Review

A Systematic Analysis of the Effectiveness of Mitochondrial-Based Therapies for the Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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A Systematic Analysis of the Effectiveness of Mitochondrial-Based Therapies for the Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Abstract: Background: This study aimed to compile and analyze an assortment of research findings concerning potential therapeutic strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The understanding of the multifaceted nature of ME/CFS and the need for varied and personalized therapeutic approaches were central to this investigation. **Methods:** A comprehensive review and analysis of various studies conducted on ME/CFS was undertaken. These studies covered a wide array of interventions, including pharmacological treatments, nutritional supplements, dietary changes, physical therapies, and lifestyle modifications. The analysis pertained to the effectiveness of these interventions, potential physiological and biochemical markers, and the response of ME/CFS patients to different treatment strategies. **Results:** The 22 selected papers investigated demonstrated varied responses to the multitude of interventions. While some interventions showed significant improvement in fatigue and biochemical parameters, others found no significant differences between the treated and control groups. Potential physiological and biochemical markers for ME/CFS, such as impaired T cell metabolism, reduced flow-mediated dilation, and decreased work rate at the ventilatory threshold, were highlighted. **Conclusion:** The findings underscored the complexity of ME/CFS and the need for personalized treatment strategies. Despite mixed results and several limitations, these studies collectively contributed to understanding ME/CFS's complex pathophysiology and treatment, laying the groundwork for future research towards more effective therapeutic strategies for this debilitating disease.

Keywords: Myalgic encephalomyelitis; chronic fatigue syndrome; therapeutic strategies; personalized treatment; pathophysiology; pharmacological treatments; nutritional supplements; dietary changes; physical therapies; lifestyle modifications

INTRODUCTION

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is an enduring, multifaceted illness, characterized by sustained fatigue, cognitive dysfunction, and various somatic symptoms, which significantly impacts the quality of life of affected individuals [1]. The etiology and pathophysiology of ME/CFS remain elusive, posing a significant challenge for the development of targeted therapeutic strategies. Despite this, there is a growing body of evidence implicating mitochondrial dysfunction as a potential contributory factor to the pathogenesis of ME/CFS [2].

Mitochondria, the cellular powerhouses, are vital for energy production via oxidative phosphorylation, and any impairment in their function can lead to a pathological energy deficit, possibly elucidating the profound, unrelenting fatigue experienced by ME/CFS patients [3]. Moreover, these organelles play a key role in several other cellular processes, including calcium homeostasis, reactive oxygen species production, and apoptosis, further implicating their dysfunction in the complex symptomatology of ME/CFS [4].

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Emerging research has focused on the use of mitochondrial-targeted therapies as a potential treatment strategy for ME/CFS. These interventions range from nutritional supplements aimed at supporting mitochondrial function, such as coenzyme Q10 and nicotinamide adenine dinucleotide, to exercise programs designed to enhance mitochondrial biogenesis [5]. However, the evidence base for these interventions remains fragmented, with studies often yielding inconclusive or contradictory results.

ME/CFS is a multifaceted ailment characterized by a wide spectrum of pathophysiological manifestations such as disruptions in immunological, endocrine, and neurological functions [1–4]. The severity of this disease varies across patients, with some experiencing mild symptoms and others becoming bedridden [1]. The exact pathomechanisms underlying ME/CFS remain elusive, and the quest for definitive biomarkers is ongoing. Thus, diagnosis is currently reliant on symptom-specific case criteria and the elimination of other potential diagnoses [1–4].

Majority of the diagnosing criteria for ME/CFS highlight fatigue as the principal symptom [1–4]. Given the pivotal role fatigue plays in the diagnosis of ME/CFS, energy metabolism, particularly mitochondrial function, is considered an essential factor in the disease's pathomechanisms and has been a focal point of recent investigations [5–23].

Mitochondria are multifunctional organelles, maternally inherited, crucial in energy production, conversion, and storage, as well as in other intracellular signaling processes [24]. The electron transport chain (ETC), located within the inner mitochondrial membrane, comprises five multi-subunit enzyme complexes (complexes I–V) and two electron carriers: coenzyme Q10 (CoQ10) and cytochrome c, which are instrumental in oxidative phosphorylation and the subsequent generation of adenosine triphosphate (ATP) [24]. Besides, mitochondria play a significant role in immune processes such as inflammasome activation and intracellular calcium signaling [25,26]. Given their physiological significance, mitochondria are implicated in a broad range of pathological conditions, including ME/CFS [5–23].

Given the potential role of mitochondrial dysfunction in ME/CFS and the growing interest in mitochondrial-targeted therapies, it is crucial to systematically evaluate the existing literature to ascertain the effectiveness of these interventions in the management of ME/CFS. This review aims to systematically analyze and synthesize the available evidence on mitochondrial-based therapies for ME/CFS, assess their efficacy in ameliorating symptoms and improving quality of life, and identify gaps in the current body of research to guide future investigations in this area.

MATERIALS AND METHODS

PRISMA and PECO for the review

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were strictly followed during the conduct of this systematic review [24], ensuring a thorough and open methodology for the selection and synthesis of studies relevant to mitochondria-centric interventions for treating ME/CFS (see Figure 1). An extensive and methodical search across multiple electronic databases was required in the first phase. The review's target group (P) was made up of people with ME/CFS from a variety of socioeconomic backgrounds. The interventions (E) primarily targeted methods to improve mitochondrial function, including nutritional supplementation, exercise programmes designed to improve mitochondrial function, dietary changes that promote mitochondrial health, and pharmaceutical drugs with known effects on mitochondrial health. The potential effects of these treatments on the development of ME/CFS were carefully examined. Control circumstances, placebo interventions, or adjunct therapies made up the comparator (C). The overarching objective (O) was to evaluate changes in aspects of ME/CFS, such as motor function, cognitive function, quality of life, the development of both motor and non-motor symptoms, and illness progression.

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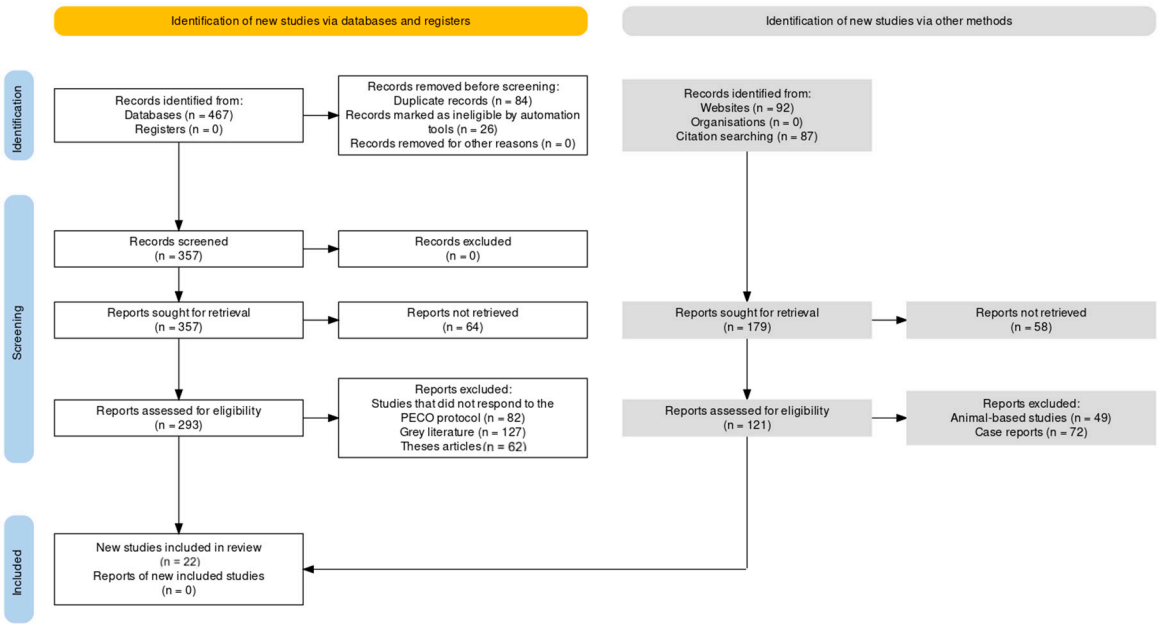

Figure 1. PRISMA protocol representing the study selection process for the review.

Database search protocol

In order to find pertinent papers across nine different databases, a rigorous and systematic strategy was utilised for the systematic review's database search methodology. The purposeful coupling of the Boolean operations AND and OR with the Medical Subject Headings (MeSH) keywords made up the search strategy, which is further described in Table 1.

Table 1. Search strings utilised across the different assessed databases for this review.

Database	Intermittent Cold Exposure	Intermittent Heat Exposure	Evolutionary Based Foods	Intermittent Fasting	Circadian-Based Interventions	Fermented Drinks	Fermented Foods	Intermittent Hypercapnia	Intermittent Hypoxia	Intermittent Exercise
PubMed	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("ME/CFS" OR "ME/CFS")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("ME/CFS" OR "ME/CFS")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("ME/CFS" OR "ME/CFS")	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("ME/CFS" OR "ME/CFS")
ScienceDirect	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND

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					("ME/CFS" OR "ME/CFS")	("ME/CFS" OR "ME/CFS")	"greek yoghurt") AND ("ME/CFS" OR "ME/CFS")			("ME/CFS" OR "ME/CFS")
IEEE Xplore	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("ME/CFS" OR "ME/CFS")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("ME/CFS" OR "ME/CFS")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("ME/CFS" OR "ME/CFS")	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("ME/CFS" OR "ME/CFS")
PsycINFO	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND

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					blocker") AND ("ME/CFS" OR "ME/CFS")	("ME/CFS" OR "ME/CFS")	yoghurt" OR "greek yoghurt") AND ("ME/CFS" OR "ME/CFS")			("ME/CFS" OR "ME/CFS")
Web of Science	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("ME/CFS" OR "ME/CFS")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("ME/CFS" OR "ME/CFS")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("ME/CFS" OR "ME/CFS")	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("ME/CFS" OR "ME/CFS")
Embase	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND

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					("ME/CFS" OR "ME/CFS")	("ME/CFS" OR "ME/CFS")	"greek yoghurt") AND ("ME/CFS" OR "ME/CFS")			("ME/CFS" OR "ME/CFS")
CINAHL	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("ME/CFS" OR "ME/CFS")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("ME/CFS" OR "ME/CFS")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("ME/CFS" OR "ME/CFS")	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("ME/CFS" OR "ME/CFS")
Scopus	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("ME/CFS" OR "ME/CFS")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("ME/CFS" OR "ME/CFS")

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					("ME/CFS" OR "ME/CFS")		yoghurt") AND ("ME/CFS" OR "ME/CFS")			
Google Scholar	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("ME/CFS" OR "ME/CFS")	("sauna" OR "infrared sauna") AND ("ME/CFS" OR "ME/CFS")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("ME/CFS" OR "ME/CFS")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("ME/CFS" OR "ME/CFS")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("ME/CFS" OR "ME/CFS")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("ME/CFS" OR "ME/CFS")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("ME/CFS" OR "ME/CFS")	("breath holding" OR "hypercapnia") AND ("ME/CFS" OR "ME/CFS")	("ihht" OR "altitude training" OR "breath holding") AND ("ME/CFS" OR "ME/CFS")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("ME/CFS" OR "ME/CFS")

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Selection criteria

RCTs, cohort studies, cross-sectional studies, case-control studies, observational studies, experimental studies, systematic reviews, and meta-analyses were among the research methodologies that were evaluated for inclusion in this systematic review. Additionally, ME/CFS patients and animal models of the disease were included. The research that complied with the requirements for reporting on the effectiveness, safety, or effect of mitochondrial treatments on ME/CFS. Changes in both motor and non-motor symptoms, alterations in quality of life, the development of the illness, changes in biochemical markers, and any necessary clinical evaluations were among the outcomes of interest. Case reports were not included in this systematic review, however, in order to support an extra layer of evidence and reduce bias brought on by specific case observations. Concerns about insufficient peer review and potential problems with methodological rigour led to the elimination of articles produced from theses and unpublished theses.

Data extraction

The systematic gathering of essential study data, such as the title, authors, year of publication, and source, was part of the data extraction technique for this systematic review. Study designs were divided into RCT, cohort, cross-sectional, case-control, observational, experimental, systematic review, and meta-analysis categories. Population information comprised the total number of participants, their ages, the distribution of their genders, and the pertinent ME/CFS inclusion criteria. The mitochondria-focused therapies were detailed in detail, including their type, dosage, duration, and schedule. Information about comparison or control groups that may have used placebos or additional treatments was also kept on file. Clinical evaluations, quality of life measures, biochemical markers of illness progression, motor and non-motor ME/CFS symptoms, and disease progression markers were all included in the primary and secondary outcomes. The key conclusions, effect sizes, statistical significance, and negative outcomes were compiled. Every statistical technique used, including tests, models, and software, was also recorded.

Assessment of Bias

As part of the bias evaluation approach used in this inquiry (see Figure 2), the quality and risk of bias of the chosen studies were assessed using the Newcastle-Ottawa Scale (NOS) [25]. When studies properly accounted for these characteristics, stars were given for comparability. The primary result was evaluated, the length of follow-up was assessed, and any loss of follow-up data was taken into account when determining the outcome.

Figure 2. Evaluation of bias in the selected papers.

RESULTS

In the first stage, a detailed identification process was used to locate pertinent studies through thorough database and register searches, which produced 467 records from various databases and zero records from registers. Additional records were found to improve these search results via websites (n=92), organisations (n=0), and citation searching (n=87). A total of 357 records that might be used for screening were left after the elimination of redundant records (n=84) and records that automated tools had declared ineligible (n=26). Each record was rigorously examined during screening to determine its applicability to the study issue, and 293 reports underwent additional eligibility review. During the eligibility assessment phase, a large number of reports were disqualified for a variety of reasons, including PECO protocol non-compliance (n=82), membership in the grey literature (n=127), and status as thesis pieces (n=62). As a consequence, 121 reports were given consideration for qualifying. Additional papers that were animal-based research (n = 49) or case reports (n = 72) were disqualified in the subsequent eligibility assessment. Due to various factors, 64 out of a total 357 reports that were attempted to be recovered could not be. Other approaches were

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used to try and retrieve 179 more reports, but only 58 of these were successful. Finally, after a thorough and multi-tiered screening process, 22 studies [26–47] in all were included in the review.

Brouwers et al [26] evaluated a polynutrient supplement containing several vitamins, minerals, and (co)enzymes, while Castro et al [27] tested the impact of oral CoQ10 and NADH supplementation. The dietary interventions of a low sugar low yeast (LSLY) diet and a healthy eating (HE) diet were compared in the study by Hobday et al [28].

Joseph et al [29] investigated the effects of a 60-mg dose of oral pyridostigmine administered after an invasive cardiopulmonary exercise test (iCPET). Keller et al [30] concentrated on the results of repeat CPETs, while both Kujawski et al [31] and Kujawski S et al [32] studied the effects of whole body cryotherapy (WBC) and static stretching (SS). Maes et al [33] proposed CoQ10 supplementation to normalize the low CoQ10 syndrome and the inflammation, oxidative & nitrosative stress (IO&NS) disorders.

Mandarano et al [34] concentrated on assessing the metabolic alterations in T cells of ME/CFS patients, though no specific intervention was evaluated. McDermott et al [35] studied the effects of BioBran MGN-3, a proposed NK cell stimulant. Physical exercise as an intervention to assess mitochondrial function was the focus of both Moore et al [36] and Nelson et al [37], with the former examining post-exercise recovery time and symptom severity, and the latter focusing on changes in the ventilatory threshold.

Rao et al [38] assessed the impact of oral administration of probiotics on mitochondrial function by observing changes in gut microbiota and its relation to ME/CFS symptoms. Rueda et al [39] studied the role of Ca(2+) in regulating respiration and activating mitochondrial metabolite transport. Sandvik et al [40] evaluated the effect of rituximab vs. placebo on endothelial function, and Sathyapalan et al [41] assessed the effect of high cocoa liquor/polyphenol-rich chocolate on fatigue and residual function compared to a simulated iso-calorific chocolate.

Strayer et al [42] assessed rintatolimod, a selective TLR3 agonist, while Sullivan et al [43] focused on the intake of a probiotic product containing Lactobacillus paracasei ssp. paracasei F19, Lactobacillus acidophilus NCFB 1748, and Bifidobacterium lactis Bb12. Thambirajah et al [44] examined the impact of Acclydine treatment for 14 weeks, and GK et al [45] evaluated the effects of Cognitive Behavioral Therapy (CBT) or Graded Exercise Therapy (GET). Lastly, Witham et al [47] investigated high-dose intermittent oral vitamin D3 therapy.

Table 2. Demographic characteristics of the included papers.

Study	Aims	Study Design	Methodology Assessed	Type of Mitochondrial Intervention Assessed
Brouwers et al [26]	To assess the effect of a polynutrient supplement on fatigue and physical activity of patients with CFS.	Prospective randomized placebo-controlled, double-blind trial.	Fifty-three patients (16 males, 37 females) fulfilling the CDC criteria of CFS.	The intervention—a polynutrient supplement containing several vitamins, minerals and (co)enzymes, or placebo, twice daily for 10 weeks.
Castro et al [27]	We conducted an 8-week, randomized, double-blind placebo-controlled trial to evaluate the benefits of oral CoQ10 (200 mg/day) plus NADH (20 mg/day) supplementation on fatigue and biochemical parameters in 73 Spanish CFS patients.	Randomized, double-blind placebo-controlled trial.	This study was registered in ClinicalTrials.gov (NCT02063126).	The intervention was oral CoQ10 (200 mg/day) plus NADH (20 mg/day) supplementation for 8 weeks.
Hobday et al [28]	This study aims to determine the efficacy of dietary intervention on level of fatigue and quality of life (QoL) in individuals with CFS.	A 24-week randomized intervention study.	Conducted with 52 individuals diagnosed with CFS.	Patients were randomized to either a low sugar low yeast (LSLY) or healthy eating (HE) dietary interventions.
Joseph et al [29]	Research question: Does neurovascular dysregulation contribute to exercise intolerance in ME/CFS, and can its treatment improve exercise capacity?	Single-center, randomized, double-blind, placebo-controlled trial.	Forty-five subjects with ME/CFS were enrolled.	Subjects were assigned to receive a 60-mg dose of oral pyridostigmine or placebo after an invasive cardiopulmonary exercise test (iCPET).
Keller et al [30]	Investigate the difference between a first and second CPET in ME/CFS patients to identify individuals with ME/CFS, document their extent of disability, and provide a physiological basis for prescribing physical activity and a metric of functional impairment.	22 subjects diagnosed with ME/CFS completed two repeat CPETs separated by 24 h.	Measures of oxygen consumption (VO2), heart rate (HR), minute ventilation (Ve), workload (Work), and respiratory exchange ratio (RER) were made at maximal (peak) and ventilatory threshold (VT) intensities. Data were analyzed using ANOVA and Wilcoxon's Signed-Rank Test (for RER).	Repeat CPETs

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Kujawski et al [31]	Explore the tolerability and effect of static stretching (SS) and whole body cryotherapy (WBC) upon fatigue, daytime sleepiness, cognitive functioning and objective and subjective autonomic nervous system functioning in those with Chronic Fatigue Syndrome (CFS) compared to a control population.	Thirty-two CFS and eighteen healthy controls (HC) participated in 2 weeks of a SS + WBC programme.	This programme was composed of five sessions per week, 10 sessions in total.	Static stretching (SS) and whole body cryotherapy (WBC)
Kujawski S et al [32]	Compare the functional interrelation of fatigue and cognitive, cardiovascular and autonomic nervous systems in a group of Chronic Fatigue Syndrome (CFS) patients with healthy individuals at different stages of analysis: at baseline and after changes induced by whole-body cryotherapy (WBC) combined with a static-stretching (SS) program.	The study included 32 patients (Fukuda criteria) and 18 healthy controls.	Fatigue, cognitive, cardiovascular and autonomic function and arterial stiffness were measured before and after 10 sessions of WBC with SS.	Whole-body cryotherapy (WBC) combined with a static-stretching (SS) program
Maes et al [33]	To examine the role of Coenzyme Q10 (CoQ10) in ME/CFS, assess its plasma levels in patients and normal controls, and explore the relationships between CoQ10 and the severity of ME/CFS as measured by the FibroFatigue (FF) scale.	Observational study	Plasma CoQ10 was assayed in patients with ME/CFS and in normal controls; the relationships between CoQ10 and the severity of ME/CFS were measured using the FF scale.	CoQ10 supplementation was suggested to normalize the low CoQ10 syndrome and the inflammation, oxidative & nitrosative stress (IO&NS) disorders.
Mandarano et al [34]	To investigate immune metabolism in ME/CFS, with a focus on T cell metabolism.	Observational study	Immune metabolism was investigated by isolating CD4+ and CD8+ T cells from patients with ME/CFS and healthy controls. Glycolysis and mitochondrial respiration in resting and activated T cells were analyzed, along with markers related to cellular metabolism and plasma cytokines.	Not specified (The study focused on assessing the metabolic alterations in T cells of ME/CFS patients rather than assessing a specific intervention).
McDermott et al [35]	To evaluate the effectiveness of BioBran MGN-3, a putative NK cell stimulant, in reducing fatigue in CFS patients.	Randomized, double-blind, placebo-controlled trial	Patients with CFS were given oral BioBran MGN-3 for 8 weeks or a placebo equivalent. The primary outcome measure was the Chalder physical fatigue	BioBran MGN-3, a putative NK cell stimulant.

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			score. Self-reported fatigue measures, self-assessment of improvement, change in key symptoms, quality of life, anxiety, and depression measures were also included.	
Moore et al [36]	To characterize the duration and severity of Post-Exertional Malaise (PEM) symptoms in ME/CFS subjects following two cardiopulmonary exercise tests (2-day CPET).	2-day CPET study on 80 ME/CFS subjects and 64 controls. Symptom Severity Scale (SSS) scores were obtained at various time points.	Use of 2-day CPET and SSS to measure PEM in ME/CFS subjects.	Physical exercise as an intervention to assess mitochondrial function by examining post-exercise recovery time and symptom severity.
Nelson et al [37]	To establish cut-off values for differentiating between ME/CFS patients and healthy controls based on the onset of ventilatory threshold (VT) during consecutive-day CPET.	CPET on a cycle-ergometer on 2-consecutive days was carried out on 16 ME/CFS patients and 10 healthy controls. Various parameters were assessed on both days.	Use of consecutive-day CPET, HR, ventilation, RPE, and work rate measurements to establish VT onset differences.	Physical exercise as an intervention to assess mitochondrial function by examining changes in ventilatory threshold.
Rao et al [38]	To determine if orally administered probiotics could improve symptoms of depression and anxiety in adult patients with chronic fatigue syndrome.	A randomized pilot study with 39 CFS patients receiving either 24 billion colony forming units of Lactobacillus casei strain Shirota (LcS) or a placebo daily for two months.	Patients provided stool samples and completed the Beck Depression and Beck Anxiety Inventories before and after the intervention.	Oral administration of probiotics as an intervention to assess mitochondrial function by observing changes in gut microbiota and its relation to ME/CFS symptoms.
Rueda et al [39]	To understand how calcium regulates respiration and whether this is dependent on the increase in ATP demand or to Ca(2+) itself.	Experimental study on intact neurons exposed to different workloads in the absence and presence of Ca(2+).	Assessed [Na(+)]i, [Ca(2+)]i and [ATP]i dynamics. Investigated the role of aspartate-glutamate exchanger ARALAR/AGC1/Slc25a12 and ATP-Mg/Pi exchanger SCaMC-3/APC2/Slc25a23 in Ca(2+)-regulated mitochondrial metabolite transport.	Studied the role of Ca(2+) in regulating respiration and activating mitochondrial metabolite transport.
Sandvik et al [40]	To investigate large-vessel and small-vessel endothelial function in ME/CFS patients.	A substudy of the RituxME trial, a national, multicenter, randomized, double-blind, placebo-controlled	Assessed Flow-mediated dilation (FMD) and post-occlusive reactive hyperemia (PORH) at baseline and after 18 months of treatment. Also measured	Evaluated the effect of rituximab vs. placebo on endothelial function.

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		phase III study on the effect of rituximab vs. placebo in ME/CFS patients in Norway.	symptom severity and various physical function measures.	
Sathyapalan et al [41]	To compare the effect of high cocoa liquor/polyphenol rich chocolate (HCL/PR) vs. simulated iso-calorific chocolate (cocoa liquor free/low polyphenols(CLF/LP)) on fatigue and residual function in subjects with chronic fatigue syndrome.	Double blinded, randomised, clinical pilot crossover study.	Assessed fatigue using the Chalder Fatigue Scale and residual function using the London Handicap scale. Also evaluated the Hospital Anxiety and Depression score.	Assessed the effect of high cocoa liquor/polyphenol rich chocolate (HCL/PR) vs. simulated iso-calorific chocolate (cocoa liquor free/low polyphenols(CLF/LP)) on fatigue and residual function.
Strayer et al [42]	To evaluate the effect of rintatolimod therapy based on disease duration in ME/CFS patients.	Phase II and Phase III double-blind, placebo-controlled, randomized, multi-site clinical trials.	The clinical activity of rintatolimod was evaluated by exercise treadmill tolerance (ETT) using a modified Bruce protocol. The ITT population (n = 208) was divided into two subsets of symptom duration.	The intervention assessed was rintatolimod, a selective TLR3 agonist.
Sullivan et al [43]	To evaluate the effect of Lactobacillus paracasei ssp. paracasei F19, Lactobacillus acidophilus NCFB 1748 and Bifidobacterium lactis Bb12 on fatigue and physical activity in CFS patients.	This was an observational study with a two-week baseline period, four weeks of probiotic intake, and a four-week follow-up period.	Fatigue, health, and physical activity were assessed by the use of the Visual Analogue Scales and the SF-12 Health Survey. Faecal samples were collected and the normal microflora was analysed.	The intervention assessed was the intake of a probiotic product containing Lactobacillus paracasei ssp. paracasei F19, Lactobacillus acidophilus NCFB 1748 and Bifidobacterium lactis Bb12.
Thambirajah et al [44]	To determine whether heat shock protein (HSP) expression is altered in CFS patients before and after exercise.	Observational study with exercise as the intervention.	HSP27, HSP60, HSP70 and HSP90 expression from 6 CFS patients and 7 age- and sex-matched controls were examined by western blot analysis of peripheral blood mononuclear cells immediately before, after, and at 1 day and 7 days following a standardized treadmill exercise.	
GK et al [45]	Measure the IGF1 and IGF binding protein (IGFBP) 3 status of CFS patients compared to age- and	A randomized, placebo-controlled, double-blind clinical trial. Fifty-seven	IGF status of 22 CFS patients was compared to that of 22 healthy age- and gender-matched	Acclydine treatment for 14 weeks.

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	gender-matched neighborhood controls, and to assess the effect of Acclydine on fatigue severity, functional impairment, and biologically active IGF1 level (IGFBP3/IGF1 ratio).	adult patients who fulfilled the US Centers for Disease Control and Prevention criteria for CFS were studied.	neighborhood control individuals. Outcome measures were fatigue severity (Checklist Individual Strength, subscale fatigue severity [CIS-fatigue]), functional impairment (Sickness Impact Profile-8 [SIP-8]), and biologically active IGF1 serum concentrations. Analyses were on an intention-to-treat basis.	
Wilshire et al [46]	Present results based on the original protocol-specified procedures and evaluate the conclusions from the trial as a whole.	Data from a recent Freedom of Information request were used to closely approximate these procedures.	The primary outcome measure was overall improvement rates. Secondary measures included rates of recovery and self-report measures.	Cognitive Behavioral Therapy (CBT) or Graded Exercise Therapy (GET).
Witham et al [47]	Test whether high-dose intermittent oral vitamin D therapy improved markers of vascular health and fatigue in patients with chronic fatigue syndrome.	Parallel-group, double-blind, randomised placebo-controlled trial. Patients with chronic fatigue syndrome according to the Fukuda (1994) and Canadian (2003) criteria were studied.	The primary outcome was arterial stiffness measured using carotid-femoral pulse wave velocity at 6 months. Secondary outcomes included flow-mediated dilatation of the brachial artery, blood pressure, cholesterol, insulin resistance, markers of inflammation and oxidative stress, and the Piper Fatigue scale.	High-dose intermittent oral vitamin D3 therapy (100,000 units every 2 months for 6 months).

Table 3. Characteristics pertaining to CD as observed in the included papers.

Study	Parameters Assessed	Inferences Observed	Results Observed
Brouwers et al [26]	Effect of a polynutrient supplement on fatigue and physical activity of CFS patients. CIS fatigue score, number of CDC symptoms, and SIP8 score.	No significant differences were found between the placebo and the treated group on any of the outcome measures.	CIS fatigue +2.16 (95%CI -4.3 to +4.39, p=0.984); CDC symptoms +0.42 (95%CI -0.61 to +1.46, p=0.417); SIP8 +182 (95%CI -165 to +529, p=0.297). No patient reported full recovery.
Castro et al [27]	Benefits of oral CoQ10 (200 mg/day) plus NADH (20 mg/day) supplementation on fatigue and biochemical parameters in CFS patients.	A significant improvement of fatigue and a recovery of the biochemical parameters were reported in the treated group versus placebo.	NAD+/NADH ($p<0.001$), CoQ10 ($p<0.05$), ATP ($p<0.05$), and citrate synthase ($p<0.05$) were significantly higher, and lipoperoxides ($p<0.05$) were significantly lower in blood mononuclear cells of the treated group.

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Hobday et al [28]	Efficacy of a low sugar low yeast (LSLY) diet or healthy eating (HE) dietary interventions on level of fatigue and QoL in CFS patients.	No statistically significant differences were observed on primary outcome measurements between the two diets.	In this randomized control trial, a LSLY diet appeared to be no more efficacious on levels of fatigue or QoL compared to HE.
Joseph et al [29]	Effect of oral pyridostigmine on exercise intolerance in ME/CFS patients. Peak exercise oxygen uptake (Vo2), exercise pulmonary and systemic hemodynamics, and gas exchange.	Pyridostigmine improves peak Vo2 in ME/CFS by increasing cardiac output and right ventricular filling pressures.	The peak Vo2 increased after pyridostigmine but decreased after placebo (13.3 ± 13.4 mL/min vs -40.2 ± 21.3 mL/min; P < .05). The treatment effect of pyridostigmine was 53.6 mL/min (95% CI, -105.2 to -2.0).
Keller et al [30]	Measures of oxygen consumption (VO2), heart rate (HR), minute ventilation (Ve), workload (Work), and respiratory exchange ratio (RER) at maximal (peak) and ventilatory threshold (VT) intensities in ME/CFS patients for two repeat CPETs separated by 24 h.	A disparity between a first and second CPET could serve to identify individuals with ME/CFS, document their extent of disability, and provide a physiological basis for prescribing physical activity as well as a metric of functional impairment.	Significant decreases from CPET1 to CPET2 in VO2peak (13.8%), HRpeak (9 bpm), Ve peak (14.7%), and Work@peak (12.5%). Decreases in VT measures included VO2@VT (15.8%), Ve@VT (7.4%), and Work@VT (21.3%). Peak RER was high (≥1.1) and did not differ between tests, indicating maximum effort by participants during both CPETs.
Kujawski et al [31]	Fatigue, daytime sleepiness, cognitive functioning, and objective and subjective autonomic nervous system functioning in Chronic Fatigue Syndrome (CFS) patients and healthy controls for 2 weeks of a SS + WBC programme.	The tolerability and effect of static stretching (SS) and whole body cryotherapy (WBC) upon aforementioned aspects in CFS patients compared to a control population.	A significant decrease in fatigue was noted in the CFS group in response to SS + WBC. Improvements in some domains of cognitive functioning (speed of processing visual information and set-shifting) were noted in both CFS and HC groups. WBC was well tolerated by those with CFS and led to symptomatic improvements associated with changes in cardiovascular and autonomic function.
Kujawski S et al [32]	Fatigue, cognitive, cardiovascular and autonomic function and arterial stiffness in CFS patients and healthy controls before and after 10 sessions of WBC with SS.	Comparison of the functional interrelation of fatigue and cognitive, cardiovascular and autonomic nervous systems in a group of CFS patients with healthy individuals at different stages of analysis.	Disturbance in homeostasis was observed in patients. Higher stress and eccentricity were observed in the CFS group. Increased fatigue was related to baroreceptor function, and baroreceptor function was in turn related to aortic stiffness in the CFS group but no such relationships were observed in the control group. Differences in the network structure underlying the interrelation among the four measured criteria were observed in both groups, before the intervention and after ten sessions of whole cryotherapy with a static stretching exercise.
Maes et al [33]	Plasma CoQ10 levels, severity of ME/CFS as measured by the FibroFatigue (FF) scale, CoQ10	Lowered levels of CoQ10 play a role in the pathophysiology of ME/CFS. Symptoms such as	Plasma CoQ10 was significantly lower in ME/CFS patients than in normal controls. Significant inverse relationships between CoQ10 and the total score on the FF scale,

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	relationship with total FF scale score, fatigue, autonomic symptoms, concentration, and memory disturbances.	fatigue, autonomic and neurocognitive symptoms may be caused by CoQ10 depletion. Lower CoQ10 is an independent predictor of chronic heart failure (CHF) and mortality due to CHF.	fatigue, and autonomic symptoms. Patients with very low CoQ10 suffered significantly more from concentration and memory disturbances.
Mandarano et al [34]	Metabolism of CD4+ and CD8+ T cells in ME/CFS patients and healthy controls, glycolysis and mitochondrial respiration in resting and activated T cells, markers related to cellular metabolism, plasma cytokines.	Patients have impaired T cell metabolism consistent with ongoing immune alterations in ME/CFS. Significant correlations between measures of T cell metabolism and plasma cytokine abundance in ME/CFS patients differ from those seen in healthy control subjects.	ME/CFS CD8+ T cells had reduced mitochondrial membrane potential compared with those from healthy controls. Both CD4+ and CD8+ T cells from patients with ME/CFS had reduced glycolysis at rest, whereas CD8+ T cells also had reduced glycolysis following activation.
McDermott et al [35]	Chalder physical fatigue score, self-reported fatigue measures, self-assessment of improvement, change in key symptoms, quality of life, anxiety, depression measures.	No significant difference observed between the effectiveness of BioBran MGN-3 and placebo in reducing fatigue in CFS patients, despite overall improvement in both groups over the study duration.	Both groups showed marked improvement over the study duration, but without significant differences. Mean improvement in the Chalder fatigue score (physical scale) was 0.3 lower in the BioBran group.
Moore et al [36]	Symptom Severity Scale (SSS), recovery time following 2-day CPET, PEM response.	ME/CFS subjects took an average of about two weeks to recover from a 2-day CPET, whereas sedentary controls needed only two days.	There was a highly significant difference in judged recovery time (ME/CFS = 12.7 ± 1.2 d; CTL = 2.1 ± 0.2 d, mean ± s.e.m., Chi2 = 90.1, $p < 0.0001$). The range of ME/CFS patient recovery was 1-64 days, while the range in CTL was 1-10 days.
Nelson et al [37]	Heart rate (HR), ventilation, ratings of perceived exertion (RPE), work rate (WR) at VT on two consecutive days of CPET.	The decrease in WR at VT of 6.3-9.8% on the 2nd day of consecutive-day CPET may represent an objective biomarker that can be used to assist with the diagnosis of ME/CFS.	WR at VT decreased from day 1 to day 2 and by a greater magnitude in ME/CFS patients ($p < 0.01$ group × time interaction).
Rao et al [38]	Beck Depression and Beck Anxiety Inventories, changes in gut microbiota, specifically Bifidobacteria and Lactobacillus levels.	Ingestion of the probiotic capsules contributed towards the predominance of bacteria that are associated with a healthy gastrointestinal system.	Compared to the placebo control group, the treatment group showed moderate increases in fecal total aerobes and anaerobes and significant increases in fecal total Bifidobacteria and Lactobacillus.
Rueda et al [39]	[Na(+)]i, [Ca(2+)]i and [ATP]i dynamics in intact neurons exposed to different workloads in the	Ca(2+) might regulate respiration by activating metabolite transport in mitochondria. ARALAR-	The lack of SCaMC-3 resulted in a smaller Ca(2+)-dependent stimulation of respiration only at high workloads. The lack of ARALAR reduced basal OCR in intact neurons using

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	absence and presence of Ca(2+). Role of aspartate-glutamate exchanger ARALAR/AGC1/Slc25a12 and ATP-Mg/Pi exchanger SCaMC-3/APC2/Slc25a23 in Ca(2+)-regulated mitochondrial metabolite transport.	MAS is a major contributor of Ca(2+)-stimulated respiration in neurons by providing increased pyruvate supply to mitochondria.	glucose as energy source and completely suppressed the OCR responses to moderate and small workloads.
Sandvik et al [40]	Flow-mediated dilation (FMD) and post-occlusive reactive hyperemia (PORH) in ME/CFS patients vs healthy controls. Symptom severity and various physical function measures.	ME/CFS patients had markedly reduced FMD and significantly lower microvascular regulation measured by PORH than healthy controls.	ME/CFS patients had markedly reduced FMD compared to healthy controls at baseline, and significantly lower microvascular regulation measured by PORH than healthy controls. There were no differences between the treatment and placebo groups in symptom changes or vascular measures. PORH, but not FMD, was similarly improved.
Sathyapalan et al [41]	Fatigue and residual function in subjects with chronic fatigue syndrome consuming high cocoa liquor/polyphenol rich chocolate (HCL/PR) vs simulated iso-calorific chocolate (cocoa liquor free/low polyphenols(CLF/LP)).	Subjects with CFS showed improvement in fatigue and residual function when consuming high cocoa liquor/polyphenol rich chocolate.	The Chalder Fatigue Scale score improved significantly after 8 weeks of the HCL/PR chocolate arm, but deteriorated significantly when subjects were given simulated iso-calorific chocolate. Residual function, as assessed by the London Handicap scale, also improved significantly after the HCL/PR arm and deteriorated after iso-calorific chocolate.
Strayer et al [42]	The clinical activity of rintatolimod, exercise treadmill tolerance (ETT) using a modified Bruce protocol; Symptom duration.	The study aimed to identify a demographic subset of ME/CFS patients that respond better to rintatolimod therapy, focusing on symptom duration.	The Target Subset, with a symptom duration of 2-8 years, showed more than twice the placebo-adjusted percentage improvements in exercise duration and vertical rise than the ITT population. The Non-Target Subset showed no significant ETT response to rintatolimod compared to placebo. Within the Target Subset, 51.2% of rintatolimod-treated patients improved their exercise duration by ≥25% ($p = 0.003$).
Sullivan et al [43]	The effect of a probiotic product on fatigue and physical activity; Fatigue and health were assessed through the Visual Analogue Scales and the SF-12 Health Survey; Analyses of faecal samples.	The study aimed to evaluate the effect of specific probiotic strains on fatigue and physical activity in CFS patients.	Neurocognitive functions improved during the study period while there were no significant changes in fatigue and physical activity scores. No major changes occurred in the gastrointestinal microflora. At the end of the study, 6 of 15 patients reported that they had improved according to the assessment described.
Thambirajah et al [44]	HSP27, HSP60, HSP70 and HSP90 expression from 6 CFS patients and 7 age- and sex-matched controls were examined by western blot analysis of peripheral blood mononuclear cells before,	The study sought to determine whether heat shock protein expression is altered in CFS patients before and after exercise.	Basal HSP27 was higher among CFS patients than in controls. These levels in CFS patients decreased immediately post-exercise and remained below basal levels at day 1 post-exercise. Similar patterns of declining HSP levels in CFS patients were also observed for HSP60 and HSP90 at day 7 post-exercise compared with basal levels. In contrast, HSP60

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	after, and 1 and 7 days following a standardized treadmill exercise.		levels in control subjects increased at day 1 and day 7 post-exercise compared to levels immediately post-exercise.
GK et al [45]	IGF1 and IGFBP3 status, fatigue severity, functional impairment, and biologically active IGF1 level	No difference in IGF status between CFS patients and healthy controls. Acclydine treatment did not result in significant differences compared to placebo across measures.	CIS-fatigue +1.1 (95% CI −4.4 to +6.5, p = 0.70), SIP-8 +59.1 (95% CI −201.7 to +319.8, p = 0.65), and IGFBP3/IGF1 ratio −0.5 (95% CI −2.8 to +1.7, p = 0.63)
Wilshire et al [46]	Overall improvement rates, rates of recovery, and secondary self-report measures	Significant effects of treatment group on primary outcome measure, but CBT or GET groups did not significantly outperform control after correcting for multiple comparisons. Modest treatment effects on self-reported measures that did not endure beyond 2 years.	Low and non-significant recovery rates across treatment groups. Self-report measure effects did not endure beyond 2 years.
Witham et al [47]	Arterial stiffness, flow-mediated dilatation of the brachial artery, blood pressure, cholesterol, insulin resistance, markers of inflammation and oxidative stress, and the Piper Fatigue scale	No effect of high-dose intermittent oral vitamin D therapy on pulse wave velocity, other vascular and metabolic outcomes, or Piper Fatigue scale.	At 6 months, adjusted treatment effect on pulse wave velocity 0.0 m/s (95% CI -0.6 to 0.6; p = 0.93), no improvement in other vascular and metabolic outcomes, Piper Fatigue scale 0.2 points (95% CI -0.8 to 1.2; p = 0.73)

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DISCUSSION

The compiled studies provided a broad perspective of potential therapeutic interventions for ME/CFS, with varying effectiveness. The significance of these studies lies in the cumulative understanding they offered into the multifaceted nature of ME/CFS, and in the individual insights they contributed to specific treatment strategies. The significant improvement in fatigue and biochemical parameters reported by Castro et al [27] underlined the potential role of nutritional supplementation in managing ME/CFS. This could stimulate further research into specific nutritional strategies and their impact on ME/CFS patients' quality of life. The studies by Keller et al [30] and Nelson et al [37] highlighted the potential of cardiopulmonary exercise testing (CPET) as both a diagnostic tool and a means to measure the extent of disability in ME/CFS patients. This could prompt the development of standardized CPET protocols for ME/CFS diagnosis and treatment efficacy evaluation.

The study by Maes et al [33] shed light on the role of CoQ10 in the pathophysiology of ME/CFS, suggesting the potential for targeted interventions to manage symptoms and improve patient outcomes. Future research may focus on the therapeutic application of CoQ10 and its effect on chronic heart failure and mortality rates in ME/CFS patients. The investigations into the effect of static stretching (SS), whole body cryotherapy (WBC), and high cocoa liquor/polyphenol-rich chocolate on ME/CFS patients indicated potential non-pharmacological interventions for symptom management. These findings could promote the exploration of a more holistic approach, incorporating lifestyle and dietary modifications alongside traditional medical treatments. The studies by Moore et al [36] and Sathyapalan et al [41] demonstrated the potential for personalized treatments based on patient characteristics and individual responses to therapy, thus underscoring the need for personalized medicine approaches in ME/CFS management. Despite the varied findings, these studies collectively underscored the complexity of ME/CFS, emphasizing the need for continued and diverse research efforts. The breadth of interventions explored and the range of observed responses may encourage the future development of personalized, multifaceted treatment strategies, potentially providing more effective and enduring relief for ME/CFS patients.

In the research conducted by Nguyen et al., no significant alterations in mitochondrial Ca2+ concentration were observed upon exposure to stimulants [14]. The same study, however, documented a decrease in cytoplasmic Ca2+ concentration within CD19+ B lymphocytes and CD56bright NK cells under the influence of stimulants. Given the dependency of mitochondrial processes, including respiratory function, on Ca2+, variations in cytosolic Ca2+ levels can affect mitochondrial uptake via Ca2+-dependent channels [39,48]. Inconsistencies in the function of Ca2+ channels, particularly transient receptor potential melastatin 3, have been associated with NK cell pathology in ME/CFS patients, resulting in diminished Ca2+ mobilization [49,50]. As Ca2+ is integral to numerous NK cell processes, including cytotoxicity, NK cell function is consequently disrupted [49,50]. This disruption may exacerbate reactive oxygen species production and contribute to the reduction of mitochondrial processes, both phenomena observed in separate studies [51]. The most persistent feature described in ME/CFS is impaired NK cell cytotoxicity [52]. Therefore, mitochondrial dysfunction may be a secondary outcome rather than a primary causative factor in ME/CFS [53,54]. Gorman et al. identified common characteristics in classical forms of mitochondrial disease and ME/CFS, with perceived fatigue being a notable attribute [55]. However, no distinctive mitochondrial gene variants characteristic of mitochondrial disease have been identified in molecular analyses of mitochondrial dysfunction in ME/CFS patients [20]. A study by Smits et al., which compared mitochondrial respiratory chain complex activity among ME/CFS patients, known mitochondrial disorder patients, and healthy controls, documented distinct differences in ATP production rate and respiratory chain complex activity. Despite these findings, the study was not included in the final review due to the inclusion of inappropriate healthy control participants [56].

Another investigation examining the presence of autoreactive antibodies in ME/CFS patients has been conducted. Despite meeting all our inclusion criteria, this article was not incorporated into the final analysis due to its publication following our screening for papers. Out of 161 ME/CFS patients, only one tested positive for anti-pyruvate dehydrogenase complex antibodies, and anti-

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mitochondrial antibodies were generally negative in ME/CFS populations. This study suggests that mitochondrial dysfunction in ME/CFS patients cannot be attributed to the presence of circulating anti-mitochondrial autoantibodies [57].

The compilation of studies presented several limitations that could potentially impact the interpretation and generalizability of their findings in relation to ME/CFS. Firstly, there was substantial variability in terms of the interventions implemented across the studies. These ranged from pharmacological treatments, dietary supplements, and dietary changes to physical therapies and lifestyle modifications. This heterogeneity of interventions might make it challenging to draw definitive conclusions or make direct comparisons across the studies. Secondly, several studies, such as those by Brouwers et al [26], Hobday et al [28], and McDermott et al [35], did not find significant differences between the treated and control groups. This could limit the conclusions that can be drawn about the effectiveness of certain interventions for ME/CFS. Thirdly, the studies often used different outcome measures, making it difficult to compare results directly. Some studies focused on fatigue levels, others on biochemical parameters, physiological measures, or quality of life. The lack of standardization in outcome measures across these studies underscores the need for unified metrics to facilitate comparative analysis. Fourthly, the sample sizes in these studies would also play a significant role in the strength of the findings. Smaller sample sizes, as often seen in such studies, can limit the statistical power and may increase the likelihood of type II errors, whereby a potentially significant effect is missed. Lastly, the studies did not uniformly account for potential confounders, such as participants' age, gender, duration of illness, and comorbidities, which could influence the results. Adjusting for these confounders in future research could help clarify the effects of the interventions studied.

CONCLUSION

The analyses of these studies collectively provided a comprehensive overview of the potential therapeutic strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The findings underscored the complexity of the disease and the need for multidimensional and personalized therapeutic approaches. The studies investigated a diverse range of interventions, from pharmacological treatments and nutritional supplements to dietary changes, physical therapies, and lifestyle modifications. The varied responses to these interventions among ME/CFS patients, as reported in the individual studies, emphasized the multifaceted nature of the disease. This suggested that a one-size-fits-all approach may not be effective for ME/CFS and underscored the need for personalized treatment strategies tailored to individual patients' needs and responses. The analyses also highlighted potential physiological and biochemical markers for ME/CFS, such as impaired T cell metabolism, reduced flow-mediated dilation, and decreased work rate at the ventilatory threshold. These findings could guide future research towards the development of objective diagnostic criteria and measurement of treatment efficacy. Despite the mixed results and several limitations, including variability of interventions, varying outcome measures, and small sample sizes, these studies collectively contributed to the understanding of ME/CFS's complex pathophysiology and treatment. The findings underscored the need for further comprehensive and rigorous research efforts to develop more effective, personalized, and enduring therapeutic strategies for ME/CFS.

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