

Study of Nutraceuticals and Phytochemicals for the Management of Alzheimer's Disease: A Review

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Abstract: Background: Alzheimer's disease (AD) affects several people worldwide and has devastating impacts on society with a limited number of approaches for its pharmacological treatment. The main causes of AD are not clear yet. However, the formation of senile plaques, neurofibrillary tangles, hyper-phosphorylation of tau protein, and disruption of redox homeostasis may cause AD. These causes have a positive correlation with oxidative stress, producing reactive ions, which are responsible for altering the physiological condition of the body.

Conclusion: Ongoing research recommended the use of phytochemicals as acetylcholinesterase inhibitors to hinder the onset and progression of AD. The natural compound structures, including lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids have anti-inflammatory, antioxidant, and anti-amyloidogenic properties. The purpose of this article is to provide a brief introduction to AD along with the use of natural compounds as new therapeutic approaches for its management.

Keywords: Alzheimer's disease, nutraceuticals, nutrients, phytochemicals, mechanism of AChE in Alzheimer's disease.

1. INTRODUCTION

Neurological disorders (ND) are considered as one of the fatal diseases, especially in the urbanized nations. Among those, Alzheimer's disease (AD) is at the highest point on the sequence of neurological disorders [1, 2]. AD was first portrayed and named by a German therapist and pathologist, Alois Alzheimer, in 1906 [3]. AD is the main reason for dementia in aging individuals [4, 5]. Cognitive dysfunction, principally memory misfortunes are the primary side effects related to this illness. Different highlights related to the later phases of AD incorporate language deficiencies, depression, behavioral problems, and psychosis. The etiology of AD is yet not clear. Many pieces of research have been attempted in recent years and concluded with some solid speculations. Some of them are cholinergic theory, amyloid cascade hypothesis, tau hypothesis, oxidative stress hypothesis, zinc dyshomeostasis hypothesis, and calpain cathepsin hypothesis

[6-11]. AD is described by neuronal misfortune and progressive cognitive weakness. AD is the main source of dementia worldwide and the rate is expanding quickly, with analysis expected to significantly increase continuously in 2050 [12]. Dementia patients totaled 24.2 million in 2005 and 4.2 million cases emerged every year from 2005 to 2011, with 70% of these cases being a consequence of AD [13]. In developed nations, 1 out of 10 individuals beyond 65 years old is influenced by dementia, with the recurrence of AD nearly doubling within this specific population every 5 years [14]. Around the world, the expense of medicinal consideration for dementia sufferers is approximately 604 billion US\$ with the yearly expense of AD per patient ranging between US\$42000 to US\$56000 in the USA [15, 16]. The average duration of ailment differs somewhere in the range of 4 and 8 years, albeit a few patients may survive up to 20 years after the beginning of the AD [17]. Alzheimer's dementia is assessed to have expanded by 35.4% in 2015, altogether raising the particular expenses of this ailment [18]. Until 1921, it was accepted that the transmission of nerve impulses was 'electrical' in nature. But this hypothesis was not worthy because of two reasons, one being the presence of a gap among neurons and effector organs and the other a decline in action because of impulses from inhibitory nerves. Otto Loewi

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demonstrated the 'Chemical' nature of impulse transmission through his analysis of two beating hearts from frogs - one associated with the vagus nerve and accelerator agent nerves; the second one without nerve association. In this investigation, he found the first neurotransmitter acetylcholine (ACh) [19, 20]. Acetylcholinesterase (AChE) is associated with the termination of neurotransmission, while the job of butyrylcholinesterase (BChE) is not comprehended. ACh is a low molecular weight neurotransmitter displayed in both the central and peripheral nervous systems. It is liable for signal transmission from nerves to terminal organs and muscles. Nicotinic (nAChR) and muscarinic acetylcholine receptors (mAChR) are available in the body and these receptors transmit information to many tissues, moreover, they can be found on leukocytes, endothelial cells, nerves, and others [21-24]. AChE is an enzyme converting acetylcholine into choline and acetate. Neurotransmission is halted by the impact of AChE [25, 26]. Acetylcholinesterase inhibitors (AChIs) have been exhibited to improve AD symptoms [27]. Medications for AD are donepezil, rivastigmine [28], and galantamine [29]. These medications were created dependent on the cholinergic hypothesis [30].

The natural sources, particularly plants, give various undiscovered properties of substrates for drug discovery pipeline and offer incredible potential for the improvement of new cholinesterase inhibitors. Past investigations have just introduced the capability of plants as crucial hotspots for cholinesterase inhibitor agents [31, 32]. Therefore, the greater part of the medication depends on the cholinergic theory, which proposes that AD starts as a deficiency in the creation of the synapse acetylcholine.

There are several inhibitors reported for AD management against AChE and BChE [33]. The way that naturally-occurring compounds from plants are viewed as a potential source of new inhibitors has prompted the revelation of a significant number of secondary metabolites and plant extracts with the capacity of inhibiting the AChE, which, as indicated by the cholinergic speculation, expands the levels of the synapse acetylcholine in the brain, hence improving cholinergic capacities in AD patients and alleviating the symptoms of this neurological issue [32]. People with AD and their parental figures are utilizing supplements to halt the movement of the illness [34]. Natural products, for example, curcumin, ginger, and *Gingko biloba* have been utilized as diets and dietary enhancements to treat human sicknesses, including malignancy, cardiovascular, respiratory, diabetes, metabolic disorders, and neurological issue [35]. It is acknowledged that natural compounds, including vitamins A, C, E, β -carotene, and minerals found in fruits and vegetables are anti-oxidants that offer medical advantages against a few distinctive oxidative stress prompted degenerative sicknesses, including AD [36]. The term vitamin E incorporates diverse fat-soluble compounds, separated into tocopherols and tocotrienols, that have antioxidant activity. α -Tocopherol is the most contemplated, yet a few investigations recommended that tocotrienols may have diverse health-promoting capacities [37]. More information on phytochemicals and their particular targets are fundamental to ensure the safe utilization of these compounds as a possibility for AD treatment [38, 39].

2. MECHANISM OF AChE

Silman and Sussman (2008) have portrayed a 'structure-function relationship' for AChE (EC 3.1.1.7) and announced that the enzyme was acquired from an enormous group of proteins that, mutually, share a typical α/β fold [40]. Neurotransmitters are called endogenous chemical messengers that empower neurotransmission. They transmit signals over a chemical synapse, for example, neuromuscular connection, from one neuron to another neuron, muscle cell, or gland cell. The essential physiological role of AChE includes the termination of chemical transmission at cholinergic synapses and secretory organs by catalyzing the hydrolysis of the neurotransmitter acetylcholine (ACh), at a high turnover rate (2.5×10^4 molecules per second) [41, 42]. During neurotransmission, ACh is released from the nerve into the synaptic part and ties to ACh receptors on the post-synaptic layer, transferring the signal from the nerve. AChE, additionally situated on the post-synaptic membrane, ends the signal transmission by hydrolyzing ACh. The liberated choline is taken up again by the pre-synaptic nerve and ACh is incorporated by adding with acetyl-CoA through the choline acetyltransferase [43, 44]. The mechanism of AChE is represented in Fig. (1).

3. ROLE OF NATURAL OR NUTRACEUTICALS COMPOUNDS IN ALZHEIMER'S DISEASE

Dietary supplements have been suggested to cure diseases [45]. Nutraceuticals are the extracts of the compounds from the foods that have health benefits. The term nutraceutical was coined by Stephen Defelice, by combining the words nutrition and pharmaceutical [46]. Nutraceuticals are consumed in the concentrated form like pills, capsules, and beverages having no side effects even at high doses [47]. Even though the causes of AD are not clear however some studies have hypothesized some reasons which include: formation of senile plaques, neurofibrillary tangles, hyperphosphorylation of tau protein, and disruption of redox homeostasis. These causes have a positive correlation with oxidative stress, producing the reactive ions, which are responsible for altering the physiological condition of the body. To overcome the side effects of known drugs, the researchers are focusing on the identification of the natural bioactive compounds present in foods to treat AD [48]. Consumption of foods consisting of bioactive compounds or appropriate administration of extracted bioactive compounds can have a prophylactic effect against various pathophysiological conditions. Although there are various sources of bioactive compounds used for AD treatment we have only discussed the commonly available. In this section, the effect of various bioactive compounds present in commonly available foods on AD has been summarized and discussed individually.

3.1. Curcumin

Curcumin is a polyphenolic compound derived from the *Curcuma Longa*. Various studies have shown the curative effect of curcumin on AD. The complete mechanism of the curative effect of curcumin is unknown. However, the three proposed mechanisms are 1) reducing the aggregation of A β peptides in the neural tissue due to their anti-inflammatory property [49]. 2) Inhibition of enzymes β -Secretase and

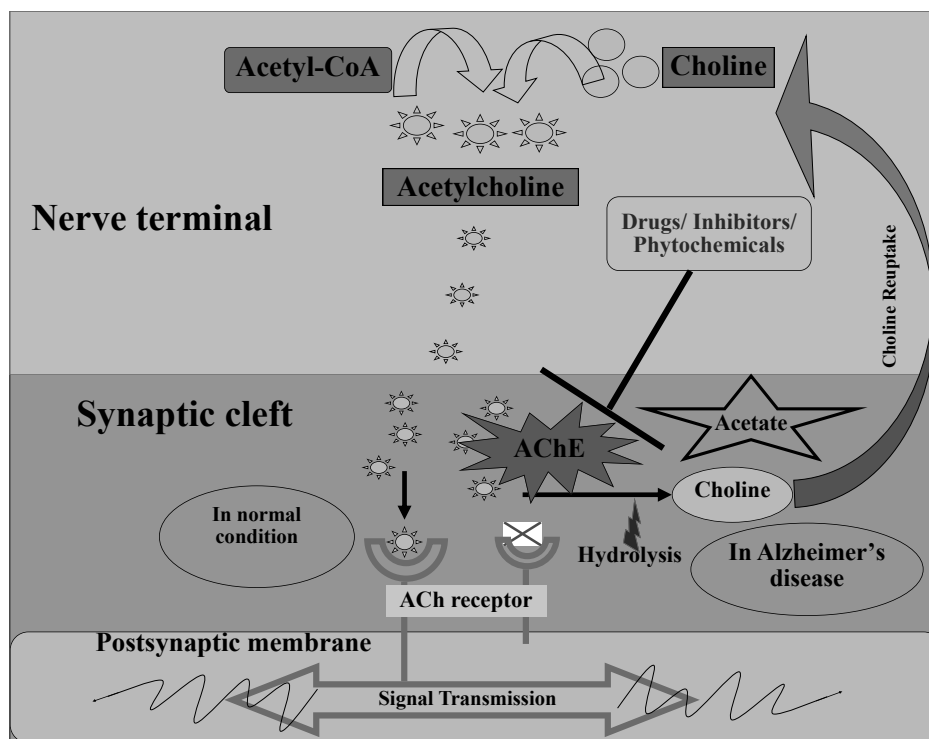


Fig. (1). Mechanism of AChE in Alzheimer disease. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

AChE responsible for the formation of A β fibril [50]. 3) Metal ions present in the synapse regions alleviate the aggregation of A β ; the phosphorylation of the tau protein bind with metal ions is the main mechanism behind its neuroprotective property [51, 52].

Using protein-ligand docking and ab initio fragment molecular orbital curcumin derivatives have been investigated to inhibit the aggregation of amyloid- β peptides (A β s) in the brain [53]. Curcumin-loaded nanocapsules have shown an antidepressant-like effect against the A β_{25-35} induced neurotoxicity in mice. Curcumin-loaded nanocapsules were also found more effective than the free curcumin [54]. A study was conducted on streptozotocin-induced rats to find the effect of curcumin on short-term spatial and recognition memory. It has been observed that the doses of 50 and 100 mg kg⁻¹ of curcumin preserved short-term object recognition memory but not short-term spatial memory suggesting a positive effect of curcumin on the former which was not related to hippocampal neurogenesis [55]. An evidence-based *in vivo* study on albino rats was tested for AD by using the steroid curcumin derivatives. These compounds showed anti-AD activity by enhancing ACh synthesis, GSh level, paraoxonase level, and BCL2 lymphoma level as compared to the untreated group [41]. A model of AD induced by A β_{1-42} peptide in aged female mice has been studied against curcumin lipid-core nanocapsules. It has been reported that after the administration of curcumin lipid-core nanocapsules, displayed significant neuroprotection against A β_{1-42} induced behavioral and neurochemical changes in Alzheimer's model [56]. In a study, selenium nanoparticles encapsulated in Poly-lactide-co-glycolide polymer with curcumin greatly

cured the memory and decreased the A β load in the brain samples of Alzheimer's mice [57]. The effect of erythropoietin and curcumin on streptozotocin-induced Alzheimer's dementia rats was studied. It has been reported that the administration of erythropoietin suppressed extrinsic apoptosis while curcumin was effective in combating oxidative stress in streptozotocin-injected rats [58]. Amyloid-binding properties of curcumin analogs *viz.*, demethoxycurcumin, bis-demethoxycurcumin and dimethoxycurcumin in AD have been conducted through *in vitro* autoradiography and it has been reported that BDMC had the highest affinity for A β containing plaques in brain tissues as compared to other curcuminoids. These findings propose that curcumin analogs may serve as a possible radio-ligand for A β plaque neuroimaging [59].

3.2. Chitosan

Chitosan is derived by partial deacetylation of chitin which is present in crustacean shells. It is composed of two basic units glucosamine and N-acetylglucosamine. Chitosan shows mucoadhesive properties because of its positive charge. It is insoluble in water and organic solvents with a weak basic nature. The biodegradability, low toxicity, and biocompatibility with other compounds make it suitable for use in biomedical and pharmaceutical formulations. In recent studies, it has been revealed that short-chain chitosan known as chitoooligosaccharides have possessed neuroprotective properties because of their ability to inhibit the A β and AChE activities. It has also been found to have anti-neuroinflammation and anti-apoptosis effects, which suggest its relation to cure AD [60-63].

In the recent study, chitosan oligosaccharides were chemically modified to prepare peracetylated and N-acetylated chitosan. Their effect against glutamate-induced PC12 cell death was analyzed and they reported that the pretreatment of PC12 cells with the peracetylated chitosan oligosaccharides markedly inhibited glutamate-induced cell death in a concentration-dependent manner. It has also decreased the lactate dehydrogenase release and reactive oxygen species production and loss of mitochondrial membrane potential. Suggesting the peracetylation is essential for the neuroprotective effects of chitosan oligosaccharides [60]. Jia *et al.* [64] reported that the chitosan oligosaccharides have shown favorable effects on the cognitive impairments in the A β ₁₋₄₂ induced rat model of AD. This was due to the inhibition of oxidative stress and neuroinflammatory responses. Other findings confirmed that due to the attenuating oxidative stress by chitooligomers a significant inhibition of dopaminergic neurodegeneration and linked physiological alteration induced by monocrotophos was observed in *C. elegans* [62]. Chitooligosaccharides with six different molecular weights were studied against the inhibition of AChE and it has been reported that the 90 molecular weight chitooligosaccharide exhibited potent AChE inhibitory activities compared to other molecular weights [65]. Pangestuti & Kim [61] has summarized the neuroprotective properties of chitosan and its derivatives. As per the data chitosan and its derivatives have shown promising properties such as suppression of A β formation, AChEs, anti-neuroinflammatory activity, apoptosis inhibitors, *etc.*, which reveal the potential of chitosan and its derivatives as potential therapeutic candidates for ND management. Zhou *et al.* [63] have reported chitooligosaccharides to protect cultured hippocampal neurons against glutamate-induced neurotoxicity, which suggests that it prevents cultured hippocampal neurons from glutamate-induced cell damage by intrusive with a raise in [Ca²⁺] and inhibiting caspase-3 activity. In addition to the above studies of chitosan has been used as a vehicle for brain drug delivery because of its good biocompatibility and biodegradability properties [66-71].

3.3. Shilajit

Shilajit is a blackish-brown powder or exudates from high mountain rocks [72]. It takes centuries to produce by the decomposition of plant material from species such as *Euphorbia royleana* and *Trifolium repens* [73]. The composition of shilajit may vary from place to place; however the common composition is composed of minerals, mainly selenium, dibenzo- α -pyrones, and humic substances, which include humins, humic acid, and fulvic acid. Other than these molecules, it contains ellagic acid, some fatty acids, resins, latex, gums, albumins, triterpenes, sterols, aromatic carboxylic acids, 3,4-benzocoumarins, amino acids, polyphenols, and phenolic lipids [74, 75].

Effects of shilajit on biogenic free radicals have been estimated by Bhattacharya *et al.* [76] and they have reported that the processed shilajit 20 and 50 mg kg⁻¹ day⁻¹ for 21 days induced a dose-related increase in free radical scavenging enzymes superoxide dismutase, catalase, and glutathione peroxidase activities in frontal cortex and striatum of rats, which suggests the use of shilajit against oxidative stress and

geriatric complaints. The improved learning and the memory engram in rats, especially in aged rats, have been reported to increase after the administration of shilajit [77]. Administration of shilajit and *Withania somnifer* in male wistar rats were studied to find their effect on memory enhancement. It has been reported that the administration of shilajit decrease the AChE straining, restricted to the basal forebrain nuclei, including the medial septum and the vertical limb of the diagonal band [78]. With the help of atomic force techniques, it has been observed that the fulvic acid present in the shilajit slows down the tau protein aggregation thus affecting the fibril length and their morphology. Thus, fulvic acid can be used as a potential nutraceutical for the treatment of AD [72, 79].

3.4. Ginkgo Biloba

Ginkgo biloba tree is widely cultivated in China as a source of food and traditional medicine. Ginkgo supplements are used to treat AD, dementia, or cognitive impairment. The bioactive components of *Ginkgo biloba* are flavonoids, terpenoids, and terpene lactones (ginkgolides and bilobalide). The proposed mechanisms of *Ginkgo biloba* against AD are the modification of the neurotransmitter system, reducing free radicals, increasing blood supply of the brain, and reducing blood viscosity [80]. Vitolo *et al.* [81] has found the protective effect of *Ginkgolide J* against A β induced irregular synaptic function and cell death. Oral administration of *Ginkgo biloba* extract showed the partial recovery of memory deficit and decreased the choline acetyltransferase activity in the hippocampus of rats treated with intraventricular infusion of A β for 14 days [82]. *Ginkgo biloba* a flavonoid-rich antioxidant showed the enhancement of spatial learning and memory of transgenic rats, which was independent of an influence on soluble A β or A β plaque burden [83]. In a 3 months study, the patient's attention and memory performance showed significant improvement compared to placebo with the oral administration of *Ginkgo biloba* extract [84]. Ismail & El-Sonbaty [85] reported the enhanced effect of *Ginkgo biloba* leaf extract with fermentation against neuroinflammation, stress hormones, apoptosis, and oxidative damage induced by gamma irradiation in the rat brain. The fermentation by *Aspergillus niger* enhanced the bio-activities of *Ginkgo biloba* leaf extract as compared to non-fermented extract. Another study has reported the reduced oxidative stress by *Ginkgo biloba* in the brain tissues of rats induced by electromagnetic waves of mobile phones [86]. The above pieces of evidence suggest the *Ginkgo biloba* is a potential remedy to treat AD.

3.5. Drumstick

Moringa oleifera is found in Asian and African countries. Its leaves and fruits are consumed by the people [87, 88]. As a food, its extracts are not toxic [87]. The leaves of *Moringa oleifera* have shown nootropics activity and protection against oxidative stress produced in AD [89]. It was also found that the leaves of *Moringa oleifera* protect hypobaric hypoxia by altering monoamines in the brain [90]. The effect of *Moringa oleifera* leaves extract on colchicines infused AD model in rats has been reported to increase superoxide dismutase and catalase activity and decrease lipid peroxidase in the cerebral cortex [91]. Ekong *et al.* [92] reported the protective effect of

Table 1. Role of alkaloid compounds in Alzheimer's disease.

S. No.	Alkaloid Compounds	Test	Result	Refs.
1	Aromoline	<i>In vitro</i>	Showed significant human BChE (hBChE) inhibitory activity.	[124]
2	Berberine	Alzheimer's like disease was induced in rats orally by a mixture of aluminum, cadmium, and fluoride	Improved cognitive behaviors and Docking results showed that berberine inhibited AChE, COX-2, and TACE.	[125]
3	Berberine	A β 25-35 induced apoptosis in primary neuron cells isolated from the hippocampus of newborn mice	Berberine reversed the effects induced by A β 25-35. Berberine attenuated the cytotoxic effect of A β 25-35. Berberine led to a decline in the apoptotic rate.	[126]
4	Berberine loaded multi-walled carbon nanotubes with polysorbate and phospholipid coating	<i>In vivo</i> pharmacokinetic studies in rats	Improvement in the rate and extent of drug absorption in the plasma and brain tissues. Phospholipid-coated and the polysorbate-coated exhibited remarkable recovery in-memory performance from 18th to 20th day.	[127]
5	Berberine	Ethanol-induced oxidative stress and memory dysfunction in rats	Prevents changes in oxidative stress and cholinesterase activity.	[128]
6	Berberine	Synaptic deficits induced by D-galactose in Male Wistar rats	Synaptic/memory impairments.	[129]
7	Berberine	Twenty-month-old male C57BL/6 mice	Alleviate postoperative cognitive dysfunction by suppressing neuroinflammation in aged mice.	[130]
8	Berberine	Diabetic neuropathy induced by streptozotocin and a high-carbohydrate/high-fat diet in rats.	Beneficial against diabetic neuropathy induced by streptozotocin and a high-carbohydrate/high-fat diet in rats.	[131]
9	Dehydroevodiamine	Rat brain slices	It activates a PP2A Tyr307 site and inhibits phosphorylation of tau in rat brain.	[132]
10	Galantamine co-administration with adenosine	Oral tremor induced by galantamine in rats.	Significantly attenuated the tremulous jaw movements induced by the galantamine. It may be beneficial in reducing parkinsonian motor impairments induced by anticholinesterase treatment.	[133]
11	Galantamine hydrobromide	Chronic effects of Galantamine hydrobromide on male albino mice.	Galantamine hydrobromide exerted severe perturbations in the cholinergic system in all regions of the brain on chronic exposure, thus eventually leading to behavioral changes.	[134]
12	Galantamine attaching to ceria-containing hydroxyapatite as well ceria-containing Carboxymethyl chitosan-coated hydroxyapatite nanocomposites.	Ovariectomized AD albino-rats	Nanoceria-containing uncoated hydroxyapatite-based-galantamine nanocomposite had been found a highly efficient anti-Alzheimer agent, where the nanoceria and hydroxyapatite also showed noteworthy useful effects to galantamine on drug-delivering action, scavenging the hazard reactive oxygen species, repairing the degenerated nerve cells, and discarding the toxic A β -amyloid plaques.	[135]
13	Galantamine	AD model mice	Administration of galantamine from the preplaque phase ameliorates the memory decline, improved the unbalanced redox state, and enhanced microglial function.	[136]
14	Huperzine A	Alzheimer Transgenic Mouse Model	It reduces the level of A β .	[137]
15	Huperzine C	<i>In vitro</i>	Showed moderate AChE inhibition with an IC50 value of 0.525 \pm 0.140 μ M	[138]
16	N-methylasimilobine	<i>In vitro</i>	Exhibited 50% inhibition of AChE at the concentration of 1.5 \pm 0.2 μ g mL ⁻¹	[139]
17	Isorhynchophylline	Amyloid- β Induced Cognitive Impairment in Rats	It restores A β -induced a cognitive impairment inhibits neuronal apoptosis and reduces phosphorylation of tau.	[140]

(Table 1) contd....

S. No.	Alkaloid Compounds	Test	Result	Refs.
18	Galanthamine	<i>In vitro</i>	The inhibitory potential of AChE with IC ₅₀ values was 0.35 μmol/L	[141]
19	Palmatine	<i>In vitro, in vivo</i> and <i>ex vivo</i>	Exhibits anti-inflammatory, anti-depressive, anti-pyretic, anti-neurodegenerative properties.	[142]
20	Palmatine and physostigmine	Swiss young male albino mice	Palmatine and physostigmine significantly improved the learning and memory of mice	[143]
21	Palmatine	<i>In vitro</i>	Inhibit PHF6 and full-length tau aggregation and disassemble pre-formed fibrils	[144]
22	Phenserine	Three-month-old male Fischer-344 rats	Possess the AChE inhibitory activity	[145]
23	Sanguinine	<i>In vitro</i>	Inhibited the activity of AChE	[146]
24	Taspine	<i>In vitro</i>	Inhibited the activity of AChE with an IC ₅₀ value of 0.33 ± 0.07 μM	[147]

Moringa oleifera leaf extract on the aluminum-induced temporal cortical degeneration in male albino Wistar rats. *Moringa oleifera* leaf extract reduced the serum aluminum concentration and fights against aluminum-induced neurohistopathology in the temporal cortex [92]. *Moringa oleifera* leaf extract was incubated with the primary culture of embryonic hippocampal neurons and it has been reported that the leaf extract promoted axodendritic maturation and neuroprotection, suggesting its well-being importance for the nervous system [93]. In a recent study, *Moringa oleifera* was tested against hyperhomocysteinemia induced AD-like pathology in rats, the results showed to prevent the oxidative stress and cognitive impairments induced by homocysteine. It has also decreased the tau hyperphosphorylation and Aβ production in the AD rat model [94]. From the above data, *Moringa oleifera* is well supported as a good candidate for the treatment of AD.

4. ROLE OF ALKALOID COMPOUNDS IN ALZHEIMER'S DISEASE

Alkaloids are a group of natural compounds with organic nitrogen, having low molecular weight primarily found in 25% of the species of higher plants as a secondary metabolite. It is abundant in the Apocynaceae, Fabaceae, Asteraceae, Rubiaceae, Papaveraceae, and Solanaceae families [95, 96]. Since ancient times plant extracts containing alkaloids like *Atropa belladonna*, *Papaver somniferum*, *Hyoscyamus niger*, and *Erythroxylum coca* have been used for medicinal purposes [97]. These compounds have been used in various pathologies like AD in Table 1.

4.1. Berberine

Berberine is isolated from the *Rhizoma coptidis* which is a perennial herb and a natural isoquinoline alkaloid. This compound is said to be beneficial for AD by inhibiting Aβ production. It has been reported that the berberine reduced and promoted the hyperphosphorylation of tau and autophagic clearance of tau, respectively, in the mouse model, which strongly supports the berberine as a potential drug candidate for AD [98]. In an experimental model of intracerebroventricular streptozotocin-induced sporadic Alzheimer's-like dementia, administration of berberine has prevented memory

loss, anxiogenic behavior, AChE activity, and cell death induced by intracerebroventricular streptozotocin by protecting the progression of neurodegeneration [99]. A neonatal rat model was induced with schizophrenia with the administration of MK-801 and the rodents treated with berberine showed improved motor and cognitive disturbances [100]. The effect of berberine on Aβ-induced impairments in learning and memory of male Wistar rats was reported to prevent memory impairment by restoring the Aβ-induced impairments [101]. Berberine administration was evaluated with western blotting, morris water maze, immunofluorescence staining enzyme-linked immunosorbent assay, and histological analysis, and against AD in mice, it has been reported that berberine significantly enhanced the mice's spatial learning capacity and memory retention by reducing the Aβ plaque deposition in the hippocampus [102].

4.2. Galantamine

This tertiary alkaloid is isolated from the flowers and bulbs of *Galanthus woronowii*, *Galanthus caucasicus*, *Narcissus*, *Leucojum aestivum*, and *Lycoris radiata* [103]. It acts as an AChIs and is approved by the FDA to cure AD, which is available in the market with a generic name as ORAL (ga-LAN-ta-meen)[104]. Galantamine reversibly inhibits cholinesterase, thus preventing the lyses of neurotransmitters [105]. Lyketsos *et al.* [106] have reported the safety and tolerability of galantamine for up to 18.5 months. The effect of galantamine on cardiac function of newly diagnosed AD patients was evaluated by Isik *et al.* [107] and they reported that no significant changes in arterial blood pressure occurred at any investigated dosage level. A study was carried to find the metabolite changes in the hippocampal after galantamine treatment for AD. It was reported that the levels of glutamate, glutamate/creatine, and glutamate/N-acetyl aspartate increased after four months of treatment with galantamine [108].

4.3. Palmatine

Palmatine is an isoquinoline alkaloid with various pharmacological effects like AD, age-related disease, cancer, cardiac hypertrophy, osteoporosis, and diabetes [109-111]. It is found in *Tinospora cordifolia* (Willd.) Miers [112], *Corydalis*

yanhusuo [113], *Coptis chinensis* Franch. [114], *Tinospora sagittata* (Oliv.) Gagnep [115], *Phellodendron amurense* Rupr. [116] and *Stephania yunnanensis* [117]. Palmatine has shown neuroprotective activity mainly by inhibiting the activity of AChE, BChE, and neuraminidase-1 [118]. It has been reported that palmatine had an antidepressant effect because it regulates brain catalase levels, lipid peroxidation, monoamine oxidase-A activity, plasma nitrite, and corticosterone levels [119]. The synergetic effect of palmatine with berberine has been reported to intensify the inhibition of AChE [120].

4.4. Chelerythrine

Chelerythrine is an alkaloid present in *Chelidonium majus* L., *Sanguinaria canadensis* L., *Dicranostigma lactucoides*, and *Zanthoxylum* spp. [121]. Chelerythrine inhibits AChE and BChE activity and A β aggregation [122]. It has been reported that chelerythrine inhibits the activity of the CYP1A1 enzyme, which can activate some toxic compound to cause cancer [123].

CONCLUSION

Phytochemicals have extraordinary biological action and keep on entering into clinical trials, like alkaloids, nutraceuticals, and nutrients from plants, and it is used for the treatment of various diseases like neurodegenerative issues, cardiovascular ailments, and malignant growth. We emphasized the use of phytochemicals for the effective management of AD in this article. Phytochemicals have the smallest toxicity along with a high level of the repairable property concerning the human body as they are used for AD management. Phytochemicals possess several biological properties like free radical scavenger, anti-inflammatory, anti-aging, and anti-ND properties. For this reason, fruits, vegetables, and spices are recommended for the daily use in the diet because they contain several antioxidant natural compounds. The earth is blessed with diverse foods having nutraceutical properties but due to lack of scientific evidence, they have not been recognized for their curative properties. There is a huge research gap in this field that should be analyzed, evaluated, and summarized in the future.

LIST OF ABBREVIATIONS

ACh	=	Acetylcholine
AChE	=	Acetylcholinesterase
AChIs	=	Acetylcholinesterase Inhibitors
AD	=	Alzheimer's Disease
A β	=	Amyloid-beta
BChE	=	Butyrylcholinesterase

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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