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Systematic Review

Natural Health Products in the Prevention and Management of Alzheimer's Disease: A Systematic Review of Randomized Clinical Trials

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Abstract: Supplementation with natural compounds, referred to as Natural Health Products (NHPs), is emerging as an applicable strategy in all phases of Alzheimer's disease (AD) management, alongside pharmacological therapy. Several studies have investigated the potential of NHPs to modulate neurochemical and inflammatory processes associated with clinical decline; however, the results remain inconclusive. To evaluate the influence of NHPs on the clinical outcomes of AD patients, a systematic review was performed by searching the PubMed, Scopus, Cochrane, and Clinical Trials.gov databases for randomized clinical trials (RCTs) exploring the effects associated with NHP supplementation for the treatment of AD. Out of the 34 RCTs analyzed, 50% reported improvements in cognitive function and reductions in neuroinflammatory markers following NHP supplementation, suggesting a potential but inconsistent therapeutic effect. The strongest evidence of benefit in AD patients was found with the use of vitamin D, selenium, and probiotics. A certain incidence of depressive disorders and delirium highlights the necessity to better evaluate the safety and tolerability of B vitamin supplements. Overall, this systematic review found mixed results regarding the use of NHPs in the management of AD. Further evidence is needed to support their use in clinical practice.

Keywords: Alzheimer's disease; supplements; vitamins; omega-3; micronutrients; herbal medicine; safety; efficacy

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1. Introduction

Due to increasing life expectancy, the annual incidence of dementia, currently estimated at approximately 10 million cases worldwide, continues to rise [1–3]. The World Health Organization predicts that 152 million people will be affected by dementia by 2050 [4].

Dementia is a degenerative neurological disorder that leads to the impairment of nerve cells and neural networks. The consequence is a gradual decline in the ability to process thoughts and cognitive function, which is often accompanied or even preceded by significant behavioural, mood, and emotional disturbances. Alzheimer's disease (AD), which is pathologically defined by the presence of amyloid plaques and neurofibrillary tangles (NFTs), is the most common form of dementia, accounting for 60–70% of all cases [1,5].

Several risk factors contribute to the onset of AD, including female sex, advanced age (typically over 65 years), smoking, excessive alcohol consumption, and pathological conditions such as hypertension, hypercholesterolemia, and diabetes mellitus [5]. In addition, the presence of at least one mutation in the ε4 allele of apolipoprotein E (APOE) is associated with a 3–4-fold increased risk of developing AD [6,7].

Despite substantial advances in understanding the physio-pathological mechanisms underlying this neurodegenerative disorder, the treatment and management of AD remain incomplete and highly challenging, with current pharmacological therapies only able to slow disease progression [8–10], rather than halt or reverse it. The therapeutic strategy currently approved by the Food and Drug Administration (FDA) for the treatment of AD is limited to just five drugs, including cholinesterase inhibitors such as rivastigmine, galantamine, and donepezil; N-methyl-D-aspartate (NMDA) receptor antagonists such as memantine for severe AD and vascular dementia; medications for blood pressure and cholesterol control, which help to prevent further brain damage due to vascular cognitive impairment; and selective serotonin reuptake inhibitors (SSRIs), used to counteract the symptoms of major depressive syndrome [1,9].

Neuroinflammation has been identified as another key factor contributing to the pathogenesis of AD. Amyloid plaques and NFTs are able to activate glial cells, which, in turn, induce an immune response in the brain. The uncontrolled activation of glial cells can lead to the loss of homeostatic functions and the triggering of a chronic inflammatory process. This inflammation is associated with the release of reactive oxygen and nitrogen species, both of which contribute to the accumulation of oxidative stress and neuronal cell death [9]. In light of these factors, and with the aim of developing more effective treatments that can halt or modify AD progression, research is focusing on several AD- related factors, including the inflammatory response and free radical damage [9].

In this context, the use of an unconventional practice belonging to "Complementary and Alternative Medicine", such as supplementation with natural compounds, referred to as Natural Health Products (NHPs), has emerged as a potentially beneficial strategy that could complement the conventional therapeutic approach in all stages of AD management [11].

Several studies have investigated the neuroprotective effects of various antioxidant agents such as omega-3 (ω-3) fatty acids (FAs) [12], vitamin (vit) E [13], and phytochemicals such as ginkgo biloba [14,15] and curcumin [16], focusing on their ability to modulate neurochemical pathways and inflammatory biomarkers responsible for the persistent neurological inflammation that characterizes AD patients. Additionally, research has explored the role of B vitamins, including vitamin B6, vitamin B9, folic acid [17,18], and dietary supplements, in mitigating the factors contributing to cognitive decline and AD progression.

Given the multifactorial nature of AD, the simultaneous use of several NHPs acting on different molecular pathways could represent a novel therapeutic strategy [17]. However, the studies that have examined the effects of these supplements, used alone or in combination, have reported conflicting results.

Furthermore, as NHPs are not inert molecules, their use may interfere with primary pharmacological treatments through drug–drug interactions (DDIs), potentially altering their pharmacodynamic or pharmacokinetic properties [18]. Such interactions could com-

promise the achievement of the desired therapeutic outcomes in several clinical fields, including neurology [11,18,19].

The aim of this systematic review is to provide an up-to-date and comprehensive overview of randomized clinical trials (RCTs) that have investigated the effects of NHPs in the prevention and treatment of AD, focusing on their mechanisms of action, assessing their potential therapeutic benefits, and analyzing factors that may influence clinical outcomes, including dosage, treatment duration, patient characteristics, and possible DDIs with conventional drug therapies.

2. Materials and Methods

The search was conducted according to the "Preferred Reporting Item for Systematic Review and Meta-Analyses" (PRISMA) guidelines [20]. This study was registered on PROSPERO (CRD42025641880). The "PICOT" algorithm was preliminarily established as follows:

- P (population): people living with AD;
- I (intervention): supplementation of NHPs (e.g., vitamins, minerals, herbal extracts, and micronutrients);
- C (comparison): placebo group or control group;
- O (outcomes): efficacy or safety of supplementation of NHPs in patients with diagnosis of AD;
- T (type of study): RCT.

2.1. Search Strategy

A systematic and comprehensive literature search was performed, using both a controlled vocabulary and free-text terms. The following "Medical Subject Heading (MESH)" terms were used, using the Boolean 'AND' operator: Herbal supplements in Alzheimer's disease; vitamins and Alzheimer's disease; micronutrients and Alzheimer's disease. The databases PubMed, Scopus, Cochrane, and ClinicalTrials.gov were searched from January 2000 to January 2025.

The selection criteria were developed by two reviewers (G.C.; V.C.). Three authors (A.Z.; A.D.S.; I.M.) independently screened the articles and judged their eligibility according to the inclusion criteria. Any disagreements were resolved by a fourth author (V.C.). The quality of this study was assessed using the Jadad Score for RCTs. Two reviewers independently assessed the study's quality and risk of bias (F.G; V.D.L.), and discrepancies were resolved by discussion with another author (V.M.).

2.2. Study Selection, Data Extraction, and Quality Assessment

Our research was limited to RCTs involving humans without gender and age restrictions. Case reports, silico/computational studies, conference paper/abstracts, editorials, reviews, systematic reviews, guidelines, in vivo studies, in vitro studies, meta-analyses, clinical trials (CTs), comments, letters and editorials, observational studies, book/book chapters, study protocols, articles not in English, articles published prior to 2000, and RCTs not reporting data in patients with an established diagnosis of AD or no data on the use of supplementation with NHPs were excluded. Only studies examining the efficacy and safety of supplements (e.g., vitamins, minerals, herbal extracts, and micronutrients) in patients with a diagnosis of AD confirmed by standardized diagnostic criteria (the "Mini-Mental State Examination, MMSE", or the "Alzheimer's Disease Assessment Scale–Cognitive Subscale, ADAS-Cog", criteria), were included in the analysis.

The quality of the included studies was assessed manually using the "Jadad scale" (Table 1), a validated tool used to assess the methodological quality of an RCT. It focuses

on three key criteria: randomization, blinding, and patients lost to follow-up. The total score ranges from 0 to 5 points. One or two points are awarded for correct randomization, depending on whether the method is described and appropriate. Similarly, up to two points are awarded for correct/adequate blinding and an additional point if the study reports withdrawals and drop-outs of participants. Studies scoring 0 to 2 points are considered to be of lower quality with a higher risk of bias, while those scoring 3 to 5 points are considered to be of high quality [21].

Table 1. Items and score of the standardized Jadad scale [21] used for reporting the quality of RCTs included in this systematic review.

Item	Description	Maximum Points
Randomization	1 point if randomization is mentioned. 1 additional point if the method of randomization is appropriate. Deduct 1 point if the method of randomization is inappropriate (minimum 0).	2
Blinding	1 point if blinding is mentioned. 1 additional point if the method of blinding is appropriate. Deduct 1 point if the method of blinding is inappropriate (minimum 0).	2
An account of all patients	The fate of all patients in the trial is known. If there are no data, the reason is stated.	1

3. Results

3.1. Search Results

Initially, 16,164 records were identified. In the end, 34 RCTs were analyzed. The PRISMA algorithm shows the flow of the research (Figure 1).

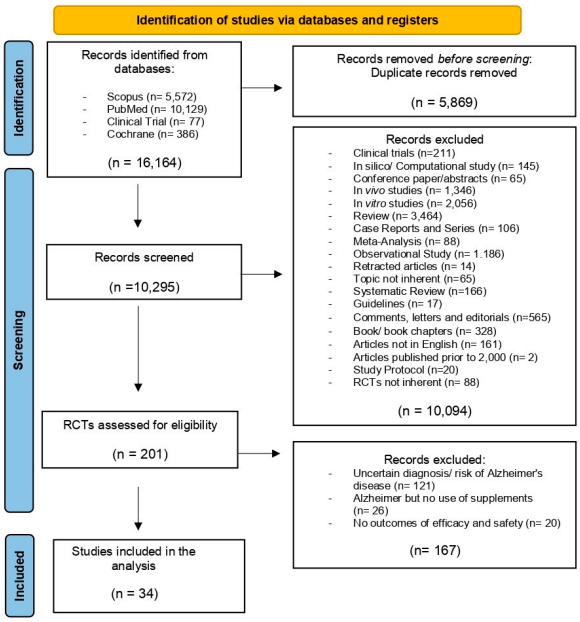

Figure 1. The PRISMA algorithm in this study.

3.2. Vitamin Supplementation in AD

The use of vitamin supplementation could play a key role in the management of AD-associated symptoms, helping to improve patients' quality of life [22,23].

Table 2 shows the results of RCTs conducted on AD patients treated with vitamins of groups B, D, and E, administered alone or in combination. Group B vit, such as vitamin B9 (folic acid), B12 (cobalamin), and B6 (pyridoxine, pyridoxal, and pyridoxamine), are widely recognized for their potential to prevent the onset of AD and preserve cognitive function in patients with established disease [24]. As elevated homocysteine (Hcy) levels (over 12 μmol/L) have been associated with an increased risk of cognitive decline and are very common in AD patients [6], the beneficial effects of these vitamins are related to their ability to reduce Hcy concentrations [25,26].

Indeed, several studies [26–29] have reported a reduction in Hcy levels in patients treated with vitamin B complex supplements. In particular, the daily use of 5 mg of folic acid, 25 mg of vitamin B6, and 1 mg of vitamin B12 was effective in providing a 7% reduction in plasma Hcy levels in the treated group compared with the placebo ($p < 0.001$) [26]. Sun et al. highlighted that the administration of 500 μg of mecobalamin (an isoform of vitamin B12), together with a complex containing 60 mg of iron, 5 mg of vitamin B6, 1 mg of folic acid, 10 mg of nicotinamide, 250 mg of calcium carbonate, 3 mg of thiamine mononitrate, 2 mg of riboflavin, 1 mg of calcium pantothenate, 100 μg of ascorbic acid, 100 μg of iodine, 150 μg of copper, 4000 IU of vitamin A, and 400 IU of vitamin D3 induced an average decrease of 2.25 μmol/L ($p = 0.008$) of Hcy concentration [27]. Similarly, Chen et al. [28] found that over a period of 12 months supplementation with 1.2 mg of folic acid and 50 μg of vitamin B12 per day significantly increased the S-adenosyl-methionine (SAM)/S-adenosyl-homocysteine (SAH) ratio ($p < 0.001$) with a consequent reduction in Hcy levels.

However, it should be noted that the studies by Aisen et al. and Sun et al. [26,27], which utilized the same treatment albeit at different dosages, showed important safety issues in the supplemented group compared to the placebo group. Aisen et al. reported a higher rate of a depressed mood, depressive episodes, and established depression [26]; Sun et al. reported a higher rate of delirium [27].

As vitamin D regulates key processes in the hippocampus, hypothalamus, and cortex [30], maintaining adequate levels of vitamin D is crucial for central nervous system (CNS) function, helping to prevent neuronal cell apoptosis, reducing synaptic degeneration, and modulating inflammation. This neuroprotective role is the main reason why vitamin D supplementation could help to slow AD progression [31]. The study by Jia et al. [31] tested whether vitamin D supplements could slow cognitive decline in AD patients by also assessing cognitive performance in relation to the amyloid-β (Aβ) 42 protein, the deposition of which is a major cause of neuronal dysfunction and cell death, progressively leading to dementia. Interestingly, the results showed reduced levels of Aβ42 in the intervention group (11.31%) compared to the control group (0.27%) ($p < 0.001$) [31].

In contrast, the study by Stein et al. [32] investigated the effect of a high dose of vitamin D2 after a nasal administration of insulin. This approach is based on the observation that nasally administered insulin improves cognitive function, while vitamin D2 increases the expression of insulin receptors and enhances the action of insulin [33]. The initial treatment consisted of 1000 IU of vitamin D2 daily for 8 weeks. Subsequently, the dosage was increased to 6000 IU, divided into two capsules and administered three times a day together with nasal insulin four times a day. The results demonstrated a significant increase in 25-hydroxyvitamin D [25 (OH)D], a recognized biomarker of vitamin D status. Specifically, the median concentration of 25(OH)D increased from 60 nM to 187 nM ($p < 0.001$) in the high-dose vitamin D group, while in the placebo group it only varied from 64 nM to 72 nM. Another significant finding was the reduction in disability assessed in 11 out of 13 participants ($p < 0.02$) using the "Disability Assessment for Dementia (DAD) score". Based on these results, the study by Stein et al. suggests that high-dose vitamin D provides

no benefit for cognition or disability compared to low-dose vitamin D in individuals with mild-to-moderate AD [32].

Vitamin E is known for its antioxidant and anti-inflammatory effects, which could protect against neurodegenerative disorders. Numerous studies have shown that people with AD or age-related cognitive decline have significantly reduced levels of vitamin E in serum and cerebrospinal fluid (CSF) compared to healthy people [23,34–36].

The potential interaction between vitamin E, memantine, and cholinesterase (ChE) inhibitors, such as rivastigmine (RIV) or donepezil (DPZ), for the treatment of AD has been investigated to test whether vitamin E could enhance the therapeutic effects of these drugs, improving cognitive function and slowing down the neurodegenerative process. The basic theory is that vitamin E combined with DPZ (which increases brain acetylcholine levels) or memantine (which modulates N-methyl-D-aspartic acid receptor activity) may have a synergistic effect in protecting neurons from oxidative damage and improving synaptic transmission [23]. Galasko et al. [37] investigated the effects of 800 IU/d of α-tocopherol, 500 mg/d of vitamin C, and 900 mg/d of α-lipoic acid (E/C/ALA) together with 400 mg of coenzyme Q (CoQ) three times a day with ChE inhibitors. This treatment provided a 19% reduction in F2-isoprostane levels in CSF and an improvement in the "MMSE" score in the treated group compared to the control group ($p = 0.02$) [37].

Dysken et al. [38] performed a study to estimate the efficacy and safety of 2000 IU/day of alpha-tocopherol (a type of vitamin E), and 20 mg/day of memantine alone or combined with alpha-tocopherol. Patients with mild-to-moderate AD treated with alpha-tocopherol showed a greater slowing of cognitive decline than those treated with a placebo ($p = 0.03$). However, unexpectedly, the combined administration of alpha-tocopherol and memantine had a smaller effect than the single treatments. The mechanism is unclear, but it is possible that memantine interfered with the action of alpha-tocopherol. Moreover, infestation or infection were reported more frequently in the groups treated with memantine (31 events in 23 subjects) and the vitamin E/memantine (44 events in 31 subjects), compared to the placebo group (13 events in 11 participants) [38]. In contrast, Thomas et al. demonstrated an improving trend of the "MMSE" score in patients taking ChE inhibitors ($p = 0.06$), whereas a worsening trend was observed in patients administered with vitamin E ($p = 0.07$) [39].

Table 2. Main characteristics and results of the RCTs, published between 2000 and January 2025, investigating the efficacy or safety of vitamin supplementation in AD patients. All drugs and supplements were orally administered with the exception of Stein et al.'s study [32] in which insulin was administered intranasally.

References	Study Design	Country	Patients (n)	Sex (F%)	Range Age (Years)	Mean Age (Years)	NHPs	Concomitant Drugs	Follow-Up	Outcomes	Main Results and Limitations	Jadad Score
Aisen et al. [26] (2008)	Multicenter, double-blind, placebo-controlled trial	USA	409 -INT-g: 240 -PL-g: 169	56 -INT-g: 57.5 -PL-g: 53.9	NA	76.3 -INT-g: 75.7 -PL-g: 77.3	Folic acid, vitamins B6, and B12	Acetylcholine esterase inhibitors	18 months	Efficacy and safety of B-vitamin supplementation	Reduced Hcy levels in the treated group compared to placebo ($p < 0.001$), without slowing AD progression. In addition, a higher incidence of depression was found (68% in the treated group vs. 18% in placebo, $p = 0.024$). Limitations: lack of measurement of basal Hcy levels.	4
Sun et al. [27] (2007)	Double-blind, placebo-controlled trial	Asia	89 -INT-g: 45 -PL-g: 44	-INT-g: 53.3 -PL-g: 45.5	NA	-INT-g: 74.9 -PL-g: 74.6	Mecobalamin (B12) + pyridoxine (B6) 5 mg, folic acid 1 mg, and other vitamins and iron.	DPZ	26 weeks	Effects of vitamins on cognitive function and serum Hcy levels in patients with mild-to-moderate AD	Reduced serum Hcy levels in the treated group compared to placebo ($p = 0.008$) was found. However, no improvement in cognitive function or activities of daily living was observed. Limitations: short follow-up and small final sample size due to adverse reactions from acetylcholinesterase inhibitors.	5
Chen et al. [28] (2021)	Single-blind placebo-controlled trial	Asia	120 -INT-g: 60 -PL-g: 60	-INT-g: 50 -PL-g: 56.67	NA	-INT-g: 68.58 -PL-g: 68.02	Folic acid and vitamin B12	NA	6 months	Effects on cognitive function and inflammation in AD	Improvement in cognitive function, reduced Hcy levels, and increased SAM/SAH ratio was observed in the intervention group compared to placebo ($p < 0.001$). These effects were observed in patients who were not on a folate-rich diet. Limitations: short follow-up and lack of assessment of the methylation grade of the inflammatory biomarkers.	3
Jia et al. [31] 2019)	Double-blind, placebo-controlled trial	Asia	210 -INT-g: 105 -CTR-g: 105	-INT-g: 55.24 -CTR-g: 58.10	≥ 65	-INT-g: 68.02 -PL-g: 67.53	Vitamin D3	NA	12 months	Effects on cognitive function and A β -related biomarkers	The supplementation induced an improvement in cognitive function and reduced A β -related biomarkers in the supplemented group compared to placebo ($p < 0.001$). Limitations: lack of assessment of confounding factors, affecting plasma A β , protein binding, and hydration.	4
Stein et al. [32] (2011)	Pilot study + double-blind, placebo-controlled trial	Oceania	31	53.1	69–80	NA	Vitamin D2	Nasal insulin, DPZ, Riv, galantamine, and memantine	16 weeks	Effects on cognition, disability, and memory in mild–moderate AD patients	No cognitive or disability-related benefits were found in either mild or moderate AD. Limitations: lack of evaluation of patient therapeutic adherence.	4
Galasko et al. [37] (2012)	Multicenter, double-blind, placebo-controlled trial	USA	78 -G1 (E/C/ALA): 28 -G2 (CoQ): 25 -PL-g: 25	-G1 (E/C/ALA): 46 -G2 (CoQ): 44 -PL-g: 48	50–85	-G1 (E/C/ALA): 73.6 -G2 (CoQ): 71.4 -PL-g: 73.2	E/C/ALA or CoQ	Acetyl cholinesterase inhibitor and memantine	16 weeks	Effects on oxidative stress biomarkers and cognitive function	Reduction in CSF F2-isoprostane levels ($p = 0.04$) and an improvement in cognitive function ($p = 0.02$) was observed in the E/C/ALA group compared to control. Limitations: the vitamin E dose of 800 IU/d in the E/C/ALA combination is lower than that generally used in neurodegenerative disorders because the literature associates increased mortality with these high levels.	4
Dysken et al. [38] (2014)	Double-blind, placebo-controlled, parallel-group clinical trial	USA	613 -Vitamin E-g: 152 -Memantine-g: 155 -INT-g: 154 -PL-g: 152	-Vitamin E-g: 4 -Memantine-g: 4 -INT-g: 3 -PL-g: 2	-Vitamin E-g: 55–93 -Memantine-g: 53–92 -INT-g: 54–94 -PL-g: 61–96	-Vitamin E-g: 78.6 -Memantine-g: 78.8 -INT-g: 78.3 -PL-g: 79.4	Vitamin E	Memantine, DPZ, galantamine, and Riv	4 years	Effects on slowing AD progression	Slowing in functional decline in treated patients compared to placebo ($p = 0.03$). No benefits in patients using memantine alone or combined with vitamin E. Limitations: several patients lost to follow-up, and a small number of women enrolled in the study.	4
Thomas et al. [39] (2001)	Double-blind + open-controlled study	EU	120 -CTR-g: 60 -G1 (DPZ): 20 -G2 (Riv): 20 -G3 (Vitamin E): 20	-CTR-g: 58.33 -G1 (DPZ): 55 -G2 (Riv): 55 -G3 (Vitamin E): 50	-CTR-g: 57–78 -G1 (DPZ): 60–73 -G2 (Riv): 59–71 -G3 (Vitamin E): 58–73	-CTR-g: 67.5 -G1 (DPZ): 66.5 -G2 (Riv): 65.0 -G3 (Vitamin E): 65.5	Vitamin E	DPZ and Riv	6 months	Effects on P300 latency and cognitive function	DPZ and Riv reduced P300 latency and improved cognitive function in the treated group compared to the control, without reaching statistical significance. In contrast, vitamin E had no similar effect. Limitations: a short follow-up.	4

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CoQ, coenzyme Q; CSF, cerebrospinal fluid; CTR-g, control group; DPZ, donepezil; E/C/ALA, vitamin E, vitamin C, and α-acid lipoic; EU, Europe; G1, group 1; G2, group 2; G3, group 3; Hcy, homocysteine; INT-g, integration group; MMSE, Mini-Mental State Examination; NA, not available; NHPs, Natural Health Products; PL-g, placebo group; Riv, rivastigmine; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; USA, United States of America.

3.3. Omega-3 Supplementation in AD

One of the most important characteristics of AD is the persistent state of neuroinflammation, driven by the activation of microglia and astrocytes [40]. The continued release of pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6, is correlated with memory impairment and a decline in cognitive performance [41,42].

The potential role of ω-3 FAs, particularly docosahexaenoic acid (DHA), which is abundant in the membrane phospholipids of brain gray matter [43], and eicosapentaenoic acid (EPA) has been investigated by several research groups because of its potential anti-inflammatory effects. Table 3 reports the main characteristics of the reviewed RCTs that evaluated the ω-3 FAs' effects in AD patients.

Faxèn-Irving et al. [44] conducted two studies to test the effects of ω-3 polyunsaturated FAs on weight and appetite in mild-to-moderate AD [44], as well as their impact on levels of transthyretin (TTR), an Aβ-binding protein that reduces brain Aβ accumulation [45]. In both studies, one group received ω-3 supplementation for 12 months, while the other group was initially treated with the placebo for the first 6 months and then switched to the same ω-3 supplementation regimen as the first group for the remaining 6 months. A progressive weigh gain was recorded in the supplemented group, whereas no weight gain was observed in the group receiving the placebo until they switched to active treatment [44,45]. This weight gain was particularly evident in participants with a body mass index at baseline of less than 23 ($p < 0.01$). Additionally, caregiver assessments indicated an increase in appetite in the ω-3/ω-3 group after 12 months ($p < 0.01$). No treatment effect related to APOE4 allele status was found. Overall, the results suggest that ω-3 FA supplementation is related to increases in weight and appetite in patients with mild AD [44].

Faxén-Irving et al., [45] in 2013, reported that after 6 months, the patients administered with the placebo showed decreased plasma TTR levels ($p < 0.001$ within a group and $p < 0.015$ between groups), whereas the ω-3 FA supplementation group did not experience this effect. During the subsequent 6 months, when both groups were supplemented with ω-3 FAs, TTR levels increased in both groups ($p < 0.01$ for the ω-3/ω-3 group and $p < 0.001$ for the placebo/ω-3 group) [45]. After 12 months, TTR increased significantly only in the group that received ω-3 FA supplementation through the entire study period ($p = 0.04$). Notably, in this group of patients, increased plasma concentrations of TTR were associated with improved cognitive function [45].

Freund-Levi et al. conducted four studies between 2008 and 2014 to test the effects of ω-3 FAs on AD-related pro-inflammatory biomarkers [46–48] and their impact on psychiatric and behavioural symptoms [49]. In 2008 [48], 174 patients with mild AD were given a dose a ω-3 FAs or placebo for 6 months, followed by 6 months of ω-3 FAs for both groups. The supplementation consisted of 1.7 g of DHA and 0.6 g of EPA. At baseline, there were no significant differences in the use of antidepressants and neuroleptics in the two groups.

The "Neuropsychiatric Inventory (NPI)", used to measure neuropsychiatric symptoms, and the "Montgomery Åsberg Depression Scale (MADRS)" for depressive symptoms showed low total scores at baseline for both groups. At 6 and 12 months, no significant differences between the groups were observed in total NPI scores. However, in the first 6 months, hallucinations ($p = 0.04$) and irritation ($p = 0.008$) improved in the ω-3 FA group and placebo group, respectively. These effects disappeared when both groups received ω-3 FA supplementation [48].

Adjusting for age, gender, and APOE genotype, no significant effects on neuropsychiatric symptoms were found, with the exception of the agitation domain. Indeed, a significant reduction in agitation scores was observed in patients carrying the APOE4 allele in the ω-3 FA group compared to placebo ($p = 0.006$).

Non-APOE4 carriers in the ω-3/ω-3 group showed a decline in MADRS scores between 0 and 6 months (p = 0.005), compared to non-APOE4 carriers receiving the placebo [48].

In summary, while treatment with ω-3 FA did not produce significant effects on neuropsychiatric symptoms or depression globally, there may be benefits in specific domains (such as hallucinations and agitation), with potential effects modulated by genetic profiles, particularly the APOE4 allele [48].

Moreover, Freund-Levi et al. [46] studied the impact of a supplementation containing 430 mg of DHA and 150 mg of EPA for six months on IL-6, TNF-α, and soluble IL-1 receptor type II (sIL-1RII) levels in plasma and CSF. A formulation containing 1 g of corn oil, including 0.6 g of linoleic acid, was used as a placebo. Both formulations contained 4 mg of vitamin E. No differences were found in IL-6 or sIL-1RII levels in CSF, whereas TNF-α significantly decreased in both groups (both $p < 0.001$). No statistically significant differences in the same markers were found in plasma [46]. Therefore, supplementation with ω-3 FAs showed no effect on pro-inflammatory biomarkers in CSF or plasma [46].

Freund-Levi et al. [47] measured levels of 8-iso-prostaglandin F2 α (8-iso-PGF2α) and 15-keto-dihydro- PGF2α, a biomarker relatable to oxidative stress and a biomarker of inflammatory response, respectively, in 37 patients who received 1.7 g of DHA and 0.6 g of EPA or placebo for 6 months [47]. No differences were observed in the urinary levels of 8-iso-PGF2α and 15-keto-dihydro-PGF2α between the supplemented group and the placebo group. At baseline, 15-keto-dihydro-PGF2α levels showed negative correlations with ω-3 FAs and a positive correlation with linoleic acid. These results suggest that ω-3 FAs for 6 months in AD patients does not significantly affect free radical-induced F2-isoprostane formation or cyclooxygenase (COX)-mediated PGF2α synthesis [47].

Freund-Levi et al. [49] also reported that patients with mild-to-moderate AD administered with 2.3 g of ω-3 FAs daily for six months showed significant increases in DHA, EPA, and total ω-3 FA levels in CSF and plasma compared to placebo ($p < 0.01$) [49]. These results suggest that oral supplementation with ω-3 FA may alter the endogenous ω-3 FA profiles in CSF, indicating the potential transfer of these FAs across the blood–brain barrier in adults [49].

Jernerén et al. [50] conducted a post hoc analysis involving 171 patients with AD. Of these, 88 patients received a daily dose of 1.7 g of DHA and 0.6 g of EPA for six months. The main goal of the analysis was to test whether the plasma levels of total Hcy affected the potential impact of ω3 FAs on cognitive decline. In patients with total Hcy levels below 11.7 μmol/L, ω3 FA supplementation induced an improvement in cognitive performance, as assessed by the MMSE score (p = 0.033), and dementia, as measured by the "Clinical Dementia Rating Scale Sum of Boxes" (CDRsob, p = 0.009) compared to placebo [50].

Quinn et al. [51] performed an RCT to evaluate whether DHA may be useful in slowing cognitive decline. DHA supplementation did not affect the ADAS-cog score, which increased by 7.98 points in the DHA group (95% CI, 6.51–9.45) compared with 8.27 points in the placebo group (95% CI, 6.72–9.82, p = 0.41). Similarly, the CDRsob increased by 2.87 points in the DHA group (95% CI, 2.44–3.30) versus 2.93 points in the placebo group (95% CI, 2.44–3.42, p = 0.68). In 53 subjects administered with DHA and 49 with placebo, the rates of brain atrophy were similar. The DHA group showed a mean decline of 24.7 cm^3 (95% CI, 21.4–28.0) in 18 months, representing an annual volume decline of 1.32% (95% CI, 1.14–1.50%), and the placebo group showed a decline of 24.0 cm^3 (95% CI, 20–28) and an annual decline of 1.29% (95% CI, 1.07–1.51%, p = 0.79) [51].

Table 3. Main characteristics and results of the RCTs, published between 2000 and January 2025, investigating the efficacy or safety of ω-3 FA supplementation in patients with AD. All drugs and supplements reported in these studies were administered orally.

References	Study Design	Country	Patients (n)	Sex (F %)	Range Age (Years)	Mean Age (Years)	NHPs	Concomitant Drugs	Follow-Up	Outcomes	Main Results and Limitations	Jadad Score
Faxèn-Irving et al. [44] (2009)	Double-blind, placebo-controlled trial	EU	174 -INT-g: 89 -PL-g: 85	-INT-g: 57 -PL-g: 46	NA	-INT-g: 72.6 -PL-g: 72.9	ω-3 FAs (DHA, EPA)	Acetylcholine esterase inhibitor	12 months	Effects on weight and appetite	ω-3 FA supplements, especially DHA, increased weight gain and appetite compared to placebo ($p < 0.01$). No correlation between APOE ε4 allele and the levels of ω-3 FAs was found. Limitations: lack of food intake data.	4
Faxèn-Irving et al. [45] (2013)	Double-blind, placebo-controlled trial	EU	174 -INT-g: 89 -PL-g: 85	-INT-g: 57 -PL-g: 46	NA	-INT-g: 72.6 -PL-g: 72.9	ω-3 FAs (DHA, EPA)	Acetylcholine esterase inhibitor	12 months	Impact on TTR levels	ω-3 FA supplementation increased plasma TTR levels in treated patients compared to placebo ($p = 0.04$). No changes in TTR levels were observed in CSF. Limitations: TTR analyses in CSF were performed only in a subgroup of patients and only at 6 months follow-up.	3
Freund- Levi et al. [46] (2009)	Double-blind, placebo-controlled trial	EU	35 -INT-g: 18 -PL-g: 17	-INT-g: 44 -PL-g: 30	NA	-INT-g: 72.2 -PL-g: 68.3	ω-3 FAs (DHA, EPA) and vitamin E	Acetylcholine esterase inhibitor	6 months	Impact on inflammatory markers in both CSF and plasma	ω-3 FAs did not influence inflammatory markers in CSF or plasma and the biomarkers of dementia. Limitations: a short treatment duration.	4
Freund- Levi et al. [47] (2014)	Double-blind, placebo-controlled trial	EU	37 -INT-g: 17 -PL-g: 20	40.5	NA	70	ω-3 FAs (DHA, EPA)	Acetylcholine esterase inhibitor	6 months	Impact on oxidative stress and systemic inflammatory biomarkers	ω-3 supplementation did not impact oxidative stress and COX-mediated inflammatory markers. Limitations: absence of a healthy control group and small sample size.	4
Freund-Levi et al. [48] (2008)	Double-blind, placebo-controlled trial	EU	174 -INT-g: 89 -PL-g: 85	-INT-g: 57 -PL-g: 46	NA	-INT-g: 72.6 -PL-g: 72.9	ω-3 FAs (DHA, EPA)	Acetylcholine esterase inhibitor, antidepressants, neuroleptics, and herbal medication	12 months	Impact on psychiatric and behavioural symptoms, functional ability, and possible association with APOE genotype	ω-3 FAs led to possible positive effects on depressive manifestation. In APOE ε4 carriers, it appears to reduce agitation in treated patients compared to placebo ($p = 0.006$). Limitations: low dose of ω-3.	4
Freund-Levi et al. [49] (2014)	Double-blind, placebo-controlled trial	EU USA	33 -INT-g: 18 -PL-g: 15	NA	NA	NA	ω-3 FAs (DHA, EPA)	Acetylcholine esterase inhibitor	6 months	Evaluation of ω-3 levels on the CSF profile	Supplementation with ω-3 FAs, particularly DHA, altered plasma and CSF levels of NHPs in the INT-g compared to placebo ($p < 0.01$). Limitations: lack of determination of the DHA amount retroconverted to EPA in plasma or CSF.	4
Quinn et al. [51] (2010)	Double-blind, placebo-controlled trial	USA	402 -INT-g: 238 -PL-g: 164	52.2 -INT-g: 47.1 -PL-g: 59.8	NA	76	DHA	Cholinesterase inhibitor and memantine	18 months	Effectiveness on AD progression	DHA supplementation did not slow cognitive decline. Limitations: many participants did not finish the study.	5
Tomaszewski et al. [52] (2020)	Placebo-controlled trial	USA	275 -INT-g: 161 -PL-g: 114	NA	NA	NA	DHA	NA	18 months	Impact of APOE ε4/ε4 genotype on plasma DHA, EPA, and AA levels and hippocampal volume	The reduced DHA/AA and EPA/AA ratios in APOE ε4/ε4 carriers impaired the effectiveness of DHA supplementation in contrast with APOE ε4/ε4 non-carriers ($p = 0.048$). Limitations: small sample size.	1
Nolan et al. [53] (2022)	Double-blind, placebo-controlled trial	EU	57 -INT-g: 38 -PL-g: 19	63.2 -INT-g: 65.8 -PL-g: 57.9	>65	-INT-g: 78.63 -PL-g: 79.74	Fish oil + carotenoids + vitamin E	NA	12 months	Impact on AD progression	INT-g showed a lower decline in AD severity and progression than individuals taking placebo ($p < 0.001$). Limitations: small sample size.	5
Lin et al. [54] (2022)	Multicenter, double-blind, placebo-controlled trial	Asia	163 -G1 (DHA): 41 -G2 (EPA): 40 -G3 (DHA + EPA): 42 PL-g: 40	-G1 (DHA): 12 -G2 (EPA): 13 -G3 (DHA + EPA): 15 PL-g: 15	65–94	-G1 (DHA): 78.95 -G2 (EPA): 77.80 -G3 (DHA + EPA): 76.73 PL-g: 78.10	DHA, EPA, DHA + EPA	NA	24 months	Effects on cognitive, functional, depressive symptoms, and circulating inflammatory cytokines levels	ω-3 had no beneficial effects on patients with cognitive impairment. Limitations: small sample size.	4

Abbreviations: AA, arachidonic acid; AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; COVID-19, coronavirus disease 2019; COX, cyclooxygenase; CSF, cerebrospinal fluid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EU, Europe; FAs, fatty acids; G1, group 1; G2, group 2; G3, group 3; INT-g, integration group; NA, not available; NHPs, Natural Health Products; PL-g, placebo group; TTR, transthyretin; USA, United States of America; ω-3 FAs, omega-3 fatty acids; ω-3 PUFAs, omega-3 polyunsaturated fatty acids.

3.4. Micronutrient Supplementation in AD

A growing body of evidence suggests that, in addition to ω-3 FAs, E, C, and B group vitamins, choline, uridine, and other micronutrients may play a role in AD progression [55,56]. Consequently, several studies have focused on the potential to enhance the structures and functions of synapses and neurons [57,58]. Table 4 reports the main characteristics of the reviewed RCTs regarding micronutrient supplementation in AD.

Souvenaid is a dietary supplement with a patented formulation (Fortasyn Connect™) [59] that contains a combination of ω-3 FA (DHA and EPA), uridine monophosphate, choline, phospholipids, selenium, B, C, and E vitamins, and folic acid, useful to improve synapse formation and activities and correlated to cognitive functions and decline [60–62].

Several studies have been conducted to evaluate the impact of administering 125 mL of this oral formulation once daily on AD progression, each with different primary endpoints.

Analyzing the results of three RCTs, Rijpma et al. [63] found that 12 to 24 weeks of supplementation with Souvenaid significantly increased the plasma and/or erythrocyte levels of several micronutrients recognized to be decreased in AD patients, such as uridine, choline, selenium, folate, vitamins B6, B12, and E, and DHA and EPA (all, $p < 0.001$), thus supporting the associated beneficial effects on AD management [63].

Some evidence suggests that the patient body mass index (BMI) may play a crucial role in the manifestation of the therapeutic effects of the supplement. Indeed, a secondary analysis of RCTs, conducted by Kamphuis et al. [64], showed that BMI was a significant factor in response to Souvenaid treatment ($p = 0.05$). Stratifying the study population according to mean BMI (26.2 kg/m^2), an improvement in activities assessed by the "Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale" was reported in the low BMI subgroup compared to the placebo ($p = 0.04$), while the higher BMI subgroup showed no improvement. These data suggest that a lower BMI may be associated with the beneficial effects of Souvenaid [64].

Scheltens et al. [61,65,66] conducted three studies to test the tolerability and efficacy of Souvenaid in AD patients. They found no significant differences in synaptic function, as assessed by the analysis of cerebral glucose metabolism using 18F-fluorodeoxyglucose [(18F) FDG] positron emission tomography (PET), between the placebo group and the group treated with Souvenaid for 24 weeks [61]. However, a significant improvement in the "delayed verbal recall" task ($p = 0.021$) was observed in patients who received the supplementation [65]. Moreover, based on the "Neuropsychological Test Battery (NTB)", Scheltens et al. [66] reported a significant enhancement in the cognitive activity of patients who received supplementation compared to the control group ($p = 0.023$) [66]. On the contrary, Soininen et al. [67] found no significant difference in NTB scores between the group that received the supplement and the control group ($p = 0.166$), although differences were observed in hippocampal atrophy and AD progression. Similarly, Shah et al. [68] found a comparable cognitive decline, as assessed by the "ADAS-cog", with no statistically significant differences between the two groups, highlighting the ineffectiveness of the Souvenaid treatment in patients with mild-to-moderate AD [68].

With regard to the tolerability of Souvenaid, the study conducted by Olde Rikkert et al. [69] showed that, even with high treatment adherence (≥95%), the adverse events (AEs) reported were generally mild and not always related to supplements [69].

Planas et al. and Laque et al. [70,71] investigated the impact of nutritional supplements containing micronutrients on weight variation in patients, yielding contrasting results. Planas et al. found no significant weight loss variation in patients supplemented with a 250 mL energy-dense, protein-rich liquid compared to the placebo group ($p = 0.590$) [70]. In contrast, Laque et al. observed weight gain in patients administered with a protein formulation called "Clinutren", compared to the control group (71.4% vs. 41.8%). However, both studies found no efficacy in the supplements administered in slowing cognitive decline [71].

Table 4. Main characteristics and results of the RCTs, published between 2000 and January 2025, investigating the efficacy or safety of nutritional supplements in patients with AD. All drugs and supplements reported in these studies were administered orally.

References	Study Design	Country	Patients (n)	Sex (F %)	Range Age (Years)	Mean Age (Years)	NHPs	Concomitant Drugs	Follow-Up	Outcomes	Main Results and Limitations	Jadad Score
Scheltens et al. [61] (2019)	Double-blind, single centre	EU	50 -INT-g: 25 -CTR-g: 25	46 -INT-g: 48 -PL-g: 44	50–85	-INT-g: 65 -PL-g: 66	Fortasyn Connect (Souvenaid)	NA	24 weeks	Impact on cognitive function	No differences were found between the INT-g and PL-g. Limitations: short duration of the study.	3
Scheltens et al. [65] (2010)	Multicenter, double-blind, controlled trial	EU USA UK	212 -INT-g: 106 -CTR-g: 106	-INT-g: 49 -CTR-g: 51	-INT-g: 54–87 -CTR-g: 52–92	-INT-g: 74.1 -CTR-g: 73.3	Fortasyn Connect (Souvenaid)	NA	12 weeks	Impact on cognitive performance	Patients with mild AD show improvements in memory, particularly in delayed verbal recall ($p = 0.021$). Limitations: short duration of the study.	3
Scheltens et al. [66] (2012)	Multi-country, double-blind, parallel-group trial	EU	259 -INT-g: 130 -CTR-g: 129	51 -INT-g: 47.7 -CTR-g: 50.4	-INT-g: 55–89 -PL-g: 51–88	-INT-g: 74.4 -CTR-g: 73.2	Fortasyn Connect (Souvenaid)	NA	24 weeks	Evaluation of efficacy and tolerability	Souvenaid is well tolerated and has a positive influence on cognitive function ($p = 0.023$). Limitations: small sample size, no AD biomarker evaluation.	5
Soininen et al. [67] (2017)	Multicenter, double-blind, parallel-group trial	EU	311 -INT-g: 153 -CTR-g: 158	INT-g: 47 CTR-g: 54	-INT-g: 50–86 -CTR-g: 52–84	-INT-g: 71.3 -CTR-g: 70.7	Fortasyn Connect (Souvenaid)	NA	24 months	Impact on cognitive decline and related parameters	No significant effect on cognitive decline was shown. Limitations: small sample size and short duration of the study.	4
Shah et al. [68] (2013)	Multicenter, double-blind	USA	527 -INT-g: 265 -CTR-g: 262	-INT-g: 52 -CTR-g: 52	NA	-INT-g: 76.6 -CTR-g: 76.9	Fortasyn Connect (Souvenaid)	Acetylch olinesterase inhibitors or memantine	24 weeks	Evaluation of efficacy and tolerability	Souvenaid is safe and well tolerated. No changes in cognitive function and functional abilities were shown.	5
Planas et al. [70] (2004)		EU	44 -INT-g: 23 -CTR-g: 21	-INT-g: 52.17 -CTR-g: 57.14	NA	-INT-g: 72.52 -CTR-g: 76.71	Nutritional supplements with micronutrient enhancement	NA	6 months	Effects on weight and AD progression	No benefits on AD progression were shown. Limitations: short treatment period.	1
Lauque et al. [71] (2004)		EU	91 -INT-g: 46 -CTR-g: 45	NA	65–92	79 -INT-g: 79.52 -CTR-g: 78.11	Nutritional supplements containing proteins, vitamins, minerals, and nutrients	NA	-Follow-up 1: 3 months -Follow-up 2: 6 months	Impact on body composition and weight, nutritional status, and cognitive functions	An increase in body weight and fat mass was demonstrated in INT-g, but no effect on cognition or biological markers was shown. Limitations: short duration of the study, small sample size, and limited number of follow-ups.	3
Levak et al. [72] (2024)	Multicentre	EU	93 -Lifestyle intervention-g: 32 -Lifestyle intervention + medical food: 31 -PL-g: 30	-Lifestyle intervention-g: 21 -Lifestyle intervention + medical food: 15 -PL-g: 14	60–85	-Lifestyle intervention-g: 72.4 -Lifestyle intervention + medical food: 72.7 -PL-g: 73.7	Fortasyn Connect	NA	6 months	Effectiveness and feasibility of a multimodal lifestyle intervention, with or without medical food	Dietary intervention improved HDI ($p = 0.042$) and MEDAS ($p = 0.007$). Limitations: Small sample size and use of questionnaires not validated in all EU countries.	1

Abbreviations: AD, Alzheimer's disease; AE, adverse events; CMRglc, cerebral glucose metabolism; CTR-g, control group; EU, Europe; FDG, fluorodeoxyglucose; HDI, Healthy Diet Index; INT-g, integration group; MEDAS, Mediterranean Diet Adherence Screener; NA, not available; NHPs, Natural Health Products; PET, positron emission tomography; PL-g, placebo group; UK, United Kingdom; USA, United States of America.

3.5. Other Supplementations for AD

Probiotics, minerals, and other NHPs such as inositol and lecithin derivatives have been evaluated as therapeutic approaches for AD patients. Probiotics could slow AD progression by reducing oxidative stress and modulating inflammation by restoring pH balance in the gut microbiota. In addition, probiotics could promote the secretion of the brain-derived neurotrophic factor (BDNF), which is essential for the survival and differentiation of neurons and whose insufficient levels are linked to cognitive disorders, such as memory deficits [73].

Hsu et al. and Akhgarjand et al. [74,75] highlighted the positive effects of probiotics in the modulating levels of the markers of inflammation and oxidative stress in AD patients.

Hsu et al. [74] found an increase in BDNF levels after a supplementation with capsules containing a mixture of five probiotic strains (*B. longum* subsp. *infantis BLI-02*, *B. breve Bv-889*, *B. animalis* subsp. *lactis CP-9*, *B. bifidum VDD088*, and *L. plantarum PL-02*, dosed in equal proportions) compared to the control group ($p = 0.049$). Furthermore, a significant reduction in the biomarkers of oxidative stress such as malondialdehyde (MDA) and protein carbonyl (PCC) ($p = 0.043$) and IL-1β levels ($p = 0.041$) was demonstrated in the group receiving supplementation. Moreover, there was an increase in the activity of the antioxidant enzyme superoxide dismutase in the 12-week treatment period ($p = 0.012$). These data suggest that probiotics could help counteract the AD-related oxidative stress [74].

Akhgarjand et al. [75] studied the effects of *Bifidobacterium longum* (*B. longum*) and *Lacticaseibacillus rhamnosus* (*L. rhamnosus*) supplementation on the modulation of the gut microbiota and on the immune response in AD patients. The results revealed an increase in serum glutathione levels in patients treated with *B. longum* ($p < 0.0001$) compared with the placebo ($p < 0.0001$) and *L. rhamnosus* groups ($p = 0.009$). In the *L. rhamnosus*-treated group, there was a significant reduction in the levels of the oxidant compound, that is, 8-hydroxy-2′-deoxyguanosine ($p < 0.0001$) compared to placebo ($p < 0.0001$) and *B. longum* ($p < 0.0001$) and in the levels of the inflammatory marker TNF-α ($p < 0.0001$) compared with the *B. longum* ($p = 0.65$) and placebo groups ($p < 0.0001$). Probiotic supplementation also led to increased levels of IL-10, with a more significant effect in the *L. rhamnosus*-treated group ($p < 0.0001$). Furthermore, both probiotic-treated groups showed improvements in patients' physical activity and quality of life [75].

Tamtaji et al. [76] investigated the combined effects of probiotic and selenium supplementation on cognitive function, markers of inflammation, oxidative stress, metabolic status, and gene expression-related insulin metabolism and lipid regulation as well as inflammation in AD patients. Results indicated that probiotic/selenium co-administration reduced TNF-α gene expression ($p = 0.005$) and increased the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) ($p = 0.002$) and the low-density lipoprotein receptor (LDL-R) ($p = 0.003$), genes involved in lipid metabolism, when compared with selenium supplementation alone or placebo. In contrast, the expression of IL-8 and transforming growth factor beta (TGF-β) did not change. In addition, the combined administration of probiotics and selenium led to significant improvements in the MMSE score ($p < 0.001$), outweighing the effects of selenium alone [76].

Similarly to what was reported by Hsu et al. [74], Foroumandi et al. [77] found that fenugreek seed supplementation significantly reduced serum MDA levels in the intervention group ($p < 0.001$), while the placebo group had higher MDA levels ($p < 0.001$). In addition, this supplementation caused a significant increase in the serum total antioxidant capacity levels ($p < 0.001$), whereas systolic and diastolic blood pressure were significantly reduced ($p < 0.001$) [77].

As selenium is essential for various brain activities, and low levels of this mineral are correlated with an increased rate of cognitive decline, Cardoso et al. [78] evaluated

the effects of sodium selenate supplementation on macroscopic AD-related symptoms. In particular, researchers showed that the use of this supplementation resulted in a significant increase in serum selenium concentration ($p < 0.01$) and central nervous system uptake ($p < 0.05$) compared to the placebo group, leading to a marked improvement in cognitive function among the enrolled patients. Further studies should evaluate the tolerability of selenium use because of recent findings showing an increase in all-cause mortality related to selenium supplementation [78].

Morè et al. and Sallowey et al. [79,80] evaluated the efficacy and safety of lecithin-derived phosphatidylserine (PS) plus phosphatidic acid (PA), and scyllo-inositol (ELND005) in AD patients, respectively. Morè et al. [79] reported that the use of PS + PA significantly improved memory. Additionally, approximately half of the participants treated with these supplements reported an improvement in general conditions, compared to 26.3% in the placebo group ($p = 0.084$). In contrast, Salloway et al. [80] assessed the safety of administering 250 mg of ELND005 in AD patients but found no significant differences in efficacy between the treatment and placebo groups, as measured by the NTB and ADCS-ADL. The main characteristics and results of the aforementioned RCTs are shown in Table 5.

Table 5. Main characteristics and results of the studies, published between 2000 and January 2025, investigating the efficacy or safety of probiotics, minerals, and other NHPs in patients with AD. All drugs and supplements reported in these studies were administered orally.

References	Study Design	Country	Patients (n)	Sex (F %)	Range Age (Years)	Mean Age (Years)	NHPs	Concomitant Drugs	Follow-Up	Outcomes	Main Results and Limitations	Jadad Score
Hsu et al. [74] (2023)	Double-blind, active-controlled trial	Asia	32 -INT-g: 16 -PL-g: 16	-INT-g: 75 -PL-g: 50	50–90	-INT-g: 75.4 -PL-g: 75.8	*Bifidobacterium longum subspecies infantis BLI-02*, *Bifidobacterium breve Bv-889*, *Bifidobacterium animalis subspecies lactis CP-9*, *Bifidobacterium bifidum VDD088*, and *Lactobacillus plantarum PL-02*	DPZ or Riv and memantine	12 weeks	Effect on BDNF levels, inflammatory and oxidative stress biomarkers, and cognitive performance	Probiotic supplementation increased BDNF ($p = 0.049$) and antioxidant levels ($p = 0.043$) and reduced levels of inflammatory biomarkers ($p = 0.041$). Limitations: lack of evaluation of all the biomarkers of AD required by updated guidelines.	3
Akhgarjand et al. [75] (2024)	Double-blind, placebo-controlled trial	Asia	90 -Lacticaseibacillus rhamnosus-g: 30 -Bifdobacterium longum-g: 30 -PL-g: 30	-Lacticaseibacillus rhamnosus-g: 33.3 -Bifdobacterium longum-g: 33.3 -PL-g: 33.3	NA	-Lacticaseibacillus rhamnosus-g: 67.93 -Bifdobacterium longum-g: 67.90 -PL-g: 67.77	*Lacticaseibacillus rhamnosus* and *Bifdobacterium longum*	NA	12 weeks	Impact on oxidative stress and inflammation markers	Probiotic supplementation leads to a decrease in serum LPS levels, inflammation, and oxidative stress ($p < 0.0001$). Furthermore, it has positive effects on quality of life and physical activity.	4
Tamtaji et al. [76] (2019)	Double-blind, placebo-controlled trial	Asia North America	79 -Selenium-g: 26 -INT-g: 27 -PL-g: 26	NA	NA	-Selenium-g: 78.8 -INT-g: 76.2 -PL-g: 78.5	Selenium, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*	NA	12 weeks	Impact on cognitive performance and metabolism	Co-supplementation improved cognitive function ($p < 0.001$). Limitations: patient compliance was not assessed.	5
Foroumandi et al. [77] (2023)	Double-blind, placebo-controlled trial	Asia	82 -INT-g: 41 -PL-g: 41	-INT-g: 65.9 -PL-g: 65.9	NA	-INT-g: 72.05 -PL-g: 71.12	Fenugreek seed extract	DPZ and sertraline	4 months	Impact on memory, depressive symptoms, quality of life, blood pressure, and serum levels of oxidative indices	Fenugreek seed extract supplementation reduced serum MDA levels, systolic and diastolic BP, and it increased serum TAC levels, memory status, and quality of life ($p < 0.001$). Limitations: small sample size, short duration of the study, and absence of patients with advanced AD.	5
Cardoso et al. [78] (2019)	Double-blind, placebo-controlled trial	Oceania	40 -Nutritional-g: 10 -Supranutritional-g: 20 -PL-g: 20	58.3 -Nutritional-g: 50 -Supranutritional-g: 75.9 -PL-g: 66.7	NA	70.2 -Nutritional-g: 73.4 -Supranutritional-g: 69.5 -PL-g: 68.7	Sodium selenate	Acetylcholine esterase inhibitor	24 weeks	Efficacy and tolerability of selenium CNS concentration	Supplementation with high-dose sodium selenate was well tolerated, and increased selenium levels in the central nervous system ($p < 0.001$) were associated with improved cognitive function ($p< 0.001$). Limitations: small sample size.	3
Morè et al. [79] (2014) (study 2)	Double-blind, placebo-controlled trial	Asia	96	63.5	50–90	75.3 years	Soy lecithin- derived PS + PA	NA	2 months	Efficacy on memory, cognitive daily functioning, and mood	Supplementation reduced cognitive impairment and improved memory. Additionally, short-term supplementation showed benefits on emotional state, mood, and self-reported general condition. However, while promising, these results did not reach statistical significance. Limitations: small sample size.	3
Salloway et al. [80] (2011)	Multicenter, double-blind, placebo-controlled, dose-ranging phase 2 study	USA	351 -INT-g1: 88 -INT-g2: 89 -INT-g3: 91 -PL-g: 83	-INT-g1: 58 -INT-g2: 53.9 -INT-g3: 56 -PL-g: 56.6	NA	-INT-g1: 73.4 -INT-g2: 73.4 -INT-g3: 72.2 -PL-g: 73.4	Scyllo-inositol (ELND005)	Acetylch olinesterase inhibitors or memantine	78 weeks	Evaluation of safety, efficacy, and tolerability	The 250 mg dose of ELND005 is safe and well tolerated. No differences in NTB or ADCS-ADL were found between treated and placebo groups ($p = 0.049$). Limitations: small sample size and lack of statistical correction for multiple analyses.	3
Sun J et al. [81] (2017)		Asia	162 -INT-g: 97 -PL-g: 65	-INT-g: 46.4 -PL-g: 46.2	NA	-INT-g: 73.3 -PL-g: 74.8	Betaine	NA	6–48 months	Association between malnutrition and Hcy levels and impact on AD progression	Betaine administration restored Hcy levels and modulated factors that promote AD progression. Furthermore, betaine appeared to improve some ADAS-Cog parameters ($p < 0.05$). Limitations: small sample size.	1

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; BDNF, brain-derived neurotrophic factor; BP, phosphatidyl bisphosphate; CNS, central nervous system; CSF, cerebrospinal fluid; DPZ, donepezil; ELND005, scyllo-inositol; Hcy, homocysteine; HHcy, hyperhomocysteine; INT-g, integration group; LPS, lipopolysaccharide levels; MDA, malondialdehyde; NA, not available; NHPs, Natural Health Products; NTB, Neuropsychological Test Battery; PA, phosphatidic acid; PL-g, placebo group; PP2Ac, protein phosphatase 2A catalytic subunit; PS, phosphatidylserine; Riv, rivastigmine; TAC, total antioxidant capacity; USA, United States of America.

4. Discussion

The lack of therapies capable of managing the full spectrum of AD-related symptoms, only being able to slow down disease progression [82], underscores the need to explore other pharmacologically active compounds, such as NHPs, that could improve the quality of life and prognosis of AD patients.

The RCTs reviewed here examined the potential of NHPs as complementary or alternative therapeutic options in AD.

We analyzed 34 RCTs published in the last two decades that evaluated the effects that vitamins [26–28,31,32,37–39], ω-3 FAs [44–49,51–54], micronutrients [61,65–68,70–72], and other forms of NHP supplementation [74–81] might have on the pathogenesis, progression, and treatment of AD symptoms.

An improvement in disease management was reported in 50% of the studies [28,31,37, 38,45,53,65–67,72,74–79,81]. Adverse reactions likely attributable to the used NHPs were found in 5.8% of the studies [26,27].

Considering that AD is characterized by a persistent neuroinflammation caused by an increased release of inflammatory and oxidative markers (e.g., TNF-α, IL-6, F2-isoprostanes, and MDA), the effectiveness of NHPs, both as monotherapy and in combination with conventional therapies, in reducing the rate of these stressors has been investigated.

Seven of the reviewed RCTs address this issue [28,37,46,47,74,75,77]. Akhgarjand et al. and Chen et al. reported a reduction in TNF-α and IL-6 levels in patients treated with the probiotic *L. rhamnosus* or vitamin B12 (50 μg) + folic acid (1.2 mg), respectively, compared to the control groups [28,75]. Chen et al. suggested that although a reduction in inflammation was observed after 6 months of treatment, longer follow-up studies are needed to assess the effect on cognitive performance [28]. In contrast, Freund-Levi et al. investigated the use of ω-3 FAs (DHA and EPA) in two consecutive studies and found no reduction in TNF-α and IL-6, even when using increasing dosages in the second study compared to the first [46,47]. These authors also found no reduction in F2-isoprostane levels [47], which, on the contrary, were reported to decrease by 19% by Galasko et al., studying the effect of an E/C/ALA regimen with CoQ [37]. Another marker of oxidative stress (MDA) was reported to decrease in the studies by Foroumadi et al. after a treatment with fenugreek seed and by Hsu et al. who investigated the effects of a mixture of five probiotic strains [74,77].

According to a 2020 meta-analysis, probiotic supplementation decreased inflammation in patients with AD and mild cognitive impairment [83]. In contrast, the study by Tamtaji et al. [76] found that the co-supplementation of probiotics and selenium improves cognitive function but has no effect on the biomarkers of inflammation. Other studies also did not attribute a beneficial effect of probiotics on inflammation status [84]. The study by Agahi et al. [84] showed no changes in the levels of IL-6 and IL-10 in 48 AD patients taking probiotic supplementation. The different severity of the disease in the participants could explain the difference in studies.

Indeed, as the severity of the disease increases, symptoms may become more difficult to improve. Consequently, as probiotics may be more effective in the early and less severe stage of the disease, the frequent lack of information on the stage of AD prevents a fair comparison between studies.

With regard to ω-3 FA supplementation, all RCTs found no benefit for the management of chronic inflammation, as well as the preservation of cognitive function and memory, and the counteraction of disability in AD patients. Freund-Levi et al. found an increase in CSF ω-3 levels after the administration of 2.3 g of ω-3 FAs (high in DHA) [49], but neither Quinn et al. using 2 g of DHA [51] nor Lin et al. using 0.7 g of DHA, 1.6 g of EPA or 0.8 + 0.35 g of DHA + EPA [54] observed a slowing of cognitive decline. However, the authors pointed out that the number of patients that completed the study in the first case,

as well as the number of patients enrolled in the second case, was insufficient to support this evidence.

Supplements containing ω-3 FAs [45], as well as vitamin D [31], may play a neuroprotective role by slowing Aβ peptide formation and its accumulation in the brain. Furthermore, Stein et al. observed an increase in the DAD score after vitamin D administration, regardless of dosage [32].

While the evidence in favor of vitamin D use seems well established, the evidence for other types of vitamins remains conflicting.

Thomas et al. [39] highlighted the ineffectiveness of 2000 IU of vitamin E daily compared to traditional drugs (DPZ and Riv) in improving cognitive function. In contrast, Dysken et al., using the same dosage in a much larger population, suggested that vitamin E might be more effective in slowing cognitive decline than treatment with memantine alone or in combination with vitamin E [38].

Both Aisen et al. [26] and Sun et al. [27] did not find an improvement in cognitive symptoms in patients treated with ChE inhibitors using vitamins B12, B6, and folic acid, although a significant reduction in plasma Hcy levels was recorded. In addition, the different incidence of depressive disorders (68% in the active group vs. 18% in the placebo group) [26] and the occurrence of delirium (8.9% in the treated group, vs. 2.3% in the control group) [27] highlight the need to better evaluate the safety and tolerability of B vitamins in AD patients. The results of these two RCTs are not confirmed by the available literature, which, on the contrary, reports considerable evidence supporting an increased likelihood of depressive disorders due to deficiencies of these vitamins [85].

The results of RCTs focused on Souvenaid and other oral liquid formulations containing micronutrients do not justify the introduction of these NHP into clinical practice. In fact, although rather large RCTs [65–68,71,72] have analyzed the effects of these supplements with different follow-ups (24 months [67], 6 months [66,68,71,72], and 3 months [65]), only the study by Soininen et al., who enrolled patients with prodromal AD, showed a reduction in hippocampal atrophy, a smaller increase in ventricular volume, and an improvement in cognitive performance [67].

Although the mechanism by which selenium exerts its antioxidant effect on the brain has not yet been fully understood [86], several pieces of evidence suggest that increasing its concentration in the CNS could be a key factor behind some improvement in disease symptoms [78]. Increasing selenium levels in the CNS, therefore, seems to be a possibility to manage the oxidative stress that characterizes AD. For example, Tamtaji et al. observed an increase in MMSE scores in patients treated with 200 μg of selenium and probiotics. However, it is important to note that the best results in terms of cognitive performance and a reduction in oxidative stress biomarkers were observed in the group treated with both selenium and probiotics, rather than in the group receiving only selenium [76]. This highlights the need for further investigations to clarify the effects of this micronutrient in AD patients, both as monotherapy and, above all, in combination with other NHPs known for their anti-inflammatory and antioxidant properties.

5. Conclusions

The strongest evidence of improved cognitive function and reduced neuroinflammatory status in AD patients appears to be associated with the supplementation of vitamin D, selenium, and probiotics. However, as these NHPs may produce distinct benefits, but have never been comprehensively studied, it may be useful to conduct RCTs involving their co-administration to prevent and improve the prognosis of AD. The RCTs examined, despite having the same main objective, showed conflicting results. This may be due to high heterogeneity in terms of sample size, study duration, stage of AD at the time of

enrolment, and inter-individual differences related to comorbidities and the drugs used to treat them.

Furthermore, no RCTS explored drug–drug interactions between NHPs and conventional drugs for AD treatment, which could lead to unfavorable efficacy and safety outcomes.

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Abbreviations

[(18F) FDG]	18F-fluorodeoxyglucose
[25 (OH)D]	25-hydroxyvitamin D
8-iso-PGF2α	8-iso-prostaglandin F2 α
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study–Activities of Daily Living
AEs	adverse events
APOE	apolipoprotein
Aβ	amyloid-β
B. longum	*Bifidobacterium longum*
BDNF	brain-derived neurotrophic factor
BMI	body mass index
CDRsob	Clinical Dementia Rating Scale Sum of Boxes
ChE	cholinesterase
CNS	central nervous system
CoQ	coenzyme Q
COX	cyclooxygenase
CSF	cerebrospinal fluid
CTs	clinical trials
DAD	Disability Assessment for Dementia
DDIs	drug–drug interactions
DHA	docosahexaenoic acid
DPZ	donepezil
E/C/ALA	vitamin E, vitamin C, and α-acid lipoic
ELND005	scyllo-inositol
EPA	eicosapentaenoic acid
FDA	Food and Drug Administration
Hcy	homocysteine
IL	interleukin
L. rhamnosus	*Lacticaseibacillus rhamnosus*
LDL-R	low-density lipoprotein receptor
MADRS	Montgomery Åsberg Depression Scale
MDA	malondialdehyde
MESH	Medical Subject Heading

MMSE	Mini-Mental State Examination
NFTs	neurofibrillary tangles
NHPs	Natural Health Products
NMDA	N-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
PA	phosphatidic acid
PCC	protein carbonyl
PET	positron emission tomography
PPAR-γ	peroxisome proliferator-activated receptor gamma
PRISMA	Preferred Reporting Item for Systematic Review and Meta-Analyses
PS	phosphatidylserine
RCTs	randomized clinical trials
RIV	rivastigmine
SAH	S-adenosylhomocysteine
SAM	S-Adenosyl methionine
sIL-1RII	soluble interleukin-1 receptor type II
SSRIs	selective serotonin reuptake inhibitors
TGF-β	transforming growth factor beta
TNF-α	tumor necrosis factor-α
TTR	transthyretin
vit	vitamin
ω-3	FAs omega-3 fatty acids

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