Letters & Reviews in Neurological Sciences

Role of Antioxidants in the Treatment of Amyotrophic Lateral Sclerosis / Motor Neuron Disease: A Narrative Review of Mechanisms, Clinical Evidence and Prospects

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND), is a fatal neurodegenerative disease in which oxidative stress is a recognised contributor to motor neuron injury. Antioxidants have therefore been tested widely, but results have been disappointing. This review summarises the evidence for edaravone, vitamins E and C, carotenoids, coenzyme Q10, melatonin, curcumin, nicotinamide riboside with pterostilbene, N-acetylcysteine, selenium and methionine. Edaravone is the only antioxidant with a positive phase 3 trial, in a selected group of patients: the mean ALSFRS-R decline over 24 weeks was 5.01 points versus 7.50 with placebo [1]. Vitamin E helped transgenic mice [2] and was associated with lower risk in cohort studies [3,4], but randomised trials were negative [5–7]. Coenzyme Q10 at 2,700 mg/day showed insufficient promise to justify phase III [8]. Melatonin, nanocurcumin and a nicotinamide riboside combination produced encouraging signals in small studies [9–11]. Mechanisms are summarised in schemes, evidence in tables and graphs, and priorities for future research are outlined.

Key words: Amyotrophic lateral sclerosis; motor neuron disease; antioxidants; oxidative stress; edaravone; coenzyme Q10; vitamin E; melatonin; curcumin; nicotinamide riboside.

1. Introduction

ALS is characterised by progressive degeneration of upper and lower motor neurons, with paralysis and death usually from respiratory failure within a few years of onset [12,13]. The discovery of mutations in the copper/zinc superoxide dismutase gene (*SOD1*) in familial ALS focused attention on oxidative stress [14], and biomarkers of oxidative damage are present in patients with sporadic disease [15]. Oxidative stress is also linked to mitochondrial dysfunction, glutamate excitotoxicity and inflammation [15] (Figure 1).

Given this rationale, antioxidant compounds of many kinds have been tried as treatment. A Cochrane review concluded that evidence for individual antioxidants, or for antioxidants in general, was insufficient [7], but newer agents have since been tested. This review brings together the preclinical and clinical evidence for the main antioxidant strategies and explains the mechanisms through which they are expected to act.

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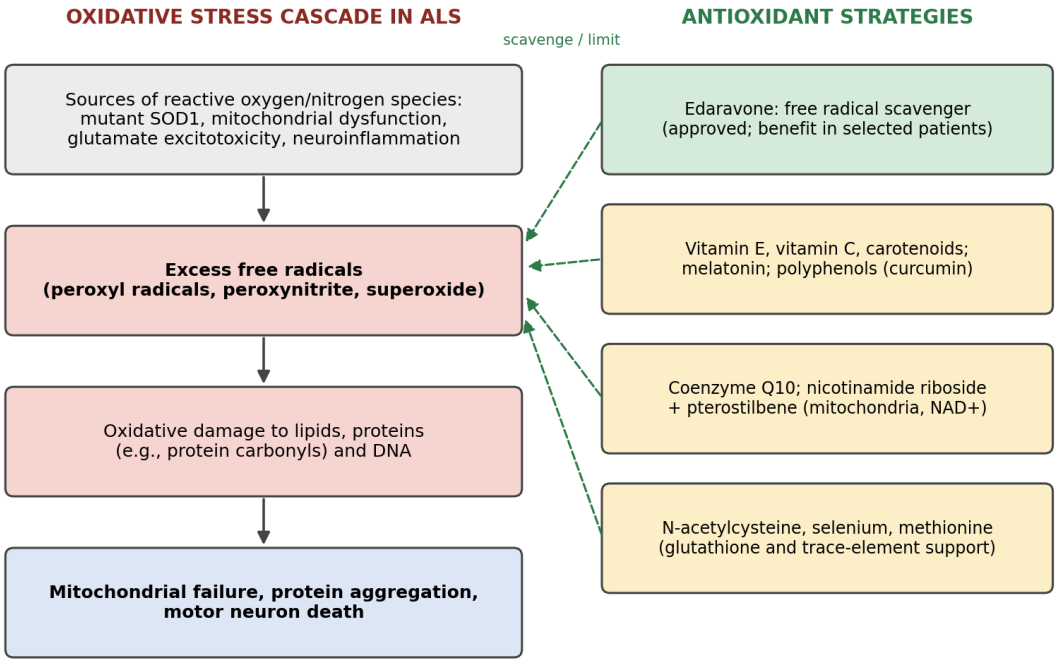


Figure 1. Oxidative stress cascade in ALS/MND and the points at which antioxidants are proposed to act.

2. Classes of antioxidants and their mechanisms

Antioxidants studied in ALS fall into several groups: Synthetic free radical scavengers (edaravone), chain-breaking vitamins (E, C and carotenoids), mitochondrial cofactors (coenzyme Q10), amphiphilic scavengers (melatonin), polyphenols (curcumin, pterostilbene), NAD^+ precursors (nicotinamide riboside) and agents supporting glutathione and selenoenzymes (N-acetylcysteine, selenium, methionine). Their proposed actions and clinical status are shown in Figure 2 and Table 1, and each class is discussed below.

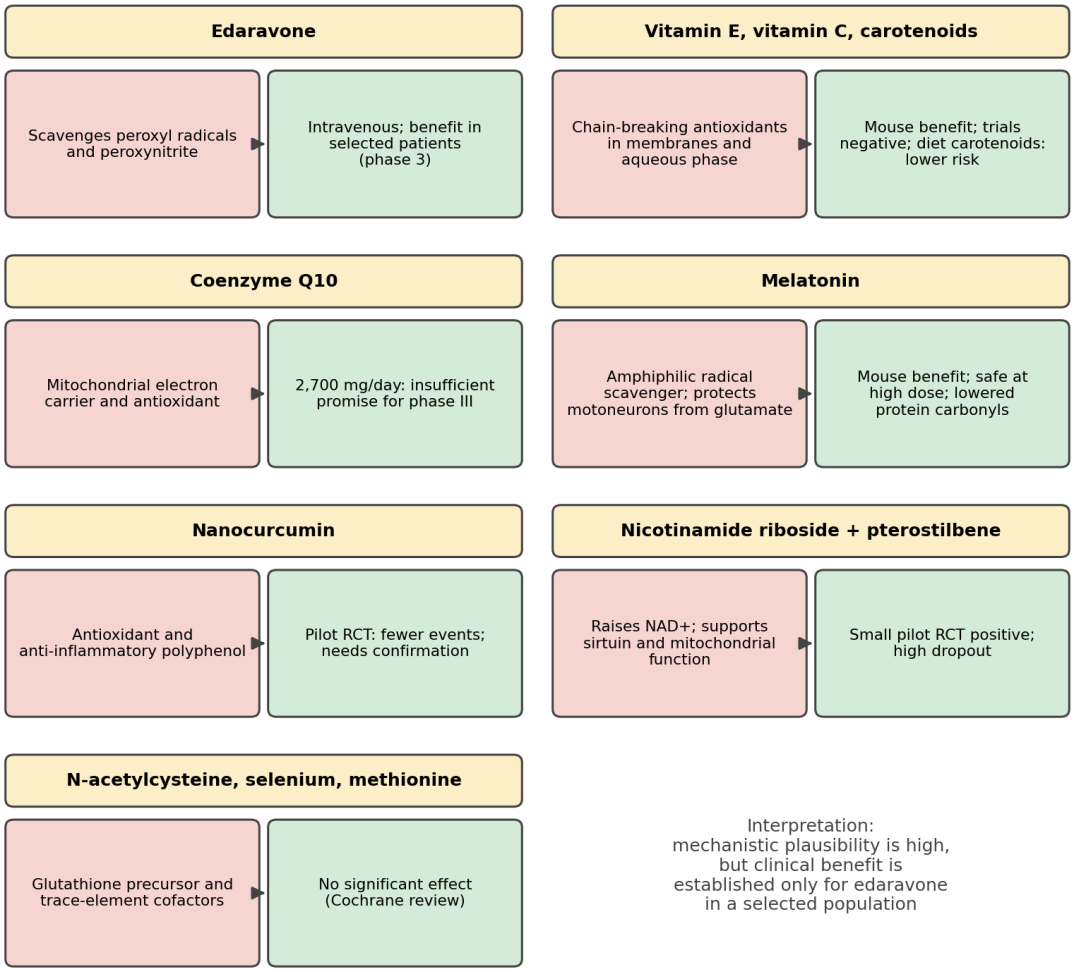


Figure 2. Proposed mechanisms of action (left) and clinical status (right) of antioxidants studied in ALS/MND.

Table 1. Antioxidant classes studied in ALS/MND and overall assessment.

Class / agent	Proposed antioxidant action	Key clinical evidence	Assessment
Edaravone	Scavenges peroxyl radicals and peroxynitrite [1]	Phase 3 benefit in selected patients [1]	Benefit in a selected population
Vitamin E	Lipid-soluble chain-breaking antioxidant [2]	Negative randomised trials [5–7]	Not effective as treatment
Vitamin C, carotenoids	Aqueous antioxidant; radical-quenching pigments	Vitamin C no association; carotenoid diet inverse [16]	Dietary pattern only
Coenzyme Q10	Mitochondrial cofactor and antioxidant [8]	Futility in phase II [8]	Not supported
Melatonin	Amphiphilic radical scavenger [9]	Safety study with biomarker effect [9]	Needs efficacy trial
Nanocurcumin	Antioxidant and anti-inflammatory [10]	Pilot RCT, fewer events [10]	Needs confirmation
Nicotinamide riboside + pterostilbene	NAD^+ and sirtuin support [11]	Small pilot RCT, positive [11]	Needs confirmation
N-acetylcysteine, selenium, methionine	Glutathione and selenoenzyme support	No significant effect [7]	Not supported

3. Edaravone

Edaravone is a free radical scavenger given by intravenous infusion in treatment cycles. A first phase 3 study did not show a significant difference in the revised ALS Functional Rating Scale (ALSFRS-R) compared with placebo; a second trial therefore enrolled a carefully defined group: patients aged 20–75 years with definite or probable ALS, independent living status, forced vital capacity of at least 80%, and disease duration of two years or less [1]. In this study, 137 patients were randomised over 24 weeks and 68 taking edaravone and 66 taking placebo entered the primary analysis; the least-squares mean ALSFRS-R change was −5.01 with edaravone versus −7.50 with placebo, a difference of 2.49 points (95% CI 0.99–3.98; p = 0.0013) [1]. Serious adverse events occurred in 16% of edaravone-treated and 24% of placebo-treated patients [1] (Figure 4a).

The result is important as the first positive phase 3 trial of an antioxidant in ALS, but it applies to a narrow, early-stage population, and the clinical meaning of a 2.5-point difference in the ALSFRS-R has been debated. Its success suggests that antioxidant strategies may work when started early in selected patients.

4. Vitamins E and C and carotenoids

In transgenic mice with an ALS-linked *SOD1* mutation, vitamin E delayed disease onset and progression [2]. Observational data are suggestive: regular vitamin E supplement users had a lower risk of ALS death, with relative risks of 0.59 for under 10 years of use and 0.38 for 10 years or more, whereas vitamin C and multivitamins showed no association [3]. A pooled analysis of five cohorts found no overall association for supplements but declining ALS rates with longer use, and a borderline inverse association with dietary intake (RR 0.79, 95% CI 0.61–1.03) [4]. Higher dietary carotenoid intake was associated with lower risk (RR 0.75, 95% CI 0.61–0.91 for the highest versus lowest quintile), driven by β-carotene and lutein, while vitamin C was not associated with risk [16] (Figure 3, Table 2).

Clinical trials did not confirm benefit. A 12-month trial of 500 mg/day of α-tocopherol did not affect survival or motor function [5], and an 18-month trial of 5000 mg/day added to riluzole did not influence survival [6]. The Cochrane review of 10 studies (1015 patients) found no significant effect of vitamin E in the individual trials or of antioxidants combined on 12-month survival [7]. The inverse associations in cohorts therefore remain unexplained and may reflect confounding by healthier lifestyles [16].

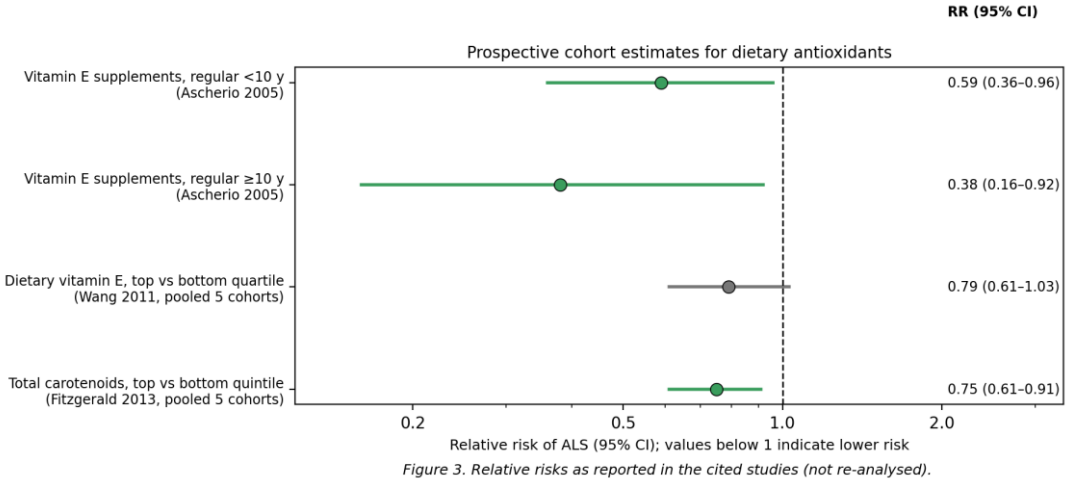


Figure 3. Relative risks as reported in the cited studies (not re-analysed).

Table 2. Observational studies of dietary and supplemental antioxidants and ALS risk.

Study	Design	Main finding (as reported)
Ascherio et al. [3]	Prospective cohort; supplement use	Regular vitamin E use associated with lower ALS mortality (RR 0.59 for <10 y; 0.38 for ≥10 y); no association for vitamin C or multivitamins.
Wang et al. [4]	Pooled analysis of 5 cohorts; 1,055,546 participants, 805 cases	Supplement use not associated overall; rates declined with years of use; dietary RR 0.79 (0.61–1.03).
Fitzgerald et al. [16]	Pooled analysis of 5 cohorts	Total carotenoids RR 0.75 (0.61–0.91); β-carotene and lutein inverse; vitamin C not associated.

5. Coenzyme Q10

Coenzyme Q10 is an electron carrier in the mitochondrial respiratory chain and an antioxidant, and it showed promise in ALS transgenic mice [8]. The QALS trial used an adaptive, two-stage, randomised, placebo-controlled phase II design in 185 participants, first choosing between 1,800 and 2,700 mg/day and then testing the preferred dose against placebo over nine months; it concluded that 2,700 mg/day showed insufficient promise to warrant phase III testing, and secondary analyses showed no significant differences [8]. The design avoided the need for a much larger phase III study.

6. Melatonin

Melatonin is an amphiphilic molecule with antioxidant effects not shared by classical antioxidants. It attenuated glutamate-induced death of cultured motoneurons, and high-dose oral melatonin delayed disease progression and extended survival in SOD1-G93A mice [9]. In a safety study of 31 patients with sporadic ALS, 300 mg/day rectal melatonin was well tolerated for up to two years, and serum protein carbonyls, which were elevated in patients, were normalised to control values by treatment [9]. The authors concluded that high-dose melatonin is suitable for clinical trials; an efficacy trial with clinical endpoints is still needed.

7. Polyphenols and NAD^+ boosters

7.1 Nanocurcumin

Curcumin is a polyphenol with antioxidant and anti-inflammatory properties. In a 12-month, double-blind, placebo-controlled pilot trial in Iran, 54 patients received nanocurcumin 80 mg daily or placebo in addition to riluzole; the primary outcome was death or dependence on mechanical ventilation, which occurred in 1 patient (3.7%) in the nanocurcumin group and 6 (22.2%) in the placebo group, with no withdrawals due to adverse effects [10] (Figure 4b). The authors concluded that nanocurcumin is safe and might improve survival, especially in patients with bulbar symptoms, but the trial was small and single-centre.

7.2 Nicotinamide riboside with pterostilbene (EH301)

EH301 combines nicotinamide riboside, an NAD^+ precursor, with pterostilbene, a stilbene related to resveratrol [11]. In a randomised pilot trial, 32 patients received EH301 (1,200 mg daily; n = 15) or placebo (n = 17) for four months, and the treated group showed improved ALSFRS-R score, pulmonary function and muscle strength compared with placebo [11]. Twelve of the 32 participants dropped out, the trial was single-centre, and some authors had commercial ties, so confirmation in a larger phase 2 trial is needed.

8. N-acetylcysteine, selenium and methionine

Agents that support glutathione and selenoenzymes have also been tested. The Cochrane review reported no significant effect of subcutaneous acetylcysteine (50 mg/kg daily) or of a combination of L-methionine, vitamin E and selenium (Alsemet) on survival at 12 months, and no differences in secondary outcomes; the antioxidants were generally well tolerated [7]. The reviewers noted that studies were generally poorly designed, underpowered and short [7].

9. Comparative evidence

Table 3 summarises the clinical studies, and Figures 4 and 5 show the main reported results and trial sizes. Only edaravone has been supported by a randomised phase 3 trial with a significant primary result [1]. The largest antioxidant trial of the group, QALS, enrolled 185 participants and was negative [8], whereas the positive signals for nanocurcumin and EH301 come from trials with 54 and 32 participants [10,11] and should be regarded as hypothesis-generating.

Table 3. Clinical studies of antioxidants in ALS/MND.

Study	Intervention	Design	Outcome (as reported)
Desnuelle et al. [5]	α-Tocopherol 500 mg/day	Randomised; 12 months	No effect on survival or motor function.
Graf et al. [6]	α-Tocopherol 5000 mg/day + riluzole	Randomised; 18 months	No influence on survival.
Kaufmann et al. [8]	Coenzyme Q10 2,700 mg/day	Phase II, adaptive; n = 185; 9 months	Insufficient promise for phase III.
Writing Group [1]	Edaravone IV, cycles	Phase 3; 137 randomised; 24 weeks	ALSFRS-R change −5.01 *vs* −7.50; difference 2.49.
Weishaupt et al. [9]	Melatonin 300 mg/day rectal	Safety study; 31 patients	Well tolerated; protein carbonyls normalised.
Ahmadi et al. [10]	Nanocurcumin 80 mg/day + riluzole	Pilot RCT; 54 patients; 12 months	Events 3.7% *vs* 22.2%.
de la Rubia et al. [11]	EH301 1,200 mg/day	Pilot RCT; 32 patients; 4 months	Improved ALSFRS-R and strength; high dropout.
Orrell et al. [7]	Various antioxidants (vitamin E, acetylcysteine, Alsemet)	Cochrane review; 10 studies, 1015 patients	No significant survival effect.

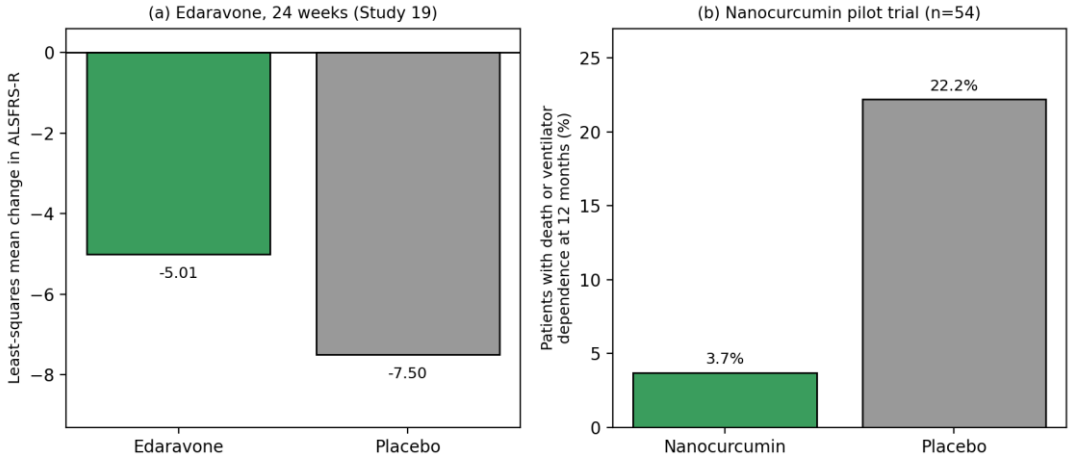


Figure 4. Reported values from Writing Group 2017 (a) and Ahmadi et al. 2018 (b); plotted from values given in the text of each paper.

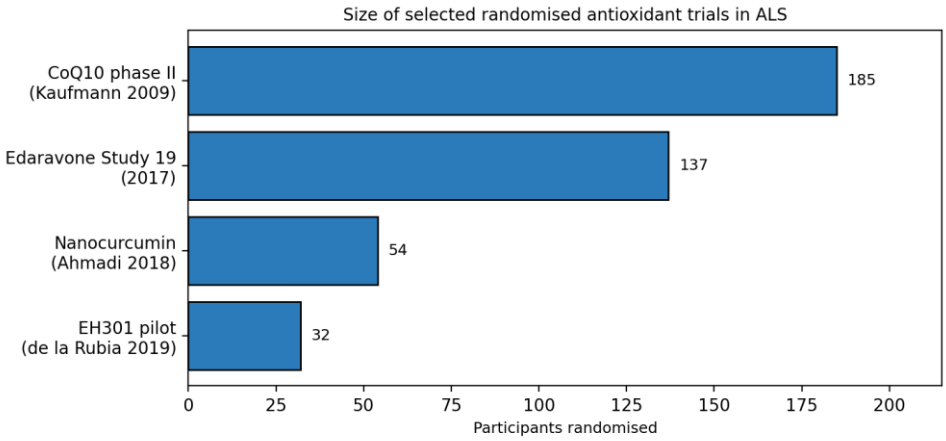


Figure 5. Randomised sample sizes reported in the cited trials.

10. Why have most antioxidants failed?

Several explanations have been proposed. First, oxidative stress may be a downstream consequence rather than a primary driver, so scavenging radicals late may have little effect. The edaravone results in early-stage, well-defined patients are consistent with the importance of timing and selection [1]. Second, doses and central nervous system exposure may be inadequate, even at very high doses such as coenzyme Q10 at 2,700 mg/day [8]. Third, a single antioxidant may not address mitochondrial, inflammatory and excitotoxic pathways at the same time [15]. Fourth, many trials were small, short and underpowered [7], which limits the ability to detect modest benefits. Finally, observational associations for vitamin E and carotenoids may be confounded by lifestyle [16].

11. Future directions

Priorities include: (i). Confirmatory, adequately powered trials of the agents with early positive signals, namely nanocurcumin, nicotinamide riboside combinations and melatonin [9–11]; (ii). enrolment of early-stage patients selected by progression rate, as in the edaravone programme [1]; (iii). biomarker-guided designs, for example using protein carbonyls or other oxidative stress markers as pharmacodynamic endpoints [9]; (iv). adaptive phase II designs with futility analysis, which can save patients and time [8]; and (v). combination regimens with approved therapies. Strategies that boost endogenous antioxidant defences, rather than only scavenging radicals, are a further area of research. Trials should report effect sizes, adverse events and adherence, and high-dose regimens should be taken under medical supervision.

12. Conclusions

Oxidative stress remains a rational therapeutic target in ALS, but the clinical record of antioxidants is mixed. Edaravone is the only agent with a positive phase 3 trial, in a selected early-stage population [1]. Vitamin E, vitamin C, coenzyme Q10, acetylcysteine, selenium and methionine have not shown benefit in trials [5–8]. Melatonin, nanocurcumin and nicotinamide riboside with pterostilbene are promising but need larger trials [9–11]. Antioxidants should therefore be used as adjuncts under medical supervision alongside approved therapy and supportive care.

Declaration, Conflict of interest and funding

The content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological disorders.

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Data availability: No new datasets were generated or analyzed.

Author Note

This manuscript is a literature review and is not a treatment recommendation for an individual patient. Antioxidants should be taken only for a clinically justified indication and with appropriate medical monitoring under the supervision of a Neurologist.

References

1. Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: A randomised, double-blind, placebo-controlled trial. *Lancet Neurol*., **2017**;16(7):505–512.
2. Gurney ME, Cutting FB, Zhai P, et al. Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial amyotrophic lateral sclerosis. *Ann Neurol*., **1996**;39(2):147–157.
3. Ascherio A, Weisskopf MG, O'Reilly EJ, et al. Vitamin E intake and risk of amyotrophic lateral sclerosis. *Ann Neurol*., **2005**;57(1):104–110.
4. Wang H, O'Reilly ÉJ, Weisskopf MG, et al. Vitamin E intake and risk of amyotrophic lateral sclerosis: A pooled analysis of data from 5 prospective cohort studies. *American J Epidemiol*., **2011**;173(6):595–602.
5. Desnuelle C, Dib M, Garrel C, Favier A. A double-blind, placebo-controlled randomized clinical trial of α-tocopherol (vitamin E) in the treatment of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*., **2001**;2(1):9–18.
6. Graf M, Ecker D, Horowski R, et al. High dose vitamin E therapy in amyotrophic lateral sclerosis as add-on therapy to riluzole: Results of a placebo-controlled double-blind study. *J Neural Transm*., **2005**;112(5):649–660.
7. Orrell RW, Lane RJM, Ross M. Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease. *Cochrane Database Syst Rev*., **2007**;(1):CD002829.
8. Kaufmann P, Thompson JLP, Levy G, et al. Phase II trial of CoQ10 for ALS finds insufficient evidence to justify phase III. *Ann Neurol*., **2009**;66(2):235–244.
9. Weishaupt JH, Bartels C, Pölking E, et al. Reduced oxidative damage in ALS by high-dose enteral melatonin treatment. *J Pineal Res*., **2006**;41(4):313–323.
10. Ahmadi M, Agah E, Nafissi S, et al. Safety and efficacy of nanocurcumin as add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: A pilot randomized clinical trial. *Neurotherapeutics*, **2018**;15(2):430–438.
11. de la Rubia JE, Drehmer E, Platero JL, et al. Efficacy and tolerability of EH301 for amyotrophic lateral sclerosis: A randomized, double-blind, placebo-controlled human pilot study. *Amyotroph Lateral Scler Frontotemporal Degener*., **2019**;20(1–2):115–122.
12. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med*., **2017**;377(2):162–172.
13. van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. *Lancet*, **2017**;390(10107):2084–2098.
14. Rosen DR, Siddique T, Patterson D, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature*, **1993**;362(6415):59–62.
15. Barber SC, Shaw PJ. Oxidative stress in ALS: Key role in motor neuron injury and therapeutic target. *Free Radic Biol Med*., **2010**;48(5):629–641.
16. Fitzgerald KC, O'Reilly ÉJ, Fondell E, et al. Intakes of vitamin C and carotenoids and risk of amyotrophic lateral sclerosis: Pooled results from 5 cohort studies. *Ann Neurol*., **2013**;73(2):236–245.