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Opinion

Amyotrophic Lateral Sclerosis as a Systemic Disease: Why Integrative and Microbiome-Focused Approaches Deserve Re-Evaluation

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Abstract

Despite decades of intensive research, therapeutic advances in amyotrophic lateral sclerosis (ALS) remain limited. Increasing evidence suggests that ALS is a multisystem disorder involving motor neuron degeneration, immune dysregulation, skeletal muscle pathology, and gastrointestinal dysfunction, thereby challenging the adequacy of current therapeutic strategies. Complementary and alternative medicine (CAM) approaches are widely used by patients with ALS. However, their efficacy remains controversial owing to limited clinical evidence and methodological limitations. The multicomponent herbal medicine and system-level characteristics of CAM conceptually align with the emerging view of ALS as a multisystemic disease. The involvement of gut microbiome dysbiosis in the pathophysiology of ALS has provided a unifying biological framework linking the peripheral, metabolic, and neuroinflammatory processes. These findings suggest that the combination of CAM and conventional therapy may serve as a potential integrative approach to target gut–brain–muscle interactions and systemic disease pathways. This article highlights critical gaps in the existing evidence and proposes that microbiome-focused, biomarker-driven clinical trials are essential to thoroughly evaluate CAM-based interventions in ALS. Embracing a system-oriented therapeutic framework may help address the complexity of ALS beyond traditional neuron-centered approaches.

Keywords: amyotrophic lateral sclerosis; gut microbiome; complementary and alternative medicine; neuroimmune modulation; multisystem therapy

1. Structural Limitations of Conventional ALS Therapies

Despite decades of intensive research, progress in treating amyotrophic lateral sclerosis (ALS) has been limited, with approved drugs providing only modest clinical benefits. Riluzole, the first disease-modifying ALS drug, extends survival by 2–3 months on average, without substantially altering disease progression [1]. Edaravone, an antioxidant agent, is effective in a narrowly defined subgroup of patients with early-stage ALS, and its real effectiveness remains controversial [2]. A limitation of both of these drugs is their single-target pharmacological paradigm—riluzole depends on glutamatergic excitotoxicity and edaravone on oxidative stress. However, the pathogenesis of ALS involves converging mechanisms, including excitotoxicity, neuroinflammation, mitochondrial dysfunction, protein aggregation, axonal transport defects, and metabolic disturbances [3,4]. Therefore, targeting a single molecular pathway is insufficient in altering this multifactorial disease process. Moreover, current pharmacological strategies predominantly focus on central motor neuron protection, often overlooking peripheral and systemic pathology, including skeletal muscle degeneration, immune dysregulation, and gut microbiome alterations. Emerging evidence suggests that these peripheral systems actively contribute to disease progression beyond epiphenomena [5,6,7]. Collectively, these limitations highlight the urgent need for a conceptual shift beyond neuron-centric, single-target therapeutic approaches in ALS patients.

1.1 ALS as a Multisystem Disease

Evidence indicates a multisystem, neurodegenerative nature of ALS, which involves dynamic interactions among the nervous system, immune system, skeletal muscle, and gastrointestinal tract (Table 1, Ref. [3,5,6,7,8,9,10,11,12]). Neuroinflammation, immune dysregulation, microbiome imbalance, and mitochondrial dysfunction interact to contribute to the progression and systemic pathology of ALS.

Neuroinflammatory activation of microglia and astrocytes is recognized as a key driver of disease progression [13]. In parallel, skeletal muscles exhibit intrinsic pathological changes, including mitochondrial dysfunction, altered myokine secretion, and impaired neuromuscular junction maintenance, which may lead to motor neuron degeneration [12]. Systemic immune dysregulation contributes to the pathophysiology of ALS, and peripheral immune cells influence neuroinflammation [14]. More recently, alterations in the gut microbiome were recognized as novel ALS pathogenesis factors. Evidence from animal models and clinical studies has demonstrated gut dysbiosis, impaired intestinal barrier function, and metabolite imbalances in ALS, suggesting the existence of a gut–brain–muscle axis

Table 1. Amyotrophic lateral sclerosis as a multisystem disease: Cellular and molecular mechanisms.

System	Pathophysiological features	Cellular alterations	Molecular mechanisms	Key references
Central nervous system	Progressive motor neuron degeneration and neuroinflammation	Loss of motor neurons; microglial and astrocyte activation	TDP-43 aggregation; SOD1 mutation; glutamate excitotoxicity; mitochondrial dysfunction	[3,8]
Immune system	Chronic systemic inflammation and immune dysregulation	Activated microglia; T-cell imbalance	NF-κB activation; cytokine dysregulation; inflammasome activation	[9,10]
Gut microbiome	Dysbiosis and impaired intestinal barrier function	Reduced microbial diversity; decreased SCFA-producing bacteria	Reduced SCFAs; increased LPS; altered microbial metabolites	[6,7]
Skeletal muscle	Muscle atrophy and neuromuscular junction degeneration	Muscle fiber atrophy; NMJ disruption	Mitochondrial dysfunction; oxidative stress; impaired proteostasis	[5,11]
Metabolic system	Energy metabolism impairment and systemic metabolic dysfunction	Mitochondrial impairment; altered lipid metabolism	Oxidative stress; metabolic dysregulation	[12]

TDP-43, TAR DNA-binding protein 43; SOD1, superoxide dismutase 1; NF-κB, nuclear factor kappa B; SCFA, short-chain fatty acid; LPS, lipopolysaccharide; NMJ, neuromuscular junction.

[6,7,15]. This multisystem perspective carries profound therapeutic implications. Diseases characterized by distributed, interconnected pathological networks are unlikely to respond adequately to narrowly targeted pharmacological interventions. Therefore, therapeutic strategies simultaneously modulating multiple pathways and organ systems may be preferable to address the complexity of ALS.

2. CAM and Microbiome in ALS—Opportunities and Challenges

2.1 Positive Outcomes and Therapeutic Potential of CAM in ALS

Accumulating preclinical evidence suggests that selected complementary and alternative medicine (CAM) interventions may provide symptomatic benefits and modulate disease-related biological pathways in ALS. Acupuncture, a CAM modality commonly used for ALS patients, improves fatigue, muscle stiffness, pain, and quality of life, with a recent systematic review indicating that it may regulate autonomic function, suppress neuroinflammatory signaling, and improve neuromuscular symptoms [16,17,18,19]. Table 2 (Ref. [17,18,20]) summarizes the major CAM approaches for ALS, highlighting their proposed mechanisms of action, including modulation of neuroinflammation, mitochondrial function, neurotransmission, and the gut microbiome. Overall, CAM approaches can potentially provide supportive benefits; however, clinical evidence remains limited, warranting the need for more well-designed studies.

Traditional herbal medicines have garnered attention owing to their potential multitarget pharmacological properties. A scoping review of clinical and preclinical studies reported that several herbal formulations exert antioxidant, anti-inflammatory, and mitochondrial protective effects in ALS models, and some clinical reports have shown stabilized functional scores and delayed symptom progression [19,21]. These multicomponent interventions may simultaneously influence excitotoxicity, oxidative stress, neuroinflammation, and metabolic dysregulation, which are central to ALS pathogenesis.

The widespread use of CAM among the ALS patients reflects patient-perceived benefits, unmet therapeutic needs, and strong interest in integrative approaches. Surveys from several countries show that over half of ALS patients use various forms of CAM, most commonly herbal medicine, acupuncture, dietary supplements, and mind–body interventions, alongside conventional therapy [17,18,19]. In South Korea, a nationwide survey revealed CAM use in virtually all respondents with ALS [19]. Together, these findings suggest that the multitarget characteristics of CAM-based interventions may offer complementary benefits for symptom control and systemic modulation in ALS, aligning with the multisystem nature of the disease.

2.2 The Gut Microbiome as a Modulator of ALS Pathophysiology

Recent studies have identified the gut microbiome as an emerging and potentially important modulator of ALS pathogenesis. Animal and human investigations have consistently revealed alterations in microbial composition, reduced diversity, and metabolic imbalances in ALS patients. A seminal study using the $SOD1^{G93A}$ mouse model demonstrated that gut dysbiosis precedes motor symptom onset and that supplementation with Akkermansia muciniphila significantly improves motor performance and survival by restoring nicotinamide metabolism [6].

Clinical studies have confirmed gut microbiome alterations in ALS patients. Fang et al. [7] reported significant differences in microbial diversity and composition between ALS patients and healthy controls, includ-

Table 2. Complementary and alternative medicine (CAM) approaches in amyotrophic lateral sclerosis (ALS): Proposed mechanisms and current evidence.

CAM approach	Representative interventions	Proposed mechanisms of action	Level of available evidence in ALS	References
Herbal medicine	Traditional East Asian herbal formulas; multi-herb prescriptions	Anti-inflammatory and antioxidant effects; modulation of neuroinflammation; mitochondrial protection; multi-target pathway regulation	Moderate but limited-quality evidence; systematic reviews and small clinical studies suggest symptomatic improvement	[17,20]
Acupuncture	Manual acupuncture; electroacupuncture	Regulation of neuroinflammation; modulation of neurotransmission; autonomic nervous system regulation	Low-to-moderate evidence; small clinical studies suggest functional improvement but methodological limitations remain	[17,18]

ing reduced abundance of beneficial commensals and enrichment of pro-inflammatory taxa . Subsequent studies confirmed that gut dysbiosis is a reproducible feature of ALS rather than a secondary epiphenomenon with associated functional metabolic disturbances [22,23]. Gut microbiota-derived metabolites, including short-chain fatty acids (SCFAs) and nicotinamide-related compounds, are known modulators of host metabolic and immune pathways, which can potentially influence neuroinflammation and mitochondrial function in ALS [6,15]. Experimental ALS models have further linked gut dysbiosis to disrupted nicotinamide metabolism and metabolic profiles associated with neuroinflammatory activation and neuromuscular vulnerability [6]. Table 3 (Ref. [7,24,25,26,27,28,29]) summarizes key microbiome-associated biomarkers reported in ALS, including alterations in microbial diversity, SCFA-producing taxa, tryptophan-related microbial metabolism, fecal inflammatory and barrier markers, and microbial functional markers. These biomarkers support the involvement of gut dysbiosis and microbiome–immune interactions as contributing factors in the multisystem pathophysiology of ALS.

These findings suggest that the gut microbiome influences ALS progression via systemic metabolic and immune mechanisms. Recognizing ALS as a multisystem disease may provide a broader framework for understanding its pathophysiology. The gut microbiome has emerged as a promising potential therapeutic target requiring further investigation.

3. CAM Approaches and Gut Microbiome Modulation in ALS

Traditional herbal medicines, a major component of CAM, have emerged as potent modulators of the gut microbiota, largely because many herbal constituents exhibit low systemic bioavailability and are extensively biotransformed by intestinal microbes into bioactive metabolites [30]. These microbially derived metabolites, including phenolic acids, SCFAs, and bile acid derivatives, exert immunomodulatory, antioxidant, and neuroprotective effects by regulating inflammatory signaling, oxidative stress responses, and mitochondrial function [31,32]. Preclinical studies have demonstrated that commonly used East Asian herbal formulations can partially restore dysbiotic microbial profiles, suppress endotoxin-producing gram-negative taxa, and enhance microbial pathways involving energy homeostasis and nicotinamide metabolism—processes which are critically impaired in neurodegenerative diseases [33,34]. Herbal medicines are critical because the resulting bioactive metabolites regulate immune responses, oxidative stress, and mitochondrial function, all of which are critically impaired in ALS [35,36]. Representative herbal bioactive compounds, such as berberine, ginsenoside Rg1, baicalin, paeoniflorin, and Astragalus polysaccharides, have been reported to reshape gut microbial composition, alter microbial metabolites including SCFA- and indole-related pathways, and attenuate inflammatory signaling, thereby supporting the plausibility of microbiome-targeted CAM strategies in ALS [37,38,39,40].

Other CAMs, such as acupuncture and mind–body interventions, indirectly influence gut microbial composition by regulating the autonomic nervous system and activity of the hypothalamic–pituitary–adrenal (HPA) axis [41,42], with evidence suggesting that vagal activation and stress reduction may improve intestinal barrier integrity, reduce systemic endotoxemia, and attenuate microglial activation, thereby reshaping the gut–brain–immune axis [43,44]. Although direct microbiome-focused studies remain limited, these findings support the notion that non-pharmacological CAM may modulate microbial ecology and host–microbiome interactions via neuroimmune mechanisms. Despite these promising observations, most studies remain heterogeneous in design, with substantial variability in intervention protocols, microbial sequencing methodologies, and outcome measures, limiting cross-study comparability [45,46]. Furthermore, most human studies are small-scale and observational, precluding causal inference and comprehensive evaluation of their effects on disease progression [47]. Nevertheless, the current evidence collectively supports the concept of CAM-based strategies representing a viable and biologically plausible approach for tar-

Table 3. Microbiome-associated biomarkers relevant to amyotrophic lateral sclerosis (ALS) research.

Biomarker category	Specific markers/examples	Reported direction in ALS	Biological/clinical relevance	References
Microbial diversity markers	α-diversity (Shannon index), community structure, OTU composition	Altered community structure; dysbiosis reported	Reflects ecological instability of the gut microbiome; useful as a broad microbiome signature	[7,24]
Short-chain fatty acid (SCFA)-producing taxa	*Roseburia*, *Faecalibacterium*, other butyrate-producing bacteria	Often decreased	Loss of SCFA-producing taxa may weaken intestinal barrier integrity and anti-inflammatory signaling	[25]
SCFAs	Butyrate, propionate, acetate	Often reduced or dysregulated	Altered SCFA profiles reflecting changes in gut microbial metabolic activity	[26]
Tryptophan-related microbial metabolism	Indole derivatives, kynurenine pathway metabolites, serotonin-related metabolites	Dysregulated microbial tryptophan metabolism reported	Relevant to immune signaling, epithelial integrity, and neuroactive metabolite production	[27]
Fecal inflammatory and barrier markers	Calprotectin, secretory IgA (sIgA), eosinophil protein X	Elevated levels observed in ALS cohorts	Indicate intestinal inflammation and mucosal immune activation	[24]
Systemic and fecal cytokines	IL-6, TNF-α, IL-1β, cytokine panels	Distinct cytokine profiles reported in ALS	Associated with systemic and intestinal immune dysregulation linked to microbiome alterations	[28]
Microbial functional biomarkers	KEGG pathway prediction	Functional differences in metabolic pathways observed	Suggest altered microbiome metabolic functional potential in ALS	[29]

OTU, Operational Taxonomic Unit; KEGG, Kyoto Encyclopedia of Genes and Genomes; IgA, immunoglobulin A; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.

geting gut microbiome dysregulation and downstream systemic pathways [48].

Therefore, there is a strong rationale for integrating microbiome-focused CAM interventions into future well-designed clinical trials incorporating microbial, metabolic, and inflammatory biomarkers, especially in complex multisystem disorders such as ALS. Emerging evidence suggests that CAM interventions may influence ALS progression by modulating the gut microbiome and its downstream neuroimmune and metabolic pathways. Growing evidence links ALS with gut microbial dysbiosis, contributing to systemic inflammation, intestinal barrier dysfunction, and microglial activation, involved in motor neuron degeneration [47,49,50].

Preclinical studies have demonstrated that microbiome-targeted interventions, including probiotic supplementation, dietary modulation, and herbal formulations, can partially restore microbial diversity, reduce neuroinflammatory signaling, and improve motor performance and survival in ALS animal models [51,52]. These effects are believed to be mediated through microbial metabolites, such as SCFAs, nicotinamide-related metabolites, and tryptophan derivatives, which regulate neuronal bioenergetics, synaptic plasticity, and mitochondrial integrity [53,54]. Accumulating evidences supports the existence of a gut–brain–muscle axis in ALS, whereby microbial metabolites and immune mediators influence neuromuscular junction stability, skeletal muscle metabolism, and myokine signaling, creating a bidirectional pathogenic loop linking intestinal dysbiosis with motor neuron vulnerability [55,56]. Recognizing ALS as a multisystem disease may provide a broader framework for understanding its pathophysiology, with the gut microbiome emerging as a promising potential therapeutic target requiring further investigation. In addition to herbal medicine, acupuncture and mind–body CAM interventions may indirectly modulate the gut microbiota through autonomic nervous system regulation and hypothalamic–pituitary–adrenal axis stabilization. These mechanisms may improve intestinal barrier integrity, reduce systemic endotoxemia, and attenuate neuroinflammatory cascades contributing to ALS progression [41,57]. Although clinical evidence remains limited, small observational studies suggest that dietary and probiotic interventions may improve gastrointestinal symptoms and inflammatory biomarkers in ALS patients, supporting the translational potential of microbiome-targeted CAM strategies [58,59]. Collectively, these findings support the hypothesis that CAM interventions targeting gut microbiome dysregulation are biologically plausible and potentially disease-modifying therapeutic strategies for ALS treatment (Fig. 1).

Future clinical trials should integrate microbiome sequencing, metabolomics, and neuroinflammatory biomarkers to clarify the causal relationships and optimize personalized microbiome-based CAM therapies for ALS patients.

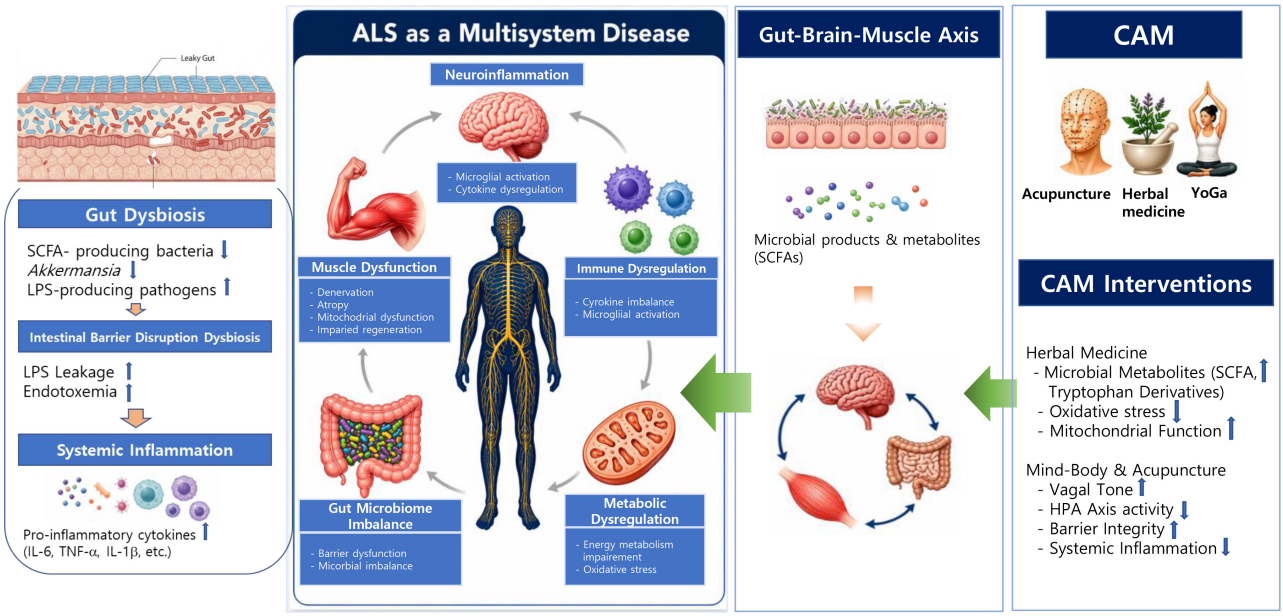

Fig. 1. Schematic illustration of the proposed role of gut dysbiosis in amyotrophic lateral sclerosis (ALS) pathogenesis and the therapeutic potential of complementary and alternative medicine (CAM) interventions. Gut dysbiosis leads to intestinal barrier disruption and systemic inflammation. ALS is a multisystem disorder involving neuroinflammation, muscle dysfunction, immune dysregulation, gut microbiome imbalance, and metabolic changes. Bidirectional interactions among the gut, brain, and muscle (gut–brain–muscle axis) are shown. CAM interventions (e.g., acupuncture, herbal medicine, and mind–body practices) that may modulate these processes are also shown. Gut microbiota imbalance may compromise intestinal barrier integrity and promote systemic inflammation, contributing to neuroinflammation, immune dysregulation, and muscle dysfunction via the gut–brain–muscle axis. Complementary approaches, including acupuncture, herbal medicine, and yoga, may help restore microbial balance and modulate disease-related pathways.

4. Conclusion

Future research should prioritize developing system-oriented, integrative therapeutic strategies for ALS treatment. Importantly, ALS should be recognized and approached as a multisystem disorder involving interconnected dysfunction across the nervous, immune, metabolic, and gut microbiome systems. Microbiome-targeted CAM interventions should be systematically evaluated in well-designed clinical trials incorporating microbial, metabolic, and inflammatory biomarkers as outcome measures, given that current evidence is largely observational and underpowered. Controlled studies (e.g., fecal microbiota transplantation trials) have demonstrated the feasibility of microbiome modulation, but larger multicenter biomarker-guided trials are necessary to clarify clinical efficacy [47,60,61].

Network pharmacology and multi-omics approaches may be powerful tools to elucidate herb–compound–target–pathway interactions and identify synergistic molecular networks relevant to ALS pathogenesis. Innovative integrative trial designs combining standard pharmacotherapy with selected CAM modalities should be explored, incorporating stratification by genetic background, disease stage, and microbiome profiles, alongside standardized safety and quality control procedures for herbal and acupuncture interventions. Collaboration among neurologists, pharmacologists, and integrative medicine specialists is essential to ensure methodological rigor and translational relevance. A microbiome-centered systems medicine approach paves the way for more effective ALS management by bridging integrative strategies with mechanism-based, disease-modifying therapies.

Author Contributions

E.J.Y. is the sole author of this manuscript and contributed to all aspects of the work, including study conception and design, literature review, manuscript drafting, revision, and submission. E.J.Y. read and approved the final manuscript and agrees to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The author declares no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The author used ChatGPT (GPT-5.5) to assist with language editing and improvement of grammar in the manuscript. The author reviewed and edited the content.

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