sclerosis

MDPI

Systematic Review

The Impact of α-Lipoic Acid Treatment on Multiple Sclerosis Disability: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Patrícia Rodrigues †, Fernanda Tibolla Viero † and Gabriela Trevisan *,†

Graduated Program in Pharmacology, Federal University of Santa Maria (UFSM), Santa Maria 97105-900, RS, Brazil; patricia.rodrigues@acad.ufsm.br (P.R.)

* Correspondence: gabrielatrevisansantos@gmail.com; Tel.: +55-55-3220-8976

† These authors contributed equally to this work.

Abstract: Background: Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination in the central nervous system (CNS). Despite the availability of interventions for disease exacerbations and symptomatic management, EM remained without a cure. Oxidative stress has been implicated in the MS demyelination mechanism. Adjuvant therapies like α-lipoic acid (ALA) have garnered interest for their potential to mitigate oxidative damage and control MS symptoms. ALA is found naturally in vegetables and red meat and can also be synthesized in mitochondria through enzymatic reactions involving octanoic acid and cysteine. However, its bioavailability from dietary sources is limited, prompting an investigation into supplemental forms. We conducted a systematic review and meta-analysis to assess the effect of ALA on disability in randomized clinical trials (RCTs) for MS. **Methods:** Records were searched until June 2023 (CRD42023397760). Five RCTs evaluated ALA's effect on MS progression using the Expanded Disability Status Scale (EDSS). The quality of evidence was assessed using GRADE, and publication bias was evaluated using Egger's and Begg's tests. **Results:** Following the selection process, five studies were included involving 179 patients (87 placebo and 92 ALA). Oral administration of racemic ALA (R/S-ALA) at 600 mg twice daily reduced EDSS, indicating a potential for ALA supplementation to mitigate MS disability. The North American trials (SPMS patients) did not show heterogeneity, while Asian studies (RRMS patients) were moderated. The quality of evidence was high without publication bias. **Conclusions:** ALA treatment reduce EDSS scores. However, further studies are warranted to establish the role of ALA as an adjuvant in clinical practice in long-term follow-up (>2 years) RCTs.

Keywords: antioxidant; RRMS; EDSS; thioctic acid; fatigue; motor symptoms

check for updates

Academic Editors: Maurizio A. Leone and Radu Tanasescu

Received: 26 November 2024
Revised: 13 January 2025
Accepted: 20 January 2025
Published: 24 January 2025

Citation: Rodrigues, P.; Viero, F.T.; Trevisan, G. The Impact of α-Lipoic Acid Treatment on Multiple Sclerosis Disability: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Sclerosis* **2025**, *3*, 4. https://doi.org/10.3390/sclerosis3010004

Correction Statement: This article has been republished with a minor change. The change does not affect the scientific content of the article and further details are available within the backmatter of the website version of this article.

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease characterized by demyelination in the brain and spinal cord [1]. MS is the leading cause of nontraumatic neurological disability and neuropathic pain, and the global prevalence is 2.8 million [2,3]. Clinically, MS manifests in different forms: relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). RRMS, the most common subtype (80% of diagnostics), is characterized by episodes of neurological dysfunction followed by partial recovery. Over time, approximately 10–20 years post-diagnosis, RRMS may progress to SPMS, characterized by a worsening of symptoms without remission. PPMS, on the other hand, involves a progressive deterioration of

neurological function without observed improvement. Accurate differential diagnosis of the MS clinical forms is essential for selecting appropriate treatment strategies [2].

Current therapeutic approaches for MS include interventions for disease exacerbations, disease-modifying therapies (DMTs), and symptomatic management [4]. Despite advancements in treatment, existing medications, such as interferon-beta (IFN-β), monoclonal antibodies, fingolimod, and glatiramer acetate, exhibit limitations, particularly in addressing progressive forms of MS, and are associated with adverse effects [5–7]. Given these challenges, adjuvant therapies like α-lipoic acid (ALA) have garnered interest for their potential to mitigate oxidative damage and control MS symptoms [8,9].

ALA is a potent antioxidant with demonstrated anti-inflammatory properties and low toxicity in randomized controlled trials (RCTs) to treat pain diseases and animal models of chronic pain [10,11]. ALA can be naturally sourced from foods or synthesized through enzymatic mitochondrial pathways [12–14]. However, its bioavailability from dietary sources is limited, prompting an investigation into supplemental forms [14,15].

While studies have explored oral or subcutaneous ALA supplementation in MS patients to address disease progression and mobility issues [12,16], the effectiveness of such interventions remains inconclusive [8,9,17]. Preclinical studies showed the effect of ALA treatment reduced the clinical score and nociception of the experimental autoimmune encephalomyelitis (EAE) model [18]. Previous clinical reviews have examined the effects of ALA in MS patients [8,12,17]. However, there is still a lack of a comprehensive meta-analysis evaluating the impact of ALA on the Expanded Disability Status Scale (EDSS). Here, we included only studies that evaluate the ALA effect on the EDSS, which measured disability of patients [19]. Therefore, this study aims to conduct a systematic review and meta-analysis to assess the efficacy of ALA supplementation in treating MS, specifically focusing on its effect on the EDSS in RCTs.

2. Material and Methods

2.1. Systematic Review and Meta-Analysis Guidelines

We conducted the systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Table S1) [20]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (CRD42023397760).

2.2. Search Strategy

A comprehensive literature search was conducted in Pubmed, Scopus, and EMBASE in February 2023, and the search was repeated in June 2023. Search terms included Medical Subject Heading (MeSH) terms related to MS and ALA. These terms were chosen according to the English-language medical metadata system (Medical Subject Heading terms). The search was formulated using the PICO (P, population: MS patients; I, intervention: treatment with ALA; C, comparison: placebo, O, outcome: change in disability as assessed by the EDSS).

Two independent researchers (G.T.S. and P.R.) performed the search, with discrepancies resolved by a third reviewer (F.T.V.). EndNote X9® software (version Bld 12062) was used for the initial removal of duplicate records, review articles, and no articles (congress abstracts, editor's notes, and letters, among others). Then, the screening of the articles followed two distinct phases, first, the title and abstract were analyzed. In the second phase, the full text was read. Finally, the references of the selected articles and reviews related to the research topic were also evaluated through manual search (G.T.).

2.3. Inclusion and Exclusion Criteria

Exclusion criteria encompassed review articles, other records that are not articles, pre-clinical articles with experimental models, articles performed with other compounds or pathologies, articles not written in the English language, and articles without a control group. Only RCT studies evaluating the effect of ALA on MS patients and presenting measures of disease progression (EDSS) were included. This selection was performed by two independent reviewers (G.T. and P.R), and possible discrepancies were analyzed by a third reviewer (F.T.V).

2.4. Data Extraction

Two reviewers (G.T. and P.R.) independently extracted relevant data from eligible studies related to the number of patients in the groups (placebo and ALA), sex distribution, age, diagnostic assessment for MS, clinical aspects, and risk of bias were entered into Table 1. The groups, MS subtype, ALA dose, route of administration, time usage, outcomes related to therapeutic effects, and risk of bias were described in Table 2.

2.5. Risk of Bias, Publication Bias and Quality Assessment

Studies were individually assessed by two independent reviewers (G.T. and P.R.) regarding the source of bias, and when necessary, a third reviewer (F.T.V.) was consulted. Studies that had characteristics such as incomplete description of clinical characteristics of patients or EDSS scores did not include the type of treatment for MS, and exclusion of EDSS > 5.5 or 6 were evaluated for bias. We classified this data in subcategories as high, low, or unclear and expressed by the Cochrane Risk of Bias Tool using the software RevMan version 5.4 [21]. Publication bias was evaluated using Egger's test, Begg's test, and funnel plots [22,23]. The quality of evidence was evaluated using GRADEprofiler (GRADEpro) 3.6.1 software for RCTs.

2.6. Data Analysis

We presented the results of the meta-analyses using forest plots generated with mean difference using the random-effects model. We used the mean change in EDSS (ΔEDSS = $EDSS_{pre\text{-}ALA} - EDSS_{post\text{-}ALA}$), standard deviation (SD), and the number of patients for both the ALA and placebo groups to demonstrate the reduction of baseline EDSS after the period of treatment. In cases where multiple articles shared the same patient groups, only the data from the first published article were considered in the total patient count to avoid duplication [24]. Moreover, subgroup analysis with continent was conducted to evaluate potential sources of heterogeneity based on trial continents. Statistical analysis was performed using RStudio software (version 2022.12.0+353) for Windows Mozilla/5.0 (Windows NT 10.0; Win64; x64) AppleWebKit/537.36 (KHTML, like Gecko) RStudio/2022.12.0+353 Chrome/102.0.5005.167 Electron/19.1.3 Safari/537.36 and RevMan software version 5.4, the Cochrane 2020 collaboration [21] with two-tailed $p < 0.05$ as the minimum significance level.

Table 1. Data extraction from clinical evaluation of the effects of α-lipoic acid (ALA) in patients with multiple sclerosis (MS).

Groups, Age, and Sex Distribution (F/M)	Diagnostic Assessment	Clinical Aspects	Risk of Bias	Reference
Placebo (N = 17, 32.2 ± 10.5 years, 15/2) ALA (N = 22, 32.3 ± 6.2 years, 15/7)	MC Donald criteria (2010).	Exclusion criteria: EDSS ≥ 5.5, pregnancy, antioxidant application during last month, diabetes, attacks during the study period and history of other autoimmune diseases or other MS subtypes. RRMS placebo: EDSS baseline = 2.2 ± 1.2; EDSS after 12 weeks: 2.3 ± 1.4; FSS = 34.4 ± 11.7; Disease duration = 4.9 ± 1.4 years. RRMS treated: EDSS baseline = 2.5 ± 1.1; EDSS after 12 weeks: 1.9 ± 1.3; FSS = 39.6 ± 16.5; Disease duration = 4.9 ± 3.6 years.	Did not mention DMTs treatment and exclusion of patient with EDSS ≥ 5.5.	Khalili et al., 2012 [25]
Placebo (N = 22, 28.7 ± 9 years, 17/5) ALA (N = 24, 31.4 ± 6.2 years, 19/5).	MC Donald criteria (2010).	Exclusion criteria: EDSS ≥ 5.5, consuming any antioxidant supplement or corticosteroid treatment, had had an attack during the previous month, had any history of other autoimmune diseases, diabetes and/or other chronic diseases or were pregnant or lactating or other MS subtypes. RRMS placebo: EDSS baseline = 1.5 ± 1.2; EDSS after 12 weeks: 1.7 ± 0.3; Disease duration = 4.5 ± 4 years. RRMS ALA treated: EDSS baseline = 2.2 ± 1.5; EDSS after 12 weeks: 2.0 ± 0.3; Disease duration = 5.1 ± 3.6 years.	Exclusion of patient with EDSS ≥ 5.5.	Khalili et al., 2014 [26]
Placebo (N = 12, 32.2 ± 10.5 years, 11/1) ALA (N = 12, 32.3 ± 6.2 years, 7/5)	MC Donald criteria (2010).	Exclusion criteria: ongoing clinical relapse, pregnancy and lactation, the use of corticosteroids, the occurrence of relapse attacks during the study, and other major medical disorders. Regular consumption of antioxidants or vitamin supplements were also considered exclusion criteria. RRMS placebo: EDSS baseline = 1.5 ± 1.3; EDSS after 12 weeks: 1.5 ± 1.5; Disease duration = 5.75 ± 5.3 years. RRMS ALA treated: EDSS baseline = 2.2 ± 1.6; EDSS after 12 weeks: 1.8 ± 1.5; Disease duration = 4.5 ± 4.5 years.	Did not mention DMTs treatment.	Khalili et al., 2017 [27]

Table 1. *Cont.*

Groups, Age, and Sex Distribution (F/M)	Diagnostic Assessment	Clinical Aspects	Risk of Bias	Reference
Placebo (N = 10, 55.7 ± 4.1 years, 5/5) ALA (N = 11, 55.8 ± 5.7 years, 6/5)	MC Donald criteria (2005).	Exclusion criteria: EDSS ≥ 6, clinical relapse in the past 5 years, age <40 or >70, recent use of specific therapies (natalizumab, immunosuppressants, chemotherapies, IV corticosteroids within 1 year, corticosteroids for relapse within 60 days, or ALA within 30 days), MRI constraints, ocular disease affecting OCT interpretation, pregnancy or breastfeeding, significant illness, uncontrolled/insulin-dependent diabetes, lack of English fluency, or non-RRMS subtypes. SPMS placebo: EDSS baseline: 6.0 ± 0.5; EDSS after 2 years: 6.0 ± 0.5; Disease duration = 22.7 ± 8.5 years; SPMS ALA treated: EDSS baseline: 5.8 ± 0.5; EDSS after 2 years: 4.8 ± 0.5; Disease duration = 28.9 ± 8.6 years.	Exclusion of patients with EDSS ≥ 6.	Loy et al., 2018 [28]
Placebo (N = 24, 59.7± 6.0 years, 15/9) ALA (N = 27, 57.9 ± 6.7 years, 16/11)	MC Donald criteria (2005).	Excluding criteria: clinical relapse in the past 5 years, age <40 or >70, recent use of natalizumab, immunosuppressants, chemotherapies, IV corticosteroids within 1 year, corticosteroids for relapse within 60 days, or ALA within 30 days, MRI constraints, self-reported ocular disease affecting OCT interpretation, pregnancy or breastfeeding, significant concurrent illness, uncontrolled/insulin-dependent diabetes, lack of English fluency, or non-RRMS subtypes. SPMS control: EDSS baseline: 6.0 ± 0.5 EDSS after 2 years: 6.0 ± 0.5 Disease duration = 29.1 ± 9.9 years. SPMS ALA treated: EDSS baseline: 5.8 ± 0.5 EDSS after 2 years: 4.8 ± 0.5 Disease duration = 30.9 ± 9.3 years.	No bias was detected.	Spain et al., 2017 [29]

α-lipoic acid (ALA); disease-modifying therapies (DMTs); Expanded Disability Status Scale (EDSS); female (F); male (M); relapsing–remitting multiple sclerosis (RRMS); secondary progressive multiple sclerosis (SPMS).

Table 2. Outcomes from randomized clinical trial that evaluated the action of α-lipoic acid (ALA) on multiple sclerosis (MS) disability.

Groups	MS Subtypes	Dose, Route, and Time of Administration	Outcomes	Risk of Bias	Reference
Placebo (N = 17) ALA (N = 22)	RRMS	Dose of 600 mg for R/S-ALA capsules, every 12 h for 12 weeks.	There was a decrease in EDSS score in the ALA group after treatment compared to the control group (for patients with EDSS > 0 at baseline).	No bias was detected.	Khalili et al., 2012 [25]
Placebo (N = 22) ALA (N = 24)	RRMS	Dose of 600 mg for R/S-ALA capsules, every 12 h for 12 weeks.	There were no statistical differences between placebo or ALA groups for EDSS.	No bias was detected.	Khalili et al., 2014 [26]
Placebo (N = 12) ALA (N = 12)	RRMS	Dose of 600 mg for R/S-ALA capsules, every 12 h for 12 weeks.	There were no statistical differences between placebo or ALA groups for EDSS.	No bias was detected.	Khalili et al., 2017 [27]
Placebo (N = 12) ALA (N = 12)	SPMS	Dose of 600 mg for R/S-ALA capsules, every 12 h for 2 years.	There were no statistical differences between placebo or ALA groups for EDSS.	No bias was detected.	Loy et al., 2018 [28]
Placebo (N = 24) ALA (N = 22)	SPMS	Dose of 600 mg for R/S-ALA capsules, every 12 h for 2 years.	There were no statistical differences between placebo or ALA groups for EDSS.	No bias was detected.	Spain et al., 2017 [29]

α-lipoic acid (ALA); Expanded Disability Status Scale (EDSS); multiple sclerosis (MS); relapsing–remitting multiple sclerosis (RRMS); secondary progressive multiple sclerosis (SPMS).

3. Results

3.1. Search Strategy

A total of 6019 studies were identified through database searches in Pubmed, Scopus, and EMBASE. After excluding duplicates (n = 1248) and non-article records (n = 1292, congress abstracts, editor's notes, letters, among others). Of these, 3459 studies were excluded based on predefined inclusion criteria, and the full texts of 20 studies were assessed to confirm the detection of a disability measure MS and treatment with ALA, and 4 articles were included. Also, 329 articles were identified from other methods by manual search from the references of the 4 previously included articles and reviews about this topic, 1 of these was included in the systematic review (Figure 1). At the end of the review, five studies were included in this systematic review and meta-analysis to evaluate the possibility of the effect of ALA on the treatment of disability of MS patients.

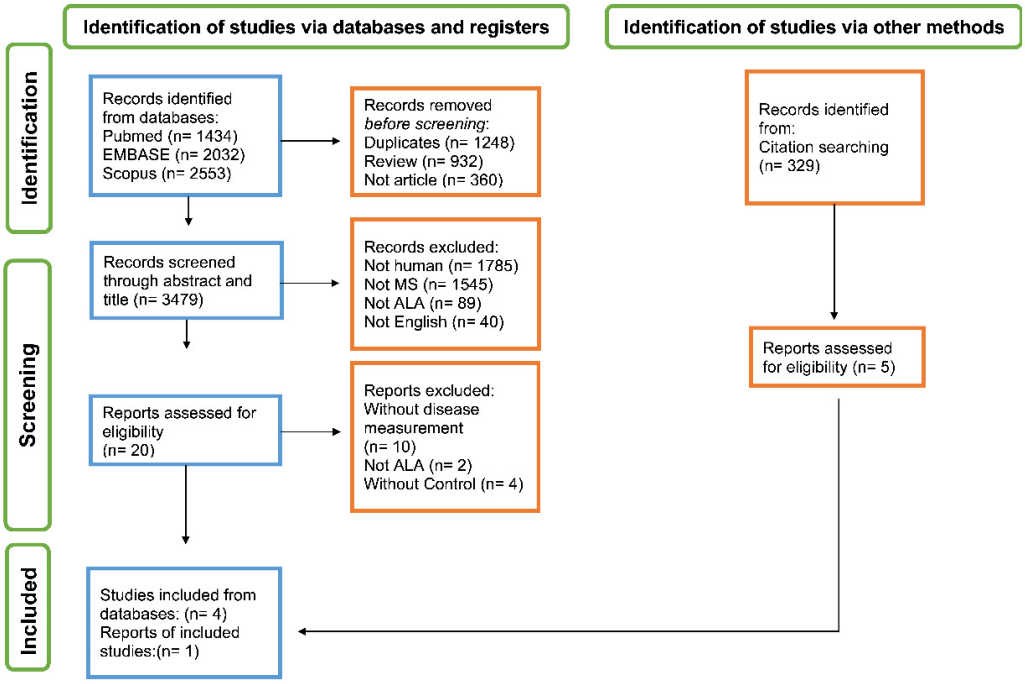


Figure 1. Flow diagram of the search of randomized clinical trials that evaluated the α-lipoic acid (ALA) treatment for multiple sclerosis (MS) patients.

The studies included in this review bring data from 181 patients, 85 with placebo treatment and 96 treated with ALA. On average, 30% were male patients, and 70% were female. The minimum age of the patients was 28.7 ± 9 years, and the maximum age was 59 ± 6 years (Table 1). In Table 2, it was observed that ALA treatment was always carried out with the racemic form (R/S-ALA). The selected dose was the same in all studies, and the administration time was 600 mg every 12 h. The studies, including RRMS patients, were treated with ALA for 12 weeks, while those with SPMS ALA were administered for 2 years.

3.2. Risk of Bias and Publication Bias

We described in Table 1 the possible bias related to patients' inclusion in the trials and in Table 2 the bias from ALA treatment. Thus, no bias was detected for the action of ALA on EDSS scores (Table 2). All included studies have a low risk of bias, but Spain 2017 had an unclear risk of selection bias (Figure 2A). We observed the low risk of selection bias (90%), performance bias, detection bias and attrition bias (100%), reporting bias (60%), and other biases (100%) (Figure 2B).

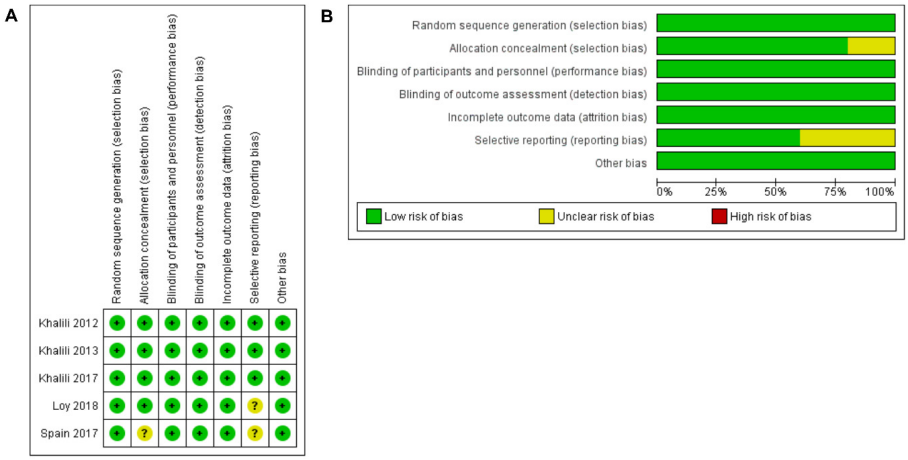


Figure 2. Risk of bias of the randomized clinical trials that accessed the α-lipoic acid (ALA) treatment for multiple sclerosis (MS) patients. (**A**) Risk of bias assessed in each included article (**B**) Percentage of risk of bias assessed by item assessed. References [25–29].

We also use the funnel plot to evaluate the publication bias shown as the standard error of the study against the mean difference (Figure 3). The funnel plot was asymmetric, but the Egger's and Beggs's tests did not show publication bias ($p = 0.0945$ and $p = 0.1932$) (Figure 3). Thus, the meta-analysis of ALA treatment for MS patients did not present publication bias.

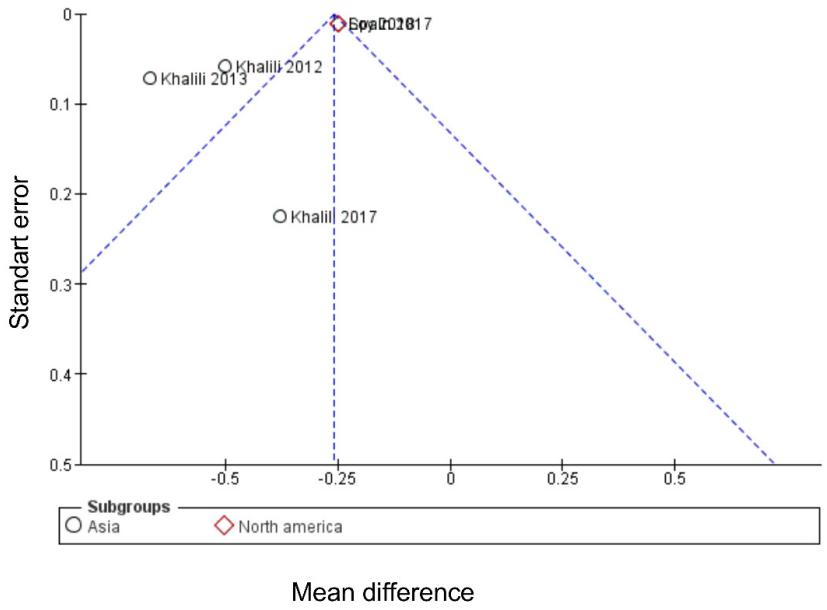


Figure 3. Funnel plot of the α-lipoic acid (ALA) treatment for multiple sclerosis (MS) patients versus placebo. References [25–29].

3.3. Meta-Analysis Results and Quality Assessment

Spain 2017 and Loy 2018 did not report the EDSS scores after ALA treatment in their published articles. However, they provided the results from each patient, which we included in the meta-analysis. Since they shared the same patient population, we counted only one study in the total number of patients.

Forest plots represented the reduction of EDSS score after ALA treatment in MS patients compared to placebo (MD = −0.37, 95% CI = −0.45 to −0.29) with higher heterogeneity ($I^2 = 92\%$) (Figure 4). To evaluate the heterogeneity source, we accomplished a sub-analysis of the continents where the RCTs were conducted. The heterogeneity of

Asian studies is moderated (I^2 = 51%), while the North American trials did not show heterogeneity (I^2 = 0%), suggesting a place effect on the RCTs heterogeneity. Moreover, the quality of evidence shows a very strong association between the reduction in EDSS and ALA treatment for both Asian and North American trials (Table S2).

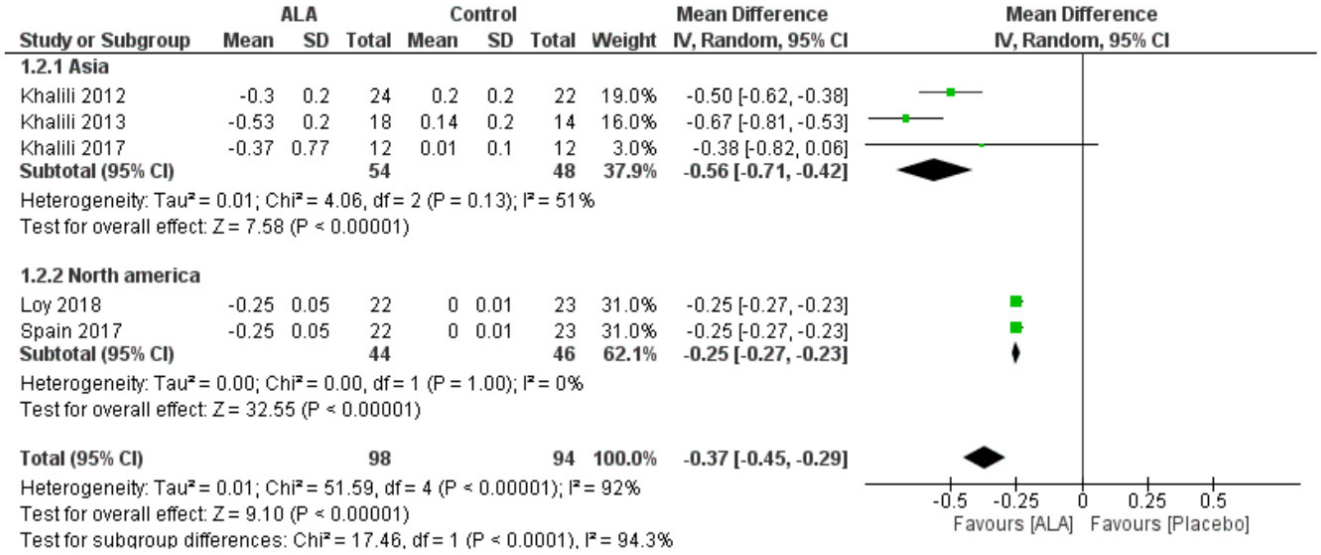


Figure 4. Forest plots from α-lipoic acid (ALA) treatment reduced the expanded disability status scale (EDSS) of multiple sclerosis (MS) patients. The forest plots used the mean of EDSS, standard deviations (SD), and the number of subjects from the studies using the random effects model for forest plots. References [25–29].

4. Discussion

MS is a disability disease in which oxidative stress is implicated in symptom development [2]. Previous research from our group has demonstrated an association between increased Expanded Disability Status Scale (EDSS) scores and elevated levels of advanced oxidative protein products, an oxidative stress biomarker [30]. In addition, our systematic review and meta-analysis of RCTs have shown that ALA treatment reduces diabetic neuropathic pain scores [10]. Thus, the primary objective of this study was to evaluate the effect of ALA treatment on the disability (EDSS) of MS patients. EDSS scores measure a patient's neurological status, the low scores (EDSS 0 to 5) corresponding to normal physical parameters, and higher scores indicating disability (EDSS > 6) [31,32]. Our findings suggest that ALA treatment may reduce MS disability by lowering EDSS scores.

Previous systematic reviews on the effects of ALA for MS treatment have included studies that did not evaluate EDSS [8,12,17]. In contrast, our meta-analysis only included articles that reported EDSS data to assess whether ALA could reduce motor alterations and disability commonly observed in MS patients [19,32]. A systematic review from 2015 evaluated different antioxidant compounds for MS treatment, but only ALA and epigallocatechin gallate (a component found in green tea) showed possible beneficial effects in this pathology. The article included both clinical and preclinical studies with ALA. However, the preliminary results of clinical studies hindered the recommendation of ALA treatment [8].

Another study published in 2020 included six studies with ALA treatment in MS patients [17]. However, two of these studies were excluded from our analysis as they did not report EDSS data. Marx and colleagues described the effect of 13 nutraceutical compounds for MS treatment, including ALA. However, so far, the limited evidence from these studies precludes the recommendation of nutraceutical compounds for MS treatment due to insufficient adverse effect data [17]. A systematic review from 2021 focused solely on

the effects of ALA in MS patients and preclinical models. While this review identified the same five articles included in our study, it also covered seven additional articles that did not report EDSS data. Similar to our results, Xie and colleagues suggested that ALA treatment exhibits promising anti-inflammatory and antioxidant effects for MS [12]. However, none of these studies conducted a meta-analysis of clinical results.

In the studies included in our review, ALA treatment was administered in its racemic form (R/S-ALA) orally via capsules at a consistent dose of 600 mg every 12 h (1200 mg/day). However, treatment duration varied, with RRMS patients receiving ALA treatment for 3 months and SPMS patients for 2 years. Similarly, another meta-analysis evaluating the analgesic effects of ALA on different types of pain identified the 600 mg dose as the most commonly used, with varying treatment durations [10]. Another systematic review and meta-analysis showed that ALA supplementation was not associated with gastrointestinal adverse effects without considering the chemical presentation (R/S-ALA) [33]. However, adverse effects specific to R/S-ALA were not assessed in our study due to a lack of reported data. Therefore, future RCTs should prioritize the evaluation of R-ALA treatment and its associated adverse effects.

Another bias that we evaluated was the patient's inclusion criteria when EDSS scores are above 6 since the patients are unable to perform daily activities and motor skills, such as walking [32]. Thus, some studies have excluded patients with EDSS scores greater than 5.5, especially studies that evaluated motor measures. In addition, the use of disease-modifying therapies (DMTs) not described in the studies may introduce bias, as certain drugs can exacerbate oxidative stress imbalance [34], possibly underestimating the ALA effect. However, our meta-analysis results indicated that ALA supplementation reduced the EDSS in two treatment periods (3 months and 2 years). Our study represents the first meta-analysis of RCTs demonstrating the efficacy of ALA supplementation in reducing EDSS for both RRMS and SPMS.

Another important result is the effect of ALA in the MS subtypes that we showed in the sub-analysis of the continent. Asian studies included only RRMS patients, while the North American studies included only SPMS patients. MS subtypes presented a distinct pathobiology and DMTs treatment response [35]. For SPMS patients, oral administration of R-ALA showed better gastrointestinal tolerance, suggesting that this chemical presentation should be preferred over the racemic mixture [16]. However, the included studies only used the racemic mixture and did not show gastrointestinal side effects for the MS subtypes. The differential response to ALA between RRMS and SPMS subgroups may reflect varying disease pathophysiology and progression patterns, emphasizing the need for targeted therapeutic approaches. This sub-analysis also demonstrates the efficacy of ALA in long treatment (2 years) and short-term treatment (12 weeks). These findings underscore the need for further research to evaluate the efficacy and tolerability of specific ALA formulations tailored to different MS subtypes and treatment duration.

We can point out some strong points of our systematic review and meta-analysis, such as we did not observe publication bias and the identification of heterogeneity sources through subgroup analysis. In addition, the quality of evidence provided by the included studies indicated that the ALA treatment showed efficacy for MS patients by reducing EDSS. However, the limited number of studies (5 articles) evaluating ALA for MS and the lack of assessment for the effects of ALA on neuropathic pain symptoms, fatigue, quality of life, MRI findings, and biomarkers of oxidative stress represent some limitations of our study. The work ability is a reliable parameter of disability in MS patients, but it was not evaluated in ALA RCTs included in this systematic review and meta-analysis, representing another limitation [36]. The highly variable nature of MS patients (RRMS and SPMS) and their clinical trajectories in studies can influence the results [19]. The lack of changes

in EDSS after a longer period of follow-up is a limitation of the RRMS-included studies (12 weeks). Future clinical studies should explore ALA supplementation's effects on these parameters over a long period of follow-up (>2 years).

This systematic review and meta-analysis provide evidence that ALA supplementation may reduce disability in MS patients, as measured by the EDSS. Our findings suggest that ALA, administered at a dose of 600 mg twice daily, is effective in both RRMS and SPMS subtypes in short-term follow-up. The analysis also highlights heterogeneity in study outcomes, influenced by differences in geographic location, disease subtype, and treatment duration. However, our analysis did not yield promising results regarding fatigue scores, and we were unable to evaluate the adverse symptoms associated with ALA supplementation.

Further studies are warranted to investigate whether ALA supplementation, in combination with DMTs, could yield beneficial effects in MS patients. Moreover, future RCTs should access MS neuropathic pain symptoms, particularly in longer-duration studies with a larger patient cohort. Although our findings indicate the beneficial effects of ALA supplementation on disability parameters as measured by the EDSS, further research is essential to determine the optimal use and implementation of ALA in clinical practice. In conclusion, this study establishes a foundation for the role of ALA in MS management, advocating for its further exploration as part of a multimodal therapeutic approach.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/sclerosis3010004/s1, Table S1: PRISMA 2020 statement: The Impact of α-Lipoic Acid Treatment on Multiple Sclerosis Disability: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Table S2: Quality of evidence using GRADE from alpha lipoic acid (ALA) versus placebo treatment for multiple sclerosis (MS) patients.

Author Contributions: P.R., F.T.V. and G.T. participated in the search design and performed the literature search and data extraction. P.R. achieved data analysis. P.R., F.T.V. and G.T. wrote or contributed to the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: We wish to acknowledge fellowships received from the Conselho Nacional de Desenvolvimento Científico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Ph.D. fellowship to P.R. [process #88887.501568/2020-00] and V.T.V. [process #88887.501615/2020-00] from CAPES. P.R. exchange fellowship [process #200483/2022-6] from CNPq. G.T. is the recipient of a fellowship from CNPq [process #303531/2020-7], a research grant from Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) [process #21/2551-0001935-2] and from CNPq N° 26/2021 [process# 401653/2022-6].

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data and program codes that support the findings of this study are openly available under request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ALA	α-lipoic acid
CNS	Central nervous system
DMTs	Disease-modifying therapies
Embase	Excerpta medical database
EDSS	Expanded disability status scale
IFN-β	Interferon-beta

MeSH	Medical Subject Heading
MS	Multiple Sclerosis
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RRMS	Relapsing–remitting multiple sclerosis
RCTs	Randomized controlled trials
SPMS	Secondary progressive multiple sclerosis
Scopus	SciVerse Scopus

References

1. Walton, C.; King, R.; Rechtman, L.; Kaye, W.; Leray, E.; Marrie, R.A.; Robertson, N.; La Rocca, N.; Uitdehaag, B.; van der Mei, I.; et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult. Scler. J.* **2020**, *26*, 1816–1821. [CrossRef]
2. Thompson, A.J.; Baranzini, S.E.; Geurts, J.; Hemmer, B.; Ciccarelli, O. Multiple sclerosis. *Lancet* **2018**, *391*, 1622–1636. [CrossRef]
3. Rodrigues, P.; da Silva, B.; Trevisan, G. A systematic review and meta-analysis of neuropathic pain in multiple sclerosis: Prevalence, clinical types, sex dimorphism, and increased depression and anxiety symptoms. *Neurosci. Biobehav. Rev.* **2023**, *154*, 105401. [CrossRef] [PubMed]
4. Yong, H.Y.F.; Yong, V.W. Mechanism-based criteria to improve therapeutic outcomes in progressive multiple sclerosis. *Nat. Rev. Neurol.* **2022**, *18*, 40–55. [CrossRef]
5. Hauser, S.L.; Cree, B.A. Treatment of Multiple Sclerosis: A Review. *Am. J. Med.* **2020**, *133*, 1380–1390.e2. [CrossRef]
6. Yang, J.H.; Rempe, T.; Whitmire, N.; Dunn-Pirio, A.; Graves, J.S. Therapeutic Advances in Multiple Sclerosis. *Front. Neurol.* **2022**, *13*, 824926. [CrossRef] [PubMed]
7. Huntemann, N.; Rolfes, L.; Pawlitzki, M.; Ruck, T.; Pfeuffer, S.; Wiendl, H.; Meuth, S.G. Failed, Interrupted, or Inconclusive Trials on Neuroprotective and Neuroregenerative Treatment Strategies in Multiple Sclerosis: Update 2015–2020. *Drugs* **2021**, *81*, 1031–1063. [CrossRef] [PubMed]
8. Plemel, J.R.; Juzwik, C.A.; Benson, C.A.; Monks, M.; Harris, C.; Ploughman, M. Over-the-counter anti-oxidant therapies for use in multiple sclerosis: A systematic review. *Mult. Scler. J.* **2015**, *21*, 1485–1495. [CrossRef] [PubMed]
9. de Sousa, C.N.S.; Leite, C.M.G.d.S.; Medeiros, I.d.S.; Vasconcelos, L.C.; Cabral, L.M.; Patrocínio, C.F.V.; Patrocínio, M.L.V.; Mouaffak, F.; Kebir, O.; Macedo, D.; et al. Alpha-lipoic acid in the treatment of psychiatric and neurological disorders: A systematic review. *Metab. Brain Dis.* **2019**, *34*, 39–52. [CrossRef]
10. Cassanego, G.; Rodrigues, P.; Bauermann, L.D.F.; Trevisan, G. Evaluation of the analgesic effect of α-lipoic acid in treating pain disorders: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.* **2022**, *177*, 106075. [CrossRef]
11. Rodrigues, P.; Cassanego, G.B.; Peres, D.S.; Viero, F.T.; Kudsi, S.Q.; Ruviaro, N.A.; Aires, K.d.V.; Portela, V.M.; Bauermann, L.D.F.; Trevisan, G. Alpha-lipoic acid reduces nociception by reducing oxidative stress and neuroinflammation in a model of complex regional pain syndrome type I in mice. *Behav. Brain Res.* **2024**, *459*, 114790. [CrossRef] [PubMed]
12. Xie, H.; Yang, X.; Cao, Y.; Long, X.; Shang, H.; Jia, Z. Role of lipoic acid in multiple sclerosis. *CNS Neurosci. Ther.* **2022**, *28*, 319–331. [CrossRef]
13. Salehi, B.; Berkay Yılmaz, Y.; Antika, G.; Boyunegmez Tumer, T.; Fawzi Mahomoodally, M.; Lobine, D.; Akram, M.; Riaz, M.; Capanoglu, E.; Sharopov, F.; et al. Insights on the Use of α-Lipoic Acid for Therapeutic Purposes. *Biomolecules* **2019**, *9*, 356. [CrossRef] [PubMed]
14. Dörsam, B.; Fahrer, J. The disulfide compound α-lipoic acid and its derivatives: A novel class of anticancer agents targeting mitochondria. *Cancer Lett.* **2016**, *371*, 12–19. [CrossRef]
15. Rochette, L.; Ghibu, S.; Muresan, A.; Vergely, C. Alpha-lipoic acid: Molecular mechanisms and therapeutic potential in diabetes. *Can. J. Physiol. Pharmacol.* **2015**, *93*, 1021–1027. [CrossRef]
16. Cameron, N.E.; Cotter, M.A.; Horrobin, D.H.; Tritschler, H.J. Effects of α-lipoic acid on neurovascular function in diabetic rats: Interaction with essential fatty acids. *Diabetologia* **1998**, *41*, 390–399. [CrossRef] [PubMed]
17. Marx, W.; Hockey, M.; McGuinness, A.J.; Lane, M.; Christodoulou, J.; van der Mei, I.; Berk, M.; Dean, O.M.; Taylor, B.; Broadley, S.; et al. The effect of emerging nutraceutical interventions for clinical and biological outcomes in multiple sclerosis: A systematic review. *Mult. Scler. Relat. Disord.* **2020**, *37*, 101486. [CrossRef] [PubMed]
18. Khan, N.; Gordon, R.; Woodruff, T.M.; Smith, M.T. Antiallodynic effects of alpha lipoic acid in an optimized RR-EAE mouse model of MS-neuropathic pain are accompanied by attenuation of upregulated. *Pharmacol. Res. Perspect.* **2015**, *3*, e00137. [CrossRef]
19. Lublin, F.D.; Reingold, S.C.; Cohen, J.A.; Cutter, G.R.; Sørensen, P.S.; Thompson, A.J.; Wolinsky, J.S.; Balcer, L.J.; Banwell, B.; Barkhof, F.; et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* **2014**, *83*, 278–286. [CrossRef]

20. Shamseer, L.; Moher, D.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A.; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ* **2015**, *350*, g7647. [CrossRef] [PubMed]
21. Higgins, J.P.; Altman, D.G.; Gøtzsche, P.C.; Jüni, P.; Moher, D.; Oxman, A.D.; Savovic, J.; Schulz, K.F.; Weeks, L.; Sterne, J.A.; et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **2011**, *343*, d5928. [CrossRef] [PubMed]
22. Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **1997**, *315*, 629–634. [CrossRef] [PubMed]
23. Begg, C.B.; Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* **1994**, *50*, 1088–1101. [CrossRef]
24. Thompson, S.G. Why sources of heterogeneity in meta-analysis should be investigated. *BMJ* **1994**, *309*, 1351–1355. [CrossRef]
25. Khalili, M.; Eskandari, G.; Ghajarzadeh, M.; Azimi, A.; Eghtesadi, S.; Ali Sahraian, M.; Motevalian, A.; Hashemi, H.; Mirshafiey, A.; Norouzi, A. Lipoic acid and multiple sclerosis: A randomized controlled clinical trial. *Curr. Top. Nutraceutical Res.* **2012**, *10*, 95–100.
26. Khalili, M.; Azimi, A.; Izadi, V.; Eghtesadi, S.; Mirshafiey, A.; Sahraian, M.A.; Motevalian, A.; Norouzi, A.; Sanoobar, M.; Eskandari, G.; et al. Does lipoic acid consumption affect the cytokine profile in multiple sclerosis patients: A double-blind, placebo-controlled, randomized clinical trial. *Neuroimmunomodulation* **2014**, *21*, 291–296. [CrossRef]
27. Khalili, M.; Eghtesadi, S.; Mirshafiey, A.; Eskandari, G.; Sanoobar, M.; Sahraian, M.A.; Motevalian, A.; Norouzi, A.; Moftakhar, S.; Azimi, A. Effect of lipoic acid consumption on oxidative stress among multiple sclerosis patients: A randomized controlled clinical trial. *Nutr. Neurosci.* **2017**, *17*, 16–20. [CrossRef] [PubMed]
28. Loy, B.D.; Fling, B.W.; Horak, F.B.; Bourdette, D.N.; Spain, R.I. Effects of lipoic acid on walking performance, gait, and balance in secondary progressive multiple sclerosis. *Complement. Ther. Med.* **2018**, *41*, 169–174. [CrossRef]
29. Spain, R.; Powers, K.; Murchison, C.; Heriza, E.; Winges, K.; Yadav, V.; Cameron, M.; Kim, E.; Horak, F.; Simon, J.; et al. Lipoic acid in secondary progressive MS: A randomized controlled pilot trial. *Neurol. Neuroimmunol. Neuroinflamm.* **2017**, *4*, e374. [CrossRef] [PubMed]
30. Rodrigues, P.; Bochi, G.V.; Trevisan, G. Advanced Oxidative Protein Products Role in Multiple Sclerosis: A Systematic Review and Meta-analysis. *Mol. Neurobiol.* **2021**, *58*, 5724–5742. [CrossRef] [PubMed]
31. Meyer-Moock, S.; Feng, Y.-S.; Maeurer, M.; Dippel, F.-W.; Kohlmann, T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol.* **2014**, *14*, 58. [CrossRef] [PubMed]
32. Cinar, B.P.; Yorgun, Y.G. What We Learned from The History of Multiple Sclerosis Measurement: Expanded Disability Status Scale. *Noro Psikiyatr. Ars.* **2018**, *55* (Suppl. S1), S69–S75. [PubMed]
33. Fogacci, F.; Rizzo, M.; Krogager, C.; Kennedy, C.; Georges, C.M.G.; Knežević, T.; Liberopoulos, E.; Vallée, A.; Pérez-Martínez, P.; Wenstedt, E.F.E.; et al. Safety Evaluation of α-Lipoic Acid Supplementation: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Clinical Studies. *Antioxidants* **2020**, *9*, 1011. [CrossRef]
34. Rafiee Zadeh, A.; Ghadimi, K.; Ataei, A.; Askari, M.; Sheikhinia, N.; Tavoosi, N.; Falahatian, M. Mechanism and adverse effects of multiple sclerosis drugs: A review article. Part 2. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2019**, *11*, 105–114.
35. Cree, B.A.C.; Arnold, D.L.; Chataway, J.; Chitnis, T.; Fox, R.J.; Pozo Ramajo, A.; Murphy, N.; Lassmann, H. Secondary Progressive Multiple Sclerosis. *Neurology* **2021**, *97*, 378–388. [CrossRef] [PubMed]
36. Ponzio, M.; Podda, J.; Pignattelli, E.; Verri, A.; Persechino, B.; Vitturi, B.K.; Bandiera, P.; Manacorda, T.; Inglese, M.; Durando, P.; et al. Work Difficulties in People with Multiple Sclerosis. *J. Occup. Rehabil.* **2024**, *34*, 606–617. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.