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Alzheimer's Disease Risk and Progression: The Role of Nutritional Supplements and their Effect on Drug Therapy Outcome

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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly population. Despite significant advancements in understanding the genetic and molecular basis of AD, the pathology still lacks treatments that can slow down or reverse the progression of cognitive deterioration. Recently, the relationship between nutrient deficiency and dementia onset has been highlighted. AD is in fact a multifactorial pathology, so that a multi-target approach using combinations of micronutrients and drugs could have beneficial effects on cognitive function in neurodegenerative brain disorders leading to synaptic degeneration. Primarily, this review examines the most recent literature regarding the effects of nutrition on the risk/progression of the disease, focusing attention mostly on antioxidants agents, polyunsaturated fatty acids and metals. Secondly, it aims to figure out if nutritional supplements might have beneficial effects on drug therapy outcome. Even if nutritional supplements showed contrasting evidence of a likely effect of decreasing the risk of AD onset that could be studied more deeply in other clinical trials, no convincing data are present about their usefulness in combination with drug therapies and their effectiveness in slowing down the disease progression.

Keywords: Acetylcholinesterase inhibitors, Alzheimer, antioxidant, metals, nutritional supplements, PUFAs.

INTRODUCTION

Alzheimer's disease (AD) represents 45-60% of dementia cases [1]. It affects an estimated 20-30 million people worldwide and more than 50% are over 85 years [2, 3]. Histopathological features in the AD brain include synaptic and neuronal loss, extracellular deposition of amyloid β (Aβ) peptide in the formation of senile plaques, and neurofibrillary tangles due to the intraneuronal hyper-phosphorylated tau protein precipitation [4]. Clinically, AD is characterized by multiple domaincognitive involvement with a progressive and irreversible deterioration. Currently, no satisfying advance in understanding the cause of this disease is available and AD still lacks disease-modifying treatments that can slow down or reverse the progression of cognitive deterioration.

The relationship between nutrient deficiency and dementia onset has been recently highlighted. Analysis of various endogenous and exogenous protective factors in the serum of AD patients detected a significant decrease in glutathione peroxidase levels, vitamin E, vitamin C, carotenoids, zinc, transferrin and albumin [5-8]. This could reflect an incorrect diet.

As suggested by recent reviews, a nutritional approach to counteract onset and progression of neurodegenerative disease might be recommended [8-19], but is still under discussion.

The purpose of this paper is to give an overall view of the role of food-derived nutrients and compounds, such as antioxidants, unsaturated fatty acids and metals on AD patients. Secondly, it aims to figure out how they influence mental health and cognition as well as therapy outcome, updating the latest findings and ideas on these topics already present in current available reviews.

ANTIOXIDANT AGENTS

The nervous system is more vulnerable to oxidative stress than other systems. The higher brain energy demand, in fact, leads to increased oxygen consumption, which in turn results in an excessive production of reactive oxygen species. Moreover, the brain is relatively poor in antioxidants and its membranes are more susceptible to free radical attack because rich in polyunsaturated fatty acids [20]. Since oxidative stress and inflammation appear to be involved in brain aging and in neurodegenerative diseases [21], it is theorized that an increased intake of antioxidants could be effective in preventing or ameliorating these changes.

The use of antioxidant agents to prevent neuronal damage or to delay its progression is currently studied at both experimental and clinical stages (Table **1**). Several antioxidants are able to protect cultured neurons against Aβ toxicity, as well as against oxidative stress produced by other important factors involved in the disease pathogenesis [22]. These antioxidants include Vitamin E. Vitamin E is fat-soluble and protects cell membranes from damage by reactive oxygen species such as peroxyl-radicals during fat oxidation. Studies in animal models of neurodegenerative

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Table 1. Summary of nutritional supplements and principal effects in different study models of Alzheimer's disease.

Treatment	Model of Study	Time	Effects/Outcome	Refs.
Vitamin E	Rat	4 months	-Upregulation of genes involved in resistance to oxidative stress counteraction of the effects of fluid percussion injury	[23]
Vitamin E	AD mouse model	1 month	-Decreased brain lipid peroxidation levels -Attenuated learning deficits	[24]
Vitamin E + Vitamin C	Human, elderly population	5 years follow-up	-Reduced prevalence and incidence of AD	[26]
Vitamin E + Vitamin C + β-carotene	Human, meta-analysis		-Lower risk of AD -Vitamin E plays the pivotal role	[28]
Vitamin E ± Vitamin C	Dementia-free community	13 years follow-up	-No delay in dementia or AD incidence	[33]
Vitamin E	Dementia-free community	5.5 years follow-up	-No protective role against dementia	[34]
Vitamin E	Human, MCI patients	3 years	-No affection of disease progression	[35]
Vitamin E	Human, AD patients	6 months	-Cognitive status maintenance, in patients where Vit E lowered oxidative stress status -Detrimental cognitive effects, in patients where Vit E did not affect oxidative stress status	[36]
Fig	AD mouse model	15 months	-Reduction of plasma Aβ(1-40) and Aβ(1-42) -Enhanced activity of antioxidant enzymes in cortex and hippocampus	[40]
Fig	AD mouse model	15 months	-Improvement of cognitive and behavioral deficits	[41]
Resveratrol	Age-related AD mouse model	2 months	-Increased mean life expectancy and life span -Decreased amyloid burden and reduced tau hyper phosphorylation	[45]
Alcohol-free wine	Human, young volunteers	1 week	- the activity of the antioxidant enzymes is not due to the alcohol content in wine but to the polyphenolic composition	[46]
Ginkbo Biloba extract (EGb 761)	Rat	2 weeks	-Cardio protective effect -Inhibition of free radical formation	[47]
Ginkbo Biloba extract (EGb 761)	N2a cell line stably expressing Swedish mutant APP695 and the exon-9 deletion mutant PS1		-Neuroprotective effects (*e.g.* attenuation of apoptosis and direct inhibition of Aβaggregation)	[48]
Ginkbo Biloba extract (EGb 761)	Human	6.1 years follow-up	-Not effective in reducing either the overall incidence rate of dementia or AD incidence	[49]
ω3 fatty acids	Mild to moderate AD patients	6 months	-No effects in the rate of cognitive decline	[125]
ω3 fatty acids	Mild to moderate AD patients	6 months	-Positive effect on weight and appetite	[68]
ω3 fatty acids	Mild to moderate AD patients	6 months	-Blood mononuclear monocytes up-regulation of genes involved in inflammation and neurodegeneration	[128]
ω3 fatty acids	Mild to moderate AD patients	6 months	-No clear effect on free radical-mediated formation of F2-isoprostane or cyclooxygenase-mediated formation of prostaglandin F2α	[63]
ω3 fatty acids	AD mouse model	7 months	-No protection against AD development in high-risk individuals	[129]
ω3 fatty acids	MCI and mild to moderate AD patients	24 weeks	-Improvement in ADAS-cog in MCI patients but not in AD patients	[65]
Souvenaid	Mild AD patients	12 weeks	-Memory improvement (delayed verbal recall)	[120]
Souvenaid	Mild AD patients	24 weeks	-Good tolerance -Improvement of memory performance	[118]
Souvenaid	Mild to moderate AD patients	24 weeks	-No slowing down of cognitive decline -Well tolerated in combination with standard AD medication	[121]
Souvenaid	Mild AD patients	24 weeks	-Preservation of the organization of brain networks	[117]

diseases have demonstrated a significant positive effect of vitamin E in ameliorating neurodegeneration [23, 24]. A 4-month 500 IU/kg vitamin E supplemented diet in rats was able to counteract the effects of fluid percussion injury by upregulating genes involved in resistance to oxidative stress (*e.g.* superoxide dismutase, Sir2) [23]. Similarly, a 4-week vitamin E supplemented diet in Tg2576 mice subjected to repetitive concussive brain injury decreased brain lipid peroxidation levels, attenuated learning deficits and did not lead to the increase of Aβ peptide deposition as in control mice [24].

On the other hand, clinical studies have demonstrated mixed or little evidence for a neuroprotective role of this vitamin [24, 25]. Similarly to most non-enzymatic antioxidants, vitamin E supplementation in humans has shown to be effective only in the case of an evident deficiency. Additionally, recent studies suggested that vitamin E could be more effective in protecting from neurodegenerative disease if combined with other supplementations in both animal models and humans. The Cache County study demonstrated that vitamin E supplementation together with vitamin C, was associated with reduced prevalence and incidence of AD in elderly population [26]. Similar results were obtained by Morris *et al*. [27]. Li *et al*. studied the role of dietary intakes, instead of supplements, of the three most common antioxidants (vitamin E, vitamin C, and β-carotene) on the risk of AD. From the meta-analysis, the authors concluded that antioxidants can lower the risk of AD, with vitamin E exhibiting the most pronounced protective effects [28].

Vitamin E administration proved to be effective also coupled with selegiline (a selective irreversible monoamine oxidase inhibitor type B) in patients with moderate or severe AD, slowing down the progression of the disease in comparison with placebo [29].

Vitamin E is easily tolerated, negative side effects are unusual [30] and a low-dose supplementation combined with other agents is associated with a statistically significant reduction in all-cause mortality [31]. Moreover, it would have a protective effect on the immunological response and on heart diseases as well [32].

Nevertheless, whilst many studies support the idea of a positive role of vitamin E, other clinical trials show the opposite.

A study performed in a 616 people dementia-free community aged 65-105 in the south-eastern US where vitamin supplement use is low, showed that the use of vitamins C and/or E did not delay the incidence of dementia or AD [33]. These results are confirmed by a 5.5-year follow-up of 2969 healthy participants aged > 65, which failed to demonstrate a protective role of vitamin E against the risk of dementia [34]. The same was observed by coupling vitamin E with vitamin C [34]. Additionally, the daily administration of vitamin E (2000UI) for three years did not have any benefit in patients with mild cognitive impairment (MCI) and did not affect the risk of disease progression [35]. On the other hand, the treatment of AD patients with 800UI of vitamin E daily for six months showed interesting results: in subjects where vitamin E lowered oxidative stress, the cognitive status was maintained but not enhanced; in those in whom vitamin E did not prevent oxidative stress, detrimental effects were observed in terms of cognition [36]. So the authors concluded with the suggestion to use vitamin E only after determining its antioxidant effect in each single patient.

Eventually, recent meta-analysis have concluded that supplementation with high doses of vitamin E may not be efficient in preventing chronic degenerative diseases and could even increase mortality [37, 38].

In addition to vitamin E, other compounds present in food were recently suggested to protect against neurodegeneration through an antioxidant mechanism. Among these, the positive role of polyphenols is widely reported in the literature. Polyphenols can in fact cross the blood-brain barrier, scavenge pathological concentrations of reactive oxygen and nitrogen species, and chelate transition metal ions [39]. These chemicals can be found in many plants such as in figs and are responsible for controlling the activity of enzymes and cell receptors, with the role to protect the plant from bacterial and fungal infections and UV radiation damage, thanks to their antioxidant properties. Subash *et al*. have recently studied the role of figs in AD mouse - models. Fig is a classical fruit tree cultivated mostly in the Mediterranean region, and its fruits are the ones containing the highest concentrations of polyphenols, especially proanthocyanidins [40], known to have excellent radical scavenging and antioxidant properties. In their AD mouse model, Subash *et al*. demonstrated positive effects of a 4% fig diet, including a reduction of Aβ (1-40) and Aβ (1-42) content in plasma, an enhanced activity of antioxidant and membrane bound enzymes in cortex and hippocampus [40], and an improvement of cognitive and behavioural deficits [41].

Another high phenol-containing food and promising neuroprotective agent is berry fruit, such as blackberry, black currant, blueberry, strawberry, bilberry, and mulberry [42]. According to what Subash *et al*. summarized in a recent review, the enhancement in motor and cognitive behavioural performance by berries could be due to their direct effect on cell signalling with the consequent improvement of neuronal communication, antioxidant and anti-inflammatory action, calcium buffering, plasticity, stress signalling pathways and inhibition of acetylcholinesterase activity [41].

Among phenol-containing compounds, the importance of red wine in the diet is widely reported in the literature. Red wine contains lower amounts of phenols than fig or berries, but a growing body of evidence shows a putative protective role against neurodegeneration other than cardiovascular disease. Moderate to mild red wine consumption is in fact associated with a decrease risk of late onset AD [43], and resveratrol could be responsible for this beneficial effect because of its anti-inflammatory and antioxidant properties [44]. In a mouse model of age-related AD, Porquet *et al*. demonstrated for the first time an increase in life expectancy in mice treated with a resveratrol-supplemented diet, other than a decrease of cognitive impairment. Moreover, reduced Aβ deposition, activation of non-amyloidogenic pathway (instead of amyloidogenic) and a decrease of tau hyper phosphorylation at serine 396 (marker of disease severity) in

resveratrol-treated mice hippocampus was also observed [45]. Eventually, in a recent paper, Noguer *et al*. demonstrated for the first time the antioxidant activity of an alcohol free red wine in humans, confirming that the activity of antioxidant enzymes (superoxide dismutase, catalase and glutathione reductase) is not due to the alcohol content in wine but to the polyphenol composition [46].

Another natural compound that was thought to be promising is *Ginkgo Biloba*. *Ginkgo Biloba* is a plant extract containing several compounds that may have positive effects on cells within the brain and the body. A major mechanism by which *Ginkgo Biloba* is proposed to exert its effect is by action of multiple antioxidants [47]. More recently, an *in vitro* study indicated that ginkgo extract has an anti-amyloid aggregation effect, suggesting another mechanism whereby *Ginkgo Biloba* may be beneficial in dementia prevention [48]. However, despite the positive *in vitro* effects, the dietary supplement of *Ginkgo Biloba* was found to be ineffective in reducing the development of dementia and AD in older people [49]. The trial, known as the Ginkgo Evaluation of Memory (GEM) enrolled 3069 participants aged 75 or older with normal cognition or MCI. The study excluded patients with dementia. Participants were randomly assigned to receive twice-daily doses of either 120 milligrams of *Ginkgo* extract or an identical-appearing placebo. During the study, 523 participants were diagnosed with dementia, 246 in the placebo group and 277 in the *Ginkgo* group, demonstrating that G*inkgo* did not have any effect in reducing AD disease risk. However, G*inkgo* did not have any adverse effects, including no evidence for increased bleeding risk in persons taking it [49].

ROLE OF SATURATED AND UNSATURATED FATTY ACIDS

Hypercholesterolemia, already known as a risk factor for atherosclerotic disease, may be a contributing factor for the development of AD [50]. The involvement of fatty acid metabolism in neurodegeneration is well established by studies investigating the role of cholesterol levels and of the ratio between saturated and polyunsaturated fatty acids (PUFAs) in the diet. A high saturated fat and cholesterol consumption increases the risk of cardiovascular disease [51]. The same feeding habit has been associated with the development of MCI [52]. On the other hand, a diet rich in PUFAs seems to protect against neurodegenerative diseases, probably because it stimulates neurogenesis [53] and reduces inflammatory response [54, 55]. It is in fact now clear that plaques *per se* are not sufficient to explain the occurrence and development of the disease. Even a normal senile brain can be rich in plaques and yet substantially retain its functions. The difference between a senescent and an AD brain is the presence of inflammatory activity. AD plaques are infiltrated by microglia that produce a large amount of inflammatory substances, responsible for cell dysfunction and death [56] (Table **1**).

In this scenario, a properly balanced intake of ω-3 and ω-6 PUFAs could play an essential role [57]. In this respect, a significant reduction in the ratio ω-3/ω-6 PUFA seems to contribute to the onset of AD [58-60]. The ω-3 PUFAs mainly involved in this process are: α-linolenic acid (ALA, only obtainable from diet), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), that are synthesizable by the desaturation of ALA. EPA is the substrate for the production of anti-inflammatory prostaglandin E3 (PGE3); it competes with arachidonic acid (AA) for incorporation into cell membrane phospholipids, and for the active site on the COX enzymes. This competition, and the resulting formation of PGE3, could result in decreased levels of pro-inflammatory prostaglandin E2 (PGE2) [61]. DHA is largely represented in the brain and is a key player in conferring fluidity to axons and neuronal membranes; this latter effect would favour the processing of APP *via* the non-amyloidogenic pathway. Deficit in dietary ω-3 PUFAs appears to contribute to inflammatory signalling, apoptosis, and neural dysfunction, and it is associated with age-related cognitive decline and neurological disorders [62]. Conversely, a diet rich in saturated fats and ω-6, such as AA contained in red meat, can alter the composition of the neuronal membrane and promote inflammation [16]. The opposite effect can be obtained with a diet rich in vegetables, fruit and fish [16]. Nevertheless, recent *in vivo* analysis in animals and humans about PUFAs supplementation show contrasting results. DHA supplementation in a transgenic mouse model of AD led to an increased DHA brain content that was associated with a reduction in various biomarkers of AD such as amyloid plaques, and Aβ levels and with an improvement of cognitive functions [63]. The same increased DHA was also observed in cerebrospinal fluid in a recent clinical trial consisting in a 6-month supplementation [63], coupled with an inverse correlation with CSF levels of total and phosphorylated tau, and a direct correlation with soluble interleukin-1 receptor type II [63]. However, the authors did not observe any clear effects on free radical-mediated formation F2-isoprostane or cyclooxygenase-mediated formation of prostaglandin F2α in urine [64]. Eventually, a 24-week ω-3 PUFAs monotherapy improved the cognitive portion of the AD Assessment Scale in MCI subjects, but did not have any effects on mild to moderate AD patients [65].

Recently a trial involving 500 subjects studied a mixture of DHA together with choline and uridine [66]. It was observed that the association of these substances facilitated the correct synthesis of the main constituents of the neuronal membrane, in particular phosphatidylcholine, the principal constituent of soya lecithin that is used to control cholesterol. The mixture under examination promotes the synthesis of both phospholipids and proteins that make up the neuronal membrane. In treated animals, it has been seen that membranes stimulate an increase in neuronal activity, thus facilitating the development of synapses. In AD, plaque deposition in the brain destroys synapses and impairs membrane function. Synapse revitalization can therefore be a very promising way to counteract cognitive decline [66].

Regarding safety, in all reported studies, no serious adverse events from PUFAs supplementation occurred [60, 64, 65, 67], indeed, it may positively affect weight and appetite in patients with mild to moderate AD [68].

METALS

Although some authors have in the past criticized the involvement of metals in the development of neurodegenerative

diseases [69], there is experimental evidence showing that dementia is associated with magnesium (Mg) insufficiency [70-73]. Mg is a metal well known for the protective action on brain tissues, although its exact role in neurodegenerative process is still not clear. Yu J. *et al*. in an *in vitro* study demonstrated that decreased total intracellular Mg level by its deprivation impairs cell viability [73]. Moreover, high extracellular Mg($[Mg^{2+}]_o$) stimulates the α-secretase cleavage (non-amyloidogenic) pathway by enhancing retention of Amyloid Precursor Protein (APP) on plasma membrane. The opposite effect is observed with low$[Mg^{2+}]_o$ [73] (Fig. **1**).

In vivo, Mg insufficiency could be caused either by a deficiency or by its depletion [72]. Mg deficiency is the result of a low dietetic intake and/or by a poor ability of the organism to maintain its physiological concentration. Mg depletion, in contrast, is due to the dysregulation in the mechanism controlling Mg metabolism [74, 75]. These insufficiencies could be corrected by increasing Mg intake [74]. An explanation of the phenomenon can be ascribed to aluminium (Al). Numerous studies have revealed the increased presence of Al in brain tissue obtained from autopsies of AD patients [72], indirectly related to intracellular Mg deposits in AD neurons. Al is in fact a neurotoxic metal capable of inhibiting the activity of enzymes that utilize Mg as a cofactor [71], such as choline acetyltransferase, glutamate decarboxylase and alkaline phosphatase [74]. The alteration of these enzymes leads to an injured brain, in terms of malfunction of cholinergic neurons, reduction in glutamatergic neurotransmission, formation of senile plaques and generation of neurofibrillary tangles [74] (Fig. **1**). Another hypothesis involves altered serum protein content (*e.g.* albumin). Altered albumin, in fact, would act by binding Al with greater affinity than Mg, facilitating the transport through the blood brain barrier. This would prevent Mg brain uptake [71]. This is confirmed by the fact that Mg depletion, especially in the hippocampus, is associated with high Al incorporation into brain neurons [72].

Moreover, Mg activates the tubulin-enzyme complex involved in the maintenance of nerve tissue cells [76]. It has been suggested that in Mg-deficiency condition Al takes its place instead. This leads to tubulin inactivation and, consequently, inadequate nerve function [74].

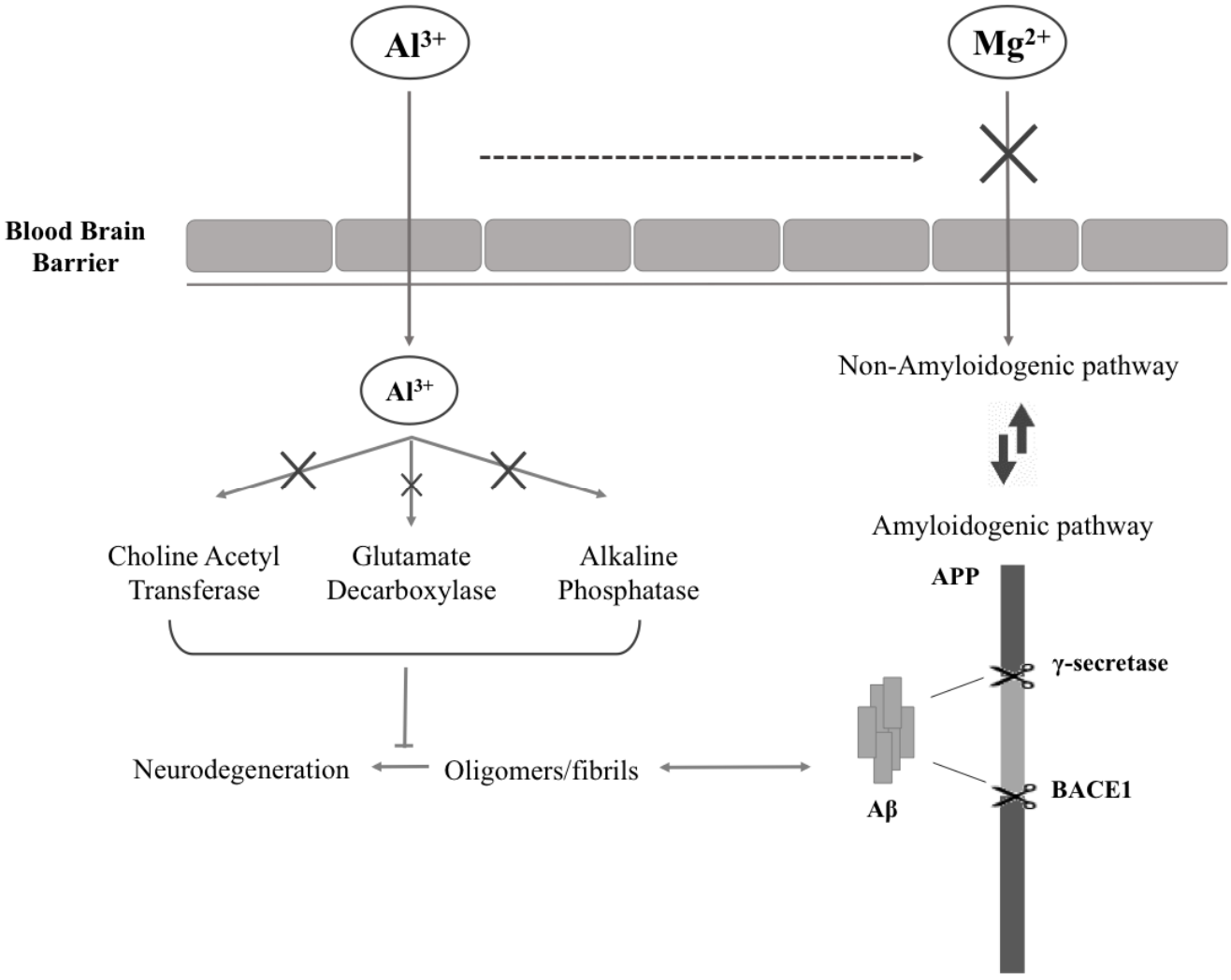


Fig. (1). Al^{3+}/Mg^{2+}competition: mechanism of action. APP = amyloid precursor protein; Aβ = amyloid beta; BACE1 = beta secretase-1.

For all his properties, Mg supplementation in the treatment of AD patients was proposed by Ozturk S. *et al*. [75]. The authors suggest that this metal used in conjunction with memantinecouldserve to increase memantine's symptomatic and neuroprotective effects, *via* its influence on N-methil D-aspartate (NMDA) receptor [75] (see paragraph 5). Unfortunately, to our knowledge, no clinical trials have been published so far. However, Mg supplementation has been studied for other pathologies, and no specific side effects were reported [67, 77-79].

Calcium (Ca) could also play a role in the pathogenesis of dementia: experimental models of neuronal pathology are based, in fact, not only on Mg deficiency, but also on the simultaneous lack of Ca and Mg and a concomitant Al intoxication [80]. The same benefit might be played by vitamin D (vit D), by enhancing antioxidant pathways, increasing neuron growth factor production, and decreasing levels of inflammatory markers [81]. Despite *in vitro* studies showed promising positive effects of vit D, a clinical trial failed to demonstrate this: neither cognition nor disability changed significantly after a 8-week high dose vit D in mild to moderate AD patients [82].

Ca and vit D are often taken together, as vit D acts by increasing Ca absorption in the intestine, and both are thought to influence neuronal functioning [83]. However, a recent randomized trial aimed to examine the effect of Ca and vit D on cognitive outcome in elderly women showed no association between the treatment and the incidence of dementia, MCI or cognitive function [83].

CURRENT DRUG THERAPIES FOR MEMORY LOSS AND COGNITIVE FUNCTION

The U.S. Food and Drug Administration (FDA) has approved two types of medications in order to treat cognitive symptoms (*e.g.* memory loss, confusion, problems with thinking and judgment) of AD. These include acetyl cholinesterase (AchE) inhibitors and memantine (Table **2**).

AchE inhibitors are mostly used for treating mild to moderate AD [84]. The therapeutic strategy is to increase the persistence of synaptic acetylcholine by blocking its degradation, leading to an increased activation of cholinergic receptor [85]. Thus, the increased residence of acetylcholine molecules within synapses by inhibiting AchE can at least partially counteract a deficiency in either the release of neurotransmitter or a reduction in cholinergic receptors/ signaling [85], delaying the breaking down process.

The most prescribed AchE inhibitor is donepezil, better known as Aricept®, the only one approved for all stages of AD. Donepezil, unlike the other AchE inhibitors, acts also in the first stages of the pathology, when cognitive symptoms are still mild and the everyday life of the patient is not compromised. According to the latest clinical trials, the drug improves cognitive functions and daily activities (*e.g.* decreased *ADAS-Cog* total scores and *Activity of Daily Living* scores) through the promotion of α-secretase activity and the decreased of β-secretase activity in platelets [86]. Donepezil decreases P300 latency (parameter involved in decision-making) together with the improvement of cognitive capability, in terms of remote memory, recent memory, visual instruction, and orientation [87], and stabilize the connectivity of medial temporal regions during resting state and of brain efficiency during a cognitive demand [88]. Moreover, it improves the *neuropsychiatric inventory* (NPI) and *Behave-AD* total scores after one-year of treatment [89], it reduces caregiver burden [90] and, if taken in the morning, can even improve the sleeping state [91]. Some studies indicate that donepezil efficacy might be influenced by a genetic factor; in particular, AD patients with mutant allele (*10) in CYP2D6 gene were found to respond better to the drug than those with wild allele (*1) [92], while rs1080985 polymorphism could be accountable for poor response [93, 94]. ApoE ε4 does not seem to be associated with the efficacy of donepezil [92]. The most effective dose is 23 mg/die instead of the 10 mg/die dose approved initially by the FDA [95, 96]. Higher concentrations of the drug in plasma, in fact, improves long-term memory in patients with

Table 2. Therapy options for Alzheimer's disease. IR = immediate release; ODT = orally disintegrating; ER = extended release; NMDA = N-methyl-D-aspartate.

Drug	Brand Name	Approved for	Year	Dosageform
Cholinesterase inhibitor				
Donepezil	Aricept®	All stages	1996	IR tablet ODT
Galantamine	Razadyne®	Mild to Moderate	2001	IR tablets ER tablets
Rivastigmine	Exelon®	All stages	2000	IR capsules Oralsolution
NMDA-receptor antagonist				
Memantine	Namenda®	Moderate to severe	2003	IR tablets
Cholinesterase inhibitor/NMDA-receptor antagonist				
Donepezil and Memantine	Namzaric®	Moderate to severe	2014	/

mild AD and imply the possible benefits for advanced stages of AD [97]. Long-term treatment with 23 mg/die dosage does not cause an elevated incidence of adverse effects, neither alone [98] nor in association with memantine [99], compared with lower dosage.

Other than AchE inhibitors, in 2003 FDA accepted thelow to moderate affinity uncompetitive N-methyl-d-aspartate (NMDA) receptor antagonistmemantine [100, 101] with similar effects on the management of disease progression (Fig. **2**). Memantine is currently approved for moderate to severe AD [100, 102], even though more recent clinical trials have shown positive effects in terms of efficacyin mild to moderate AD patients [102-104]. NMDA receptors are heteromeric ligand-gated ion channelsphysiologically activated by glycine and glutamate [105,106], highly permeable to Ca^{2+} and voltage-dependent blocked by endogenous Mg. Under resting conditions, Mg blocks the ion channel. Post-synaptic depolarization forces Mg to unbind, leading to Ca^{2+} influx. In AD, NMDA receptor is continuously stimulated, leading to a continuous Ca^{2+} influx, the principal cause of cognitive deficit and neuronal loss [101]. Memantine's principal mechanism of action is the blockade of current flow through NMDA-receptors channels [106, 107]. Recent studies suggest that memantine may work also by reducing the activity of phosphatase A2 (PA2) [108]. PA2 activity is in fact compromised in AD brain and it is one of the main causes of the abnormal hyperphosphorylation of tau protein and neurofibrillary degeneration [108].

The use of combination therapy (AchE inhibitors with memantine) for the treatment of moderate to severe AD has been recently investigated, but results show uncertain efficacy [84]. The combination therapy results in significantly better outcome than donepezil alone in terms of cognition, activities of daily living, global outcome, behavior and tolerability in moderate to severe AD [109-111]; moreover, it reduces agitation/aggression, irritability, as well as appetite eating disturbances [112]. However, in mild to moderate AD memantine does not exert any advantage on patients already under an AchE inhibitors regimen [113, 114].

ASSOCIATION BETWEEN ALZHEIMER DRUG THERAPY AND NUTRACEUTICAL SUPPLEMENTATION

Several clinical trials have recently tried to figure out if the drug therapy outcome would beameliorated by coupling the therapy with micro and macronutrients supplementation. Studying the literature, contrasting results were found (Table **3**).

Souvenaid® (Nutricia N.V., Zoetermeer, The Netherlands) is the first medical nutrition product to be designed to enhance synapse formation and function in early AD, and has undergone an extensive, 12-year development program [115]. Souvenaid® is a 125-ml (125-kcal) once-daily drink [116] intended as a medical food for oral consumption aimed to address disease-specific nutrient requirements [117]. Souvenaid® contains ω-3 PUFAs (EPA and DHA), uridine (as uridine monophosphate) and choline, together with phospholipids and other cofactors [115]. Trials in drug-naïve mild-AD patients demonstrated an enhancement in memory function, an improvement on brain functional connectivity [118] (confirmed also in an animal study [119]), and a preservation of the organization of brain networks hypothetically counteracting the progressive network disruption

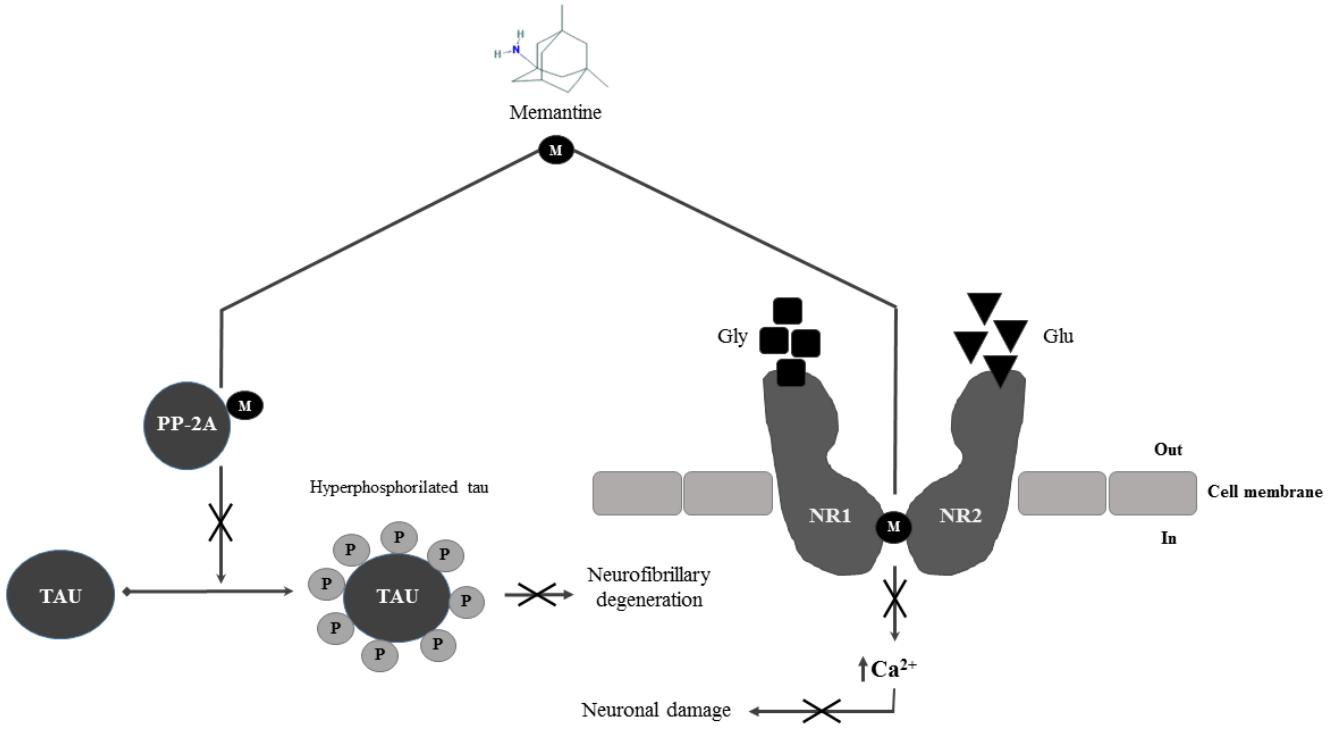


Fig. (2). Memantine's mechanism of action. M = memantine; PP-2A = protein phosphatase 2A; Gly = glycine; Glu = glutamate; NR1 = NMDA Receptor subunit 1; NR2 = NMDA Receptor subunit 2.

Table 3. Molecular formula and structure of the principle compounds cited in the text.

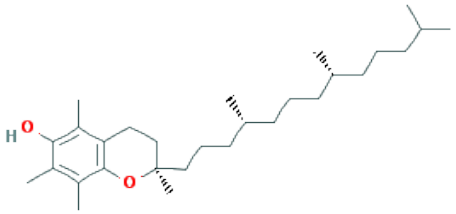
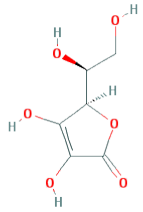
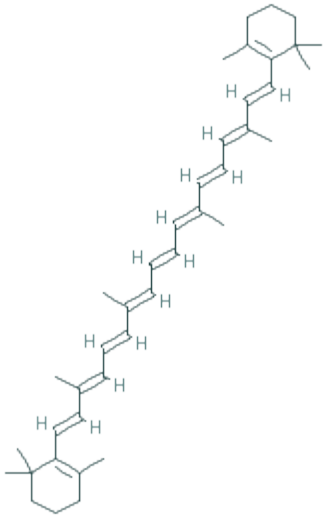
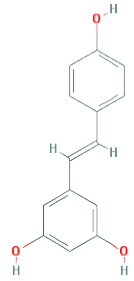
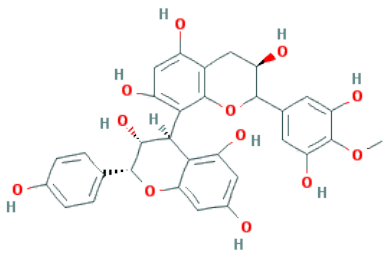
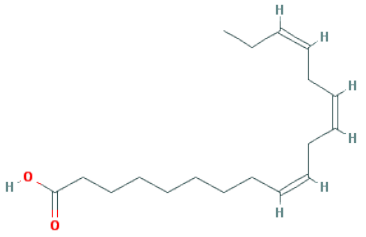
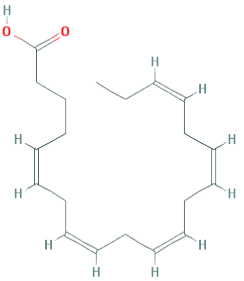
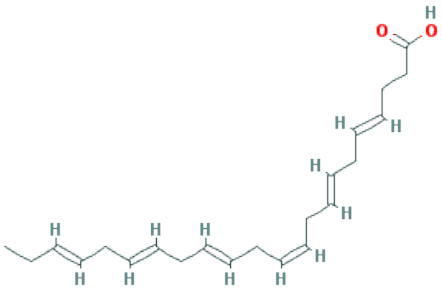
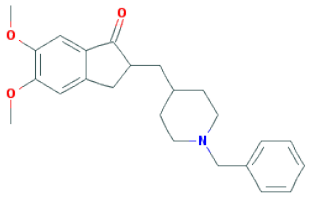
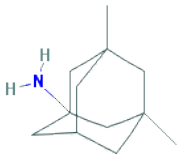
Name	Molecular Formula	Structure
Antioxidants		
Vitamin E	$C_{29}H_{50}O_2$	
Vitamin C	$C_6H_8O_6$	
β-carotene	$C_{40}H_{56}$	
Resveratrol	$C_{14}H_{12}O_3$	
Proanthocyanidins	$C_{31}H_{28}O_{12}$	

Table 3. contd….

Name	Molecular Formula	Structure
Unsaturated fatty acids		
Linolenic acid (ALA)	$C_{18}H_{30}O_2$	
Eicosapentaenoic acid (EPA)	$C_{20}H_{30}O_2$	
Docosahexaenoic acid (DHA)	$C_{22}H_{32}O_2$	
Drugs		
Donepezil	$C_{24}H_{29}NO_3$	
Memantine	$C_{12}H_{21}N$	

over time in AD [117]. However, it did not affect Modified AD Assessment Scale-cognitive subscale and other outcome scores [120]. Despite the positive effects in naïve-drug patients, Souvenaid® did not slow cognitive decline in patients taking medications for mild-to-moderate AD [121].

The same negative outcome in improving the slowdown of the disease combining therapy with nutrients supplementation was found in vitamin E treated patients. In a three-year trial including 769 subjects, vitamin E (2000IU)did not slowdown the probability of progression or development of AD in donepezil MCI treated patients [30]. Similarly, a one-year follow up of AD subjects taking AchE inhibitors coupled with vitamin E and C supplementation did not show any effects in the pathology clinical course compared with control group [122]. Interestingly, the TEAM-AD VA randomized trial integrated the AchE inhibitors and vitamin E treatment with memantine. There were no significant differences in the groups receiving memantine alone or

memantine plus vitamin E, suggesting a benefit of vitamin E in AD by slowing functional decline [123].

More promising are the results obtained with AD therapy combined with either folic acid [124] or PUFAs [125], which showed slight amelioration in cognitive function, especially in mild AD [125]. Anyway, they are all studies that need to be confirmed with other research trials.

Several authors also took into consideration the use ofa multi-target therapy. Cornelli *et al*. observed a significant improvement in MMSE II score in moderate AD patients treated concurrently with donepezil ± formula F, a formula containing the most common antioxidant (carnosine, coenzyme Q_{10}, vitamin E, vitamin C, beta-carotene, selenium, L-cysteine, *Ginkgo Biloba* and vitamins B) for two months [126], compared with a group treated with donepezil and placebo [126]. Sun *et al*. did not obtain the same positive results using a multivitamin (vitamins B6 and B12 and folic acid) approach for 26 weeks, in mild-to-moderate AD patients already taking AchE inhibitors [127].

CONCLUSIONS

In this mini-review different approaches to counteract AD onset and progression were examined. Currently, there is no cure for AD, but drug and non-drug treatments may help with both cognitive and behavioral symptoms (*e.g.* memory loss and confusion), at least for a limited time. AD is a multifactorial pathology, so that a multi-target approach using combinations of micronutrients and drugs could have beneficial effects on cognitive function in neurodegenerative brain disorders leading to synaptic degeneration, instead of a single target therapy. From the literature analysis, we ended up with the conclusion that nutritional supplementation could in part attenuate AD risk but, although animal studies seem to be promising, human trials results are contrasting. Moreover, to our knowledge, there is no sufficient evidence to consider nutritional supplementation a factor that can help to slow down the disease progression either alone or coupled with drug therapies, especially in mild-to-moderate stage. Therefore, more clinical trials are needed, and a personalized approach should be taken into consideration.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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