


REVIEW

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The potential therapeutic approaches targeting gut health in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a narrative review

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Abstract

Background Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex disorder characterized by persistent fatigue and cognitive impairments, with emerging evidence highlighting the role of gut health in its pathophysiology. The main objective of this review was to synthesize qualitative and quantitative data from research examining the gut microbiota composition, inflammatory markers, and therapeutic outcomes of interventions targeting the microbiome in the context of ME/CFS.

Methods The data collection involved a detailed search of peer-reviewed English literature from January 1995 to January 2025, focusing on studies related to the microbiome and ME/CFS. This comprehensive search utilized databases such as PubMed, Scopus, and Web of Science, with keywords including “ME/CFS,” “Gut-Brain Axis,” “Gut Health,” “Intestinal Dysbiosis,” “Microbiome Dysbiosis,” “Pathophysiology,” and “Therapeutic Approaches.” Where possible, insights from clinical trials and observational studies were included to enrich the findings. A narrative synthesis method was also employed to effectively organize and present these findings.

Results The study found notable changes in the gut microbiota diversity and composition in ME/CFS patients, contributing to systemic inflammation and worsening cognitive and physical impairments. As a result, various microbiome interventions like probiotics, prebiotics, specific diets, supplements, fecal microbiota transplantation, pharmacological interventions, improved sleep, and moderate exercise training are potential therapeutic strategies that merit further exploration.

Conclusions Interventions focusing on the gut-brain axis may help reduce neuropsychiatric symptoms in ME/CFS by utilizing the benefits of the microbiome. Therefore, identifying beneficial microbiome elements and incorporating their assessments into clinical practice can enhance patient care through personalized treatments. Due to the complexity of ME/CFS, which involves genetic, environmental, and microbial factors, a multidisciplinary approach is also necessary. Since current research lacks comprehensive insights into how gut health might aid ME/CFS treatment, standardized diagnostics and longitudinal studies could foster innovative therapies, potentially improving quality of life and symptom management for those affected.

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Keywords Chronic fatigue syndrome, Health, Myalgic encephalomyelitis, Microbiota-gut-brain-axis, Microbiome-gut-brain-axis, Therapeutics

Background

The multifaceted condition known as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) poses significant challenges to both patients and healthcare professionals. Characterized by persistent fatigue, post-exertional malaise, and cognitive dysfunction, ME/CFS affects approximately 1% of the global population, with a higher prevalence in women [1, 2]. The complexity of this disorder arises from its unclear etiology and the lack of definitive diagnostic tools, making it difficult to differentiate from other overlapping illnesses [3, 4]. Research has increasingly highlighted the relationship between gut health and the symptoms of ME/CFS, particularly chronic inflammation and dysbiosis, which may exacerbate fatigue and cognitive issues [1, 5, 6]. Hence, exploring therapeutic approaches that target gut health could provide promising avenues for alleviating ME/CFS symptoms and improving patient quality of life [7–9]. Recent investigations into the gut microbiome reveal a concerning prevalence of dysbiosis in ME/CFS patients, characterized by reduced microbial diversity and an imbalance between beneficial and harmful bacteria [1, 10–14]. This microbial dysregulation contributes to systemic inflammation and immune dysfunction, further complicating the clinical picture of ME/CFS [15–17]. Moreover, gastrointestinal symptoms often reported by individuals with ME/CFS underscore the potential gut-brain axis involvement in disease manifestation [8, 13]. As chronic inflammation can lead to increased gut permeability, also known as “leaky gut,” the interactions between gut health and neurological function become increasingly relevant [1, 10, 11, 13, 18]. These insights suggest that interventions aimed at restoring gut microbiota balance—through dietary modifications, probiotics, fecal microbiota transplantation, etc.—may offer novel therapeutic strategies to alleviate the debilitating symptoms of this complex condition [1, 8]. Furthermore, the recognition of gut health as a pivotal aspect of ME/CFS management opens the door to a range of therapeutic approaches that warrant further exploration [1, 10, 11, 13]. Prebiotics, probiotics, and dietary interventions have shown promise in preliminary studies, pointing toward the potential for restoring microbial balance and combating dysbiosis [10, 13]. Adjunct therapies focusing on digestive health may not only mitigate fatigue but could also enhance cognitive function, presenting a comprehensive approach to treatment [6, 7]. Integrating these

gut health-focused strategies into clinical practice could transform the management of ME/CFS, fostering a more holistic perspective on the condition that places emphasis on underlying biological mechanisms [5, 10, 15]. Ultimately, as research progresses, the significance of gut health in ME/CFS may lead to more effective and personalized treatment modalities that better address this challenging syndrome [8, 9, 19].

Research objectives and significance

The primary objectives of this review are multifaceted; firstly, it aims to synthesize existing literature on the gut microbiome’s composition in individuals with ME/CFS, identifying whether specific dysbiotic patterns correlate with the severity of ME/CFS symptoms. Secondly, this article addresses the possible biological pathways that link dysbiosis to the symptoms of ME/CFS. Thirdly, the paper will evaluate a spectrum of interventions focused on restoring gut health. Lastly, the research seeks to generate recommendations for clinical practice, outlining how such interventions could be integrated into existing ME/CFS treatment protocols. The significance of this research extends beyond the academic realm; it holds practical implications for patients suffering from ME/CFS, who often find themselves with limited treatment options that adequately address their complex symptoms. By elucidating the connections between gut health and ME/CFS, this study not only contributes to the existing body of knowledge but also seeks to empower healthcare providers to implement evidence-based strategies that could significantly enhance patient outcomes. Moreover, understanding these relationships may catalyze future research endeavors aimed at developing more effective therapies tailored to ME/CFS, potentially reshaping the clinical landscape for this frequently overlooked condition. Consequently, this section emphasizes the urgency of addressing gut health as a viable therapeutic target, thereby optimizing patient care within the ME/CFS community and fostering a more integrative approach to chronic illness management.

Methods

In this narrative review, data collection techniques included a comprehensive search of English peer-reviewed literature from January 1995 to January 2025 to ensure that an extensive range of studies addressing the microbiome and ME/CFS were included. Databases such as PubMed, Scopus, and Web of Science were utilized,

employing relevant keywords related to the “ME/CFS,” “Gut-Brain Axis,” “Gut Health,” “Intestinal Dysbiosis,” “Microbiome Dysbiosis,” “Pathophysiology,” and “Therapeutic Approaches.” The goal was to extract qualitative and quantitative data from studies that investigate gut microbiota composition, assess inflammatory markers, and evaluate the therapeutic outcomes of interventions targeting the microbiome. Additionally, when available, insights from clinical trials and observational studies were included to enrich the findings and support the overarching narrative being developed. Finally, the method of narrative synthesis was utilized to organize and convey the findings effectively, adhering to the framework suggested by MacLure [20]. This approach emphasizes the critical role of researcher engagement in various activities including reading, writing, thinking, interpretation, argumentation, and justification.

Overview of gut microbiota composition in ME/CFS patients vs. healthy individuals

Research on ME/CFS patients compared to healthy controls has identified changes in intestinal microbiota, although no specific microbial signature has been consistently found (see Table 1) [12, 21–31]. This inconsistency in results makes it difficult to establish a direct link between changes in gut microbiota and the disease mechanisms [32–34]. In this regard, a systematic review by Newberry et al. indicates conflicting study results, but the overall evidence suggests dysbiosis in ME/CFS patients [35]. A study identified microbial dysbiosis in individuals with ME/CFS, showing 83% classification accuracy using gut microbiome dysbiosis and elevated inflammatory blood markers due to microbial translocation. Despite a small sample size of 48, these findings need further validation. The 16S rRNA stool analysis revealed reduced bacterial diversity and richness, lower anti-inflammatory species, and higher pro-inflammatory species like *Enterobacteriaceae* in ME/CFS patients [27]. Typically, high microbial diversity correlates with good health and fitness, as cardiorespiratory fitness accounts for roughly 20% of gut diversity variation

Table 1 Overview of microbial alterations in ME/CFS patients relative to healthy controls

Enhanced microbiota	Reduced microbiota	Intestinal dysbiosis	Subjects	Country	Authors’ names (year)
<i>Enterobacteriaceae</i> (e.g. <i>Proteus mirabilis</i>)	None	Yes	29 cases and 11 healthy controls (Fukuda criteria)	Belgium	Maes et al. (2007) [21]
Aerobic bacteria, D-lactic acid producing: <i>E. faecalis</i> , <i>S. sanguinis</i>	<i>E. coli</i> , Gram-positive/Gram-negative bacteria ratio	Yes	108 cases and 177 healthy controls (Holmes, Fukuda and Canadian criteria)	Australia	Sheedy et al. (2009) [22]
<i>Lactonifactor</i> and <i>Alistipes</i>	<i>Firmicutes</i>	Yes	35 cases, 36 healthy controls (Fukuda criteria)	Belgium	Frémont et al. (2013) [23]
<i>Bacteroidetes</i> (non-significant)	<i>Actinobacteria</i> ; <i>Firmicutes</i> (non-significant)	Yes	10 cases, 10 healthy controls (Fukuda criteria)	Italy	Shukla et al. (2015) [24]
Aerobic bacteria (non-significant), <i>Clostridium spp.</i>	Anaerobic bacteria, <i>Bacteroides spp.</i>	Yes	34 cases and 25 healthy controls (Canadian Criteria)	Australia	Armstrong et al. (2016) [25]
None	<i>Faecalibacterium</i> , <i>Bifidobacterium</i>	Yes	1 case, 1 healthy control (34-year-old monozygotic male twins) (Fukuda Criteria)	United States	Giloteaux et al. (2016) [26]
Pro-inflammatory species, <i>Proteobacteria</i> (e.g. <i>Enterobacteriaceae</i>)	<i>Firmicutes</i> (non-significant), anti-inflammatory species (non-significant)	Yes	48 cases, 39 healthy controls (Fukuda Criteria)	United States	Giloteaux et al. (2016) [27]
<i>Alistipes</i> (with IBS), <i>Bacteroides</i> (without IBS)	<i>Faecalibacterium</i> (with IBS), <i>Bacteroides vulgatus</i> (without IBS)	Yes	50 cases, 50 healthy controls (Fukuda, Canadian Criteria)	United States	Nagy-Szakal et al. (2017) [28]
None	None	No	17 cases und 17 healthy controls (Fukuda Criteria)	United States	Mandarano et al. (2018) [29]
<i>Blautia</i> , <i>Coproacillus</i> , <i>Eggerthella</i>	None	Yes	48 cases, 52 healthy controls (Fukuda und International Consensus Criteria)	Japan	Kitami et al. (2020) [30]
<i>Bacteroidetes</i>	<i>Firmicutes</i>	Yes	35 cases, 70 healthy controls (Fukuda Criteria)	Italy	Lupo et al. (2021) [12]
Anaerobic bacteria (e.g., <i>Paraprevotella</i> , <i>Ruminococcaceae</i> UCG_014)	None	Yes	2076 cases, 460,857 healthy controls	11 countries	He et al. (2023) [31]

[36]. This suggests that reduced gut diversity in ME/CFS might relate to different physical fitness levels; notably, ME/CFS patients show lower VO₂ peaks [37]. While one study reported a decrease in anaerobic bacteria in ME/CFS patients [25], another observed an increase, indicating varied findings regarding intestinal bacteria changes in this condition [22]. Recent studies have also identified alterations in gut microbiota among individuals with ME/CFS. These changes include higher levels of *Enterococcus* and *Streptococcus* species and increased *Enterobacteriaceae*, while beneficial *Bifidobacteria* and anti-inflammatory *Firmicutes* are decreased [21–23, 27]. Metagenomic analysis reveals that specific bacterial taxa, including the *Firmicutes* phylum and genera such as *Faecalibacterium*, *Roseburia*, and *Clostridium*, show associations with ME/CFS. Notably, increased levels of *Alistipes* and reduced butyrate-producing *Faecalibacterium* are emerging as potential diagnostic biomarkers [28]. However, findings about *Clostridium* genus abundance remain inconsistent [27]. In a case study involving ME/CFS discordant identical twins, the affected twin showed reduced abundance of *Bifidobacterium* and *Faecalibacterium* compared to the non-affected twin, coupled with decreased gut alpha diversity [26]. Furthermore, high-throughput 16S rRNA sequencing from stool samples identified increased gut inflammation markers, such as elevated levels of *Lactonifactor* and *Alistipes* [23]. A study involving 48 ME/CFS patients and 52 controls identified 26 distinct bacterial markers between the two groups. The abundances of *Coprobacillus*, *Eggerthella*, and *Blautia* were key differentiators. Additionally, a decrease in *Faecalibacterium* and an increase in *Coprobacillus* were observed [30], which aligns with previous studies' findings [27, 28]. Another recent study with 35 patients and 70 controls identified a distinct microbial pattern, showing decreased anti-inflammatory *Firmicutes* [12], supporting previous findings [23, 27]. The research compared patients with internal vs. external controls and found overlaps between patients and their relatives, highlighting the importance of considering lifestyle and genetic factors [12]. Although these findings of dysbiosis in ME/CFS are evident [12, 21–31], their exact role in the disease mechanism remains unclear [10]. The studies vary significantly in sample sizes, recruitment strategies, and microbiota characterization methods, with most using culturing or 16S amplicon sequencing and only one employing whole genome shotgun sequencing. However, the hypothesis that restoring gut health could play a key role in managing ME/CFS emphasizes the importance of integrating microbiome research into current therapeutic frameworks, thereby advancing the understanding and treatment of this complex and multifaceted condition [1].

Hypothetical theoretical frameworks linking dysbiosis and ME/CFS

Research shows that gut microbiota can affect individuals' clinical conditions by influencing the central nervous system (CNS) and the immune system, causing physical or mental symptoms. Although it seems this bidirectional connection is guided by various mechanisms, there is no definitive epidemiological evidence linking gut dysbiosis, the CNS, and the peripheral immune system (see Fig. 1). This highlights the necessity for further research into the microbiome-gut-brain axis to fully understand its role and implications [38]. In this context, the exploration of ME/CFS pathogenesis has increasingly focused on the microbiome-gut-brain axis, revealing a complex interplay between intestinal dysbiosis and the multifaceted symptomatology of this debilitating condition [10]. The convergence of these influences suggests that disruptions in microbial homeostasis could contribute significantly to the development and perpetuation of ME/CFS [10, 33]. Despite the lack of sufficient and solid information on this topic, the following sections attempt to discuss the current evidence supporting hypothetical theoretical frameworks that connect dysbiosis with ME/CFS (see Fig. 2).

Increased lipopolysaccharides (LPS) theory

In a healthy gut environment, bacterial translocation across the intestinal barrier is typically prevented [39]. However, numerous studies indicate that individuals with ME/CFS experience increased intestinal permeability, supporting the theory that Gram-negative bacterial endotoxins, also known as LPS, may enter the mesenteric lymph nodes and the blood stream through the loosening of tight-junction proteins (e.g., Zonulin), triggering an immune response and resulting in systemic inflammation [10, 21, 24, 39–42]. Leaky gut may also stem from systemic inflammation, where cytokines like interleukin (IL)–1 β , IL-6, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ disrupt gut permeability and promote bacterial translocation by weakening tight junctions [21]. Additionally, decreased production of ceramides may potentially harm gut epithelial cells by reducing LPS hydrolysis and increase gut permeability [28]. Consequently, two pathways may be triggered by commensals entering from the gut. The first involves binding with the Toll-Like Receptors (TLR) complex, which activates nuclear factor κ B and leads to the production of pro-inflammatory cytokines, including IL-1 and TNF- α , as well as reactive oxygen species (ROS) and reactive nitrogen species (RNS). This can potentially cause neuroinflammation and symptoms of depression and fatigue. The second pathway involves the translocation of gram-negative commensals, resulting in immunoglobulin (Ig)

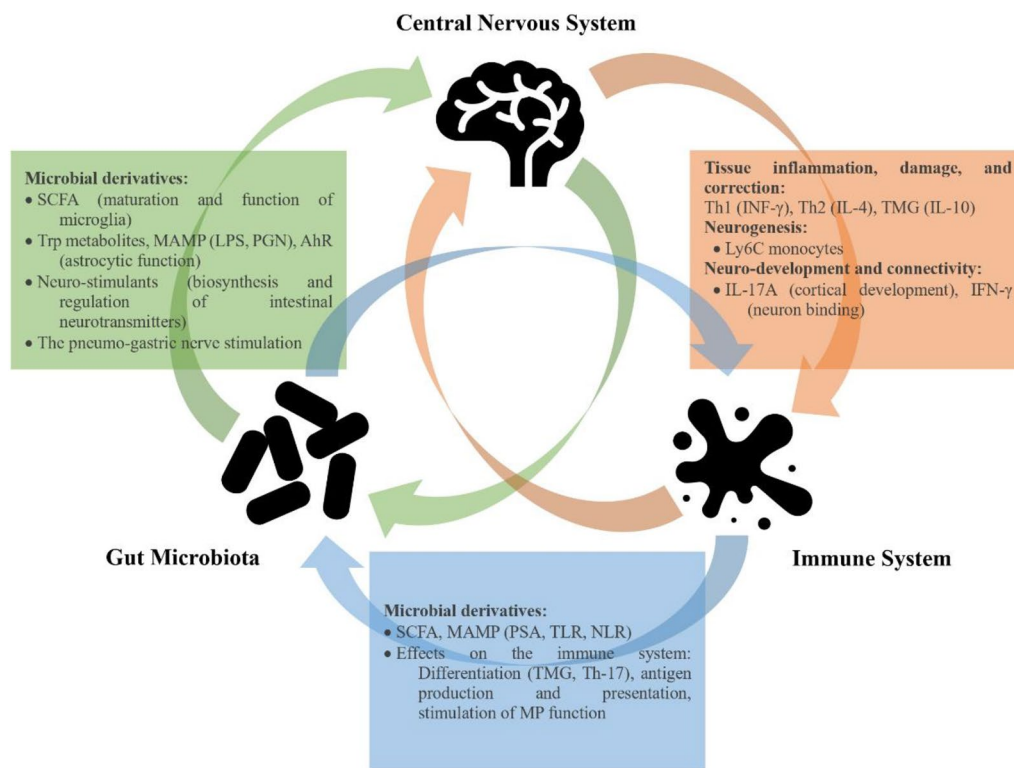


Fig. 1 The impact of the bidirectional relationship between the gut microbiota and the brain on the peripheral immune system and metabolome. SCFA: Short-Chain Fatty Acids; Trp: L-tryptophan; LPS: Lipopolysaccharides; AhR: Aryl hydrocarbon receptor; MAMP: Microbe-Associated Molecular Patterns; PGN: Peptidoglycan; PSA: Polysaccharide; TLR: Toll-Like Receptor; NLR: NOD-Like Receptor; TMG: Thymoglobulin; Th-17: T helper 17; MP: Mononuclear Phagocyte; INF- γ : Interferon-Gamma; IL: Interleukin. (Adapted from Montagnani et al. [38])

A and IgM responses against bacterial LPS. This can act as a superantigen for T lymphocytes, inducing autoimmunity against neuronal lipid structures like gangliosides, potentially causing autoimmune conditions. This phenomenon helps explain the unusually high levels of IgA and IgM antibodies against LPS found in the blood of these patients, with 67% and 40% of ME/CFS patients respectively showing elevated antibody levels, compared to none in the control group [21]. Regardless of these events, gut-derived inflammation may also activate TLR and intracellular signaling pathways like NF κ B, p38, and MAP kinase, coordinating the expression of inflammatory genes [21].

Decreased short-chain fatty acids (SCFA) theory

Gut hyperpermeability may also be linked to the by-products of amino acid fermentation, which produce SCFA [25]. A decrease in SCFA-producing bacteria, especially butyrate producers like *Faecalibacterium* and *Roseburia* from the *Firmicutes* phylum, along with certain *Bacteroides* species, has been observed in ME/CFS patients [10, 25, 28]. Butyrate essentially fuels colon cells and is crucial for the neuroimmunoendocrine system,

promoting gut health through its anti-inflammatory properties and strengthening the intestinal barrier [43]. This molecular pathway may be influenced by the level of daily physical activity, as a study using high-throughput sequencing found that physically fit individuals had higher fecal butyrate levels, better VO₂ max values, more diverse gut microbiota, lower LPS biosynthesis, and consequently, less systemic inflammation [22, 44]. In ME/CFS patients, the scarcity of butyrate-producing bacteria could be due to low levels of SCFA, potentially causing post-exertional malaise and a cycle of inactivity. This inactivity might increase LPS levels, exacerbating the condition. Alternatively, chronic inactivity from ME/CFS could itself reduce SCFA production over time. Additionally, the depletion of SCFA might result from an overgrowth of D-lactate producing bacteria, which are found at elevated levels in ME/CFS patients and have been studied previously [36]. However, a study challenged the butyrate deficiency theory by identifying higher fecal concentrations of butyrate, isovalerate, and valerate in ME/CFS specimens, linked to increased bacterial fermentation. Researchers suggest that elevated gut pH, gut dysbiosis (i.e., a higher *Firmicutes*:*Bacteroidetes* ratio),

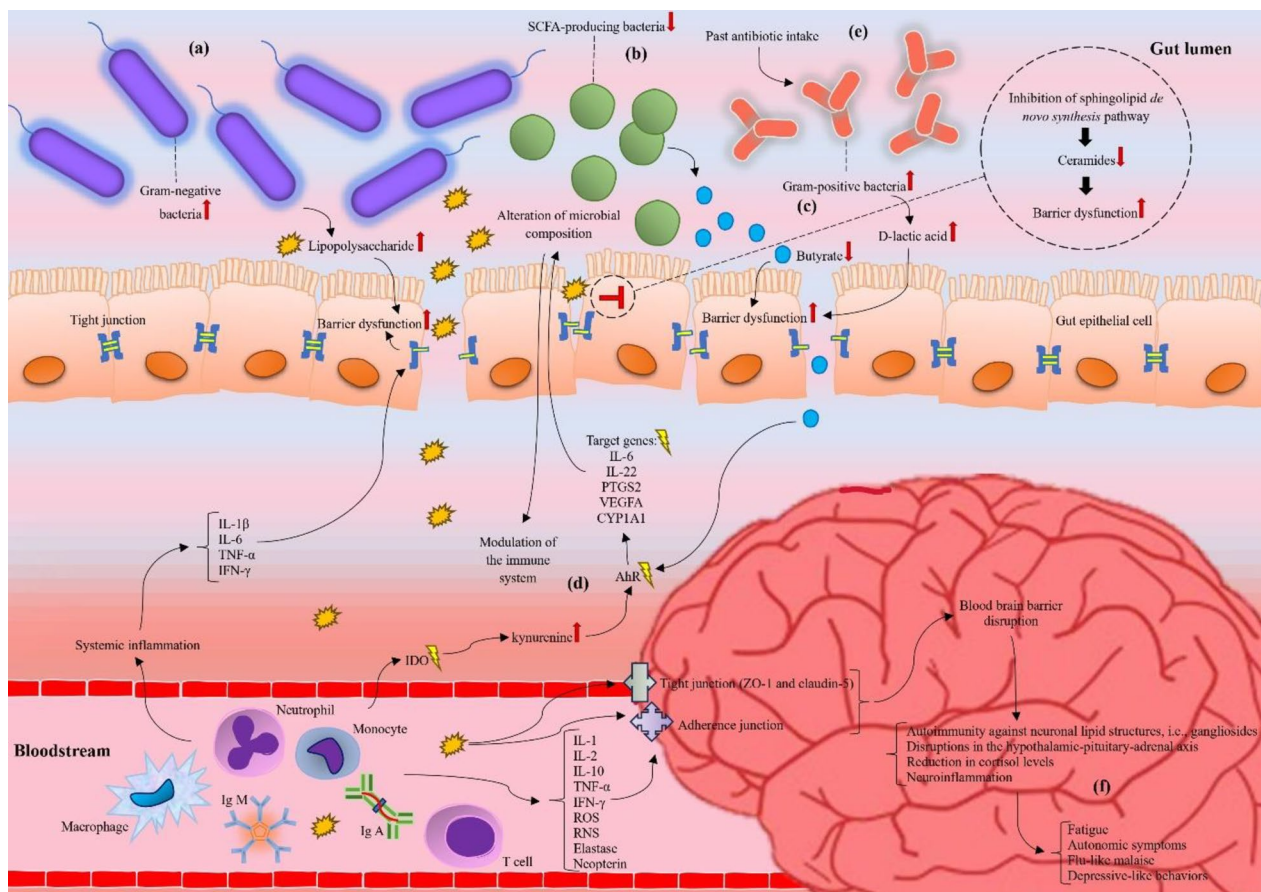


Fig. 2 Different hypothetical theoretical frameworks connect dysbiosis with ME/CFS: **a** Increased Lipopolysaccharides (LPS) Theory: Endotoxins, or LPS, from Gram-negative bacteria can enter mesenteric lymph nodes and the bloodstream by disrupting tight-junction proteins, leading to an immune response and systemic inflammation. This inflammation can result in a leaky gut, with cytokines such as IL-1 β , IL-6, TNF- α , and IFN- γ further compromising gut permeability and allowing bacterial translocation. Reduced ceramide production also harms epithelial cells by decreasing LPS hydrolysis and increasing gut permeability. Additionally, translocated commensals activate IgA and IgM against bacterial LPS—these act as superantigens for T lymphocytes, possibly causing autoimmune conditions against neuronal lipid structures like gangliosides. Gut-derived inflammation also activates signaling pathways that coordinate inflammatory gene expression; **b** Decreased short-chain fatty acids (SCFA) theory: A reduction in SCFA-producing bacteria weakens the intestinal barrier by decreasing butyrate production; **c** Increased D-lactic acid theory: Overgrowth of Gram-positive bacteria raise D-lactic acid production, lowering intestinal pH and increasing gut permeability; **d** Kynurenine production insufficiency theory: When proinflammatory cytokines induce the activation of the enzyme indoleamine-2,3-dioxygenase (IDO), it results in the production of kynurenine, which binds to the aryl hydrocarbon receptor (AhR) and plays a vital role in immune regulation by promoting regulatory T-cell generation and preventing excessive inflammation. Additionally, microbial metabolites such as SCFA and tryptophan derivatives can activate AhR, influencing the expression of genes like IL-6, IL-22, prostaglandin G/H synthase 2 (PTGS2), vascular endothelial growth factor A (VEGFA), and cytochrome P450 1 A1 (CYP1 A1) in the intestine. This AhR signaling can modify gut microbial composition, serving as a key regulator of host-microbiota communication, affecting metabolism, and modulating immune responses; **e** Past antibiotic intake hypothesis: Using antibiotics can disrupt the microbiome, impair anti-inflammatory metabolite production, and increase D-lactate-producing bacteria, potentially leading to conditions like D-lactic acidosis and intestinal barrier dysfunction; **f** The stress crash theory: Physiological stress may alter the gut microbiota by decreasing beneficial bacteria, potentially contributing to ME/CFS. This imbalance can increase harmful bacteria and LPS production, triggering inflammation through IL-22, affecting the HPA axis, and reducing cortisol levels [10, 21, 22, 24, 25, 28, 36, 39–80]. ROS: Reactive oxygen species; RNS: Reactive nitrogen species

obesity, or malabsorption might increase fecal SCFA, such as butyrate, which could have potential neurotoxic effects [25, 45, 46]. Accordingly, it is crucial to understand that fecal SCFA excretion does not entirely reflect their concentration and production within the gut. A comprehensive analysis of SCFA serum levels is required

to gain a more accurate understanding of their dynamics in the body [10, 45–48].

Increased D-lactic acid theory

Another theory regarding the reduced intestinal pH and increased gut permeability in ME/CFS patients is the

increased production of D-lactic acid due to the overgrowth of Gram-positive bacteria such as Enterococci and Streptococci, which leads to systemic inflammation, immune activation, and oxidative stress [22, 44]. However, targeting bacterial overgrowth with antibiotics and probiotics hasn't improved fatigue symptoms, questioning D-lactate's role. Additionally, differences between cerebrospinal fluid and fecal lactate levels suggest an incomplete understanding of intestinal lactate metabolism's impact on ME/CFS patients [25, 44, 49].

Kynurenine production insufficiency theory

Recent research has identified the aryl hydrocarbon receptor (AhR) and the enzyme indoleamine-2,3-dioxygenase (IDO) as key players in the increased gut permeability and bacterial endotoxin translocation seen in ME/CFS patients. These components are crucial in linking microbial L-tryptophan (Trp) catabolism and host endogenous Trp metabolites to regulatory T-cell function, particularly in maintaining AhR-dependent T-cell immune homeostasis at mucosal surfaces. When induced by proinflammatory cytokines, the enzyme IDO is activated, leading to the production of kynurenine [50]. These kynurenines act as ligands for the AhR, playing a crucial role in regulating immune homeostasis by fostering the generation of regulatory T-cells, thereby protecting against hyper-inflammatory responses. This interaction is part of a coevolutionary relationship between hosts and microbes, with particular relevance to tryptophan-derived AhR ligands [50, 51]. Several factors, such as diet, microbial metabolism of tryptophan, and endogenous enzymatic activity, can provide critical signals to the host, aiding in resisting colonization and defending against mucosal inflammation [51]. Specifically, Lactobacilli species, as probiotics, can convert tryptophan into AhR ligands like indole-3-aldehyde, which activate innate lymphoid cells. These cells subsequently induce the production of IL-22, which regulates the release of antimicrobial peptides and enhances their expression in the gut epithelium, thereby reducing pathogen infectivity by sequestering metal ions [52]. This intricate interplay underscores the importance of microbial metabolites in immune regulation and host defense mechanisms [52, 53]. In this regard, previous studies emphasize the bidirectional interaction between the AhR and the microbiome, indicating that this microbiome-AhR axis influences host metabolism. Microbial metabolites like SCFA and Trp derivatives can activate AhR and its target genes, including IL-6, IL-22, prostaglandin G/H synthase 2 (PTGS2), vascular endothelial growth factor A (VEGFA), and cytochrome P450 1A1 (CYP1A1) in the intestine or liver. Additionally, AhR signaling can alter microbial composition in the small intestine, acting as

a crucial regulator of host-microbiota communication, thereby affecting host metabolism and modulating the immune system [54–58]. However, the potential for using these findings in treating or diagnosing ME/CFS remains under investigation and requires further study to draw definitive conclusions [55–57]. For example, Kashi et al. [58] proposed a “metabolic trap hypothesis” that suggests ME/CFS patients suffer from insufficient kynurenine production due to gene mutations in IDO2 [58]. This leads to elevated tryptophan levels, affecting the central nervous system, gastrointestinal tract, immune system, and energy metabolism. Their study found multiple IDO2 gene mutations in ME/CFS patients, correlating with symptom severity. The resulting lack of IDO2 activity hinders tryptophan conversion to kynurenine. Elevated tryptophan and reduced kynurenine levels were confirmed in these patients, disrupting serotonin and melatonin pathways and contributing to ME/CFS symptoms. Contrarily, while elevated tryptophan levels do not safeguard intestinal integrity from damage induced by LPS, reduced levels of kynurenine appear to offer some protection [58, 59]. The “metabolic trap hypothesis” explores the potential metabolic and immunological mechanisms in ME/CFS, focusing on serotonin and tryptophan metabolism and their effects on patient microbiomes. Crucially, decreased IDO enzyme activity can disrupt tryptophan fermentation, affecting the gut microbiome and potentially leading to an impaired intestinal mucosal barrier, increased endotoxin translocation, and chronic inflammation. These insights are vital for understanding ME/CFS mechanisms and identifying therapeutic targets [60–62]. Recent research into ME/CFS investigates increased kynurenine production rather than decreased levels proposed by the “metabolic trap hypothesis.” The balance between tryptophan depletion and kynurenine generation, marked by the kynurenine and tryptophan (KYN/TRP) ratio, indicates IDO activity and immune responses. High IDO activity, often linked with chronic inflammation, supports theories of increased kynurenine production. This is significant since elevated KYN/TRP ratios and neuroactive metabolites like quinolinic acid are linked with symptoms in disorders, including ME/CFS. Additionally, viral infections such as Epstein-Barr virus activating IDO may convert tryptophan to kynurenine, supporting this hypothesis [63–66]. Although studies suggested that tryptophan and its derivatives could influence the gut microbiome and interact with the gut mucosal immune system, recent clinical investigations proposed that changes in immunity and kynurenine metabolism may trigger fatigue in ME/CFS but do not sustain it over time [61, 67, 68].

Past antibiotic intake hypothesis

There is also a potential link between antibiotic use and ME/CFS development, as altered microbiota can be influenced by antibiotics. While no specific studies have examined antibiotics as a trigger, many patients with ME/CFS have frequent infections treated with antibiotics [47, 69–72]. This may alter the microbiome, impairing anti-inflammatory metabolite production or fostering conditions like D-lactic acidosis by increasing D-lactate-producing bacteria [22, 25, 49]. Women are more often diagnosed with ME/CFS, potentially due to higher antibiotic exposure compared to men [73, 74]. Antibiotics may contribute to oxidative stress by increasing reactive oxygen species (ROS), aligning with observations of elevated ROS levels in ME/CFS patients. Despite this, antibiotics have been explored as a treatment for ME/CFS, targeting the overgrowth of certain bacteria [75–77]. A pilot study by Jackson et al. demonstrated that antibiotics improved sleep quality by reducing lactic acid-producing bacteria and balancing the microbiome with a reduction in Gram-positive bacteria, which lowers proinflammatory cytokines [78]. Similarly, Wallis et al. found that a four-week treatment combining antibiotics and probiotics enhanced neurological symptoms and sleep quality, though it did not alleviate fatigue symptoms linked to ME/CFS [44]. These findings suggest a microbiome-related approach may improve certain aspects of the condition but underline the complexity of addressing fatigue specifically [44, 78].

The stress crash theory

The stress crash theory suggesting that hypothalamic–pituitary–adrenal (HPA) axis hypofunction triggers immune-inflammatory pathways in ME/CFS cannot be substantiated. This theory faces contradictions, such as HPA axis hypofunction being limited to certain patients, no early-stage changes in ME/CFS, and heightened immunosuppressive effects of glucocorticoids in these patients. Alternatively, the HPA axis hypofunction might arise from several mechanisms, including chronic inflammation with elevated TNF- α levels, a regulatory T cells response with increased IL-10 and transforming growth factor (TGF)- β , heightened oxidative and nitrosative stress pathways, notably elevated nitric oxide (NO) production, and infection-related factors like LPS tolerance and viral infections affecting the HPA axis (see Table 2) [79]. These factors may independently or interactively contribute to ME/CFS. For instance, physiological stress is believed to play a role in modifying gut microbiota, reducing beneficial bacteria like *Bifidobacterium* and *Lactobacillus*, which could contribute to ME/CFS by enabling harmful bacteria to thrive. This imbalance might cause LPS to be increasingly produced and enter the bloodstream, triggering widespread inflammation through IL-10, disruptions in the HPA axis, and a reduction in cortisol levels, another factor linked with ME/CFS [79, 80]. These intertwined factors potentially maintain a disturbed homeostasis within individuals suffering from

Table 2 Impacts of immune-inflammatory and nitrosative pathways on reducing the functionality of the HPA axis in patients with ME/CFS (Adapted from Morris et al. [79])

Biomarkers	Effects
↑ TNF- α	↓ ACTH production ↓ Cortisol synthesis ↓ ACTH-stimulated cortisol secretion
↑ IL-10	↓ Glucocorticoid synthesis ↓ Progesterone levels ↑ Steroid suppression ↑ Dexamethasone binding sites act synergistically with glucocorticoids
↑ TGF- β	↓ Glucocorticoid secretion ↓ Steroid production ↓ DHEA-S synthesis
↑ NO	↓ CRH secretion ↓ Steroidogenesis ↓ Transcription of steroidogenesis proteins
↑ LPS	↑ IL-10 and its effects ↓ HPA axis responses to LPS ↓ Cortisol levels
↑ Poly I:C	↓ Adrenal sensitivity to ACTH ↑ Negative feedback

TNF- α : tumor necrosis factor- α ; IL-10: Interleukin-10; TGF- β : Transforming growth factor- β ; NO: Nitric oxide; LPS: Lipopolysaccharides; ACTH: Adrenocorticotropic hormone; DHEA-S: Dehydroepiandrosterone sulfate; CRH: Corticotropin-releasing hormone

ME/CFS. Nevertheless, future research should focus on examining temporal relationships between HPA axis function and immune-inflammatory or nitrosative stress pathways through biomarkers like TNF- α , IL-10, TGF- β , inducible NO synthase, NO production, protein nitrosylation, and bacterial translocation in ME/CFS patients to better understand their roles [79].

The potential therapeutic approaches targeting gut health in ME/CFS

Considering the common links between ME/CFS and dysbiosis, increased gut permeability, and chronic inflammation [12, 21–31, 40, 41], it is reasonable to hypothesize that strategies focused on restoring microbial equilibrium, enhancing mucosal barrier function, and reducing inflammation could have therapeutic potential. In this context, the use of probiotics, prebiotics, specific diets, dietary supplements, fecal microbiota transplantation, some pharmacological interventions, and improved sleep has been suggested.

Probiotics

Probiotics are live microorganisms that can enhance gut health and reduce inflammation [81]. Although this treatment option might benefit ME/CFS treatment [82, 83], only two studies on ClinicalTrials.gov explore this, despite theories linking microbiota to the disease's progression [12, 84]. An Italian pilot study found that an 8-week course of various probiotics improved well-being and reduced inflammation in patients with ME/CFS, though the study was limited by a small sample size and lack of a control group [12]. Another study assessed *Lactobacillus paracasei* ssp. *paracasei* F19, *Lactobacillus acidophilus* NCFB 1748, and *Bifidobacterium lactis* Bb12 in 15 ME/CFS patients, observing improvements in neurocognitive function but no significant reduction in fatigue or physical activity levels in only nine patients [84]. The systematic review by Corbitt et al. reveals a lack of evidence for probiotics as a treatment for gastrointestinal symptoms in ME/CFS patients, largely due to poor study quality [85]. This finding aligns with an evaluation in *Nature* that highlights insufficient impact assessments and therapy recommendations for probiotics, citing conflicting and industry-driven study results [83]. Existing studies typically focus on stool samples, yet recent findings suggest biopsies might better reveal gut interactions, as the small intestine may exhibit distinct patterns. It is also advised to conduct a before-and-after analysis of the gut microbiota due to its highly individual-specific and somewhat resistant nature [86].

The use of *Bifidobacterium infantis* 35,624 in 48 ME/CFS patients further confirmed probiotics' capacity to

lower systemic inflammatory markers like CRP, TNF- α , and IL-6 [87]. Given the frequent occurrence of anxiety, depression, and other psychiatric conditions in individuals with ME/CFS, exploring alternatives to traditional psychotropic drugs is essential [88]. A 12-week randomized, double-blind, placebo-controlled study found that a combination of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 effectively reduced inflammation and alleviated psychiatric symptoms in patients with Major Depressive Disorder (MDD) who were on a gluten-free diet [89]. Considering the overlap in psychiatric symptoms between MDD and ME/CFS, it raises the possibility that probiotics could similarly benefit those with chronic fatigue [90]. Early indications suggest that administering *Lactobacillus casei* strain Shirota daily for two months may significantly lessen anxiety and restore eubiosis in ME/CFS patients [91]. Additionally, notable improvements in neurocognitive functions have been observed in individuals diagnosed with ME/CFS taking *L. paracasei* spp. *paracasei* F19, *L. acidophilus* NCFB 1748, and *B. lactis* Bb12 [84]. Collectively, these findings indicate that probiotics, whether used alone or in combination, are likely to become an effective component of therapy for ME/CFS.

Prebiotics

Prebiotics, which are indigestible carbohydrate nutrients, serve as sustenance for the gut microbiota. The primary categories of prebiotics include fructo-oligosaccharides and galacto-oligosaccharides [92]. These compounds undergo bacterial breakdown, leading to the production of SCFA that enter systemic circulation, thereby affecting both gastrointestinal and systemic health [46]. Due to their selective enhancement of certain beneficial gut bacteria and their ability to modify the composition and function of the gut microbiota, prebiotics are considered a potential supportive treatment for various disorders such as IBS, Crohn's disease, issues with bowel motility, autism, obesity, and colorectal cancer [92]. Research has shown that various oligosaccharides can counteract imbalances in the microbiota by encouraging the growth of *Lactobacilli*, reducing *Proteobacteria* populations, and lowering the *Firmicutes/Bacteroidetes* ratio in diet-induced obese rodents [93–95]. Moreover, improvements in gut barrier integrity and reductions in systemic inflammation have been observed. Rodents consuming prebiotics like bovine milk oligosaccharides, oligofructose-enriched inulin, spirulina platensis, and a combination of Fructooligosaccharide/Galactooligosaccharide have exhibited decreased plasma levels of lipopolysaccharides, lower serum concentrations of pro-inflammatory

cytokines, diminished intestinal inflammation, and enhanced tight-junction integrity [93–97]. Collectively, these findings indicate that prebiotics could be beneficial for managing conditions such as ME/CFS characterized by dysbiosis, increased intestinal permeability, and chronic inflammation. However, further clinical studies are essential to substantiate these potential benefits.

Specific diets

Altering dietary habits provides a swift, consistent, and effective method for altering the composition of the gut microbiota [98]. Recent evidence has shown diets rich in glucose/fructose or prolonged high-protein diets have been linked to negative outcomes such as dysbiosis, increased intestinal permeability, heightened systemic inflammation, and elevated plasma endotoxin levels [99, 100]. Conversely, adopting gluten-free diets or those low in starch and sucrose, as well as calorie-restricted eating plans, can lower levels of C-reactive protein and LPS binding protein, improve gut barrier function, and alleviate both gastrointestinal and systemic symptoms associated with IBS and obesity [89, 101, 102]. The Mediterranean diet and low FODMAP diet may also serve as the models for dietary recommendations. They promote foods that enhance gut microbiota richness and alleviate systemic inflammation and fatigue [103–105]. Moreover, Small partly non-controlled clinical pilot studies have explored the efficacy of ketogenic diets in alleviating fatigue symptoms associated with multiple sclerosis, Parkinson's disease, and the impact of short-term fasting on cancer-related fatigue [106–108]. Although the exact mechanisms by which ketogenic diets exert their effects are not fully known, it is believed that these effects are partially mediated through interactions with the gut microbiome [109–111]. Consumption of cocoa and dark chocolate has been linked to beneficial health outcomes in relation to chronic diseases. This review highlights a randomized controlled crossover study that explored the therapeutic benefits of cocoa on reducing fatigue and enhancing residual functions in ME/CFS patients, as measured by the London Handicap Scale. The study compared the effects of high-polyphenol cocoa to those of an iso-caloric low polyphenol chocolate. Although the findings were promising, the study's credibility is tempered by its small sample size ($n = 10$), short duration of treatment, and the absence of detailed dietary intake data during the trial period [112].

Contrary to the positive findings mentioned above, a systematic review determined that there is no supportive evidence indicating that elimination or modified diets benefit patients with ME/CFS [113]. It is important to acknowledge the potential risk of bias in these

dietary studies due to the inability to implement blinding. Additionally, extreme dietary interventions should be approached with caution and implemented under the supervision of qualified healthcare professionals, particularly because it is uncertain if they might exacerbate symptoms in ME/CFS patients, especially during the initial weeks. Overall, further clinical trials in humans are necessary to demonstrate that dietary interventions can simultaneously influence the microbiome, intestinal permeability, inflammation, and neurocognitive symptoms, making them a compelling complementary strategy in the treatment of ME/CFS [10, 11, 13].

Dietary supplements

Enhancing the intake of omega-3 fatty acids and polyphenols has been shown to increase microbiota diversity and reduce metabolic endotoxemia [114]. Specifically, eicosapentaenoic acid found in omega-3 rich fish oil has been effective in reducing symptoms in cases of ME/CFS [115, 116]. In experimental models using diet-induced obese rats and mice, targeted nutrient supplementation has yielded benefits. For instance, treatments with apple polysaccharides, flos lanicera, and Bofutsushosan—an herbal remedy from Japan—have been successful in promoting the growth of beneficial bacteria like *Lactobacillus* and *Bacteroidetes*, improving intestinal barrier integrity, and decreasing pro-inflammatory cytokines such as TNF- α and IL-6 [117–119]. Furthermore, incorporating *Sarcodon imbricatus* or consuming a blend of *Angelica gigas*, *Cnidium officinale*, *Paeonia lactiflora*, moxibustion, cistanche, ginkgo extracts, and ginseng has shown potential in restoring antioxidant balance and reducing fatigue in ME/CFS models in mice [120–124]. In line with these studies, the findings from a recent systematic review article including 68 patients have highlighted a potential benefit of ginseng therapy in the treatment of ME/CFS [125–127]; results that have also been repeated in an open-label, pilot trial of HRG80™ red ginseng, but this time with a larger sample size ($n = 188$) [128].

CoQ10–selenium combination, β -nicotinamide adenine dinucleotide (NADH), and NADH–CoQ10 combination were also found to alleviate fatigue in patients with ME/CFS [129–131]. However, the studies did not include assessments of dietary intake either before or after the treatment periods, leaving it uncertain whether changes in diet may have affected the outcomes. Additionally, the reliability of these findings is compromised by the small number of participants and the short duration of the treatments, which lasted only 4 and 8 weeks. Consequently, there is a need for long-term studies with more substantial participant numbers to verify the sustained effectiveness of NADH and CoQ10 in treating ME/CFS [129]. Moreover, the study by Forsyth et al.

utilized a questionnaire developed by the researchers to assess symptoms, which, despite undergoing reproducibility tests, raises questions about its ability to accurately capture ME/CFS symptoms [132]. Future research should employ validated measurement tools to ensure reliable results and facilitate comparisons across different studies.

Ubiquinol-10, also known as CoQ10, plays a crucial role in cellular energy production and acts as an antioxidant [7]. Studies have shown that CoQ10 levels are lower in ME/CFS patients than in healthy individuals [133–135]. A single randomized controlled trial examining the effects of 12-week supplementation with Ubiquinol-10 in ME/CFS patients reported no significant improvements in fatigue as measured by Chandler's Fatigue Scale. However, improvements were noted in other symptoms associated with ME/CFS, such as reduced night-time awakenings, suggesting potential long-term benefits for fatigue management [131]. An animal model study has also shown that the administration of CoQ10 for 21 days significantly altered the gut environment, resulting in an increase in hydrogen concentration and SCFA like butyrate in feces. Additionally, it reduced trimethylamine levels and the relative abundance of *Helicobacter* while boosting beneficial groups like *Ruminococcus* and *Lachnospiraceae*. These changes suggest that CoQ10's antioxidant effects may involve modifying the gut microbiota's taxonomic composition and increasing molecular hydrogen production. The rise in butyrate levels could enhance gut barrier protection, contributing to overall gut health [136]. All in all, although the results of a recent meta-analysis have shown that CoQ10 is an effective and safe supplement for reducing fatigue symptoms, more extensive and controlled studies are essential to further substantiate the advantages of Ubiquinol-10 supplementation [137].

Aside from this, recent evidence has found that melatonin and zinc supplementation is safe and possibly effective in managing ME/CFS symptoms. In this respect, a 16-week randomized, placebo-controlled trial was conducted with 50 ME/CFS patients to test the effects of oral melatonin (1 mg) and zinc (10 mg) supplements. The study showed significant reductions in physical fatigue and improvements in quality of life [138].

Thiamine, a crucial co-factor in the TCA cycle and glycolysis, is partially produced by gut bacteria like *Bacteroides*, which are often reduced in ME/CFS patients [139]. Another bacterium, *Faecalibacterium*, also found to be diminished in these patients, relies on thiamine for growth [27, 28, 35, 140]. Although gut microbes produce only small amounts of thiamine, its availability significantly influences the competitive microbial ecosystem in the gut. This highlights the potential impact of reduced thiamine levels on gut health in ME/CFS sufferers [141].

Overall, although most clinicians commonly recommend that patients with ME/CFS consume supplements such as vitamin A, vitamin C, vitamin D, Vitamin B1, Vitamin B12, vitamin E, folic acid, ferritin, iron, selenium, calcium, magnesium, L-tryptophan, L-carnitine and etc. [129, 142–144], a recent meta-analysis was unable to definitively establish a significant connection between overall vitamin and mineral deficiencies and fatigue in patients with ME/CFS [145], although some uncertainty about the role of vitamin E deficiency persists [146]. Furthermore, this analysis found no clear advantages of nutritional interventions, noting that only a limited number of such trials were assessed [145]. Additionally, another systematic review indicated some potential benefits of nutritional supplements like d-ribose, particularly in symptom management [147]. Despite these findings, the existing limitations of the studies mentioned make it impossible to reach a conclusive verdict at this time [7, 145, 147, 148].

Fecal microbiota transplantation

Fecal microbiota transplantation, also referred to as stool transplantation or bacteriotherapy, involves transferring fecal matter from a healthy donor into the gastrointestinal tract of a patient [149]. This procedure aims to correct imbalances in the gut microbiome by introducing a diverse and healthy microbial community. Typically, this is done through colonoscopy, though other methods such as enemas and oral capsules are also used [150, 151]. Currently, fecal microbiota transplantation is officially sanctioned only for treating persistent or severe infections caused by *Clostridium difficile* [152]. However, its use is being explored as a potential treatment for a range of conditions including obesity, insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, fibromyalgia, ulcerative colitis, Crohn's disease, functional constipation, IBS, and even cancer [153–156]. The technique is also being investigated for its potential benefits in various neuropsychiatric disorders such as autism, Parkinson's disease, Alzheimer's disease, and multiple sclerosis, although the outcomes of these studies remain uncertain [157–159]. Fecal microbiota transplantation is also being explored in ME/CFS research due to indications that the microbiome may significantly impact the disease, particularly its neurological symptoms [160, 161]. The ability of fecal microbiota transplantation to reduce inflammation, enhance intestinal barrier integrity through the production of SCFA, and rebalance immune function highlights its potential as an emerging treatment modality, particularly for ME/CFS [162]. Interest in fecal microbiota transplantation for treating ME/CFS emerged from a retrospective study involving 60 ME/CFS patients, many of whom also had IBS.

This study administered a culture of 13 common fecal bacteria via colon infusion, resulting in 70% of patients responding positively after four weeks. Remarkably, 58% of contactable patients-maintained resolution of ME/CFS symptoms for 15–20 years [160]. Another recent retrospective study showed promising results when comparing fecal microbiota transplantation to an oral treatment consisting of dietary and lifestyle changes, pre- and probiotics, and natural remedies. In this study, 17 out of 21 patients receiving fecal microbiota transplantation from ten different donors achieved at least a 60% improvement [161]. However, in the only randomized, placebo-controlled pilot study to date examining fecal microbiota transplantation in 11 patients with ME/CFS—where 5 patients received transplants from a universal donor and 6 underwent autologous fecal microbiota transplantation through colonoscopy—there were no notable differences in health-related quality of life metrics between the treatment and placebo groups at both 1- and 6-months post-treatment [163]. It seems this contradiction arises from several challenges that remain in the broader application of fecal microbiota transplantation. These include inconsistencies in protocols, a lack of standardized criteria for donor selection and treatment regimens, and unresolved questions regarding long-term safety and efficacy [149, 155, 159, 164–166]. Additionally, the scientific community has yet to reach firm conclusions due to the limited scale of existing studies, underscoring the need for more extensive clinical trials to better understand the effectiveness of fecal microbiota transplantation across various conditions [149, 159, 162, 167, 168]. There is also interest in comparing the effectiveness of using multiple donors versus a single donor in fecal microbiota transplantation procedures, as some preliminary findings suggest potential benefits [169]. Moreover, antibiotic treatment prior to fecal microbiota transplantation significantly enhances engraftment [170, 171]. The success of fecal microbiota transplantation is most strongly linked to the method of administration, especially when combining both upper and lower gastrointestinal applications [172]. *Bacteroidetes* and *Actinobacteria* species exhibit better engraftment rates compared to *Firmicutes* and *Proteobacteria*, while gram-positive bacteria have lower engraftment compared to gram-negative ones. These findings highlight the importance of characterizing and standardizing donor stool for fecal microbiota transplantation to improve outcomes [172]. While numerous hurdles still exist, the data thus far suggests that leveraging fecal microbiota transplantation for treating a variety of diseases linked to intestinal dysbiosis could soon offer a new therapeutic avenue for cases of ME/CFS [11].

Pharmacological interventions

The exploration of pharmacological interventions for the treatment of ME/CFS reveals both potential benefits and risks, particularly concerning gut health [7]. Numerous studies demonstrate that pharmacological agents can influence gut microbiota, which is increasingly recognized as a factor in ME/CFS pathology [173–176]. For instance, medications that modulate the gut microbiome, such as antibiotics, have been shown to improve some gastrointestinal symptoms associated with ME/CFS, thereby enhancing overall patient well-being [5, 10, 12, 32, 161]. In this context, a study on antibiotics for ME/CFS patients with high stool *Streptococcus* counts indicated that reducing these counts led to improved sleep [78]. Additionally, neomycin was tested in ME/CFS patients with small intestinal bacterial overgrowth, resulting in reported improvements in pain, depression, and cognitive function [177]. However, the application of these interventions poses a risk of dysbiosis, where medication-induced changes may lead to an imbalance in microbial populations, exacerbating symptoms rather than alleviating them [178–180]. Careful consideration must be given to the individual responses and the existing discrepancies among the microbiomes of ME/CFS patients compared to healthy individuals, emphasizing the delicate interplay between pharmacological treatments and gut health [181–184]. Furthermore, existing literature indicates that drugs aimed at treating specific ME/CFS symptoms may inadvertently affect the gut microbiota, influencing both therapeutic outcomes and overall patient health [10, 11]. For example, non-steroidal anti-inflammatory drugs often prescribed for pain management have been associated with gastrointestinal disturbances, raising concerns about their long-term use in ME/CFS patients who already report high levels of gut-related issues [185, 186].

Research into the effects of various antidepressants on ME/CFS has yielded mixed results [7]. Moclobemide was found to enhance vitality and energy in patients without notably alleviating depression [187]. Conversely, phenelzine showed no significant benefits [186]. A small trial exploring escitalopram for ME/CFS patients with major depressive disorder indicated substantial reductions in both ME/CFS and depression symptoms [189]. However, fluoxetine generally did not show significant improvement in symptoms for either depressed or non-depressed patients, except in one study where it improved depressive symptoms without significantly affecting fatigue levels [190, 191]. Meanwhile, duloxetine, assessed for its analgesic potential, did not reduce general fatigue but resulted in notable improvements in mental fatigue, pain relief, and overall symptom perception compared to a placebo [192]. Nevertheless, antidepressants posed

a risk of altering gut flora in several animal models via inhibition of efflux pumps and/or amino acid transporters, which may exacerbate issues related to inflammation and immune responses [193–197]. Additionally, in ME/CFS, the salivary glands undergo pathological changes, including mast cell accumulation and targeting by autoantibodies against muscarinic receptors [198]. These changes affect saliva production, consequently impacting nutrition and oral health. Antidepressants, unlike pyridostigmine or pilocarpine, which are saliva stimulants, may worsen these effects [199]. Recognizing this duality highlights the need for a comprehensive approach that balances symptom relief with potential impacts on gut health, ensuring that interventions contribute positively to the multifactorial nature of ME/CFS [7]. Anti-inflammatory and immunomodulatory agents may also be critical in the context of ME/CFS [7, 10, 200]. Chronic inflammation has been identified as a central feature in many patients, linking immune dysregulation to symptomatology such as fatigue and cognitive impairments. Pharmacological interventions targeting cytokine pathways, particularly those involving TNF- α and ILs, may present viable options for managing these complex immune responses. These agents could foster a more favorable immune profile by reducing inflammation stemming from gut dysbiosis, thereby enhancing the quality of life for patients [201–203].

Ultimately, while pharmacological interventions can offer symptomatic relief for ME/CFS patients, an understanding of the potential benefits and risks associated with such treatments is crucial. The intersections of gut health, microbiome integrity, and medication effects underscore the importance of personalized medicine in this context [6]. By appreciating the potential adverse effects of pharmacological agents on the gut microbiota, researchers and clinicians can develop more effective, tailored therapies that prioritize not only the alleviation of ME/CFS symptoms but also the maintenance of gut health [6, 7, 10, 11]. As the literature expands on the links between gut dysbiosis and the broader symptomatology of ME/CFS, it becomes increasingly necessary to integrate this knowledge into clinical practice, reinforcing perspectives that prioritize holistic treatment methodologies in an often fragmented care landscape.

Improved sleep

Research on sleep disorders, both in animal models and humans, has been aimed at understanding how sleep deprivation or disturbance can impact the gut microbiome [204–207]. A study has found that short-term sleep deprivation can indirectly affect human microbiota by altering the balance between *Firmicutes* and *Bacteroidetes*, with the ratio of these bacteria doubling after just

two days of partial sleep deprivation compared to normal sleep conditions [208]. Similar findings have been observed in mice; those subjected to experimentally induced sleep fragmentation and fed a low-fat diet exhibited increased food consumption and shifts in gut microbiota, including changes in the *Firmicutes/Bacteroidetes* ratio and a decrease in *Actinobacteria* species. These shifts disrupt metabolic balance, potentially leading to inflammation in systemic and adipose tissues, possibly due to the translocation of microbial metabolites and insulin resistance. However, these effects were found to be reversible when sleep fragmentation occurred intermittently [209, 210]. Further studies in mice have revealed that a five-day sleep disruption affects both the microbiome and metabolome, with consequences lasting at least four days post-interruption. This disruption results in decreased levels of beneficial bacteria, altered metabolic functions within the microbiome, and changes in fecal bacterial metabolite levels [211]. A recent study examined the connection between the gut microbiome and sleep patterns in young males, utilizing tools such as actigraphy, cognitive assessments, and gut microbiome sequencing. The research found a positive correlation between the diversity and richness of gut microbes and sleep quality, as well as a negative correlation with sleep fragmentation. Notably, increased richness in the *Bacteroidetes* and *Firmicutes* phyla was linked to improved sleep efficiency. Conversely, *Bacteroidetes* alone was negatively related to post-sleep onset wakefulness. *Actinobacteria* diversity showed a negative correlation with awakening frequency. The study also investigated the role of IL-6, an immune system marker regulating sleep, finding its levels positively associated with microbiota diversity and various sleep metrics, including time in bed and total sleep duration. Certain *Proteobacteria* were associated with increased IL-6 levels. Despite these findings, the precise mechanisms connecting gut microbes, sleep, and immune functions remain unclear [212]. Liu et al. discovered that insomnia is associated with significant changes in the structure and function of gut microbiota, showing reduced diversity (both α -diversity and β -diversity) and altered microbial interactions in individuals with insomnia compared to healthy controls [213]. The study observed a reduction in the *Firmicutes/Bacteroidetes* ratio in the gut microbiota of individuals with insomnia, alongside an increase in gram-negative and potentially pathogenic bacteria compared to a control group. This finding contrasts with prior research on sleep deprivation, which reported increased ratios. While insomnia and sleep deprivation both lead to reduced sleep, they differently affect gut microbiota and metabolic processes. Liu and colleagues also noted increased vitamin B6 catabolism and folate biosynthesis but reduced

arachidonic acid biosynthesis in the insomnia group [213]. Although further research is necessary, numerous studies have demonstrated that there is a bidirectional relationship between gut microbiota and sleep disorders. Disruptions in circadian rhythms can adversely affect sleep quality and lead to imbalances in gut microbiota, resulting in alterations to the community structure, ecological parameters of the microbial ecosystem, and the inflammatory state of the body [45, 214–221]. This overview highlights the complex relationship between sleep patterns and gut microbiota, suggesting a possible bidirectional influence where disturbances in one can lead to changes in the other. However, specific investigations into intestinal dysbiosis following improvements in sleep quality among individuals with ME/CFS have not been conducted, indicating a need for further research in this area.

Moderate exercise training

Physical activity, particularly moderate exercise, is a common approach for self-rehabilitation among ME/CFS patients due to its potential to reduce fatigue symptoms [222]. Research indicates that structured regimens of moderate physical activity over 12 to 26 weeks can significantly help in reducing fatigue compared to conventional or passive therapies [223]. A survey in Norway revealed that about 80% of ME/CFS patients experienced a decline in health after participating in graded exercise therapy [224]. This observation contrasts with research suggesting the combination of graded exercise therapy and cognitive behavioral therapy can alleviate fatigue, indicating ongoing debate about these therapies' effectiveness [225]. Nevertheless, although moderate exercise training reduces gut transit time, prolonged strenuous exercise can increase gut permeability, leading to issues like diarrhea, bacterial translocation, gastrointestinal bleeding, and disorders [9]. In a study by Shukla et al., the relationship between bacterial translocation and post-exertional malaise was investigated. The researchers observed phenotypic characteristics, post-exertional malaise, and microbiome changes shortly after a maximal exercise test at intervals of 15 min, 48 h, and 72 h. They noted significant changes in pain, fatigue, and confusion levels post-exercise. Furthermore, they discovered interesting shifts in the relative abundance of intestinal microbiota compared to a control group. Specifically, the genus *Clostridium* appeared in the blood 15 min following exercise, while Bacilli levels significantly increased after 48 h. These findings suggest that increased bacterial translocation may occur after exertion. The authors emphasized that future research should focus more on changes in

intestinal composition following exercise rather than just examining dysbiosis itself [24].

Conclusions

In summary, research has identified a link between the gut microbiome and ME/CFS, although causation has not been established. Changes in the gut microbiome may significantly impact ME/CFS, potentially due to increased gut permeability that allows bacteria to enter the body, or through fermentation products affecting cells and immune responses, exacerbating cognitive and physical impairment in ME/CFS patients. In this respect, future research should explore diagnostic methods like fecal and plasma analyses and consider treatments such as fecal microbiota transplantation. However, the widespread use of prebiotics and probiotics needs careful reconsideration because it is unclear whether gut dysbiosis contributes to the disease or results from it, or if it is related to factors like inactivity or antibiotic use. Additionally, to advance the understanding of ME/CFS pathophysiology, longitudinal studies should account for variables like physical activity and antibiotic use before disease onset. The role of other life events, including pregnancy, should also be examined as potential risk factors. Moreover, analyzing the microbiome in ME/CFS patients presents significant challenges, as studies often produce conflicting findings, particularly concerning gut imbalances. These discrepancies may arise from the varied diagnostic criteria employed across different research efforts, leading to diverse participant groups that exhibit distinct neurological, immune, infectious, muscular, and hormonal issues. Additionally, it is crucial to recognize the existence of ME/CFS subtypes, such as those arising post-infection versus other causes, as well as the fluctuating nature and intensity of symptoms. There is a general agreement in the scientific community on the need for improved research methodologies. This includes the consistent application of case definitions, enhancing study quality, and conducting more longitudinal research to gain clearer insights into ME/CFS. Future studies should take these considerations into account to advance understanding in this field. Furthermore, as highlighted in the existing literature, integrating microbiota assessments into clinical practice can serve as a significant step toward implementing individualized treatment strategies, thereby enhancing patient care and recovery prospects. Finally, it is imperative to acknowledge the complexity and heterogeneity of ME/CFS, which challenges researchers and clinicians in identifying effective therapeutic approaches. The intersection of genetic, environmental, and microbial factors emphasizes the need for a multidisciplinary approach in addressing this condition; systematic reviews point out inconsistencies

in methodologies and outcomes in current research, indicating a critical gap in our understanding of how gut health can be effectively targeted for therapeutic gain in ME/CFS patients. By fostering collaborative research efforts that prioritize standardized diagnostic criteria and enhanced longitudinal studies, the potential for innovative treatments targeting gut health can be realized. Ultimately, the development of targeted therapeutic interventions related to gut health for ME/CFS can lead to improved quality of life and symptom management for those affected by this often-misunderstood disorder.

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