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Therapeutic Efficacy of Natural Phytochemicals as Acetylcholinesterase Inhibitors Against Alzheimer's Disease

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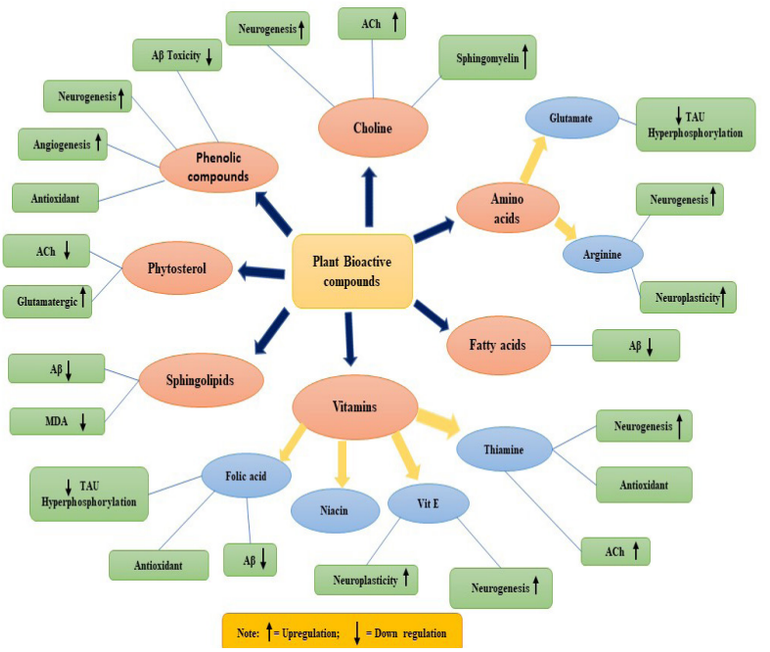
Abstract

Alzheimer's Disease (AD) is a chronic degenerative brain illness marked by a slow, steady loss in cognitive function and behaviour. AD is an aging-related dementia that begins with memory loss and progresses to the destruction of brain functions as the neocortex suffers neuronal, synaptic, and dendritic connections. The formation of amyloid plaques causes the entire phenomenon to spread. Although there is presently no treatment, cholinesterase inhibitors give excellent temporary alleviation of symptoms in some individuals. The cholinergic hypothesis, which promotes cognition enhancement by regulating the production and release of acetylcholine in the brain, is now the basis for medication research and development. Acetylcholinesterase inhibitors and N-Methyl-D-Aspartate (NMDA) receptor antagonists are two drugs authorised to treat Alzheimer's disease. Caregivers who do not have enough information on Alzheimer's disease may feel that there is nothing they can do to manage the illness's symptoms. This article aims to highlight the plant extract/compounds and FDA approved drugs which play the most significant role as acetylcholinesterase inhibitors in AD.

Graphical Abstract



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1. Introduction

Alzheimer's Disease (AD) is a chronic neurodegenerative disease that has been designated as a worldwide public health priority by the World Health Organization. Aloysius Alzheimer initially characterised the clinical condition in his 51-year-old patient in 1907. At autopsy, he noted neuritic plaques, neurofibrillary tangles, and amyloid angiopathy, all of which are markers of Alzheimer's disease. In 2018, there were around 5.7 million people living with Alzheimer's disease in the United States; this number is expected to rise by nearly 30% to 7.1 million by 2025, and to 13.8 million by 2050[1] . It is the most prevalent kind of dementia, accounting for 60–70% of all cases. The primary factors of the rising number of common dementia cases are population ageing and growth. In 2016, dementia was the fifth leading cause of mortality worldwide (2.4 million fatalities) and the second leading cause of death in those over the age of 70. It is now widely accepted that Alzheimer's disease is a complex illness caused due to hereditary and environmental factors. The dominant autosomal mutations affecting the genes coding for the amyloid precursor protein, presenilin 1, and presenilin 2 have been linked to the development of early-onset AD, which occurs before the age of 65 years and accounts for around 5% of all AD cases[2]. Though a large number of hypothesis have been proposed to explain the pathophysiology and symptoms of Alzheimer's disease, including the amyloid hypothesis, cholinergic deficit hypothesis, hyperphosphorylated tau protein hypothesis, neuro-inflammation, and many more. Currently FDA-approved pharmacotherapy focuses primarily on the cholinergic hypothesis.

Cholinergic neurotransmitters are important in memory, learning, behaviour, and attention. Acetylcholinesterase and Butyrylcholinesterase are the two major enzymes in the brain that hydrolyse Ach[3]. Reduced brain acetylcholine levels, particularly in the nucleus basalis of Meynert, are considered the cause of cognitive impairment in Alzheimer's disease, according to the cholinergic hypothesis[4]. According to the amyloid hypothesis, the overproduction and/or impaired clearance of Aβ peptides produced from APP proteolysis via the amyloidogenic pathway initiated by β-secretase is the primary pathogenic event in AD (or BACE1). Aβ40 and Aβ42 are the most hazardous Aβ types in Alzheimer's disease; the second one is more hydrophobic and amyloidogenic. The β-sheet configuration of the misfolded Aβ monomers leads to soluble and insoluble oligomeric complexes. These oligomers of various sizes aggregate in protofibrils, fibrils, and amyloid plaques in a sequential manner[5]. Aβ42 oligomers have been found to cause oxidative damage, increase Tau hyperphosphorylation, and have deleterious effects on synapses and mitochondria. Hyperphosphorylation of Tau protein, which occurs as a result of increased kinase activity and reduced phosphatase activity, is another significant component in the development of Alzheimer's disease. Glycogen synthase kinase 3 beta (GSK-3β) is the main kinase linked to Tau phosphorylation[6]. Detachment of hyperphosphorylated Tau protein from microtubules causes cytoskeletal instability, poor axonal transport, and synaptic dysfunction. Tau's hyperphosphorylation causes it to self-assemble into soluble Tau Oligomers (TauOs) of various sizes. Tau may also cluster form insoluble polymers like granular oligomers (gTauOs), Straight Filaments (SFs), Paired Helical Filaments (PHFs), and neurofibrillary tangles are three types of filaments seen in the brain (NFTs). Tauos, which are seen in the early stages of AD disease and are characterised by neurotoxicity and the capacity to spread to neighbouring neurons and microglial cells, appear to be the most toxic amongst all Tau proteins[7].

In Alzheimer disease, the changes in AChE and BChE activity, which were the targets for the action of ChEIs. Immunotherapy-based methods have failed in phase II or III clinical trials, while additional therapeutic options addressing the amyloid and tau theories have not proven successful[8]. Despite repeated attempts to create preventive and disease-modifying treatments, ChEIs continue to play an important role in treating symptoms and maybe delaying the development of AD. This article examines the safety and efficacy of different acetylcholine esterase inhibitors in the treatment of Alzheimer's disease and/or other serious neurocognitive disorders.

This review also includes a review of the relevant literature on the beneficial effects of medicinal plants in dementia, particularly Alzheimer's disease-related dementia, as well as an assessment of the claims of therapeutic effects of various medicinal plants used in various traditional systems of medicine and a comparison of folkloric and scientific evidence. We also wanted to compile high-quality studies and highlight medicinal plants with the greatest potential to prevent, mitigate, and treat Alzheimer's disease, as well as provide insights into future strategies, research directions, and identify bottlenecks that prevent widespread ethnopharmacological use of medicinal plants in healthcare systems around the world.

2. Cholinestrase Inhibitors

Three Cholin-Esterase Inhibitors (ChEIs) – donepezil, galantamine, and rivastigmine – and a glutamate receptor antagonist – memantine – are already FDA-approved

medications for the symptomatic treatment of mild to severe AD. Despite the fact that ChEIs only produce little improvement in cognition in dementia patients, they are the most commonly utilised pharmaceutical treatments for this illness[9]. AChE is an enzyme that converts ACh to acetate and choline, putting an end to its activity. It is membrane bound and may be found both pre- and post-synaptically in the nerve terminal. A similar enzyme, BChE, is a nonspecific protein that hydrolyzes a wide range of choline-based esters. AChEIs bind to the enzyme and offer an indirect cholinergic effect by inhibiting its breakdown, resulting in the buildup of ACh and eliciting a reaction that aids in the symptomatic relief[10]. Current ChEIs, on the other hand, are commonly related to adverse side effects. Weight loss and anorexia are two of the most underreported and underappreciated side effects of ChEIs. Both of these factors are linked to mortality, especially among the elderly. Patients commonly have bradycardia in addition to Gastro-Intestinal (GI) problems[11].

As a result, new and safer ChEIs are urgently required. Numerous phytocompounds have a promising future as next-generation ChEIs. Galanthamine, donezepil, tacrine, and rivastigmine are only a few of the AChE inhibitors now being utilised to treat Alzheimer's disease in which only glutamine is a naturally occurring alkaloid first isolated from Galanthus spp.

Tacrine was the first Alzheimer's disease medication to be approved in the United States. The medicine (dual inhibitor) inhibits the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes, limiting acetylcholine metabolism and increasing its availability for binding to muscarinic receptors. It has been shown that as Alzheimer's disease progresses, AChE levels fall but BChE levels remain constant or rise, which might explain why dual cholinesterase inhibitors are more effective. Tacrine has had mixed outcomes in clinical studies in terms of effectiveness. Although some trials showed a statistically significant reduction in cognitive decline, the medication was stopped in 2013 owing to serious side effects, the most frequent of which were gastrointestinal and, less occasionally, hepatotoxicity (elevated transaminases), which might lead to death[12].

Donepezil was the second FDA-approved cholinesterase inhibitor to hit the market. The first formulations, 5 and 10 mg, were approved by the FDA in 1996 for the treatment of mild to moderate Alzheimer's disease, and a 23 mg dosage was approved in 2010 for the treatment of moderate to severe Alzheimer's disease[13]. Donepezil works by increasing the quantity of acetylcholine in the synaptic cleft by functioning as a highly selective, centrally acting, reversible inhibitor of acetylcholinesterase. This method of action is based on the cholinergic theory of Alzheimer's disease (AD), which states that raising the concentration of acetylcholine improves neuronal function[14].

Donepezil was shown to be more effective than galantamine or rivastigmine in improving global AD symptomatology in a 2017 meta-analysis by Blanco-Silvente *et al.*, 2017[15]. The most common side effects (AEs) reported after taking donepezil are related to the drug's mechanism of action, which is to increase cholinergic activity. Nausea, vomiting, diarrhoea, and abdominal cramps have all been described as GI adverse effects[1].

The FDA authorised oral rivastigmine in 2000 for the treatment of mild-to-moderate Alzheimer's disease and subsequently (2006) for the treatment of mild-moderate Parkinson's dementia, with an optimum therapeutic dosage of 6-12 mg/day[16]. Rivastigmine is as low ly reversible dual inhibitor of AChE and BChE. Rivastigmine is also not metabolised by the CYP-450 system, which means it has a lower risk of drug-drug interactions. Donepezil, on the other hand, despite these advantages, rivastigmine has been linked to the greatest risk of adverse events and a poorer all-cause discontinuation result when compared to other cholinesterase inhibitors in its oral form. Rivastigmine's role as a disease-modifying medication for AD has moved to that of a symptomatic treatment, hand, which is metabolised by CYP-450 and is solely selective for AChE inhibition[1]. However, rivastigmine has been demonstrated to change the ratio of AChE-R and -S isoforms and enhance nicotinic receptor expression, both of which have been linked to better cognition in Alzheimer's patients.

Galantamine Commercially known as Razadyne®, is a selective reversible inhibitor of AChE that was originally launched in the United States in 2000 as a therapy for AD. The medication inhibits acetylcholinesterase in a reversible and competitive manner, increasing ACh activity at the synapse level and improving cholinergic tone. Users of the substance report enhanced central cholinergic tone as a result of its inherent capacity to penetrate the blood-brain barrier. Galantamine is an allosteric modulator of nicotinic ACetylcholine Receptors (nAChRs), boosting the expression and activity of these receptors in central cholinergic neurotransmission, in addition to its inhibitory action on AChE. This action helps to partially repair deficits in the septo-hippocampal cholinergic pathway that are prevalent in Alzheimer's patients. Patients taking medication for the treatment of Alzheimer's disease have shown better cognitive performance and a considerable delay in the onset of behavioural abnormalities associated with the illness after chronic delivery[1].

3. Plant Extract/Compounds as Acetylcholine Esterase Inhibitor

The majority of currently authorised medicines, such as acetylcholinesterase inhibitors, are used to treat the cognitive symptoms of Alzheimer's disease. Current strategies can only

delay the progression of symptoms associated with AD. Many research teams have concentrated their efforts on naturally occurring plant chemicals as possible sources of novel or more effective AChEI. These researches resulted in the identification of a large number of secondary metabolites as well as plant extracts, both of which have the potential to inhibit AChE. The alkaloid family includes indoles, isoquinolines, quinolizidine, piperidines, and steroidal alkaloids, together constituting the majority of these AChEI. Natural sources, on the other hand, have yielded several non-alkaloidal and potent AChEI, including terpenoids, flavonoids, and other phenolic agents.

Table 1 represents the plant extract having cholinesterase inhibiting activity and Table 2 represents the natural compound isolated from the plant having anti-cholinestrase activity. The medicinal herb *Nelumbo nucifera*, which belongs to the Nelumbonaceae family, has been investigated for its therapeutic potential. This plant recently yielded N-methylasimilobine and an aporphine alkaloid with an IC50 of 1.5 µg/ml that was discovered to be a noncompetitive inhibitor[17]. Two *Beilschmiedia* species extracts were shown to inhibit AChE and phytochemical analysis of *B. alloiophylla* and *B. kunstleri* indicated the presence of various alkaloids with IC50 values ranging from 2.0 to 10.0 µM[18]. 2-hydroxy-9-methoxyaporphine, laurotetanine, liriodenine, and oreobeiline were shown to be the most powerful AChEI (IC50 = 2.0-5.0 µM), with anti-AChE activity equivalent to huperzine A (IC50 = 1.8 µM). Secoboldine, boldine, isoboldine, asimilobine, and 3-methoxynordomesticine all have substantial AChE inhibitory action (IC50 = 8.4 - 10.0 µM). The existence of benzylisoquinoline alkaloids with anti-AChE activity has been discovered in plants from the genus *Corydalis* (Papaveraceae) that are used in traditional medicine to treat memory impairment. The ethanolic extract from the tuber of *C. turtschaninovii*, which had previously been discovered to inhibit AChE, was chosen for a chemical investigation, which led to the separation of the isoquinoline alkaloids stylopine, epiberberine, pseudodehydrocorydaline, pseudocopsitine and pseudoberberine with IC50 15.8, 6.5, 8.4, 4.3 and 4.5 µM, respectively[19].

Table1. Plant extract as ChE Inhibitor

Plant	Family	Extract/fraction	Plant part	Activity	Ref.
Salsola oppositifolia	Amaranthaceae	Alkaloids		AChE inhibitory activity with 70.0 µg/ml IC50 value.	54
Adhatoda vasica	Acanthaceae	methanolic extract	leaves, seed and root	AChE inhibitory activity	20
Rhinacantus nastutas	Acanthaceae	methanolic extract	Leaf	highest inhibitory activity against AchE	21
Acorus calamus	Acoraceae	methanolic extract	Rhizome	AChE inhibitory activity with IC50 of 82 µg/mL	22
Acorus tatarinowii	Acoraceae	Hydroalcoholic	Rhizome	inhibitory activity against both AChE and BChE	23
Eucharis bonplandii	Amaryllidaceae	Alkaloids	leaf and bulb	IC50 value 0.72 ± 0.05 µg/mL against human recombinant AChE	24
Crinum jagus	Amaryllidaceae	Alkaloids	leaf and bulb	IC50 was 8.51 ± 0.56 µg/mL against human serum BChE	24
Galanthus nivalis	Amaryllidaceae	Alkaloids	whole plant	potent inhibitory activities against AChE in both in vitro and invivo experiments	25
Sesuvium portulacastrum	Aizoaceae	Methanolic	Leaf	cholinergic inhibitory activity was observed with IC50 value of 1.18 ± 0.005 mg/mL for TChE and 1.0 ± 0.017 mg/mL for BChE.	26
Suaeda monoica	Amaranthaceae	methanolic extract	Leaf	dual cholinergic inhibitory activity was observed with IC50 value 1.42 ± 0.007 mg/mL for TChE and 0.52 ± 0.018 mg/mL for BChE	26
Atriplex laciniata L.	Amaranthaceae	Methanolic	whole plant	showed AChE and BChE inhibition	27
Aerva javanica	Amaranthaceae	Methanolic	Flower	inhibitory activity against AChE and BchE	28
Haloxylonsalicornicum	Amaranthaceae	Hydroalcoholic	Rhizome	Inhibitory activity against ChE enzymes	29

Mutellina purpurea,	Apiaceae		Fruits	percentage inhibition was found to be 9.30 ± 1.86% and 91.62 ± 1.53% against AChE and BChE, respectively	30
Angelica decursiva	Apiaceae	Methanolic extract	whole plant	inhibitory activity against α-glucosidase, protein tyrosine phosphatase 1B (PTP1B), acetylcholinesterase (AChE), and butyrylcholinesterase (BChE).	20
Chaerophyllum aromaticum	Apiaceae	Methanolic	Roots and aerial parts	inhibit AChE activity	74
Hemidesmus indicus	Apocynaceae	Methanolic	root	phenolic compounds as AChE inhibitors	31
Holarrhena pubescens	Apocynaceae	alkaloid extract	Bark	strong AChE inhibition. IC50 values ranged from 1.44 to 23.22 μM	32
Rauvolfia reflexa	Apocynaceae	Alkaloid	Bark	most potent inhibitor of AChE and BchE	33
Acanthopanax henryi	Araliaceae	Alkaloid	Leaves	strong AChE inhibitory activity with IC50 values ranging from 62.6 to 121.9 μM.	34
Panax japonicas	Araliaceae	Alkaloid	Leaves	AChE inhibitors	35
Eleutherococcus gracilistylus	Araliaceae	Chloroform	Leaves	strong inhibitory effect against AChE and BChE	36
E. setchuenensis	Araliaceae	Ethanolic	whole plant	potent inhibitor of AChE	36
Acanthopanax henryi	Araliaceae	Alcoholic	Leaves	strongest inhibitors of AChE	34
Aralia cordata	Araliaceae	n-hexane	Root	potent inhibitors of BChE but not for AchE	37
Phagnalon saxatile	Asteraceae	Methanolic	whole plant	showed inhibition of both AChE and BchE	38
Pulicaria stephanocarpa	Asteraceae	Chloroform	whole plant	AChE inhibitory activity of greater than 50% at a concentration of 200 μg	39
Artemisia annua,	Asteraceae	Ethanolic	whole plant	AChE inhibitory activity	40
Carthamus tinctorius	Asteraceae	Alcoholic	Seed	exhibited inhibition of AChE	41
Xeranthemum annuum L.	Asteraceae	chloroform and ethylacetate	flower and root-stem	Most effective extracts towards BChE inhibition	42
Zephyranthes carinata	Amaryllidaceae	Alkaloidal	Bulb	inhibitory activity of AChE with IC50 value 18μg/ml.	43
Pavetta indica L.	Rubiaceae	methanolic extract	aerial part	inhibitory activities towards acetylcholine-esterase, butyrylcholine-sterase, and α-glucosidase (α-Glc) with IC50 value of 17.8μg/ml.	44
Carpolobia lutea	Polygalaceae	Ethyl acetate	Root	anti-AChE activity with 0.3μg/ml IC50 value.	45
Morus alba L.	Moraceae	Ethyl acetate	root-bark	strong AChE- and BChE-inhibitory activities	46
Buchanania axillaris	Anacardiaceae	Methanolic extract	aerial parts	inhibition against AChE, BuChE, α- and β-glucosidase enzymes	44
Huperzia squarrosa	Lycopodiaceae	Ethyl acetate	aerial parts	anti-AChE activity	47
Ochna obtusata	Ochnaceae	Chloroform	aerial parts	inhibitory activities towards acetylcholine-sterase, butyrylcholine-sterase, and α-glucosidase (α-Glc).	44
Phlegmariurus tetragonus	Lycopodiaceae	Alkaloidal	Aerial	AChE inhibitory activity	48
Scadoxus puniceus	Amaryllidaceae	Ethyl acetate	Bulb	AChE inhibitory activity	49

Table 2. Natural compounds as AChE Inhibitor

Plant	Family	Compound	Activity	IC50	Ref.
Skimmia laureola	Rutaceae	3-hydroxy-2,2,6-trimethyl3,4,5,6-tetrahydro-2H-pyrano[3,2-c] quinoline-5-one	AChE and BChE inhibitory activity	110μM	[59]
		Ribalinine	AChE and BChE inhibitory activity	30μM	[59]
		Methyl isoplatydesmine	AChE and BChE inhibitory activity	30μM	[59]
Esenbeckia leiocarpa	Rutaceae	Leptomerine	AChE inhibitory activity	2.5μM	[50]
		Kokusaginine	AChE inhibitory activity	46μ M	[50]
Zanthoxylum nitidum	Rutaceae	Skimmianine	very low AChE inhibitory activity	8.6 μg/ml	[51]
		Furoquinoline	very low AChE inhibitory activity	8.6 μg/ml	[51]
Nelumbo nucifera	Nelumbonaceae	N-methylasimilobine	non-competitive inhibitor of AchE	1.5 μg/ml	[54]
Corydalis turtschaninovii	Papaveraceae	Stylopine	Inhibit AchE	15.8μM	[19]
		Epiberberine	Inhibit AchE	6.5μM	[19]
		Pseudodehydro-corydaline	Inhibit AchE	8.4μM	[19]
		Pseudocopsitine	Inhibit AchE	4.3μM	[19]
		Pseudoberberine	Inhibit AchE	4.5μM	[19]
Coptis chinensis	Ranunculaceae	Berberine	anti-AChE activity	ranged between 0.44 and	[37]
		Palmatine			
		Jateorrhizine		0.80 μM	
		Coptisine			
		Groenlandicine			
		Epiberberine	anti-AChE activity	1.07 μM	[37]
Stephania venosa	Menispermaceae	Stepharanine	high AChE-inhibtion	14.10μM	[52]
		Cyclanoline	High AChE-inhibtion	9.23μM	[52]
		N-methyl stepholidine	High AChE-inhibtion	31.30μM	[52]
Chelidonium majus	Papaveraceae	8-hydroxydihy-drochelerythrine	AChE inhibitory activity	0.61μM	[72]
		8-hydroxydihy-drosanguinarine	AChE Inhibitory activity	1.37 μm	[72]
Magnolia x soulangiana	Magnoliaceae	Taspine	long-lasting inhibitory effect on AchE	0.33 μM	[55]
Catharanthus roseus	Apocynaceae	Serpentine	potent in vitro AChEi	0.775 μM	[53]
Ervatamia hainanensis	Apocynaceae	Coronaridine	AChE inhibitory activity	8.6μM	[66]
		Voacangine	AChE inhibitory activity	4.4μM	[66]

Tabernaemontana divaricata	Apocynaceae	19,20-dihydrotabernamine	AChE inhibitory activity	0.227	[69]
		19,20-dihydroervahanine A	AChE inhibitory activity	0.071 μM,	[69]
		Conodurine	no AChE inhibitory activity		[69]
		Tabernaelegantine	no AChE inhibitory activity		[69]
Uncaria rhynchophylla	Rubiaceae	Geissoschizine methyl ether	inhibit AChE in a reversible and non-competitive way	3.7μg/ml	[67]
Himatanthus lancifolius	Apocynaceae	Uleine		0.45μM	[68]
Hippeastrum papilio	Amaryllidaceae	11β-hydroxygalantha-mine	AChE inhibition	14.5μM	[69]
Leucojum aestivum	Amaryllidaceae	N-allylnorgalantha-mine	potent AChEi than galanthamine	0.18μM	[56]
		N- (14-methylallyl) norgalanthamine	potent AChEi than galanthamine	0.16μM	[56]
Galanthus rizehensis	Amaryllidaceae	incartine N-oxide	moderate inhibitory activity	34.5μM	[73]
		lycorine N-oxide	AChE inhibition	106.97μM	[73]
Nerine bowdenii		Undulatine	AChE inhibition	37 μM	[70]

Two Zingiberaceae plants were examined to inhibit AChE. At 0.1 mg/mL, ethanolic extracts of *Kaempfera parviflora* inhibited AChE by 64%. Bioactive compounds from *Curcuma longa* inhibited AChE with IC50 values of 19.67, 16.84, 33.14, and 67.69 μM for curcuminoids, bisdemethoxycurcumin, demethoxycurcumin, and curcumin[57]. In an investigation, the researcher reported that *Hedychium gardnerianum* leaf essential oils were tested for inhibitory effect on AChE with IC50 value of 1 mg/mL. The main component identified in the oil was sesquiterpenes[71]. *Aframomum danielli* and *A. melegueta* seeds were used to make phenolic extracts that were tested for AChE inhibitory activity in a separate research[58].

The quinoline alkaloids methyl isoplatydesmine, ribalinine, and 3-hydroxy-2,2,6-trimethyl-3,4,5,6-tetrahydro-2H-pyrano[3,2-c] quinoline-5-one were found to be linear mixed inhibitors of AChE with inhibition constant 30.0μM, 30.0μMand 110.0μM respectively, isolated from the aerial parts of *Skimmia laureola* (Rutaceae). However, leptomerine and kokusaginine, both isolated from the crude extract of *Esenbeckia leiocarpa* belongs to Rutaceae family, have been shown to inhibit AChE with IC50 values of 2.5 and 46 μM, respectively. The same authors also reported the discovery of skimmianine, a furoquinoline alkaloid with very moderate AChE inhibitory activity (Rahman *et al.*, 2006)[58].

The plant was tested for the presence of cholinesterase inhibitory components in an investigation of *Avicennia officinalis* relevance in the treatment of Alzheimer's disease. At doses of less than 2 mg/mL, the methanolic leaf extract of *Avicennia officinalis* reduced TChE and BChE activity by 50%[26].

The potential cholinesterase inhibitory effect of *Taxus baccata* extract was investigated. Taxiresinol, 3′-demethylisolariciresinol-9′-hydroxyisopropylether, Lariciresinol, isolariciresinol and 3-demethylisolariciresinol are among the taxoids and lignans isolated. The compounds demonstrated significant inhibition of BChE, but no action against AChE was discovered in any of the analysed compounds[60].

In two independent experiments, the cholinesterase inhibitory activity of *Delphinium denudatum* and *Coptis chinensis* was examined. In the first experiment, Isotalatazidine hydrate, extracted from the aerial portions of *Delphinium denudatum*, inhibited both AChE and BChE with IC50 values of 12.13 μM and 21.41 μM, respectively[61]. In another research, *Coptis chinensis* was shown to be 10 times more effective than galantamine at inhibiting AChE. The IC50 values of the methanolic and aqueous extracts of the plant were 0.031 μg/mL and 2.5 μg/mL, respectively. The synergistic combination of the individual alkaloids berberine, coptisine, and palmatine discovered in the crude extract of *Coptis chinensis* was thought to be responsible for the significant inhibitory activity[62].

According to the in vitro Ellman technique, chloroform and methanolic extracts of the *Boswellia socotran* plant show substantial inhibitory effects on AChE. At a concentration of

200 µg, chloroform extract showed inhibitory activity against AChE of higher than 50%[39]. Ethyl acetate and essential oil from *Boswellia dalzielii* leaves were shown to exhibit AChE inhibitory effects in a separate research, with IC50 values of 76.20 and 67.10 mg/L, respectively[36].

Albizia adianthifolia fractions and extracts were tested for their ability to inhibit AChE. Methanolic extract, ethylacetate fraction, chloroform fraction, and n-hexane fractions were shown to have potent inhibitory effects. The IC50 values for these fractions and extracts were 11.80±0.88, 10.04±1.67, 17.44±1.74, and 124.38±1.51 (µg/mL), respectively (Sonibare *et al.*, 2017). Plants of the Cucurbitaceae family have long been used to treat neurological disorders. Green fruits of *Momordica charantia* were utilised in a separate investigation to isolate several chemicals and assess anti-cholinesterase efficacy. With an IC50 value of 32.20 µM, ligballinol was found to have the greatest inhibitory action against BChE among the isolated phytocompounds[63]. It was observed that the inhibition was reversible and noncompetitive. The AChE inhibitory action of saffron extract and its components from *Crocus sativus* stigmas was investigated in research to see whether they might be used to treat Alzheimer's disease. The saffron extract was shown to have AChE inhibitory action in the study. Safranal, crocetin, and dimethylcrocetin all have IC50 values in the low micromolar range[64]. *Iris germanica* var. Florentina was utilised in separate research to isolate phenolic and flavonoid content. Isolated fractions inhibited both AChE and BChE, indicating that they may be utilised to treat Alzheimer's disease[65].

The majority of the plant extracts investigated had an antagonistic effects on acetylcholinesterase, indicating that they could be studied further for the treatment of Alzheimer's disease. Species from the Amaryllidaceae, Apiaceae, Asteraceae, Fabaceae, Amaranthaceae, Acanthaceae, Acoraceae, Amaryllidaceae, Amaranthaceae, Apocynaceae, Araliaceae, Amaryllidaceae, Rubiaceae, Polygalaceae, Rutaceae, Papaveraceae and Fumariaceae families were the most examined. The higher activity of these extracts might be owing to their high alkaloidal component, as most acetylcholinesterase inhibitors are known to have nitrogen. The alkaloids are the primary components isolated from this species, and they have acetylcholinesterase inhibitory action. More study is needed to better understand the effects of these alkaloids to find a potential therapy for Alzheimer's disease.

4. Conclusion

This review aims to give a complete overview of the many medicinal plants, extracts, fractions, and phytocompounds that can be utilised to inhibit AChE for the treatment of Alzheimer's disease. A variety of medicinal plants, their herbal extracts, fractions, and phytochemicals have been reported to have AChE inhibitory activities in the literature gathered and evaluated. The findings show that medicinal plants and bioactive phytoconstituents have a lot of promise against Alzheimer's disease.

Discovering new AChE inhibitory lead compounds and scaling up the synthesis of different biomolecules generated from these plants will require further effort. This might be accomplished by utilising current advancements and complexity in genome and metabolomics technologies. Moreover, genome and transcriptome data must be used to design secondary metabolic pathways in plants to increase the synthesis of high-value neuroprotective compounds from medicinal plants. This will aid in attaining the objective of the AChE inhibitory natural compounds study, which is to develop a low-cost and effective herbal medication that may be used to treat AChE.

5. Consent for Publication

Not applicable.

6. Funding

None

7. Conflict of Interest

The authors declare no conflict of interest.

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9. References

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