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Multiple Approaches for the Management of Alzheimer's Disease: Natural Compounds, FDA Approved Drugs, and Nanotechnology Interventions

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ABSTRACT

Alzheimer's disease is the most common in the elderly population. Due to its irreversible and progressive nature, it gained more attention for early management. In this regard, several new therapeutic targets, such as degrading neurotransmitter enzymes, amyloid cascade enzymes, and monoamine oxidases, have been explored. Inhibition of these targets with natural and synthetic compounds and dietary supplements has been traditionally exercised for decades in the etiology of AD. Secondary metabolites obtained from natural resources are in the trend to use against these targets. The purpose of this review is to provide a brief introduction to AD along with the related concept of several therapeutic compounds involved in the progression of the disease and its management using different natural compounds against selected targets.

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Introduction

Among neurodegenerative diseases, Alzheimer's disease (AD) is the most common in the elderly population. Due to its irreversible and progressive nature, it gained more attention for early management. AD is the most prevalent neurodegenerative cause of dementia, causing considerable individual morbidity and death as well as a large financial burden on the healthcare system (1-4). Dementia is a word used to describe a decrease in a cognitive capacity. AD accounts for about three-quarters of dementia cases, with vascular dementia, combined Alzheimer's, and dementia with Lewy bodies, and frontotemporal dementia accounting for the rest (5, 6). AD is described as Early-onset Alzheimer's disease (EOAD) and late-onset form (LOAD). EOAD is found at the age of 65 and is more progressive. 5-10% cases are found in EOAD, while 10-15% of cases of AD are related to the mutation in amyloid precursor protein (APP), Presenilin-1 (PSEN1), and Presenilin-1 (PSEN2) (7). Alzheimer's dementia affects an estimated 6.2 million Americans aged 65 and over. In 2019, 121,499 official deaths were recorded, making it the sixth leading cause of death in the United States and the fifth leading cause of death among Americans aged 65 and older. Fatalities from stroke, heart disease, and HIV declined between 2000 and 2019, while recorded deaths from AD increased by more than 145%. Health care, long-term care, and hospice services for persons 65 and older with dementia are expected to cost $355 billion in 2021. In 2020, unpaid dementia care was estimated to be worth $256.7 billion. In 2020, an estimated 15.3 billion hours of unpaid care were provided to persons with AD or other dementia by more than 11 million family members and other unpaid caregivers (8).

There are three defined clinical phases present in AD, such as pre-symptomatic, pre-dementia phase, and clinically defined dementia phase (9) as shown in Figure 1.

In AD, age is a major risk factor and it accounts for 50–75% of dementia cases. Amyloid-beta (Aβ) 40, Aβ42, total tau, p-tau, and neurofilament, an intraneuronal protein and component of the axonal cytoskeleton showing neuronal degeneration, are the most prevalent biomarkers tested to represent AD pathology in biofluids (7, 10). About 70% of AD is caused by genetics, while obesity, cardiovascular disease, hypertension, and diabetes elevate the risk of AD (11). More than 30 dominant mutations in the *APP* gene (present in chromosome 21q21) have previously been discovered and account for 15% of cases of early onset. Mutations in the *PSEN1* gene (14q24.3) are connected with 80% of cases of early-onset AD, whereas 5% of cases are linked with *PSEN2* mutations (1q31-q42) (12). Three *APOE* alleles such as ε2 (5-10%), ε3 (65-70%), and ε4 (15-20%) are defined and give rise to apoE2, apoE3 and apoE4 isoforms with different frequencies range (13). The ε4 allele is the foremost risk factor for late-onset AD, having 3-fold of heterozygosity and 12-fold for homozygosis (14, 15). Karch and Goate, 2014 describe the new genes associated with AD risk, including ABCA7, BIN1, CASS4,

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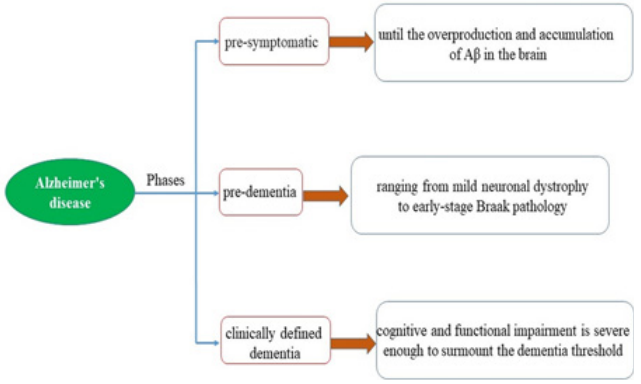

Figure 1. The different phases of Alzheimer's disease.

CD33, CD2AP, CELF1, CLU, CR1, DSG2, EPHA1, FERMT2, HLA-DRB5-DBR1, INPP5D, MS4A, MEF2C, NME8, PICALM, PTK2B, SLC24H4-RIN3, SORL1, and ZCWPW1 (14).

Amyloid imaging tracers like Pittsburgh Compound-B, Neuraceq™ (florbetaben F18), Amyvid™ (florbetapir F18), and Vizamyl™ (flutemetamol F18) and tau ligand (Tauvid™; 18F-flortaucipir) are FDA approved technique for AD pathology (16). While whole-exome sequencing is now available for regular screening in the clinic, its interpretation (and accompanying genetic counseling) is primarily confined to known mutations in APP, PSEN1, PSEN2, GRN, and MPT, which account for only a tiny percentage of EOAD patients before age 65 (7). In recent years, there has been a lot of attention on developing alternative methods that target the AChE enzyme as well as additional targets, including BuChE, Aβ, β-secretase-1, metal antioxidant capabilities, and free radical scavenging capability (17). As a result, the proteins Aβ, BACE-1, RAGE, AChE, BuChE, Caspase 8, P2X7 receptors, and Monoamine Oxidase are being effectively targeted for the therapy of AD (18-21). The several known compounds against different target enzymes of AD were reported in Table 1. The aim of this review is to provide a brief introduction to AD along with the related concept of several therapeutic compounds involved in the progression of the disease and its management using different natural compounds against selected targets.

Mechanism of Cholinesterase enzyme

AChE and BuChE are encoded by separate genes on human chromosomes 7 (7q22) and 3 (3q26), respectively, and have 65 percent amino acid sequence homology. Both AChE and BuChE feature a mainly hydrophobic active gorge, which is 20 Å deep in AChE and 20 Å deep in BuChE (29). When ACh hits this active site, it binds to two sites: a catalytic area near the gorge's bottom and a choline-binding site around halfway. ChE enzymes hydrolyze acetylcholine (ACh) to choline and acetate, rendering it useless as a neurotransmitter (30). The most widely used medicines for the treatment of AD target the enzyme AChE, which is involved in the breakdown of the neurotransmitter ACh. However, most of the treatments only give symptomatic relief (17).

Monoamine oxidases (MAOs)

MAOs are enzymes that are covalently linked to a cysteine residue and include flavin adenine dinucleotide. MAOs' physiological activities are influenced by the type of their substrates, which include indoleamines like serotonin and tryptamine, as well as epinephrine19 and trace amines (31, 32). MAO-A and MAO-B are two isoforms of the enzyme that are found mostly in the outer membrane of mitochondria in neuronal, glial, and other cells. MAO-A and MAO-B have 527 and 520 amino acid residues, respectively, and their amino acid sequences are identical up to 70% (33, 34). The deamination of norepinephrine and serotonin is preferentially catalyzed by MAO-A (35, 36). Thus, MAO-AIs result in a rise in norepinephrine levels and lower 3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxyphenylglycol and reduce 5-hydroxyindoleacetic acid. Furthermore, following MAO inhibition, trace monoamines such as tryptamine and octopamine are elevated. MAO-AIs have been widely utilized as antidepressant drugs because deficits of these two neurotransmitters have been related to the development of depression (37-39). The crystal structure of human MAO-A (hMAO-A) in combination with harmine was determined. (PDB: 2Z5X) (40), in which harmine interacts with the residues of amino acids Tyr69, Asn181, Phe208, Val210, Gln215, Cys323, Ile325, Ile335, Leu337, Phe352, Tyr407, and Tyr444 within the active center cavity of hMAO-A (40). The crystal structure of hMAO-B was also established for the first time (PDB: 1GOS) (41). hMAO-B has two cavities in its active site: a hydrophobic substrate cavity and an entrance cavity. The entrance cavity is lined by the residues Phe103, Pro104, Trp119, Leu164, Leu167, Phe168, Leu171, Ile199, Ile316, and Tyr326 (42).

Natural Compounds

The main kind uses natural resources to treat diseases and the most widely used resources belong to the plant kingdom. Various plant foods have medicinal values which are known as nutraceutical foods and can be used for the prevention of AD(1). The medicinal properties of plants are due to the bioactive compounds present in them. These

Table 1. The list of reported natural and synthetic compounds as an inhibitor of the selected target for managing Alzheimer's disease.

Target name	Compounds name	References
AChE	Indirubin and dehydroevodiamine, Quinoline, Carbamates	(17, 22)
BuChE	Fluorobenzylcymserine	(23)
Caspase 8	rutaecarpine	(24)
Aβ	Vincamine, Ajmalicine, Emetine	(25)
BACE	Ajmalicine, Yohimbine, Huperzine A, Physostigmine, LY2811376, LY2886721, E2609	(26, 27)
MAO	Ladostigil, Selegilline, Rasaglime	(20)
apoE4 protein	Epicatechin Gallate, Fulvic acid, and Tideglusib	(28)

bioactive compounds have antioxidant, anti-inflammatory, antiapoptotic, antithrombotic, acetylcholinesterase, and monoamine oxidase inhibition, and neurotrophic activities. These properties are required to treat AD (43, 44). The role of plant-based AD treatment has been verified within *in-vitro*, *in-vivo,* and *in-silico* studies. The examples of various studies are described below:

Apigenin (4',5,7-trihydroxyflavone), a common compound of parsley, celery, oranges, onions, chamomile, tea, wheat sprouts, and some seasoning (45) is a flavonoid has shown a decrease in inflammatory cytokines, Aβ burden, oxidative stress, cortical hyperexcitation, and β-amyloid neurotoxicity in an *in-vitro* induced neurogenesis and *in-vivo* mouse model of AD (45, 46). Crocin extracted from *Gardenia jasminoides* has been tested in *in-vivo* mouse model of AD. It was suggested that crocin might be a promising drug to improve cognitive and memory impairment, with multiple targets (47). Berberine extracted from 80 traditional Chinese medical plants was tested for their *in-vitro* model of AD based on Ellman's colorimetric assay has shown the inhibition of acetylcholinesterase which is required for the treatment of AD (48). Catechin present in *Camellia sinensis* has shown cognition contributes to the inhibition of acetylcholinesterase in an *in-vivo* rat model of AD (49). Genistein and chrysin isolated from C. villosus were investigated by molecular docking simulation and *in-vitro* models of AD. Both compounds have shown a potential neuroprotective ability along with the inhibition of human monoamine oxidase A and B (50). By molecular docking simulation and *in-vivo* rat model of AD, Hesperidin isolated from *Valeriana offcinalis* has shown a neuroprotective effect by strongly inhibiting the Beta-secretase 1 activity and Aβ aggregation (51, 52). In another study, flavonols (morin and isoquercitrin) and flavanones (hesperidin and neohesperidin) showed a decrease in Beta-secretase 1, γ-secretase, Aβ fibrillogenesis, caspase-3, caspase-9, apoptosis, amyloid plaque, and tau hyperphosphorylation in an *in-vivo* rat model of AD. This suggested that the consumption of foods rich in these compounds may be beneficial in neurodegenerative disorders (53). Naringenin is a flavonoid commonly found in citrus fruits, which has been reported to decrease inflammatory cytokines, NF-κB, and oxidative stress in an *in-vitro* rat model (54). Withanone and withanamides A and C extracted from a medicinal plant *Withania somnifera,* which is also known as Indian ginseng, have been reported to protect neurons and glial cells and decrease Aβ fibril formation in an *in-vivo* rat model of AD (46). *In-vitro* rat model and *in-silico* results of berberine derived from various plants like European barberry against AD showed improved cognitive behavior and downregulated the AChE expression respectively (55). Dehydroevodiamine, a major phytochemical of *Evodia rutaecarpa,* has been tested in rat brain slices with AD and was reported to activate a PP2A Tyr307 site and inhibit tau phosphorylation (56). Galantamine is mainly found in the plants of the genera Amaryllis. It has been tested against AD in the mouse model, which showed that the preplaque phase ameliorates memory decline and improved the unbalanced redox state (57). Huperzine A is isolated from plants of the Huperziaceae family. In an Alzheimer's transgenic mouse model, it has been reported to have anticholinesterase activity and reduces the level of Aβ (58). In an *In-vitro* study, N-methylasimilobine, an alkaloid extracted from *Nelumbo nucifera,* has been reported to have strong inhibition of acetylcholinesterase (59). Isorhynchophylline, a major compound of *Uncaria rhynchophylla,* possesses potential neuroprotective effects. In a rat model, it has been shown to restore Aβ–induced cognitive impairment, reduce phosphorylation of tau, and inhibit neuronal apoptosis (60). Lycorine and galanthamine extract of *Crinum L.,* bulbous monocot, have been reported to have the inhibitory potential of acetylcholinesterase in an *in-vitro* study (61). Palmatine, present in different plants, including Berberidaceae, Papaveraceae, Ranunculaceae, and Menispermaceae, is a yellow isoquinoline alkaloid that has been used to treat various diseases (62). In an *in-vitro*, *in-vivo*, and *ex-vivo* experiment, it has been reported to show anti-inflammatory, anti-depressive, antipyretic, anti-neurodegenerative, inhibited tau aggregation and disassembled pre-formed fibrils (63, 64). Sanguinarine is an alkaloid present in the rhizomes of *Sanguinaria Canadensis* and has been shown to Inhibit the activity of acetylcholinesterase in an *in-vitro* study (65). Taspine extracted from the bark and leaves of Magnolia x soulangiana has also shown the inhibitive activity of acetylcholinesterase in an *in-vitro* study (66).

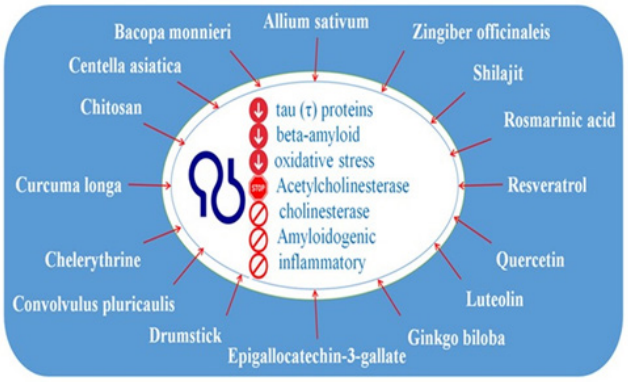

Figure 2. Natural resources having AD-preventing properties.

From the above studies, the natural compounds have the potential to prevent AD. However, no permanent cure for AD has been found until now and natural compounds can retard its progression. There are other plant sources and compounds having anti-inflammatory, anti-Amyloidogenic, anti-cholinesterase, acetylcholinesterase inhibition, tau protein, beta-amyloid, and oxidation stress reduction properties as shown in Figure 2.

Synthetic FDA-approved drugs

Tacrine was introduced in 1945 by Adrian Albert and is known as one of the main FDA-approved drugs for AD (67). The IUPAC name of Tacrine is 9-Amino-1,2,3,4-tetrahydroacridine and is available in the market by the name Cognex (67). It shows the reversible inhibition of acetylcholinesterase prevention of the cholinergic enzyme to stop the neuronal signal transmission between the synapses (68). The use of tacrine is associated with side effects and is believed to have hepatotoxicity (69). Tacrine-derived compound Velnacrine has the same activity as AD, but in 1994 FDA banned its use due to its toxicity (70). Thus, other hybrids have been developed to overcome the side effects by altering the basic structure of Tacrine (71).

Memantine is a synthetic compound with IUPAC name as 1-amino-3,7-dimethyladamantane. It was synthesized by Eli Lilly in 1968 and patented as an antidiabetic agent.

Currently, it has been approved by Food and Drug Administration to decrease the progression of moderate to severe AD. However, it has not been approved for mild to moderate treatments of AD (72). It is being produced in many countries with 114 brand names in three forms, capsules, oral solution, and oral tablets. It also has various derivatives and isomers like 1-amino-3,7- diethyladamantane, 1-amino-5,7-dimethyladamantane, and 1-amino-3-ethyladamantane (73). It is against the N-Methyl-D-Aspartate receptor and blocks it, thus preventing over-activation of glutamine receptors (72).

Donepezil is an inhibitor of acetylcholinesterase used to enhance cortical acetylcholine for the cure of AD (74). It is synthesized by an aldol condensation/dehydration reaction between the piperidine and the indanone moieties (75). It was approved by the FDA in 1996 to delay the decline of cognition in moderate to severe AD patients (76). It is available on the market in the form of tablets, capsules, jelly, and transdermal patches (77).

A derivative of a toxic compound alkaloid physostigmine known as rivastigmine(77) has been used for the treatment of AD since 1997. In 2006, it was approved for the treatment of mild, moderate, and severe AD (78). It is available on the market in the form of capsules, liquid form, and transdermal patches (77). The mechanism of action of rivastigmine against AD is believed to have dual inhibition of acetylcholinesterase and butyrylcholinesterase activity (78). Mostly these FDA-approved drugs have some side effect such as Nausea, vomiting, and loss of appetite (https://www.alz.org/media/documents/fda-approved-treatments-alzheimers-ts.pdf).

Application of nanotechnology in AD treatment

Nanoparticles are nanosized particles with high surface area and have wide applications in food (79), packaging (80, 81), medicines (82), agricultural (83), etc. Nanotechnology can be used in AD treatment in two ways, viz. Diagnosis and treatment. Biocompatible nanoparticles, after increasing their magnetic and optical properties, can be used for early AD diagnosis (84). This diagnosis can be performed inside the body *in-vivo* or outside the body *in-vitro* for biomarker detection (85). The various *in-vivo* and *in-vitro* nanotechnologies used for AD diagnosis are shown in Figure 3.

All FDA-approved synthetic drugs do not completely cure AD but can reduce its occurrence. Moreover, almost all these drugs have some side effects like nausea, vomiting, and diarrhea. During their injection, they cross the intestines and spread throughout the body with blood, and finally cross the blood-brain barrier to produce a curing effect (86). Creating nanoparticle drugs can help us to minimize these side effects in various ways. The surface area of nanoparticles is more than their original form. Thus, the required quantity for the injection can be minimized. Nanocarriers are not dependent on albumin binding for their half-lives. Moreover, these nanocarriers can bypass the blood-brain barrier by being administered directly intranasally(87).

Nanotechnology has been used to deliver drugs through nanocarriers which are more effective than without carriers. The various nanocarriers used to treat AD are colloidal polymeric nanoparticles (88), phosphorus dendrimers (89), colloidal dispersion of lipid nanoparticles (90), microemulsions (91), oil-in-water nanoemulsions (92), and liposomes(93).

Donepezil loaded on polymeric nanoparticles (poly-lactic-co-glycolic acid) showed high concentration uptake of donepezil in the brain, which may improve the effect of donepezil in AD treatment (88). Nanoparticles in the range of 1-100 nm in diameter have been reported to deliver rivastigmine effectively through the blood-brain barrier with fewer side effects (84). Rivastigmine has high aqueous solubility and poor penetration due to which high doses are required to cure AD. Ferulic acid was entrapped in lipid nanoparticles for the AD treatment. The results demonstrated that the nanocomplex has higher protective activity against AD due to its antioxidant property (90). For this reason, microemulsion and mucoadhesive microemulsions of rivastigmine were formulated for nasal-to-brain delivery (91). The highly branched nature of dendrimers has application in the regulation of amyloid fibril development. Phosphorus dendrimers have been reported to affect Aβ1-28 peptide and MAP-Tau protein aggregation (89). Nanoemulsions have been successfully used for the release of phytotherapeutics through the nasal membrane for AD treatment (92). Resveratol and curcumin co-encapsulated with hyaluronic acid have shown good results for the transnasal treatment of AD (88). In a study, the preparation of curcumin nanoemulsions for intranasal delivery has been optimized with the help of Box-Behnken design. The optimum formulation has shown successful results and did not show in toxicity (94). Galantamine-loaded polymeric nanoparticles showed successful results in drug delivery of AD treatment because of their biocompatible, biodegradability, and safety (95). The creation of complex galantamine hydrobromide and chitosan nanoparticles for nasal treatment of AD has been reported to not affect the efficiency of galantamine hydrobromide(87). Liposomal drug delivery has been suggested to have improved drug delivery to the brain. The intranasal liposomal formulation was found safe and a promising drug delivery mode(93).

Conclusion

There are ample natural and synthetic compounds available for the treatment of AD. Unfortunately, until now, there is no permanent cure for AD except for slowing its progression. These compounds also have some side effects, which reduce their effectiveness. To overcome this, natural compounds and some novel approaches are new to be investigated. Nanotechnology can play a vital role in AD treatment. It can be used for the early diagnosis and drug delivery system. The above discussion suggests that

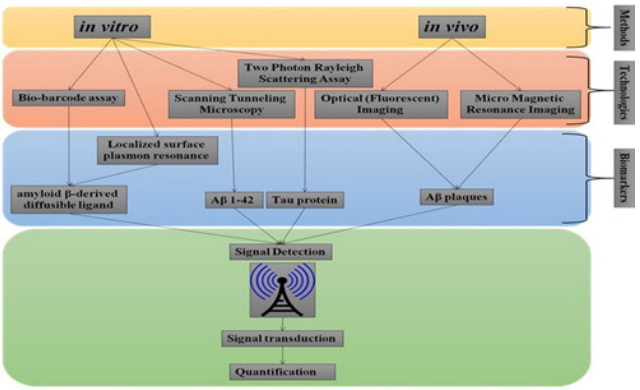

Figure 3. Role of nanotechnology in AD diagnosing.

nanotechnology is a promising method of drug delivery that not only is safe for use but also reduces the amount of drug intake.

List of Abbreviations

AD Alzheimer's disease
EOAD Early-onset Alzheimer's disease
LOAD Late-onset form
Aβ Amyloid-beta
AChE Acetylcholinesterase
BuChE Butyrylcholinesterase
FDA Food and Drug Administration
MAO Monoamine oxidases

Consent for Publication

Not applicable.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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