

# Alzheimer's Disease and Treatment



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# Current vs Emerging Natural Compounds-Based Treatments for Alzheimer's Disease

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## Abstract

Alzheimer's disease is a progressive and irreversible neurodegenerative disease that affects millions of people globally. Presently, AD is considered a serious health concern, a social and economic burden. There is still no medically accepted cure for AD. Current therapeutics that are marketed for AD treatment only attenuate the symptoms and have several side effects. To avoid the side effects associated with synthetic drugs, natural compounds have gained huge attention in the last 20 years, since they have been part of our common diet and have shown neuroprotective effects. This chapter presents a brief review on the existing medication and ongoing research on natural compounds in clinical trials for AD treatment. However, natural compounds alone have low permeability through the Blood Brain Barrier (BBB) and have low bioavailability. Therefore, a combination of natural compounds with nanocarriers could be a potential therapeutic strategy for AD.

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## Introduction

Alzheimer's disease (AD) is a global health concern that is accountable for 60% to 80% of dementia cases in today's population [1]. It is an irreversible and progressive neurodegenerative disease which leads to deterioration of healthy brain cells, loss of memory and inevitable cognitive impairment [2]. The exact mechanism lying behind the destructive symptoms of AD is not entirely comprehended and is still debatable in academia [3].

There is no medically accepted cure for AD. It is a gradually advancing brain disease that begins 15-20 years before symptoms emerge [4]. Generally, this neurological disorder observes at the age of 65 years and older, and the survival rate after the first diagnosis approximately ranges from 3 to 9 years [5]. Estimates from the United States data shows that the population of AD will almost triple by 2050 and this raises a serious health concern [1].

With the advancement in science and research, deaths reported between 2000 and 2018 from stroke, HIV and heart diseases have decreased, although the mortality rate from AD have increased to 146.2% [6]. According to the World Alzheimer's 2020 report, the annual cost of care provided by more than 16 million family members or caregivers for people with Alzheimer's or other dementias was estimated to be 18.6 billion hours with the value cost of 244 billion dollars [6]. This makes AD a social and economic burden in present.

The scarcity of treatments for AD demands an urgent need for new therapies. Natural compounds have been proposed in the last decades for the prevention and treatment of AD due to their neuroprotective effects. These bioactive compounds present some advantages over synthetic drugs as they are originated from natural sources and have been part of our diet, which



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further facilitate them for clinical approval [7]. This chapter presents the main challenges of the current therapeutic strategies used for AD. Additionally, a brief overview of natural compounds with positive outcomes in clinical trials is given here. The drawbacks associated with natural compounds administration and the future perspectives on scientific investigation for AD therapy are also discussed.

**The current treatments for alzheimer’s disease**

Current pharmaceuticals available for AD treatment cannot cure, only slow down the progression of the disease. Only four cholinergic inhibitors and one uncompetitive antagonist at glutamatergic NMDA receptors have been commercially promoted till now for AD treatment [8,9].

For attenuating the symptoms of early to moderate AD stages, the current medications approved and normally prescribed are the cholinesterase inhibitors. That way, the breakdown of acetylcholine (a-SEA-til-KOH-lean), a chemical messenger important for learning and memory is prevented. So, this class of medicines could delay the symptoms related with memory, thinking, language and judgment. However, this effect varies from person to person. The current cholinesterase inhibitors available commercially are galantamine, rivastigmine and donepezil, also called Razadyne, Exelon and Aricept, respectively. Donepezil can also be used from moderate to severe cases as well as with mild to moderate dementia associated with Parkinson’s disease. They are normally well tolerated. However, a couple of side effects could occur. Both galantamine and rivastigmine could cause nausea, vomiting, loss of appetite and increased frequency of bowel movements. Therefore, it is strongly recommended that a medical doctor and the caregivers monitor the patients that are taking that medicines.

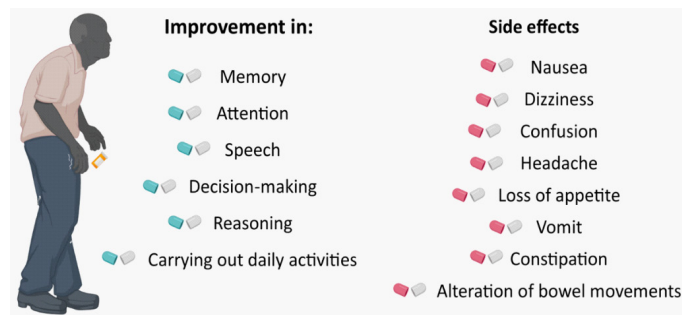
Out of these therapeutics, another cholinesterase inhibitor (Tacrine) has been withdrawn from the market because of its hepatotoxicity [10].

Memantine (commercially called Namenda) is also commonly used to attenuate the moderate to severe AD symptoms. Memantine improves the memory, attention, reason, language and the ability to carry out the daily activities. This drug has the capacity to regulate the activity of glutamate, a molecule involved in information processing, storage and retrieval. However, some side effects are associated with this medicine, such as headache, constipation, confusion and dizziness. Memantine, is less preferred than cholinergic inhibitors and generally is used for patients who have a contraindication to those inhibitors.

More recently, another approach was applied to treat moderate to severe AD symptoms. This includes the use of drugs

combination, the memantine and donepezil (commercially called Namzaric). Although, this drugs combination strategy seemed to have significantly improved the cognitive decline, still the side effects remained the same. With this strategy, nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness are pretty common side effects.

Hence, it is necessary to find more drugs/strategies for AD treatment that attenuates the symptoms with less side effects. Figure 1 summarizes the main symptoms management and side effects of clinically used drugs for AD therapy.



**Figure 1:** Schematic representation of symptoms management and side effects of clinically used drugs for AD therapy.

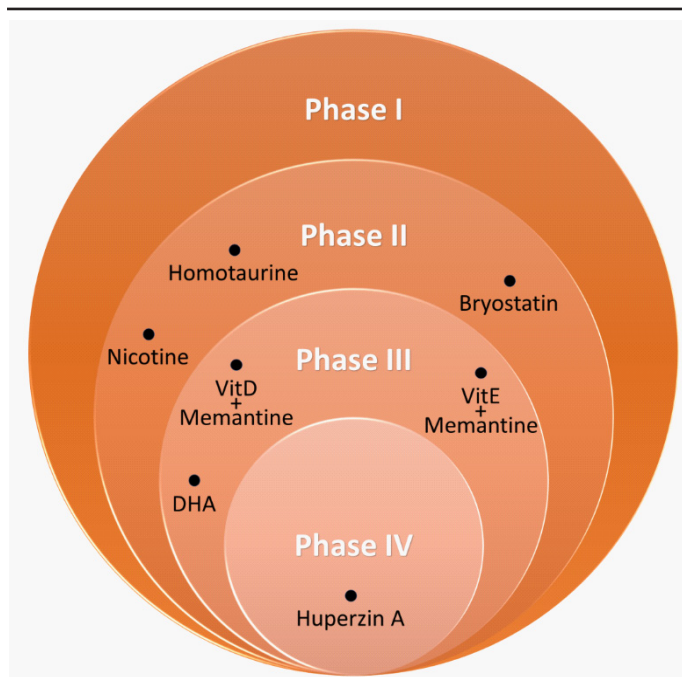
**Natural compounds in AD prevention and therapy**

Since the currently used drugs for AD only can delay or slow down the symptoms of the disease, it is urgent to find new therapeutic strategies. The process of developing new drugs is very expensive and time-consuming and is often delayed due to the failure of drug candidates in the clinical trials phase. Recently, natural compounds have been proposed for the prevention of AD and its therapy since these are commonly consumed in daily life, and therefore presumably safe for human intake. Several natural compounds have shown neuroprotective effects in *in vitro* studies, however, just a small percentage have reached the clinical trials stage. The majority of the studied bioactive compounds are from vegetable sources, with only a few natural compounds derived from animal sources [7].

In the last years, clinical trials using natural compounds have been performed to validate their safety and efficacy for AD prevention or therapy (Table 1). Clinical studies have allowed a better evaluation of safety, tolerance, and effective therapeutic doses of natural compounds for AD therapy. In the first stage, the compounds are required to be safe for human use and then can further proceed to the other successive phases. The majority of the studied natural compounds for AD therapy are currently in phase II and III of clinical trials (Figure 2).

**Table 1:** Natural compounds in clinical trials for AD therapy.

Compound	Trial phase	Trial status	Number of participants	Duration	Results
Bryostatin	II	Completed	150	12 weeks	Cognitive functions improved
Homotaurine	II	Completed	1052	78 weeks	Cognitive functions improved
Nicotin	II	Ongoing	300	2 years	No results yet
Docosahexaenoic acid (DHA)	III	Completed	485	24 weeks	Cognitive functions improved
Vitamin D and memantine	III	Ongoing	90	24 weeks	No results yet
Vitamin E and memantine	III	Completed	613	5 years	Slowed cognitive decline
Huperzine A	IV	Ongoing	300	52 weeks	No results yet



**Figure 2:** Natural compounds in different phases of clinical trials for AD therapy.

Nicotine was the first natural compound to be tested in human trials for AD prevention or treatment in 1992. Interesting, although nicotine had improved the perceptual and visual attentional deficits in a pilot study conducted for 2 weeks with 70 AD patients, it was not further studied for several years [11]. Nicotine supplementation is controversial due to its association with tobacco consumption and high dependence. However, several *in vitro* studies showed the potential of this natural compound for AD therapy [12]. Only most recently, nicotine has attracted attention in the scientific community and is now currently being studied in an ongoing randomized, placebo-controlled phase II trial with 300 participants with mild cognitive impairment. In this 2-year trial, subjects will be randomized (50:50) and a transdermal patch containing nicotine (21 mg/day) will be used or placebo (ClinicalTrials.gov Identifier: NCT02720445).

Another natural compound, bryostatin was also studied in a phase II clinical trial for AD therapy. Farlow et al. (2018) [13] evaluated the effects on cognitive function of bryostatin on AD patients in a placebo-controlled trial with 150 participants. The subjects were randomly divided into two groups, the placebo group and one group of patients administered with 20 or 40  $\mu$ g of bryostatin for 12 weeks. This study showed the ability of the natural compounds in improving the cognitive functions of patients.

Other natural compounds have revealed to be more promising for AD therapy and have already been able to reach the phase III of clinical trials, such as Docosahexaenoic Acid (DHA). Quinn et al. (2010) started placebo-controlled phase III clinical trial to evaluate the effect of DHA supplementation on cognitive impairment [14]. 485 healthy participants with age-related cognitive decline were randomly divided into two groups and daily administered orally with placebo or 900 mg of DHA orally for 24 weeks. The treated patients showed improved cognitive and memory functions.

The effects of homotaurine intake were also evaluated in a phase III placebo-controlled clinical trial with AD patients from mild to-moderate symptoms. 1052 were randomly divided into

three groups, one group receiving placebo, and the other two groups treated with 100 or 150 mg of homotaurine for 78 weeks. The obtained results showed that this natural compound has the ability to improve cognitive functions [15]. [100, 101]

The concomitant administration of natural compounds with currently used therapeutic drugs for AD have been also evaluated in phase III clinical trials, such as the co-administration of memantine with different vitamins. Dysken et al. (2014) studied the combination effects of vitamin E and memantine in a placebo-controlled clinical trial with 613 AD patients from mild to moderate symptoms [16]. The subjects were randomized in three groups, being the first treated with a combination of vitamin E and memantine, and the second and the third groups being administered with only vitamin E or only memantine, respectively. Treatment with vitamin E alone has proved to be effective in slowing down the cognitive decline, however co-administration with vitamin E did not improved memantine effects.

The combination effect of memantine with other natural compound, vitamin D, was also evaluated in a phase III clinical trial. The co-administration of vitamin D and memantine was first evaluated in a pilot study with 43 AD patients for 24 weeks [17]. The subjects were randomized in three groups, being the first treated with a combination of vitamin D and memantine, and the second and the third groups being administered with only vitamin D or only memantine, respectively. The results showed that co-therapy with both compounds is more effective in improving cognitive function than vitamin D or memantine alone. After the promising results obtained in this pilot study, the co-administration of both compounds has been further studied in human trials. Currently there is an ongoing phase III clinical trial to study their concomitant use in 90 patients with diagnosis of moderate AD. In this 24-week trial, subjects will be randomly divided into two groups (only memantine and vitamin D plus memantine) to assess if co-administration with vitamin D increases the efficacy of memantine (ClinicalTrials.gov Identifier: NCT01409694).

Huperzine A is currently the only natural compound in phase IV of clinical trials after being proven to improve cognitive functions in mild to moderate AD patients in a study conducted in 2011 with 177 patients for 16 weeks [18]. This natural compound is now being evaluated in an ongoing phase IV clinical trial. In this placebo-controlled trial, 300 AD patients with mild cognitive impairment will be randomized (50:50) and administered with huperzine A (200  $\mu$ g/day) or placebo for 52 weeks (ClinicalTrials.gov Identifier: NCT02931136).

Other natural compounds can also be a promising approach for AD prevention and therapy in present and near future. For example, other natural compounds such as curcumin and melatonin have presented promising results in *in vitro* and therefore have been studied in small-scale pilot studies. Despite having a limited size of subjects, pilot studies can provide useful information for the preparation of further clinical trials. Valuable information can also be obtained from human trials with no positive outcomes. For example, resveratrol has been studied in phase III clinical trials for AD therapy but did not show significant improvement for AD treatment [19]. A similar result was verified in two different phase III clinical trials to study the combination effect of vitamin E with AD drugs (vitamin E/donepezil [20] and vitamin E/selenium [21], respectively), where no positive outcomes were verified.

### Delivery systems to improve the natural compounds' therapeutic efficiency

Despite their promising value in the treatment of AD, natural compounds have some limiting features that prevent them from becoming effective drug candidates. Among them, the low solubility in water, poor bioavailability, difficulty to cross the Blood-Brain Barrier (BBB), lack of specificity and rapid metabolism of the compound stand out [22]. Such characteristics hinder the bioactive compounds from reaching the brain tissue in effective concentrations. Nanoparticles (NPs) are a promising strategy to overcome these challenges by protecting compounds from biological degradation and masking their limiting physicochemical properties. Additionally, the controlled and sustained release provided by NPs allow to maintain active doses of therapeutic agents for long periods [23]. Moreover, nanocarriers allow to reduce the dosage of compounds that are needed to produce therapeutic effects due to the improvement in their pharmacological activity, thus decreasing the side effects. Generally, nano-scaled Drug Delivery Systems (DDS) present numerous beneficial properties such as biodegradability, biocompatibility, nontoxicity, non-immunogenicity, high stability in body fluids and ability to interact with specific receptors [24].

More than the molecules' properties to be delivered, the ability of NPs to cross the BBB depends on their physicochemical characteristics such as surface charge, hydrophobicity, and size. Besides, the NPs' functionalization by conjugating specific ligands to the NPs' surface is an attractive approach to improve the nanosystems' brain delivery by enhancing their recognition by the BBB receptors [25].

In recent years, numerous efforts have been made to develop suitable DDS to deliver natural compounds with clinical interest for AD. From the compounds covered in this chapter, only vitamin E, huperzine A, resveratrol and curcumin were encapsulated and tested for AD therapy [26]. With more than two dozen described studies, NPs for curcumin delivery are the most promising nanocarrier so far. Lipid and polymeric NPs are the most used types of NPs. However, the development of NPs to deliver natural products is still in early stages. In fact, among the natural product-based nanoformulations described till date for the treatment of AD, only 60% of the formulations proved to be effective in *in vivo* studies, and out of these, only 30% adopted the functionalization strategy to increase the efficiency of the compound (only for curcumin [27-31] and huperzine A [32]). However, despite the promising preclinical results, much more efforts are needed since no clinical trials were reported so far. It is urgent to perform further experiments to develop effective strategies to improve the therapeutic activity of these molecules for AD.

As reported in the previous section, the synergistic effect of natural compounds is an interesting approach to increase their therapeutic benefits, and so, the co-encapsulation of bioactive molecules can also represent a valuable strategy to improve their medicinal activity in *in vivo*. However, no study attempting such approach was reported so far.

### Concluding remarks and future perspectives

The stagnation in the appearance of new therapies for AD is mainly due to the fact that the exact mechanisms of the disease are not known yet. The available medicines, including memantine and cholinesterase inhibitors, are able to relieve the symptoms, but frequently induce undesired side effects. To

overcome this problem associated with synthetic drugs, a suitable strategy would be using natural compounds. Since natural compounds have been part of our daily life and are originated from natural sources, the expected side effects are lower.

Some natural compounds have been tested in clinical trials with the aim of slowing down the AD symptoms. Huperzine A has shown positive results in clinical trials and is already in phase IV. Other promising natural compounds that are in phase III are DHA, vitamins D and E.

Similar to the synthetic compounds' association memantine and donepezil, the association of natural compounds with synthetic ones have been tried. The case of the association of memantine with vitamin E already finish the phase III and demonstrates to be promising. The association of memantine with vitamin D have already proven to be effective in the phase II stage and is now in the phase III stage. However, some of the limiting factors of the efficacy of the natural compounds are related with their low bioavailability and difficulty to cross the BBB.

A promising strategy to overcome these limitations is a combination of natural compounds with nanocarriers. Many preclinical studies in the previous years have already proven nanocarriers as a safe and biocompatible tool for AD therapy. It is expected that in near future more nanocarriers for natural compounds delivery will reach the clinical trials and will bring a significant improvement in AD therapy.

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