosed ALS patients (8 females)	12 controls (6 females) matched for age and sex, among spouses and caregivers	Cases with GI diseases or those treated with drugs (such as antibiotics) that could alter nutritional balance and affect intestinal microbiota. Antibiotic use within 2 months	16S rRNA gene sequencing (V3–V4 region)	Spain	Fontdevila et al., 2024 [13]
Spinal ALS patients showed higher fecal F/B ratios in contrast with bulbar ALS patients who had decreased oral F/B. The Shannon index in ALS patients evidenced decreased richness. In spinal ALS, there was an enrichment of the <i>Ruminococcaceae</i> and a depletion of the <i>Bacteroidaceae</i> . In the oral microbiota of bulbar ALS, there was a depletion of <i>Veillonellaceae</i> and an increased abundance of the <i>Prevotellaceae</i> family.	36 Patients with bulbar or spinal ALS (24 spinal onset with 15 females; 12 bulbar onset with 8 females)	20 healthy controls living with patients	Exposure to antibiotics/probiotics, immunocompromising illness/therapy, previous abdominal/anorectal surgery, GI-/respiratory-/gynecological-tract infection, food poisoning, or major epistaxis requiring treatment; active/persistent primary disease of GI-/respiratory-/gynecological-tract, endocrinal disease, heart failure, severe renal-insufficiency, current pregnancy, drug/alcohol abuse, and active smoking within 6 months	Deep sequencing the V4 hypervariable region of bacterial 16S rRNA	USA	Kim et al., 2022 [44]

¹ Abbreviations: FVC: Forced-vital capacity; OTU: Organizational Taxonomic Unit; MI: Body-mass index; GI: gastrointestinal.

Further complicating the matter is the substantial heterogeneity of the human microbiome, influenced by individual factors such as living environment, ethnicity, diet, lifestyle, and medical history. This variability and differences in study populations, recruitment methods, sample processing, and data analysis techniques across studies make it difficult to compare and synthesize results. For example, a genome-wide association study of 18,340 individuals from 24 international cohorts revealed significant variability in microbiome composition, with only 9 out of 410 genera detected in over 95% of participants [134]. The sparsity of microbiome data further complicates the ability to discern real signals from noise, especially in studies with limited sample sizes.

The selection of cases and controls also introduces potential biases. Many studies rely on prevalent ALS cases, which may overrepresent patients with longer survival and may not accurately reflect the broader ALS population. Additionally, the timing of sample collection post-diagnosis raises concerns about reverse causation, as the disease and its treatments can significantly alter the gut microbiome. Using different control groups, such as healthy volunteers versus relatives of patients, presents its own advantages and limitations, potentially leading to residual confounding or over-matching.

Finally, methodological inconsistencies across studies, including variations in sample processing, sequencing data handling, and statistical methods, further contribute to the heterogeneity of results. The use of inappropriate statistical methods and the lack of correction for multiple comparisons in several studies also raise concerns about the validity of the findings. Indeed, advanced statistics, such as cross-sectional approaches using probabilistic generative event-based models to stage patients using microbiome associations, could also help clarify the potential role of the microbiome in ALS clinical heterogeneity.

3.4.3. Mechanistic Understanding of Microbiota's Role in ALS

While correlations between gut microbiota dysbiosis and ALS have been established, the mechanistic pathways linking microbial changes to neurodegeneration remain unclear. For instance, it is still not fully understood how microbial metabolites such as SCFAs or bacterial amyloids directly influence motor neuron health and neuroinflammatory pathways. In particular, the role of curli-like amyloids in promoting protein misfolding in ALS-specific proteins like TDP-43 and SOD1 needs further exploration. Investigating these mechanisms could help identify specific microbial targets for therapeutic intervention. Indeed, the possibility of testing them *in vitro* in relevant cell cultures, such as those derived from induced pluripotency human stem cells, could help to design therapeutical approaches rationally.

3.4.4. Therapeutic Trials of Microbiota-Based Interventions

Although preliminary studies have suggested the potential benefits of probiotics, prebiotics, and FMT in other neurodegenerative diseases, robust clinical trials in ALS are still lacking. The efficacy and safety of these microbiota-based interventions must be thoroughly tested in ALS patients before they can be widely recommended as part of treatment protocols. Additionally, the long-term impact of dietary interventions, particularly those aimed at modulating the gut microbiota, should be studied in the context of ALS. Future research should focus on developing randomized controlled trials that assess the microbiota composition and clinical outcomes in ALS patients [21] based on anecdotal evidence of FMT-related changes in ALS [135]. In this line, a very recent review lists at least four ongoing studies of this type [53].

3.4.5. Role of Environmental and Dietary Factors in Modulating Microbiota

Environmental exposures, such as diet, antibiotics, and geographical factors, are critical in shaping gut microbiota. However, the specific impact of these factors on ALS progression

remains under-explored. For example, the potential link between environmental toxins like BMAA and gut microbiota dysbiosis in ALS requires further investigation [21]. Indeed, recent reports show that specific microbiota, under stress, could generate D-amino acids, such as D-glutamate, which could contribute to neurotoxicity, adding another layer of complexity in the sense that not only specific microbiota but selected conditions could confer pathogenicity to microbiome [136]. Future research should aim to dissect how dietary patterns, antibiotic use, and environmental exposures interact with microbiota changes in ALS and whether these factors could be modified to slow disease progression.

3.4.6. Developing Personalized Microbiota-Based Therapies

As our understanding of the microbiota's role in ALS grows, the potential for personalized microbiota-based therapies becomes increasingly evident. Just as ALS patients respond differently to pharmacological treatments, they are likely to exhibit diverse responses to microbiota-modulating interventions. Future research should focus on identifying biomarkers that predict individual responses to probiotics, prebiotics, or FMT. Personalized approaches could involve tailoring interventions based on an individual's microbiota profile, genetic background, and ALS phenotype, allowing for more targeted and effective treatments.

4. Conclusions

The potential role of gut microbiota in the pathogenesis and progression of ALS represents a promising yet underexplored avenue of research. As ALS remains a multifactorial neurodegenerative disorder with limited therapeutic options, the emerging links between gut dysbiosis and neuroinflammation open new possibilities for intervention. Microbial metabolites, such as SCFAs, have been shown to influence key inflammatory and metabolic pathways, and their reduced production in ALS patients may exacerbate disease progression. Furthermore, bacterial amyloids and neurotoxins like BMAA suggest an environmental and microbial component to ALS that warrants further investigation.

The gut–brain axis provides a critical framework for understanding how gut health impacts neurodegenerative diseases. In ALS, the interplay between the liver, gut, and CNS suggests that systemic metabolic disturbances, driven by dysbiosis, may contribute to neuroinflammation and motor neuron death. These insights highlight the need for targeted therapies that restore microbial balance, reduce harmful metabolites, and support neuroprotective pathways.

Future research should prioritize larger, longitudinal studies that can establish causality and further elucidate the specific microbial pathways involved in ALS. Personalized microbiota-based therapies, such as probiotics, prebiotics, and FMT, represent exciting prospects but require robust clinical validation. Ultimately, the modulation of gut microbiota could complement existing treatments, offering a new dimension of therapeutic strategies aimed at mitigating the progression of ALS.

In conclusion, while the relationship between the gut microbiota and ALS is still in its infancy, the evidence, thus far, suggests that microbiota-targeted therapies hold potential as adjunctive treatments. As our understanding of the microbiota's role in ALS deepens, so will the opportunities for novel interventions that could enhance the quality of life for ALS patients and potentially slow disease progression.

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