Multiple Sclerosis and Related Disorders 37 (2020) 101486

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

The effect of emerging nutraceutical interventions for clinical and biological outcomes in multiple sclerosis: A systematic review

Wolfgang Marx[a,b,*], Meghan Hockey[a], Amelia J. McGuinness[a], Melissa Lane[a], John Christodoulou[b,c], Ingrid van der Mei[d], Michael Berk[a], Olivia M. Dean[a,e,f], Bruce Taylor[d], Simon Broadley[g], Jeannette Lechner-Scott[h,i], Felice N Jacka[a], Robyn M. Lucas[j,k], Anne-Louise Ponsonby[b,j], the RELIEF Trial team

[a] Deakin University, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Australia
[b] Murdoch Children's Research Institute, Royal Children's Hospital, Australia
[c] Department of Paediatrics, University of Melbourne, Parkville, Melbourne, Australia
[d] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
[e] Florey Institute for Neuroscience and Mental Health, University of Melbourne, Kenneth Myer Building, Australia
[f] University of Melbourne, Department of Psychiatry, Level 1 North, Main Block, Royal Melbourne Hospital, Parkville, Australia
[g] School of Medicine, Griffith University, Gold Coast, Queensland Australia
[h] School of Medicine and Public Health, University Newcastle, Australia
[i] Department of Neurology, John Hunter Hospital, Hunter New England Health, Newcastle, Australia
[j] National Centre for Epidemiology and Population Health, Research School of Population Health, The Australian National University, Canberra, Australia
[k] Centre for Ophthalmology and Visual Sciences, University of Western Australia, Perth, Australia

ARTICLE INFO

Keywords:
Dietary supplement
Nutraceutical
Multiple sclerosis
Vitamin

ABSTRACT

Background: Due to the considerable burden of multiple sclerosis (MS)-related symptoms and the need to identify effective interventions to prevent disease progression, various nutraceutical interventions have been trialed as adjunctive treatments. The aim of this review was to investigate the efficacy and safety of nutraceutical interventions for clinical and biological outcomes in people with MS.

Methods: In accordance with PRISMA reporting guidelines, a systematic literature search was conducted using three electronic literature databases. Risk of bias was assessed using the Jadad scale.

Results: Thirty-seven randomized controlled trials, investigating fourteen nutraceuticals, were included in the review. Trials that investigated alpha lipoic acid (n = 4/6), ginkgo biloba (n = 3/5), vitamin A (n = 2/2), biotin (n = 1/2), carnitine (n = 1/2), green tea (n = 1/2), coenzyme Q10 (n = 1/1), probiotics (n = 1/1), curcumin (n = 1/1), *Andrographis paniculata* (n = 1/1), ginseng (n = 1/1), and lemon verbena (n = 1/1) were reported to improve biological (e.g. MRI brain volume change, antioxidant capacity) and/or clinical (e.g. fatigue, depression, Expanded Disability Status Scale) outcomes in multiple sclerosis compared to control. However, most trials were relatively small (average study sample size across included studies, n = 55) and there were few replicate studies per nutraceutical to validate the reported results. Furthermore, some nutraceuticals (e.g. green tea and inosine) should be used with caution due to reported adverse events. Risk of bias across most studies was low, with 31 studies receiving a score between 4 and 5 (out of 5) on the Jadad Scale.

Conclusion: The existing literature provides preliminary support for the use of a number of nutraceutical interventions in MS. However, sufficiently powered long-term trials are required to expand the currently limited literature and to investigate unexplored nutraceuticals that may target relevant pathways involved in MS such as the gut microbiome and mitochondrial dysfunction. Prospero ID: CRD42018111736.

1. Introduction

Multiple sclerosis (MS) is characterized by the development of central nervous system inflammatory demyelination and neurodegeneration resulting in irreversible axonal loss and gliosis (Reich et al., 2018). While highly effective therapies for MS are now available for

* Corresponding author.
E-mail address: wolf.marx@deakin.edu.au (W. Marx).

https://doi.org/10.1016/j.msard.2019.101486
Received 24 May 2019; Received in revised form 11 September 2019; Accepted 28 October 2019

early active disease, later-stage disease is more refractory to therapy. Persistent MS-related symptoms are a significant problem for many people with MS and effective symptomatic therapies are not always available. For example, despite fatigue affecting up to 80% of people with MS (Simpson et al., 2016), a meta-analysis concluded that current pharmacotherapy has little effect on MS-related fatigue (effect size 0.07 (95%CI −0.22, 0.37); $p = 0.63$) (Asano and Finlayson, 2014).

Due to the considerable burden of MS-related symptoms and the need to identify effective interventions to prevent or limit disease progression, various nutraceutical interventions that target specific pathways implicated in MS pathology (such as inflammation, oxidative stress, and mitochondrial dysfunction) (Lassmann, 2013) have been trialed for their efficacy as adjunctive treatments in MS. The most well explored nutraceutical interventions are omega-3 fatty acids and vitamin D, which have been covered in previous systematic reviews and meta-analyses (Farinotti et al., 2012; Zheng et al., 2018; Yadav et al., 2014; McLaughlin et al., 2018). A meta-analysis of 12 randomized controlled trials ($n = 950$ participants) of vitamin D supplementation reported no significant improvement in the Expanded Disability Status Scale (EDSS), annualized relapse rate, T2 MRI lesions, or gadolinium-enhancing MRI lesions compared to placebo (Zheng et al., 2018; McLaughlin et al., 2018). Similarly, a Cochrane review reported that omega-3 supplementation provided no significant improvements to disease progression (Farinotti et al., 2012).

Clinical trials that have investigated other nutraceutical interventions are emerging and the use of such nutraceuticals is of considerable interest to patients (Dunn et al., 2015; Claflin et al., 2018). For example, vitamin or dietary supplement-related queries were the third most common in a recent analysis of terms used by MS-related social media, websites, and call centers conducted by the National Multiple Sclerosis Society (Dunn et al., 2015). With a need to inform both clinical interest and research directions, the aim of this review is to investigate the efficacy and safety of emerging nutraceutical interventions for clinical and biological outcomes in people with MS.

2. Methods

2.1. Literature search

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) and as registered on PROSPERO (CRD42018111736), relevant studies were retrieved from PubMed, Embase, and The Cochrane Library for articles published since journal inception up to August 2018. Google Scholar and the Natural Medicines Database were also searched. Search terms related to commonly used nutraceuticals (e.g. carnitine, alpha lipoic acid) and multiple sclerosis were used (Supplementary Material 1).

To be included in this review, studies needed to meet each of the following eligibility criteria: used a randomized, parallel or cross-over trial study design; investigated a nutraceutical as a stand-alone intervention either as an adjunctive to standard medication or as a monotherapy; recruited only participants with MS; measured any biological or clinical outcome related to multiple sclerosis pathology or symptoms.

Interventions that investigated nutraceuticals in combination with other medical or lifestyle interventions (e.g. diet or exercise) were excluded. Studies that investigated vitamin D or omega-3 polyunsaturated fatty acids were excluded due to the extensive systematic review literature already published on these interventions (Farinotti et al., 2012; Zheng et al., 2018).

2.2. Data extraction

Screening of the publication title and abstract for individual studies was conducted in duplicate by three authors (WM, AJM or MH) with disagreements resolved by consensus. Articles deemed eligible for full-text review were assessed for eligibility independently by three authors (WM, AJM, MH). The following parameters were extracted from included studies: author and date, study design, sample size, total study period, sample characteristics (including age, gender, EDSS score), intervention characteristics (including type of nutraceutical, dose), length of follow up and outcomes.

2.3. Assessment of study risk of bias

Risk of bias was assessed using the Jadad Scale (Jadad et al., 1996). This is a five-item scale that assesses risk of bias due to randomization, blinding, and follow up. Studies can receive a score between zero and five, with lower scores indicating a higher risk of bias.

2.4. Data analysis

Due to the heterogeneous data included in this review and the small number of trials per nutraceutical, a meta-analysis was not conducted. Instead, all results reported in this review are based on between-group differences in the end-of-intervention measures, unless otherwise indicated. Data were considered statistically significant if the reported p-value was <0.05.

3. Results

3.1. Study selection

As represented in Fig. 1, the search strategy resulted in 4532 de-duplicated studies that were screened to identify 37 eligible studies for inclusion (see Table 1).

3.2. Trial characteristics

All studies were randomized controlled trials with 31 being parallel designs and 6 being cross-over. Most studies were conducted in Iran ($n = 13$) or the USA ($n = 10$). The most common trial duration was 12 weeks, with the longest trial running for 3 years. Sample sizes ranged from 11 to 171 participants with an average of 55 participants. All but one trial compared the nutraceutical intervention to placebo (Tomassini et al., 2004). Risk of bias across most studies was low with 31 studies receiving a score between 4 and 5 (out of 5) on the Jadad Scale.

The average age of participants was 40 years old. Most participants were women (71%). Studies mostly recruited a cohort of mixed MS types ($n = 12$) or relapsing remitting only ($n = 21$), with an average EDSS of 3. In order of frequency, the interventions investigated in the included studies were alpha lipoic acid ($n = 6$) (Khalili et al., 2014a,b, Khalili et al., 2017; Khallli et al., 2012; Spain et al., 2017; Yadav et al., 2005), ginkgo biloba ($n = 5$) (Diamond and Bailey, 2013; Johnson et al., 2006; Lovera et al., 2007; Lovera et al., 2012; Brochet et al., 1995), inosine ($n = 3$) (Gonsette et al., 2010; Markowitz et al., 2009; Munoz Garcia et al., 2015), acetyl-L-carnitine ($n = 2$) (Tomassini et al., 2004; Ledinek et al., 2013), biotin ($n = 2$) (Tourbah et al., 2018; Tourbah et al., 2016), green tea extract ($n = 2$) (Lovera et al., 2015; Mahler et al., 2015), retinyl palmitate ($n = 2$) (Bitarafan et al., 2016; Mohammadzadeh Honarvar et al., 2016), melatonin ($n = 2$) (Drake et al., 2018; Roostaei et al., 2015), creatine monohydrate ($n = 2$) (Malin et al., 2008; Lambert et al., 2003), lemon verbena ($n = 1$) (Mauriz et al., 2014), a multi-strain probiotic ($n = 1$) (Kouchaki et al., 2017), curcumin ($n = 1$) (Dolati et al., 2018), MS14 (a propriety herbal formulation; $n = 1$) (Nabavi et al., 2012), coenzyme Q10 ($n = 1$) (Sanoobar et al., 2016), cranberry extract ($n = 1$) (Gallien et al., 2014), glucosamine sulphate ($n = 1$) (Shaygannejad et al., 2010), and gamma-tocopherol ($n = 1$) (Pantzaris et al., 2013), riboflavin ($n = 1$) (Naghashpour et al., 2013),

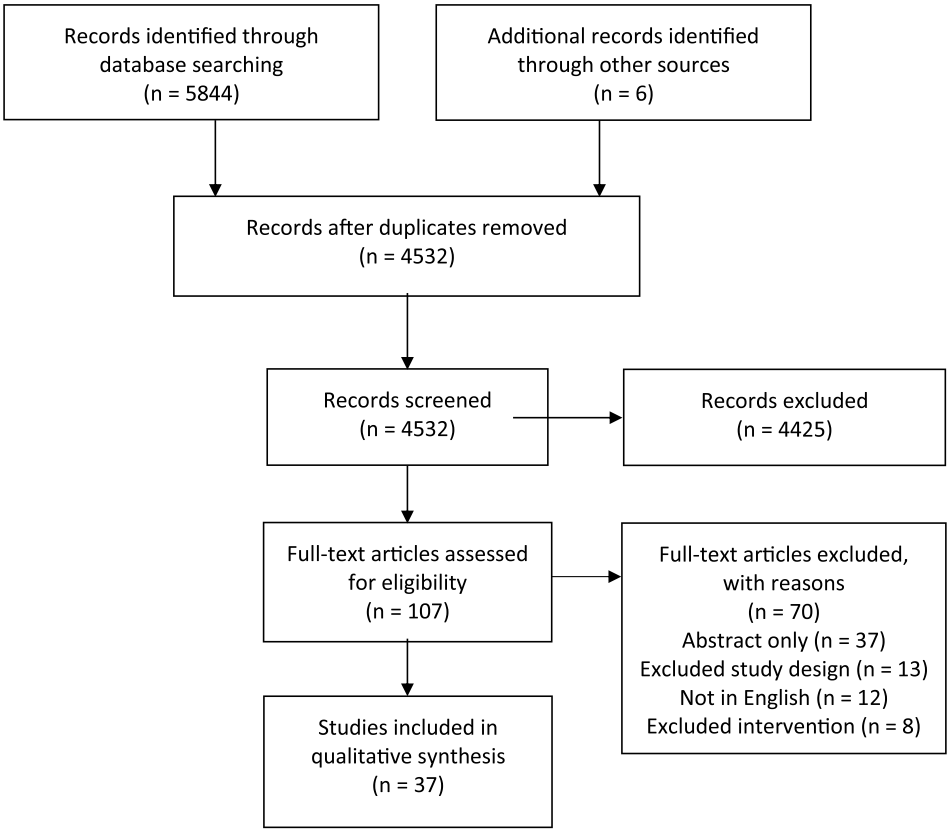

Fig. 1. PRISMA Flow diagram.

Andrographis paniculata ($n = 1$) (Bertoglio et al., 2016), and ginseng ($n = 1$) (Etemadifar et al., 2013).

3.3. Trial results

3.3.1. Alpha lipoic acid

Six studies investigated the use of alpha lipoic acid (Khalili et al., 2014a,b; Khalili et al., 2017; Khallli et al., 2012; Spain et al., 2017; Yadav et al., 2005). All studies used a dose of 1200 mg per day, with one trial including an additional arm that received 2400 mg per day. Yadav et al. (2005) In a 2-year trial, participants ($n = 54$) that received alpha lipoic acid had a significantly lower percentage change in brain volume compared to placebo ($p = 0.002$) but there was no effect on quality of life (using the RAND 36-Item Short Form Health Survey), mobility, cognition (using the single digit modality test), or EDSS (Spain et al., 2017). One 12-week trial ($n = 39$) found alpha lipoic acid improved EDSS in patients with a baseline EDSS >0 ($p = 0.036$) (Khallli et al., 2012). Another 12-week trial ($n = 54$) reported that 1200 mg of alpha lipoic acid improved serum total antioxidant capacity, transforming growth factor-β (TGF-β), Interferon-gamma (IFN-γ), vascular cell adhesion molecule-1, Intercellular Adhesion Molecule-1 (ICAM-1), and interleukin-4 compared to placebo but not superoxide dismutase, glutathione peroxidase activity, and malondialdehyde (Khalili et al., 2014a,b). Four 12-week studies reported no significant between-group difference in one or more of the following measures: EDSS (Khallli et al., 2012), fatigue (Khallli et al., 2012), plaque formation (Khallli et al., 2012), and serum measures including asymmetric dimethylarginine (Khalili et al., 2017), tumor necrosis factor-alpha (TNF-α) (Khalili et al., 2014a,b), interleukin-6 (IL-6) (Khalili et al., 2014a,b), tissue inhibitor of metalloproteinases-1 (Yadav et al., 2005), sICAM-1 (Yadav et al., 2005), and matrix metallopeptidase-9 (Khalili et al., 2014a,b; Yadav et al., 2005).

3.3.2. Ginkgo biloba

Five studies investigated the use of ginkgo biloba extracts. One study investigated the use of 240 mg/day or 360 mg/day of ginkgolide B over a 7-day period in 104 participants experiencing a relapse (Brochet et al., 1995). No significant between-group differences were reported for all outcomes: EDSS, the Hauser ambulation index, and fatigue.

In the four remaining studies, the use of a standardized extract (29.7 mg of flavoglycosides and 7.3 mg of terpene lactones per 120 mg) of ginkgo biloba, EGb 76, was investigated at a dose of 240 mg per day (Diamond and Bailey, 2013; Johnson et al., 2006; Lovera et al., 2007; Lovera et al., 2012). One 4-week trial ($n = 23$) reported an improvement in fatigue using the Modified Fatigue Impact Scale ($p = 0.024$) but no significant difference in depression, anxiety, symptom severity, and functional capacity (Johnson et al., 2006). Using the same dataset, another study reported improvements in processing speed (using the Visual Threshold Serial Addition Test; $p = 0.05$) and performance on the California Verbal Learning Test ($p = 0.03$) compared to the placebo group (Diamond et al., 2013). A 12-week trial ($n = 43$) reported significant improvements in a quality of life sub-score, retrospective memory ($p = 0.015$), and measures of concentration using the Stroop Color-Word test ($p = 0.015$) but no benefits for other cognitive measures (Lovera et al., 2007). There were no significant differences between the ginkgo and placebo group on visual-spatial memory and attention/concentration (using the Rey-Osterreith Complex Figure Test and digit span test, respectively) (Diamond et al., 2013). In a larger 12-week follow-up trial ($n = 120$), no significant difference was reported for any cognitive measure or fatigue (using the Modified Fatigue Impact Scale) and depression (using the Beck Depression Inventory II) (Lovera et al., 2012).

3.3.3. Inosine

Three studies investigated the use of inosine, either as a stand-alone

Table 1
Summary table of included studies.

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Alpha Lipoic acid						
Khalili et al. (2017)	**Study design:** RCT **Country:** Iran **Sample size (n):** 31 **Total study period (weeks):** 12	**MS diagnosis**: Relapse remitting **Age in years (mean):** 32	Alpha lipoic acid (1200 mg/day)	ADMA, EDSS	No significant between-group differences reported.	5
Spain et al. (2017)	**Study design:** RCT **Country:** USA **Sample size (n):** 54 **Total study period (years):** 2	**MS diagnosis**: Secondary progressive **Age in years (median):** 57.9 (intervention), 59.7 (control)	Alpha Lipoic Acid (1200 mg/day)	Annualized percent change brain volume, mobility, QoL (using the RAND 36-Item Short Form Health Survey), cognition, EDSS	Annualized PCBV was significantly less in the intervention group compared to placebo ($p = 0.002$). No other significant between-group differences reported	5
Khalili et al. (2014a,b)	**Study design:** RCT **Country:** Iran **Sample size (n):** 52 **Total study period (weeks):** 12	**MS diagnosis**: Relapse remitting **Age in years (mean):** 30	Alpha lipoic acid (1200 mg/day)	Total antioxidant capacity, superoxide dismutase, glutathione peroxidase activity, malondialdehyde,	Total antioxidant capacity significantly improved in the intervention group compared to placebo ($p < 0.004$)	5
Khalili et al. (2014a,b)	**Study design:** RCT **Country:** Iran **Sample size (n):** 52 **Total study period (weeks):** 12	**MS diagnosis**: Relapse remitting **Age in years (mean):** 30	Alpha lipoic acid (1200 mg/day)	TGF-β,INF-γ, VCAM-1, ICAM-1, IL-4, TNF-α, IL-6, EDSS, MMP-9	TGF-β,INF-γ, VCAM-1, ICAM-1, IL-4, significantly improved in the intervention group compared to placebo ($p < 0.01$)	5
Khallli et al. (2012)	**Study design:** RCT **Country:** Iran **Sample size (n):** 39 **Total study period (weeks):** 12	**MS diagnosis**: Relapse remitting **Age in years (mean):** 32	Alpha lipoic acid (1200 mg/day)	Fatigue (using the Fatigue Severity Scale), EDSS, plaque formation (via MRI)	No significant between-group differences reported. In participants with a baseline EDSS >0, there was a significant decrease in EDSS ($p = 0.036$)	4
Yadav et al. (2005)	**Study design:** RCT **Country:** USA **Sample size (n):** 37 **Total study period (weeks):** 2	**MS diagnosis**: Mixed diagnoses **Age in years (median):** 49	Alpha Lipoic Acid 1200mg (either once or twice per day), 2400mg (1200mg twice per day)	MMP-9, TIMP-1, sICAM-1	No significant between-group differences reported. A dose response relationship was observed for mean change in sICAM-1 ($p = 0.03$)	5
Ginkgo Biloba						

(*continued on next page*)

Table 1 (*continued*)

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Brochet et al. (1995)	**Study design:** RCT **Country:** France **Sample size (n):** 104 **Total study period (days):** 7	**MS diagnosis**: RRMS **Age in years (mean):** 35	ginkgolide B (240 mg/day or 360 mg/day)	EDSS, Hauser ambulation index, fatigue (using the FSS)	No significant between-group differences reported.	4
Diamond et al. (2013)	**Study design:** RCT **Country:** USA **Sample size (n):** 23 **Total study period (weeks):** 4	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 50.75	Ginkgo Biloba (Egb 761 extract, 240 mg/day)	Visual-spatial memory, attention/ concentration, processing speed, verbal intrusions	Processing speed ($p = 0.05$) and verbal intrusions ($p = 0.03$) improved in the intervention group compared to the placebo group. No other significant between-group differences reported.	5
Johnson et al. (2013)	**Study design:** RCT **Country:** USA **Sample size (n):** 23 **Total study period (weeks):** 4	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 50.75	Ginkgo Biloba (Egb 761 extract, 240 mg/day)	Depression (using the Center for Epidemiologic Studies of Depression Scale), anxiety (using the State-Trait Anxiety Inventory)Fatigue (using the Modified Fatigue Impact Scale), symptom severity (using the Symptom Inventory) and functional performance (using the Functional Assessment of Multiple Sclerosis)	Fatigue significantly improved in the intervention group ($p = 0.024$), compared to the placebo group. No other significant between group differences.	5
Lovera et al. (2012)	**Study design:** RCT **Country:** USA **Sample size (n):** 120 **Total study period (weeks):** 12	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 52	Ginkgo Biloba (Egb 761 extract; 240 mg/day)	California Verbal Learning Test II, Stroop Test, Controlled Oral Word Association Test, Paced Auditory Serial Addition Task, Perceived Cognitive deficits, Perceived Cognitive deficits (using the Sclerosis Neuropsychological Screening Questionnaire), Social integration (using the Community Integration Questionnaire), Fatigue (using the Modified Fatigue Impact Scale), Depression (using the Beck Depression Inventory II)	No significant between-group differences reported.	5

(*continued on next page*)

Table 1 (*continued*)

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Lovera et al. (2007)	**Study design:** RCT **Country:** USA **Sample size (n):** 43 **Total study period (weeks):** 12	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 49	Ginkgo Biloba (Egb 761 extract; 240 mg/day)	Working memory and sustained attention, phonemic fluency, information processing speed and visual tracking, visual information processing, divided attention and selective attention, which measures cognitive processing speed, concentration, selective attention, mental flexibility and interference susceptibility, verbal memory and learning, depression (using the Beck Depression Index II), QoL (using the MS Quality of Life Index)	Stroop Color and Word Test ($p = 0.015$) and the Retrospective Memory Scale subscale of quality of life ($p = 0.015$), improved in the intervention group compared to the placebo group. No other significant between-group differences reported.	5
Inosine						
Markowitz et al. (2009)	**Study design:** RCT with a cross-over placebo arm **Country:** USA **Sample size (n):** 16 **Total study period (years):** 1	**MS diagnosis**: Relapse remitting **Age in years (mean):** not listed	Inosine (2-3g/day), administered with interferon	EDSS, MRI	No significant between-group differences reported.	5
Gonsette et al. (2010)	**Study design:** RCT **Country:** Belguim **Sample size (n):** 159 **Total study period (years):** 2	**MS diagnosis**: Relapse remitting **Age in years (mean):** 37	Inosine, Individualized dose based on serum uric acid levels	EDSS, Multiple Sclerosis Functional Composite, relapse rate	No significant between-group differences reported.	5
Munoz Garcia et al. (2015)	**Study design:** RCT **Country:** Spain **Sample size (n):** 36 **Total study period (years):** 1	**MS diagnosis**: Relapse remitting **Age in years (mean):** 32	Inosine (3g/day), administered with interferon	MRI	No significant between-group differences reported.	4
Acetyl L Carnitine						
Ledinek et al. (2013)	**Study design:** RCT **Country:** USA **Sample size (n):** 30 (medication groups not included) **Total study period (weeks):** 4	**MS diagnosis**: Relapse remitting **Age in years (mean):** 39	Acetyl L Carnitine (2000 mg/day)	Fatigue (using the Modified Fatigue Impact Scale), QoL (using the 36-item Short Forum Health Survey Questionnaire)	No significant between-group differences reported.	2

(*continued on next page*)

Table 1 (*continued*)

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Tomassini et al. (2004)	**Study design:** RCT-cross over **Country:** Italy **Sample size (n):** 93 **Total study period (months):** 6 (6-month open label extension phase not extracted)	**MS diagnosis**: Primary progressive or secondary progressive **Age in years (mean):** 44	Acetyl L Carnitine (1000 mg/day)	Fatigue (using the Fatigue Severity Scale and the Fatigue Impact Scale), depression (using the Beck Depression Inventory), social interaction (using the Social Experience Checklist)	Fatigue significantly improved in the intervention group compared to placebo. ($p = 0.039$) No other significant between-group differences reported.	3
Biotin						
Tourbah et al. (2018)	**Study design:** RCT **Country:** France/UK **Sample size (n):** 93 **Total study period (weeks):** 24 (6-month open label extension phase no extracted)	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 41	Biotin (MD1003; 300 mg/day)	Impairment of the optic nerve, VEPs, automated perimetry, and OCT including RNFL and thickness, QoL (using the Multiple Sclerosis Quality of Life-54 and the National Eye Institute 25-Item Visual Function Questionnaire), patient- and clinician evaluated global impression scale	No significant between-group differences reported.	5
Tourbah et al. (2016)	**Study design:** RCT **Country:** France **Sample size (n):** 154 **Total study period (months):** 12 (12-month open label extension phase not extracted)	**MS diagnosis**: Primary progressive or secondary progressive **Age in years (mean):** 51	Biotin (MD1003; 300 mg/day)	Improved disability, EDSS, clinician global impression of change, patient impression of change, QOL (using the Short Form 36 Health Survey), fatigue (using the modified Fatigue Impact Scale)	MS-related disability ($p = 0.005$), EDSS ($p = 0.01$), CGI scores ($p < 0.001$), SGI scores ($p = 0.009$) significantly improved in the intervention group compared to placebo. In as post-hoc analysis, there were significantly more participants with >20% improvement in TW25 times at month 9, compared with the placebo group ($p = 0.03$)." Intervention group reported significantly worse on general health QOL subscale ($p = 0.03$) No other significant between group differences.	4
Green tea extract						
Lovera et al. (2015)	**Study design:** RCT **Country:** Slovenia **Sample size (n):** 13 (halted early) **Total study period (weeks):** 52	**MS diagnosis**: Relapse remitting **Age in years (mean):** 48	Polyphenon E (Epigallocatechin-3-gallate Green tea extract)	NAA (using magnetic resonance spectroscopic imaging), EDSS, MSFC	Not assessed, trial halted early due to adverse liver events	5

(*continued on next page*)

Table 1 (*continued*)

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Mahler et al. (2015)	**Study design:** RCT Cross-over **Country:** Germany **Sample size (n):** 20 **Total study period (weeks):** 16 weeks per intervention	**MS diagnosis**: Relapse remitting **Age in years (mean):** 42	Epigallocatechin-3-gallate (600 mg/day)	Postprandial increase in fat oxidation, efficiency of muscle work, postprandial profiles of plasma glucose, insulin, and free fatty acids	The intervention group had a significantly lower postprandial energy expenditure during exercise than placebo ($p = 0.004$). No other significant between-group differences reported.	4
Retinyl palmitate						
Bitarfen et al. (2016)	**Study design:** RCT **Country:** Iran **Sample size (n):** 101 **Total study period (months):** 12	**MS diagnosis**: Relapse remitting **Age in years (mean):** 31.3	Retinyl palmitate (25000 IU/d and 10000 IU/d for 6 months each)	Depression (using the Beck Depression Inventory-II), fatigue (using the modified fatigue impact scale)	Depression significantly improved significantly in the intervention group, compared to the placebo group ($p = 0.01$). Total fatigue ($p = 0.004$) and subscales for physical ($p = 0.02$), cognitive ($p = 0.02$), and psychosocial ($p = 0.02$) function significantly improved in the intervention group, compared to the placebo group	5
Mohammadzadeh Honarvar et al. (2016)	**Study design:** RCT **Country:** Iran **Sample size (n):** 39 **Total study period (weeks):** 24	**MS diagnosis**: RRMS **Age in years (mean):** 32.2	Retinyl palmitate (25,000IU/day)	IFN-γ and T-bet gene expression	IFN-γ ($p = 0.002$) and T-bet ($p = 0.001$) gene expression improved in the intervention group compared to placebo.	4
Melatonin						
Drake et al. (2018)	**Study design:** RCT-cross over **Country:** UK **Sample size (n):** 34 **Total study period (weeks):** 12 (6 weeks per intervention phase)	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 54.8	Melatonin (sustained release, 2 mg/day)	Nocturia episodes, subjective severity, QoL (using the MS Quality of Life Scale), sleep quality (using the Pittsburgh Sleep Quality Index), EDSS, urinary tract symptoms	No significant between-group differences reported.	5
Roostaei et al. (2015)	**Study design:** RCT **Country:** Iran **Sample size (n):** 26 **Total study period (weeks):** 52	**MS diagnosis**: Relapse remitting **Age in years (mean):** 33.9	Melatonin (3 mg/day)	Relapse rate, EDSS, number and volume of brain lesion, Fatigue (using the Modified Fatigue Impact Scale), Depression (using the Beck Depression Inventory-II), Multiple Sclerosis Functional Composite	No significant between-group differences reported.	5
Creatine monohydrate						

(*continued on next page*)

Table 1 (*continued*)

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Malin et al. (2008)	**Study design:** RCT Cross-over **Country:** USA **Sample size (n):** 11 **Total study period (weeks):** 2 weeks per intervention	**MS diagnosis**: MS subtype not stated **Age in years (mean):** 44	Creatine monohydrate 20grams (first week), 5grams (second week)	Fatigue (using the Fatigue Severity Scale), rates of perceived exertion, knee extension total work, muscle power (knee extension), muscle power (knee flexion)	No significant between-group differences reported.	4
Lambert et al. (2003)	**Study design:** RCT **Country:** USA **Sample size (n):** 16 **Total study period (days):** 5	**MS diagnosis**: Relapse remitting **Age in years (mean):** 40.3	Creatine monohydrate (20g/day)	Body composition, exercise capacity and muscle metabolites (phosphocreatine, ATP, total creatine)	No significant between-group differences reported.	3
Lemon Verbena						
Mauritz et al. (2015)	**Study design:** RCT **Country:** Spain **Sample size (n):** 32 **Total study period (weeks):** 4	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 49	Lemon Verbena (600mg) standardized to 10% verbascoside	IFN-y, IL-12, IL-23, IL-6, TNF-a, TGF-a, IL-4 and IL-10, CRP	Secondary progressive MS- supplemented participants had significantly lower CRP ($p < 0.005$) and IFN-y ($p < 0.003$) and higher IL-4 and IL-10 compared to placebo ($p < 0.05$). IL-12 was reduced in the relapsing-remitting supplemented group compared to placebo ($p < 0.05$). IFN-y levels decreased for all MS-treated groups	3
Probiotics						
Kouchaki et al. (2017)	**Study design:** RCT **Country:** Iran **Sample size (n):** 60 **Total study period (weeks):** 12	**MS diagnosis**: Relapse remitting **Age in years (mean):** 34	Probiotics (Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum and Lactobacillus fermentum, 2 x 10^9 CFU/g each)	EDSS, QoL(using the general health questionnaire), depression and anxiety (using the Beck Depression Inventory and the Depression Anxiety and Stress Scale), CRP, nitric oxide metabolites, malondialdehyde, insulin, HOMA IR, beta cell function, total/HDL cholesterol, insulin sensitivity check index, HDL cholesterol, BMI, total antioxidant capacity, fasting plasma glucose, glutathione	EDSS ($p = 0.001$), QOL ($p < 0.001$), Depression and anxiety ($p < 0.001$), CRP ($p = 0.01$), Nitric oxide metabolites ($p = 0.002$), malondialdehyde ($p = 0.04$), insulin, HOMA IR ($p = 0.001$), beta cell function ($p < 0.001$), total/HDL cholesterol ($p = 0.02$), insulin sensitivity check index ($p < 0.001$), HDL cholesterol ($p = 0.02$) improved in the intervention group compared to the placebo group. No other significant between group differences.	5
Curcumin						

(*continued on next page*)

Table 1 (*continued*)

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Dolati et al. (2018)	**Study design:** RCT **Country:** Iran **Sample size (n):** 50 **Total study period (months):** 6	**MS diagnosis**: RRMS **Age in years (mean):** 34.9	Curcumin (nano-encapsulated, 80 mg/day)	Gene expression levels of miR-32, miR-16, miR-45. mRNA expression of genes (NF-κB, AP-1, STAT-1, STAT5, IL-1β, IL-6, IL-8, TNF-α, IFN– γ, CCL2 and CCL5) miRNA-dependent targets (FoxP3, PDCD1, Sirtuin1, Sox2), Serum inflammatory cytokines (IFN–γ, CCL5, CCL2, , IL-1β, IL-6, IL-8, TNF-α), EDSS	miR-45 ($p < 0.001$), miR-32 ($p = 0.0039$), IFN–γ ($p = 0.0025$), CCL5 ($p = 0.0003$), CCL2 ($p = 0.0029$), FoxP3 ($p = 0.02$), PDCD1 ($p = 0.0012$), Sirtuin1 ($p = 0.0062$), Sox2 ($p = 0.0032$), STAT1 ($p = 0.0001$), STAT5 ($p = 0.0001$), NFKB ($p < 0.0001$), AP-1 ($p = 0.047$) significantly improved in the intervention group compared to placebo. No other significant between-group differences reported.	4
MS14, a proprietary herbal formulation						
Nabavi et al. (2009)	**Study design:** RCT-cross over **Country:** Iran **Sample size (n):** 38 **Total study period (weeks):** 3	**MS diagnosis**: Relapse remitting or Secondary progressive **Age in years (mean):** 30.8	MS14, a proprietary herbal formulation containing 90% Penaeus latisculatus, 5% Apium graveolens and 5% Hypericum perforatum (50 mg/kg/day)	QoL (using the Hamburg quality of life questionnaire on multiple sclerosis)	Lower limb mobility sub score significantly improved in the intervention group ($p = 0.048$), compared to the placebo group. No other significant between-group differences reported.	3
Coenzyme Q10						
Sanoobar et al. (2015)	**Study design:** RCT **Country:** Iran **Sample size (n):** 48 **Total study period (weeks):** 12	**MS diagnosis**: Relapse remitting **Age in years (mean):** 32	Coenzyme Q10 (500 mg/day)	Fatigue (using the Fatigue Severity Scale), depression (using the Beck Depression Inventory)	Fatigue ($p < 0.001$) and depression ($p < 0.001$) was significantly decreased in participants receiving the intervention compared to the placebo group	3
Cranberry extract						
Gallien et al. (2014)	**Study design:** RCT **Country:** France **Sample size (n):** 171 **Total study period (years):** 1	**MS diagnosis**: Mixed diagnoses **Age in years (mean):** 49	Cranberry extract (36mg proanthocyanidins per day)	First symptomatic urinary tract infection, number of UTIs, QoL (using the Qualiveen scale), EDSS, symptomatology of urinary disorders, relapses antibiotic consumption	No significant between group differences except at month 9 where placebo group had higher QoL compared to intervention ($p = 0.02$)	5
Glucosamine sulphate						
Shaygannejad et al. (2010)	**Study design:** RCT **Country:** Iran **Sample size (n):** 97 **Total study period (months):** 6	**MS diagnosis**: Relapse remitting **Age in years (mean):** 30.25	Glucosamine sulphate (1000 mg/day)	EDSS progression, relapse rate	No significant between-group differences reported.	5
Gamma-tocopherol						

(*continued on next page*)

Table 1 (*continued*)

Author/Date	Study details	Sample details	Intervention	Outcomes	Results	Jadad score
Pantzaris et al. (2013)	**Study design:** RCT **Country:** Cyprus **Sample size (n):** 40 (omega 3 groups not included) **Total study period (months):** 30	**MS diagnosis**: Relapse remitting **Age in years (mean):** 37.9	Gamma-tocopherol (760 mg/day)	Annualized relapse rate, EDSS progression, T2 lesions progression	No significant between-group differences reported.	5
Riboflavin						
Naghashpour et al. (2013)	**Study design:** RCT **Country:** Iran **Sample size (n):** 29 **Total study period (months):** 6 with 3 months washout	**MS diagnosis**: Relapse remitting or secondary progressive **Age in years (mean):** 33	Riboflavin (10 mg/day)	EDSS, serum homocysteine	No significant between-group differences reported.	4
Andrographis paniculata						
Bertoglio et al. (2016)	**Study design:** RCT **Country:** Chile **Sample size (n):** 24 **Total study period (years):** 1	**MS diagnosis**: Relapse remitting **Age in years (mean):** 37	Andrographis paniculata (340 mg/day, total andrographolides: 170 mg)	Fatigue (using the FSS), EDSS	Fatigue was significant improvement in the intervention group compared to placebo (p value not reported). No other significant between-group differences reported.	5
Ginseng						
Etemadifar et al. (2013)	**Study design:** RCT **Country:** Iran **Sample size (n):** 60 **Total study period (months):** 3	**MS diagnosis**: Relapse remitting **Age in years (mean):** 33	Ginseng (500 mg/day)	Fatigue (using the Modified Fatigue Impact Scale) and QoL (using the Multiple Sclerosis Quality Of Life Questionnaire	Fatigue ($p = 0.046$) and QoL ($p \leq 0.0001$) were significantly improved in the intervention group compared to placebo.	4

ADMA, asymmetric dimethylarginine; CCL, Chemokine Ligand; CRP, C reactive protein; EDSS, Expanded Disability Status Scale; HOMA IR, Homeostatic model assessment insulin resistance; IFN, interferon; IL, interleukin; MMP-9, MRI, Magnetic resonance imaging; Matrix metallopeptidase 9; MSFC, Multiple Sclerosis Functional Composite; NAA, N-acetyl aspartate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OCT, optical coherence tomography; PCBV, percent change brain volume; PDCD1, Programmed Cell Death 1; QOL, quality of life; RNFL, retinal nerve fiber layer; sICAM-1, Soluble intercellular adhesion molecule-1; TIMP-1, Tissue inhibitor matrix metalloproteinase 1; TGF-alpha, transforming growth factor alpha; TNF-alpha, Tumor necrosis factor alpha; UTI, Urinary Tract infection; VEPs, visual evoked potentials.

intervention or combined with interferon, compared to placebo in 16–159 participants over 1–2 years (Gonsette et al., 2010; Markowitz et al., 2009; Munoz Garcia et al., 2015). Doses were either 2–3 g/day or individually determined based on serum uric acid levels. EDSS (Gonsette et al., 2010; Markowitz et al., 2009), MRI (Markowitz et al., 2009; Munoz Garcia et al., 2015), functional capacity (Gonsette et al., 2010), inflammatory markers (Markowitz et al., 2009), and relapse rate (Gonsette et al., 2010) were measured in at least one study; however, no significant differences were reported in any study.

3.3.4. Acetyl-L-Carnitine

One cross-over trial (3 months per intervention) investigated 1000 mg of acetyl-L-carnitine compared to amantadine in 36 participants. There was improvement in fatigue as measured using the Fatigue Severity Scale ($p = 0.039$), but not when using the Fatigue Impact Scale (Tomassini et al., 2004). No significant difference was found for depression (using the Beck Depression Inventory) or social interaction (using the Social Experience Checklist). In contrast, another 4-week trial ($n = 30$) that investigated the use of 2000 mg of acetyl-L-carnitine reported no improvement in fatigue (using the Modified Fatigue Impact Scale) or quality of life when compared to placebo (Ledinek et al., 2013).

3.3.5. Biotin

Two randomized controlled trials by the same research group investigated the use of 300 mg/day of a biotin formulation (MD1003) (Tourbah et al., 2018; Tourbah et al., 2016). The first trial ($n = 154$) was a 12-month randomized, double-blind, placebo-controlled trial with a subsequent open-label 12-month extension phase (Tourbah et al., 2016). This trial reported a significant improvement in the primary outcome, disability reversal (defined as EDSS decrease of ⩾1 point, ⩾0.5 for EDSS 6–7, or a ⩾20% decrease in timed 25-foot walk time, compared to baseline; $p = 0.005$). The proportion of patients with EDSS progression during the blinded phase was not significantly different across the arms of the trial ($p = 0.07$). However, there was a significant improvement during the following open-label phase in the group that initially received the intervention compared to those that initially received the placebo ($p = 0.005$). A *post hoc* analysis showed that there was a significantly higher number of patients in the treatment group that had >20% improvement in 25-foot walk times from baseline during the blinded phase compared to the placebo group ($p = 0.03$). The intervention group also had significantly better clinician-assessed Clinical Global Impression Scale scores ($p < 0.001$) and subject-assessed Clinical Global Impression Scale scores ($p = 0.009$) at month 12 compared with the placebo-treated participants.

The second trial ($n = 93$) was also a randomized, double-blind, placebo-controlled trial with an open-label extension phase; however, each phase ran for 6 months instead of 12 (Tourbah et al., 2018). This trial reported no significant difference in measures of visual acuity, quality of life, and subject- or clinician- assessed Clinical Global Impression Scale scores. EDSS was not assessed as a study outcome in this trial.

3.3.6. Green tea extract

Two studies investigated the use of a green tea extract standardized to 600–800 mg/day of epigallocatechin gallate (EGCG), a polyphenol compound abundant in green tea (Lovera et al., 2015, Mahler et al., 2015). One cross-over trial ($n = 20$) reported that a 16-week intervention of green tea extract resulted in lower postprandial energy expenditure during exercise than placebo ($p = 0.004$). The same trial also reported sex differences in energy expenditure in response to EGCG (Mahler et al., 2015). Another trial investigated the effect of a propriety green tea extract ($n = 13$), Polyphenon E, on N-acetyl aspartate (using brain magnetic resonance spectroscopic imaging), EDSS, and Multiple Sclerosis Functional Composite score, but was halted early due to adverse liver outcomes (See Adverse Events section for further details) (Lovera et al., 2015).

3.3.7. Retinyl palmitate (Vitamin A)

A trial ($n = 101$) using retinyl palmitate (25000 IU and 10000 IU per day for 6 months each) reported a significant improvement in depression using the Beck Depression Inventory II and fatigue using the Modified Fatigue Impact Scale ($p = 0.004$; total score) and its subscales for physical ($p = 0.02$), cognitive ($p = 0.02$), and psychosocial ($p = 0.02$) function compared to placebo (Bitarafan et al., 2016). A second trial ($n = 39$) reported that retinyl palmitate (25000 IU per day) significantly improved gene expression of inflammatory markers IFN-γ ($p = 0.002$) and T-bet ($p = 0.001$) in a 6-month intervention (Mohammadzadeh Honarvar et al., 2016).

3.3.8. Melatonin

In a 52-week trial that investigated melatonin supplementation (3 mg/day) ($n = 26$), there were no significant differences between the intervention group and the control group in the following outcomes: relapse rates, EDSS, number and volume of brain lesions, fatigue (using the Modified Fatigue Impact Scale), depression (using the Beck Depression Inventory-II), and Multiple Sclerosis Functional Composite score (Roostaei et al., 2015). Similarly, a cross-over trial of 34 participants receiving 2 mg per day of melatonin for 12 weeks reported no significant difference in nocturia episodes, subjective severity of nocturia, quality of life (using the MS Quality of Life Scale), lower urinary tract symptoms, sleep quality (using the Pittsburgh Sleep Quality Index), or EDSS (Drake et al., 2018).

3.3.9. Creatine monohydrate

Two studies investigated the effect of creatine monohydrate. Using a cross-over trial design, the first trial ($n = 11$) reported that a two-week regimen of creatine monohydrate (20 g/day first week, 5 g/day second week) did not significantly influence fatigue (using the Fatigue Severity Scale), rates of perceived exertion, or muscle power (Malin et al., 2008). The second ($n = 16$) found that a 5-day regimen of creatine (20 g/day) did not improve body composition, exercise capacity, or muscle metabolites (phosphocreatine, ATP, total creatine), relative to placebo (Lambert et al., 2003).

3.3.10. Lemon verbena

Lemon verbena (600 mg/day, standardized to 10% verbascoside) reduced serum C-reactive protein and IL-4 and IL-10 levels compared to placebo in one 4-week trial in people with secondary progressive MS ($n = 32$) (Mauriz et al., 2014). The same trial reported no significant between-group differences in serum IFN-y, IL-12, IL-23, IL-6, TNF-α, or TGF-β.

3.3.11. Probiotics

One 12-week trial ($n = 60$) that investigated the use of a multi-strain probiotic formulation (containing *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum* and *Lactobacillus fermentum*; $2 \times 10[9]$ CFU/g each) reported significant improvement in EDSS ($p < 0.001$), depression (using the Beck Depression Inventory and the Depression Anxiety and Stress Scale; $p < 0.001$), quality of life (using the General Health Questionnaire; $p < p < 0.001$), C-reactive protein ($p = 0.01$), nitric oxide metabolites ($p = 0.002$), malondialdehyde ($p = 0.04$), insulin ($p < 0.001$), Homeostatic Model Assessment of Insulin Resistance (HOMA IR; $p < 0.001$), beta cell function ($p < 0.001$), total/HDL cholesterol ($p = 0.02$), insulin sensitivity check index ($p < 0.001$), and HDL cholesterol ($p = 0.02$). No significant difference was reported for BMI, total antioxidant capacity, fasting plasma glucose, or glutathione (Kouchaki et al., 2017).

3.3.12. Curcumin

One 6-month trial ($n = 51$) reported that curcumin (80 mg/day) modulated gene expression of the following inflammatory and immune

markers: micro-RNA 45 ($p < 0.001$), micro-RNA 32 ($p = 0.0039$), IFN–γ ($p = 0.0025$), Chemokine ligand (CCL) 5 ($p = 0.0003$), CCL2 ($p = 0.0029$), forkhead box P3 (FOXP3; $p = 0.02$), Programmed Cell Death 1 (PDCD1; $p = 0.0012$), Sirtuin1 ($p = 0.0062$), sex determining region Y box-2 (Sox2; $p = 0.0032$), Signal transducer and activator of transcription (STAT) 1 ($p = 0.0001$), STAT5 ($p = 0.0001$), nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB; $p < 0.0001$), Activator protein 1 (AP-1; $p = 0.047$) (Dolati et al., 2018). There was also an improvement in the following serum inflammatory cytokines: IFN–γ ($p = 0.0025$), CCL5 ($p = 0.0003$), CCL2 ($p = 0.0029$). There were no between-group differences in serum IL-1β, IL-6, IL-8, TNF-α.

3.3.13. MS14, propriety herbal formulation

MS14, a propriety herbal formulation (500 mg/day) containing 90% Penaeus latisculatus, 5% Apium graveolens and 5% Hypericum perforatum, was reported in one 6-week (3 weeks per trial arm) cross-over trial ($n = 38$) to improve the lower limb motion sub-score ($p = 0.048$) of a quality of life measure (the Hamburg Quality of Life Questionnaire on Multiple Sclerosis). There was no significant difference in total score or in other subscores of the quality of life measure (Nabavi et al., 2012).

3.3.14. Co-enzyme Q10

After a 12-week intervention ($n = 48$) using co-enzyme Q10 (500 mg/day), participants reported reduced fatigue (using the Fatigue Severity Scale), and depression (using the Beck Depression Inventory) compared to the placebo group ($p < 0.001$) (Nabavi et al., 2012).

3.3.15. Cranberry extract

No significant differences between placebo and intervention were reported in a one year trial ($n = 171$) of cranberry extract (36 mg proanthocyanidins per day) for first symptomatic urinary tract infection, number of urinary tract infections, quality of life (using the Qualiveen scale), EDSS, relapses, or antibiotic consumption (Gallien et al., 2014).

3.3.16. Glucosamine sulphate

One trial ($n = 97$) that investigated a 26-week intervention of glucosamine sulphate (1000 mg/day) reported no significant between-group differences in relapse rate and EDSS progression (Shaygannejad et al., 2010).

3.3.17. Gamma-tocopherol

In one trial ($n = 40$) that investigated a 30-month intervention of gamma-tocopherol (760 mg/day), there were no significant between-group differences in annualized relapse rate, EDSS progression, and change in T2 lesions (Pantzaris et al., 2013).

3.3.18. Riboflavin (Vitamin B2)

One 6-month study of 29 participants investigated the use of 10 mg/day of riboflavin and reported no significant difference in EDSS ($p = 0.25$) or homocysteine levels ($p = 0.9$)_at follow-up (Naghashpour et al., 2013).

3.3.19. Andrographis paniculata

In 24 participants, a 1-year trial investigated the effect of *Andrographis paniculata* at a dose of 340 mg/day (total andrographolides: 170 mg) and a reported significant between group improvement in fatigue (p-value not reported) but not EDSS in intervention group compared to placebo (Bertoglio et al., 2016). The study also reported that 4 participants that received the placebo had new T2 lesions or new gadolinium-enhancing lesions at 12 months compared to 1 in the intervention group (no statistical analysis reported).

3.3.20. Ginseng

A 3-month study in 60 participants investigated the use of 500 mg/day ginseng and reported significant improvements in fatigue ($p = 0.046$) and quality of life ($p \leq 0.0001$) at follow-up compared to placebo (Etemadifar et al., 2013).

3.4. Adverse events

In studies that reported adverse events, gastrointestinal-related side-effects such as nausea were most commonly reported. One trial reported vomiting and dehydration requiring hospitalization in one participant receiving alpha lipoic acid; symptoms, resolved once alpha lipoic acid was ceased (Spain et al., 2017). This trial also reported that two participants who received alpha lipoic acid experienced glomerulonephritis or renal failure. However, the consulting nephrologist did not consider these adverse events to be related to the intervention (Spain et al., 2017). Two of the three studies that investigated the use of inosine reported adverse events. One study reported renal colic ($n = 2$ participants) and asymptomatic hyperuricemia ($n = 10$ participants) (Munoz Garcia et al., 2015). Another study reported that $n = 4$ of the 16 participants receiving inosine experienced kidney stones (Markowitz et al., 2009). One trial that investigated a green tea extract was terminated early due to abnormal liver function test results detected in most participants undergoing the intervention (5 of 6) with one considered a grade 4 serious adverse event (AST and ALT levels 15 times the normal range in conjunction with elevated bilirubin) (Lovera et al., 2015). One trial that investigated biotin reported that the incidence of MS relapse was higher in the intervention group (13.8%) than in the placebo group (3.6%) (Tourbah et al., 2018). Another trial that investigated biotin identified one participant with a mucocutaneous rash, which was considered as possibly relating to the intervention (Tourbah et al., 2016). In the one study that investigated the use of *Andrographis paniculata*, one participant in the intervention arm experienced a skin rash that resolved with anti-histamines (Bertoglio et al., 2016).

4. Discussion

This review identified multiple nutraceutical interventions that have been investigated for their effect on a range of clinical and biological outcomes in people with MS. In sixteen of the 30 included studies, nutraceuticals including alpha lipoic acid, ginkgo biloba, vitamin A, biotin, carnitine, green tea, coenzyme Q10, probiotics, curcumin and lemon verbena were reported to improve biological (e.g. MRI brain volume change, antioxidant capacity) and clinical (e.g. fatigue, depression, EDSS) outcomes in people with MS.

Fatigue and depression were the most commonly reported MS-related symptoms to improve following nutraceutical intervention. Seven studies reported improvement in measures of fatigue and/or depression when investigating coenzyme Q10, retinyl palmitate, probiotics, acetyl L carnitine, ginseng, Andrographis paniculate, or gingko biloba (Tomassini et al., 2004; Johnson et al., 2006; Bitarafan et al., 2016; Kouchaki et al., 2017; Sanoobar et al., 2016; Bertoglio et al., 2016; Etemadifar et al., 2013). Clinical improvements in EDSS were reported in three trials, involving biotin, alpha lipoic acid, and probiotics (Khallli et al., 2012; Tourbah et al., 2016; Kouchaki et al., 2017). Inflammatory markers were the most commonly reported biological outcomes with five studies reporting significant improvement when using the following interventions: curcumin, probiotics, lemon verbena, retinyl palmitate, or alpha lipoic acid (Khalili et al., 2014a,b; Mohammadzadeh Honarvar et al., 2016; Mauriz et al., 2014; Kouchaki et al., 2017; Dolati et al., 2018).

Although the existing evidence provides preliminary evidence for the use of nutraceuticals in MS, most trials had relatively small sample sizes and there are few replicate studies per nutraceutical to confirm the reported results. In addition, most included studies have been relatively short-term, which may be unable to capture potential longer-term changes. Until sufficiently powered long-term studies are conducted

that can replicate the existing studies, recommendations regarding the use of the included nutraceuticals remains premature. In line with the limited number of trials identified in this review, The National MS Society Wellness Research Working Group has recently stated that the investigation of individual and/or combined nutrients (as well as dietary interventions) in the management of physical health and disease course is a research priority (Motl et al., 2018). However, despite insufficient evidence of their benefit, the use of commercially available nutraceuticals by people with MS is high with an estimated 82.1% of respondents saying they take at least one dietary supplement per day (O'Connor et al., 2012). Due to this high prevalence of existing use, there is a need to improve the evidence-base to inform clinical recommendations.

In addition to further trials to assess efficacy, it will also be important to assess the safety of these interventions within the MS population to ensure they do not interfere with MS-specific medication or exacerbate MS symptoms. For example, resveratrol was reported in one study to exacerbate clinical signs including demyelination and inflammation in an animal model of MS (Sato et al., 2013). Furthermore, while many nutraceutical compounds are present in food, nutraceutical extracts that deliver compounds far in excess of what is regularly consumed may pose safety concerns. For example, in this review, one trial that investigated green tea extract was halted due to abnormal liver enzymes. Green tea extracts have been reported in other populations to also be associated with liver-related adverse events (Isomura et al., 2016; Molinari et al., 2006). In another trial, incidence of relapse was almost four-fold higher in the group that received a biotin formulation than in the placebo group (Tourbah et al., 2018). However, this was not replicated in a *post hoc* analysis of another trial that used the same biotin formulation (Tourbah et al., 2018; Tourbah et al., 2016).

In contrast to single-compound nutraceuticals (e.g. coenzyme Q10, Acetyl-L-Carnitine), food-derived extracts (e.g. green tea, lemon verbena) contain a complexity of various bioactive compounds that can significantly differ between products (Marx et al., 2017). Given the complexity of food-derived nutraceuticals, there is a need for clinical trials to investigate formulations that are standardized to a specific level of bioactive compounds and for researchers to report the level of bioactive compounds to improve between-study comparison.

As new evidence uncovers pathways implicated in MS symptoms and severity, there is a need to investigate nutraceuticals that specifically target these pathways. Assessing markers of underlying pathways may also provide insight into inter-individual variations in response to specific nutraceutical interventions. Nitric oxide-mediated impaired mitochondrial dysfunction has been implicated in the pathogenesis and progression of MS. Proposed mechanisms include direct damage of mitochondrial DNA, damage of, or interaction with, respiratory chain complex proteins with consequent impairment of the respiratory chain function, or through damage to mitochondrial membranes (Lan et al., 2018). Others have suggested that in the early neuroinflammatory process, axonal mitochondrial trafficking dynamics could be affected, with consequent perturbation of local energy levels (Errea et al., 2015). A recent review identified several nutraceuticals that may target mitochondrial dysfunction including some nutraceuticals that have been trialed in preliminary studies in people with MS such as alpha lipoic acid, vitamin D, and coenzyme Q10 (Pereira et al., 2018).

Metabolites within the kynurenine pathway have also been implicated in MS as well as other neurological disorders. For example, the metabolites kynurenic acid, quinolinic acid, and tryptophan were critical determinants in predicting MS severity (Lim et al., 2017). Few studies have evaluated interventions that target the kynurenine pathway in humans. However, probiotics and polyphenols have been demonstrated to affect the kynurenine pathway in non-MS subjects and in animal models (Strasser et al., 2016; Marques et al., 2018).

A rapidly expanding area of research has now implicated changes in the composition and function of commensal bacteria within the gut microbiome in MS pathophysiology and symptomology (Berer et al., 2017). Pro- and pre- biotic interventions that target the gut microbiota are currently being investigated for a wide-range of chronic diseases. While one trial in our review reported a significant improvement in a range of outcomes from probiotic supplementation (Kouchaki et al., 2017), further studies are required to confirm these results.

Several nutraceuticals including polyphenol compounds such as apigenin Ginwala et al. (2015), and naringenin Wang et al. (2015) have demonstrated improvements in outcomes in animal models of neuroinflammation used to study MS. However, they have not yet been investigated in people with MS. In addition, composite interventions of selected nutraceuticals that exhibit synergistic effects may provide additional benefit beyond single compound nutraceutical interventions and should be investigated in future trials. Finally, while there have been multiple interventions investigated for their effect on outcomes such as EDSS, fatigue, and depression, other commonly reported outcomes such as cognitive function, quality of life and bowel/bladder/sexual dysfunction have been less explored. It is recommended that these areas be investigated in future trials.

5. Conclusion

The results of this review provide preliminary evidence for the emerging use of nutraceutical interventions in the MS setting. However, due to the small sample sizes and a lack of replication or validation studies using the same agent and outcome measures, recommendations for clinical use are premature. Sufficiently powered trials are required to expand the currently limited literature and to investigate currently unexplored nutraceuticals that may target relevant underlying pathways involved in MS such as the gut microbiota and mitochondrial dysfunction.

We would like to thank and acknowledge the RELIEF trial investigator team for supporting this publication. OMD is supported by the National Health and Medical Research Council (APP 1145634) and gratefully acknowledges their support.

Funding and sponsorship

No direct funding was used to create this manuscript. WM is funded by a Deakin University postdoctoral fellowship. The research conducted at the Murdoch Children's Research Institute was supported by the Victorian Government's Operational Infrastructure Support Program. MB is supported by a NHMRC Senior Principal Research Fellowship (APP1059660 and APP1156072). MH is funded by Australian Rotary Health PhD Scholarship. OMD is a R.D. Wright Biomedical Research Fellow (APP 1145634) and has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical Research Institute, Deakin University, Lilly, NHMRC and ASBDD/Servier. She has also received in kind support from BioMedica Nutraceuticals, NutritionCare and Bioceuticals. ML is funded by a Deakin University PhD Scholarship. FJ has received Grant/Research support from the Brain and Behaviour Research Institute, the National Health and Medical Research Council (NHMRC), Australian Rotary Health, the Geelong Medical Research Foundation, the Ian Potter Foundation, Eli Lilly, Meat and Livestock Australia, The A2 Milk Company, BeFit Foods, Woolworths Limited, Fernwood Foundation, The Wilson Foundation, and The University of Melbourne and has received speakers honoraria from Sanofi-Synthelabo, Janssen Cilag, Servier, Pfizer, Health Ed, Network Nutrition, Angelini Farmaceutica, Eli Lilly and Metagenics. She is supported by an NHMRC Career Development Fellowship(2) (#1108125). Felice Jacka is currently writing two books for commercial publication and has a personal belief that good diet quality is important for mental and brain health. AJM is funded by an Australian Rotary Health/Ten Island Tassie Tag Along Tour Funding Partner PhD Scholarship. RL is funded by a NHMRC Senior Research Fellowship (#1107343)

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.101486.

References

Asano, M., Finlayson, M.L., 2014. Meta-Analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Mult. Scler. Int. 2014, 798285.

Berer, K., Gerdes, L.A., Cekanaviciute, E., Jia, X., Xiao, L., Xia, Z., Liu, C., Klotz, L., Stauffer, U., Baranzini, S.E., Kümpfel, T., Hohlfeld, R., Krishnamoorthy, G., Wekerle, H, 2017. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc. Natl Acad. Sci. 114 (40), 10719–10724.

Bertoglio, J.C., Baumgartner, M., Palma, R., Ciampi, E., Carcamo, C., Caceres, D.D., Acosta-Jamett, G., Hancke, J.L., Burgos, R.A, 2016. Andrographis paniculata decreases fatigue in patients with relapsing-remitting multiple sclerosis: a 12-month double-blind placebo-controlled pilot study. BMC Neurol. 16, 77.

Bitarafan, S., Saboor-Yaraghi, A., Sahraian, M.A., Soltani, D., Nafissi, S., Togha, M., Moghadam, N.B., Roostaei, T., Honarvar, N.M., Harirchian, M.H, 2016. Effect of Vitamin A supplementation on fatigue and depression in multiple sclerosis patients: a double-blind placebo-controlled clinical trial. Iran. J. Allergy Asthm Immunology 15 (1), 13–19.

Brochet, B., Guinot, P., Orgogozo, J.M., Confavreux, C., Rumbach, L., Lavergne, V, 1995. Double blind placebo controlled multicentre study of ginkgolide B in treatment of acute exacerbations of multiple sclerosis. The Ginkgolide Study Group in multiple sclerosis. J. Neurol. Neurosurg. Psychiatr. 58 (3), 360–362.

Claflin, S.B., van der Mei, I.A.F., Taylor, B.V, 2018. Complementary and alternative treatments of multiple sclerosis: a review of the evidence from 2001 to 2016. J. Neurol. Neurosurg. Psychiatry 89 (1), 34.

Diamond, B.J., Bailey, M.R, 2013. Ginkgo biloba. indications, mechanisms, and safety. Psychiatr. Clin. N. Am. 36 (1), 73–83.

Diamond B.J., Johnson S.K., Kaufman M., Shiflett S.C., Graves L. A randomized controlled pilot trial: the effects of EGb 761 on information processing and executive function in multiple sclerosis. Explore (New York, NY). 2013;9(2):106–7.

Dolati, S., Ahmadi, M., Aghebti-Maleki, L., Nikmaram, A., Marofi, F., Rikhtegar, R., Ayromlou, H., Yousefi, M, 2018. Nanocurcumin is a potential novel therapy for multiple sclerosis by influencing inflammatory mediators. Pharmacol. Rep. 70 (6), 1158–1167.

Drake, M.J., Canham, L., Cotterill, N., Delgado, D., Homewood, J., Inglis, K., Johnson, L., Kisanga, M.C., Owen, D., White, P., Cottrell, D, 2018. Results of a randomized, double blind, placebo controlled, crossover trial of melatonin for treatment of Nocturia in adults with multiple sclerosis (MeNiMS). BMC Neurol. 18 (1) 107–.

Dunn M., Bhargava P., Kalb R. Your patients with multiple sclerosis have set wellness as a high priority—and the National Multiple Sclerosis Society is responding. Your Patients with Multiple Sclerosis have Set Wellness as a High Priority—And the National Multiple Sclerosis Society is Responding. 2015.

Errea, O., Moreno, B., Gonzalez-Franquesa, A., Garcia-Roves, P.M., Villoslada, P, 2015. The disruption of mitochondrial axonal transport is an early event in neuroinflammation. J. Neuroinflammation 12, 152.

Etemadifar, M., Sayahi, F., Abtahi, S.H., Shemshaki, H., Dorooshi, G.A., Goodarzi, M., Akbari, M., Fereidan-Esfahani, M, 2013. Ginseng in the treatment of fatigue in multiple sclerosis: a randomized, placebo-controlled, double-blind pilot study. Int. J. Neurosci. 123 (7), 480–486.

Farinotti, M., Vacchi, L., Simi, S., Di Pietrantonj, C., Brait, L., Filippini, G, 2012. Dietary interventions for multiple sclerosis. Cochrane Database Syst. Rev. 12 Cd004192.

Gallien, P., Amarenco, G., Benoit, N., Bonniaud, V., Donze, C., Kerdraon, J., de Seze, M., Denys, P., Renault, A., Naudet, F., Reymann, J.M, 2014. Cranberry versus placebo in the prevention of urinary infections in multiple sclerosis: a multicenter, randomized, placebo-controlled, double-blind trial. Mult. Scler. 20 (9), 1252–1259.

Ginwala, R., McTish, E., Singh, N., Raman, C., Nagarkatti, M., Jain, P., Khan, Z.K, 2015. Apigenin, a natural flavonoid, attenuates EAE severity through modulation of dendritic and other immune cell functions. J. Neurovirol. 21 (Supplement 1), S24–SS5.

Gonsette, R.E., Sindic, C., D'Hooghe M, B., De Deyn, P.P., Medaer, R., Michotte, A., Seeldrayers, P., Guillaume, D, 2010. Boosting endogenous neuroprotection in multiple sclerosis: the Association of Inosine and Interferon beta in relapsing- remitting Multiple Sclerosis (ASIIMS) trial. Multiple sclerosis (Houndmills, Basingstoke, England) 16 (4), 455–462.

Isomura, T., Suzuki, S., Origasa, H., Hosono, A., Suzuki, M., Sawada, T., Terao, S., Muto, Y., Koga, T, 2016. Liver-related safety assessment of green tea extracts in humans: a systematic review of randomized controlled trials. Eur. J. Clin. Nutr. 70, 1221.

Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J, 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17 (1), 1–12.

Johnson S.K., Diamond B.J., Rausch S., Kaufman M., Shiflett S.C., Graves L. The effect of Ginkgo biloba on functional measures in multiple sclerosis: a pilot randomized controlled trial. Explore (New York, NY). 2006;2(1):19–24.

Khalili, M., Azimi, A., Izadi, V., Eghtesadi, S., Mirshafiey, A., Sahraian, M.A., Motevalian, A., Norouzi, A., Sanoobar, M., Eskandari, G., Farhoudi, M., Amani, F, 2014a. Does lipoic acid consumption affect the cytokine profile in multiple sclerosis patients: a double-blind, placebo-controlled, randomized clinical trial. NeuroImmunoModulation 21 (6), 291–296.

Khalili, M., Eghtesadi, S., Mirshafiey, A., Eskandari, G., Sanoobar, M., Sahraian, M.A., Motevalian, A., Norouzi, A., Moftakhar, S., Azimi, A, 2014b. Effect of lipoic acid consumption on oxidative stress among multiple sclerosis patients: a randomized controlled clinical trial. Nutr. Neurosci. 17 (1), 16–20.

Khalili, M., Soltani, M., Moghadam, S.A., Dehghan, P., Azimi, A., Abbaszadeh, O, 2017. Effect of alpha-lipoic acid on asymmetric dimethylarginine and disability in multiple sclerosis patients: a randomized clinical trial. Electron. Physician. 9 (7), 4899–4905.

Khallli, M., Eskandari, G., Ghajarzadeh, M., Azimi, A., Eghtesadi, S., Sahraian, M.A., Motevalian, A., Hashemi, H., Mirshafiey, A., Norouzi, A, 2012. Lipoic acid and multiple sclerosis: a randomized controlled conical trial. Curr. Top Nutraceutical Res. 10 (2), 95–100.

Kouchaki, E., Tamtaji, O.R., Salami, M., Bahmani, F., Daneshvar Kakhaki, R., Akbari, E., Tajabadi-Ebrahimi, M., Jafari, P., Asemi, Z, 2017. Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. Clin. Nutr. (Edinburgh, Scotland) 36 (5), 1245–1249.

Lambert, C.P., Archer, R.L., Carrithers, J.A., Fink, W.J., Evans, W.J., Trappe, T.A, 2003. Influence of creatine monohydrate ingestion on muscle metabolites and intense exercise capacity in individuals with multiple sclerosis. Arch. Phys. Med. Rehabil. 84 (8), 1206–1210.

Lan, M., Tang, X., Zhang, J., Yao, Z, 2018. Insights in pathogenesis of multiple sclerosis: nitric oxide may induce mitochondrial dysfunction of oligodendrocytes. Rev. Neurosci. 29 (1), 39–53.

Lassmann, H., 2013. Pathology and disease mechanisms in different stages of multiple sclerosis. J. Neurol. Sci. 333 (1–2), 1–4.

Ledinek, A.H., Sajko, M.C., Rot, U, 2013. Evaluating the effects of amantadin, modafinil and acetyl-L-carnitine on fatigue in multiple sclerosis - Result of a pilot randomized, blind study. Clin. Neurol. Neurosurg. 115 (SUPPL.1), S86–SS9.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D, 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6 (7), e1000100.

Lim, C.K., Bilgin, A., Lovejoy, D.B., Tan, V., Bustamante, S., Taylor, B.V., Bessede, A., Brew, B.J., Guillemin, G.J, 2017. Kynurenine pathway metabolomics predicts and provides mechanistic insight into multiple sclerosis progression. Sci. Rep. 7, 41473.

Lovera, J., Bagert, B., Smoot, K., Morris, C.D., Frank, R., Bogardus, K., Wild, K., Oken, B., Whitham, R., Bourdette, D, 2007. Ginkgo biloba for the improvement of cognitive performance in multiple sclerosis: a randomized, placebo-controlled trial. Mult. Scler. 13 (3), 376–385.

Lovera, J., Ramos, A., Devier, D., Garrison, V., Kovner, B., Reza, T., Koop, D., Rooney, W., Foundas, A., Bourdette, D, Polyphenon, E., 2015. Non-futile at neuroprotection in multiple sclerosis but unpredictably hepatotoxic: phase I single group and phase II randomized placebo-controlled studies. J. Neurol. Sci. 358 (0), 46–52.

Lovera, J.F., Kim, E., Heriza, E., Fitzpatrick, M., Hunziker, J., Turner, A.P., Adams, J., Stover, T., Sangeorzan, A., Sloan, A., Howieson, D., Wild, K., Haselkorn, J., Bourdette, D, 2012. Ginkgo biloba does not improve cognitive function in MS: a randomized placebo-controlled trial. Neurology 79 (12), 1278–1284.

Mahler, A., Steiniger, J., Bock, M., Klug, L., Parreidt, N., Lorenz, M., Zimmermann, B.F., Krannich, A., Paul, F., Boschmann, M, 2015. Metabolic response to epigallocatechin-3-gallate in relapsing-remitting multiple sclerosis: a randomized clinical trial. Am. J. Clin. Nutr. 101 (3), 487–495.

Malin, S.K., Cotugna, N., Fang, C.S, 2008. Effect of creatine supplementation on muscle capacity in individuals with multiple sclerosis. J. Diet Suppl. 5 (1), 20–32.

Markowitz, C.E., Spitsin, S., Zimmerman, V., Jacobs, D., Udupa, J.K., Hooper, D.C., Koprowski, H, 2009. The treatment of multiple sclerosis with inosine. J. Altern. Complem. Med. (New York, NY) 15 (6), 619–625.

Marques, C., Fernandes, I., Meireles, M., Faria, A., Spencer, J.P.E., Mateus, N., Calhau, C, 2018. Gut microbiota modulation accounts for the neuroprotective properties of anthocyanins. Sci. Rep. 8, 11341.

Marx, W., Isenring, E.A., Lohning, A.E, 2017. Determination of the concentration of major active anti-emetic constituents within commercial ginger food products and dietary supplements. Eur. J. Integr. Med. 10, 19–24.

Mauriz, E., Vallejo, D., Tunon, M.J., Rodriguez-Lopez, J.M., Rodriguez-Perez, R., Sanz-Gomez, J., Garcia-Fernandez Mdel, C, 2014. Effects of dietary supplementation with lemon verbena extracts on serum inflammatory markers of multiple sclerosis patients. Nutr. Hosp. 31 (2), 764–771.

McLaughlin, L., Clarke, L., Khalilidehkordi, E., Butzkueven, H., Taylor, B., Broadley, S.A, 2018. Vitamin D for the treatment of multiple sclerosis: a meta-analysis. J. Neurol. 265 (12), 2893–2905.

Mohammadzadeh Honarvar, N., Harirchian, M.H., Abdolahi, M., Abedi, E., Bitarafan, S., Koohdani, F., Siassi, F., Sahraian, M.A., Chahardoli, R., Zareei, M., Salehi, E., Geranmehr, M., Saboor-Yaraghi, A.A, 2016. Retinyl palmitate supplementation modulates T-bet and interferon gamma gene expression in multiple sclerosis patients. J. Mol. Neurosci. 59 (3), 360–365.

Molinari, M., Watt, K.D.S., Kruszyna, T., Nelson, R., Walsh, M., Huang, W.-Y., Nashan, B., Peltekian, K, 2006. Acute liver failure induced by green tea extracts: case report and review of the literature. Liver Transpl. 12 (12), 1892–1895.

Motl, R.W., Mowry, E.M., Ehde, D.M., LaRocca, N.G., Smith, K.E., Costello, K., Shinto, L., Ng, A.V., Sullivan, A.B., Giesser, B., McCully, K.K., Fernhall, B., Bishop, M., Plow, M., Casaccia, P., Chiaravalloti, N.D, 2018. Wellness and multiple sclerosis: The National MS Society establishes a Wellness Research Working Group and research priorities. Multiple sclerosis (Houndmills, Basingstoke, England) 24 (3), 262–267.

Munoz Garcia, D., Midaglia, L., Martinez Vilela, J., Marin Sanchez, M., Lopez Gonzalez, F.J., Arias Gomez, M., Dapena Bolano, D., Iglesias Castanon, A., Alonso Alonso, M., Romero Lopez, J, 2015. Associated inosine to interferon: results of a clinical trial in multiple sclerosis. Acta Neurol. Scand. 131 (6), 405–410.

Nabavi, S.M., Naseri, M., Rezaeezadeh, H., Ghareguzli, K., Shayegannejad, V., Ghafarpoor, M., Faghihzadeh, S, 2012. A double-blind, placebo-controlled, study of oral MS14, a herbal-marine drug, on walking ability in multiple sclerosis patients. J.

Neurol. (1), S153.
Naghashpour, M., Majdinasab, N., Shakerinejad, G., Kouchak, M., Haghighizadeh, M.H., Jarvandi, F., Hajinajaf, S, 2013. Riboflavin supplementation to patients with multiple sclerosis does not improve disability status nor is riboflavin supplementation correlated to homocysteine. Int. J. Vitamin Nutr. Res. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung Journal international de vitaminologie et de nutrition 83 (5), 281–290.
O'Connor, K., Weinstock-Guttman, B., Carl, E., Kilanowski, C., Zivadinov, R., Ramanathan, M, 2012. Patterns of dietary and herbal supplement use by multiple sclerosis patients. J. Neurol. 259 (4), 637–644.
Pantzaris, M.C., Loukaides, G.N., Ntzani, E.E., Patrikios, I.S, 2013. A novel oral nutraceutical formula of omega-3 and omega-6 fatty acids with vitamins (PLP10) in relapsing remitting multiple sclerosis: a randomised, double-blind, placebo-controlled proof-of-concept clinical trial. BMJ Open 3 (4).
Pereira, C., Chavarria, V., Vian, J., Ashton, M.M., Berk, M., Marx, W., Dean, O.M, 2018. Mitochondrial agents for bipolar disorder. Int. J. Neuropsychopharmacol. 21 (6), 550–569.
Reich, D.S., Lucchinetti, C.F., Calabresi, P.A, 2018. Multiple sclerosis. N. Eng. J. Med. 378 (2), 169–180.
Roostaei, T., Sahraian, M.A., Hajeaghaee, S., Gholipour, T., Togha, M., Siroos, B., Mansouri, S., Mohammadshirazi, Z., Aghazadeh Alasti, M., Harirchian, M.H, 2015. Impact of melatonin on motor, cognitive and neuroimaging indices in patients with multiple sclerosis. Iran J. Allergy Asthma Immunol. 14 (6), 589–595.
Sanoobar, M., Dehghan, P., Khalili, M., Azimi, A., Seifar, F, 2016. Coenzyme Q10 as a treatment for fatigue and depression in multiple sclerosis patients: a double blind randomized clinical trial. Nutr. Neurosci. 19 (3), 138–143.
Sato, F., Martinez, N.E., Shahid, M., Rose, J.W., Carlson, N.G., Tsunoda, I, 2013. Resveratrol exacerbates both autoimmune and viral models of multiple sclerosis. Am. J. Pathol. 183 (5), 1390–1396.
Shaygannejad, V., Janghorbani, M., Savoj, M.R., Ashtari, F, 2010. Effects of adjunct glucosamine sulfate on relapsing-remitting multiple sclerosis progression: preliminary findings of a randomized, placebo-controlled trial. Neurol. Res. 32 (9), 981–985.
Simpson Jr., S., Tan, H., Otahal, P., Taylor, B., Ponsonby, A.L., Lucas, R.M., Blizzard, L., Valery, P.C., Lechner-Scott, J., Shaw, C., Williams, D., van der Mei, I, 2016. Anxiety, depression and fatigue at 5-year review following CNS demyelination. Acta Neurol. Scand. 134 (6), 403–413.
Spain, R., Powers, K., Murchison, C., Heriza, E., Winges, K., Yadav, V., Cameron, M., Kim, E., Horak, F., Simon, J., Bourdette, D, 2017. Lipoic acid in secondary progressive MS: a randomized controlled pilot trial. Neurol. Neuroimmunol. Neuroinflammation 4 (5), e374.
Strasser, B., Geiger, D., Schauer, M., Gostner, J.M., Gatterer, H., Burtscher, M., Fuchs, D, 2016. Probiotic supplements beneficially affect tryptophan–kynurenine metabolism and reduce the incidence of upper respiratory tract infections in trained athletes: a randomized, double-blinded, Placebo-Controlled Trial. Nutrients 8 (11), 752.
Tomassini, V., Pozzilli, C., Onesti, E., Pasqualetti, P., Marinelli, F., Pisani, A., Fieschi, C, 2004. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. J. Neurol. Sci. 218 (1–2), 103–108.
Tourbah, A., Gout, O., Vighetto, A., Deburghgraeve, V., Pelletier, J., Papeix, C., Lebrun-Frenay, C., Labauge, P., Brassat, D., Toosy, A., Laplaud, D.A., Outteryck, O., Moreau, T., Debouverie, M., Clavelou, P., Heinzlef, O., De Seze, J., Defer, G., Sedel, F., Arndt, C, 2018. MD1003 (High-Dose pharmaceutical-grade biotin) for the treatment of chronic visual loss related to optic neuritis in multiple sclerosis: a randomized, double-blind, Placebo-Controlled Study. CNS Drugs 32 (7), 661–672.
Tourbah, A., Lebrun-Frenay, C., Edan, G., Clanet, M., Papeix, C., Vukusic, S., De Seze, J., Debouverie, M., Gout, O., Clavelou, P., Defer, G., Laplaud, D.A., Moreau, T., Labauge, P., Brochet, B., Sedel, F., Pelletier, J, 2016. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: a randomised, double-blind, placebo-controlled study. Mult. Scler. 22 (13), 1719–1731.
Wang, J., Niu, X., Meydani, S., Wu, D, 2015. Dietary supplementation with naringenin attenuates experimental autoimmune encephalomyelitis in mice. FASEB J. Conf. 29 (1 Meeting Abstracts).
Yadav, V., Bever Jr., C., Bowen, J., Bowling, A., Weinstock-Guttman, B., Cameron, M., Bourdette, D., Gronseth, G.S., Narayanaswami, P, 2014. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. Neurology 82 (12), 1083–1092.
Yadav, V., Marracci, G., Lovera, J., Woodward, W., Bogardus, K., Marquardt, W., Shinto, L., Morris, C., Bourdette, D.N, 2005. Lipoic acid in multiple sclerosis: a pilot study. Multiple Sclerosis 11 (2), 159–165.
Zheng, C., He, L., Liu, L., Zhu, J., Jin, T, 2018. The efficacy of vitamin D in multiple sclerosis: a meta-analysis. Mult. Scler. Relat. Disord. 23, 56–61.