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Lead Discovery for Cholinesterase Inhibitors from Botanicals

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Abstract: Acetylcholinesterase inhibitors (AChE) are effective treatments for a number of neurological conditions, including Alzheimer's disease (AD), myasthenia gravis, ataxia and senile dementia. Few synthetic drugs with side effects are there for treating the memory loss and cognitive impairment brought on by these disorders. Many plants have been found to have AChE inhibitory activity Alzheimer's disease (AD), which makes them potentially useful in neurodegenerative diseases. The current need is to create possible AChE inhibitors using botanicals. The therapeutic strategy for the treatment of Alzheimer's disease (AD) and dementia is to rebuild the level of acetylcholine by impairing the major forms of cholinesterase such as butyrylcholinesterase (BChE) and acetylcholinesterase (AChE). The decrease in concentration of neurotransmitter acetylcholine is one of the critical elements in the formation of dementia. As a result, scientists have concentrated their efforts on discovering cholinesterase inhibitors from natural compounds. These inhibitors are isolated in significant quantities from the medicinal plants. The chapter offers a comprehensive review of advancements made in the study of phytoconstituents that are cholinesterase inhibitors and discusses some of the encouraging acetylcholinesterase inhibitors extracted from plants.

Keywords: Alzheimer's disease, phytoconstituents, acetylcholinesterase, butyrylcholinesterase, natural compounds, ataxia, senile dementia, myasthenia gravis.

INTRODUCTION

Alzheimer's disease affects the cholinergic cells propagating to the neocortex as well as hippocampus, resulting in substantial memory problems, emotional instability, and personality abnormalities in the final stages [1]. According to cholinergic theory, AD's memory dysfunction is caused by a loss in cholinergic functioning in the brains, resulting in lower hippocampal as well as cortical levels of the cholinergic system, Acetyl Choline (ACh) and indeed the related enzyme choline transferase [2]. Acetylcholinesterase (AChE) is the important enzyme in the normal brain for regulating ACh levels, whereas butyrylcholinesterase (BChE) performs a limited role [3]. In Alzheimer's disease patients, AChE activity increases and BChE shows better therapeutic effects in AD [4, 5]. As a result, inhibiting AChE as well as BChE is the most efficient therapeutic method for treating AD manifestations [6,7]. As a result, inhibitors of cholinesterase enzyme are the medications for providing relief to people with extremely serious Alzheimer's disease [8,9]. While synthetic medications including rivastigmine, neostigmine and donepezil are accessible for symptomatic therapy of Alzheimer's disease. Researchers all over the globe are looking for novel compounds from natural ingredients. As little more than a result, a variety of botanicals considered as memory stimulants in different traditional medical systems have indeed been investigated for anticholinesterase action. Among the medicinal plants employed as performance enhancing drugs by traditional healing include *Bacopa monniera, Ginkgo biloba, Buxus sempervirens, Acorus calamus, Epimedium koreanum, Glaucium corniculatum, Corydalis solida, Rhododendron ponticum, Rhododendron luteum* etc [10-11].

1.1. Acetylcholinesterase

The cholinergic system, which consists of the CNS and PNS, relies heavily on acetylcholinesterase [12]. Choline and acetate ions are produced when ACh is hydrolyzed by AChE. A huge hydrophobic cavity serves as AChE's enzymatic active site. The

Esteratic subsite and binding site of anionic substrate are the two halves of AChE. The neurotransmitter acetylcholine (ACh) is found abundantly throughout the central nervous system. This positive charge present in the quaternary amine of Acetyl choline is a good binding partner for the anionic binding site, and it also allows this site to bind to other cationic substrates and inhibitors [13]. Glu327, His440, Ser200 form a catalytic trinity in the esteratic site [14]. About 20 angstroms out from location of the protein, this catalysis triad is located at bottom side of a narrow gorge which widens the base. The Ser 200 participates in the catalytic site that allows for the protonation necessary for the breakdown of acetylcholine esters [15,16]. The aromatic amino group as well as the quaternary ammonium of ACh also interact with one another through cation [17]. Torpedo californica acetylcholinesterase (TcAChE) is a prototype acetylcholine protein that binds with a highly aromatic active aromatic center (fourteen aromatic motifs) [18]. Many AChE-ACh interactions rely on the amino acid that is aromatic Trp84; replacing this one with alanine reduces the interaction's reactivity by a factor of three thousand. In addition to such locations, AChE also has a 'acyl pocket' that determines substrate selectivity and a 'oxyanion hole' that interacts with negative oxygen ions during catalysis to boost the enzyme's catalytic performance [20].

1.2. PATHOGENESIS

1.2.1. Cholinergic hypothesis

Mental health problems have been linked to neuronal degeneration. In 1976, Peter Davies made a seminal discovery that paved the way for current neurochemistry [21] by connecting the particular cholinergic anomalies in the brain of individuals who have Alzheimer's contribute to the medical signs and symptoms (memory loss). This hypothesis postulates that increased acetylcholinesterase functioning or reduced synthesis of the acetylcholine neurotransmitter contribute to cholinergic deficit in the nervous system [22]. As a result of the disruption in cholinergic neurotransmission, the intellectual capacities decline when this neurotransmitter is present in low concentrations. By extension, this theory predicts that enhancing cholinergic function will lead to better mental performance in AD patients It has been shown in Fig. 1.

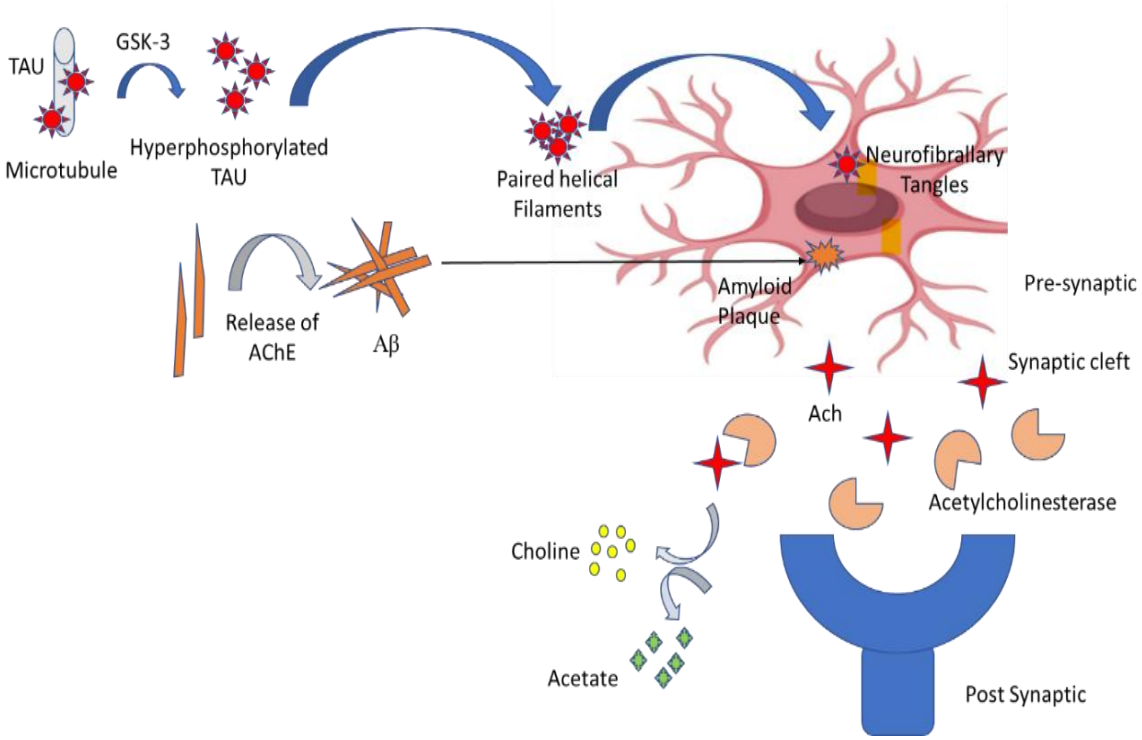

Fig.1. Systemic illustration of pathogenesis of cholinergic with respect to cholinergic hypothesis

Whereas the two most significant clinical characteristics of AD are believed to be the development of extracellular A plaques as well as intracellular neurofibrillary tangles (NFTs) in distinct locations of patients with Alzheimer's disease. The aberrant phosphorylation of tau proteins neurofibrillary [23], which leads to the instability of microtubules with changes in axonal transport [24] and causes memory deficits and neuronal loss [25], is currently thought to be a major contributor to these NFTs. These occurrences suggest a link between aberrant tau proteins and the cognitive deterioration linked to AD. Fig. 2 is a diagrammatic representation illustrating the top five therapy targets for Alzheimer's disease.

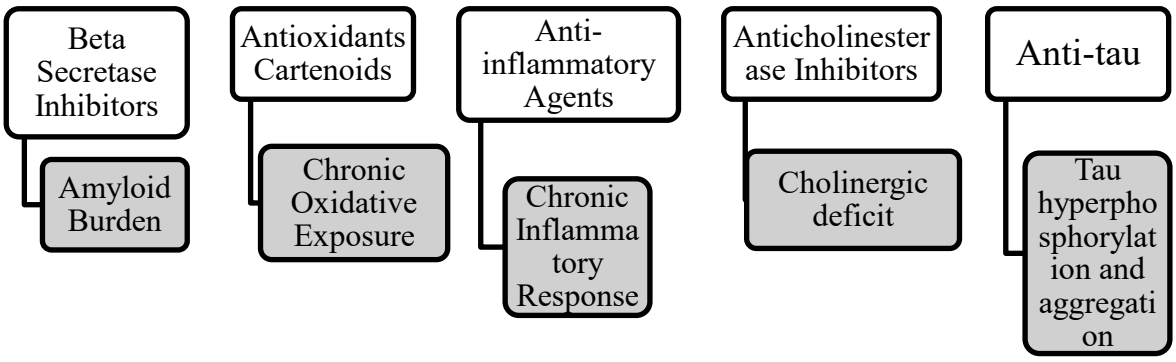

Fig. 2. Diagrammatic representation of the top five treatment targets for Alzheimer's disease.

It was once thought that A peptides accumulation caused the pathogenic abnormalities in tau function, but it has since been considered that the two mechanisms work in tandem, amplifying one other's harmful effects, and causing the cognitive loss seen in AD [26]. Because of their solubility and mobility, tau oligomers have been implicated in the systemic dissemination of their harmful effects [27]. In accordance with the hypothesis of amyloid cascade, the buildup of A peptides results from the enzyme production of β- and γ—secretase, that cleaves amyloid precursor proteins (APP) [28]. The former is more likely to accumulate and accumulate in the brain of AD [29].

There are a variety of physiological pathways that work together to remove Aβ from our brain. 1) Breakdown by peptidase enzymes such neprilysin, degrading enzyme of insulin and endothelin-converting enzyme [30], and 2) Transfer to bloodstream via the BBB, interstitial bulk flow, arachnoid villi, and glymphatic-lymphatic routes [31] mand 3) Microglial, perivascular macrophages, and astrocyte degradation as well as phagocytosis. A lower A clearance can result from flaws in any of the aforementioned procedures. The build-up of A peptides, which can be caused by this drop in addition to an increase in synthesis [32], can lead to neuronal malfunction and death.

There is currently proof showing that plaque formation is not a primary source of the impairments seen in Alzheimer's disease. Many efforts have been made to revise our understanding of Ad pathology [33] in light of the idea that oligomers of Aβ are the primary source of neuronal damage and cognitive decline. Such plaques are assumed to be part of a reservoir that stores soluble A oligomers and also play a role in their sequestration. Several studies have indicated that AD patients' brains accumulate these aqueous oligomers, and they are also linked to the brain synapses of individuals showing memory loss symptoms. Dementia is caused by the pathological changes in the synaptic architecture that are promoted by these oligosaccharides. These findings further bolster a previous theory that synaptic disruption contributes to AD impairment in addition to Aβ buildup and aberrant tau proteins. Research has shown that A peptides connect to cellular receptors and activate numerous signal transduction pathways, notably calcium transmission and different oxidative pathways [35].

They increase in the release of glutamate neurotransmitter in the synaptic region that interact with receptors related with synaptic plasticity, disrupting the function of these receptors with in process. In addition, they are implicated in memory impairment and suppression of longer - term stimulatory effects (LTP), leading to weaker neuron connections [38], and induce tau hyperphosphorylation [36]. There has been a lot of research into the effects of A peptides, but the specific mechanism of their cytotoxicity is still unclear. There is a need for more research because research has indicated that receptors interaction of Aβ aggregates may modify certain critical neuronal processes [39]. Nevertheless, studies have not shown the full profile of these sites or the accompanying signal transduction pathways linked with them. The use of acetylcholine esterase (AChE) inhibitors is discussed here, but there are numerous more avenues being explored as well. AD pathogenic mechanisms include: oxidative stress [40], inflammatory pathways (particularly NF-B), hyperphosphorylation of tau protein as well as aggregation, and secretases essential for APP degradation. Antioxidants along with -secretase inhibitors constitute two examples of drugs that alter these systems and have been considered elsewhere [41] as possible future therapies for AD.

2. DUAL ROLE OF ACHE IN ALZHEIMER

The acetylcholinesterase enhancement theory puts primary emphasis on this enzyme's increased activity. According to the findings, AChE is liable for multiple non-catalytic effects, along with the pro-

aggregating ability of Aβ. Alzheimer's patients have lower levels of the acetylcholine because their acetylcholinesterase activity is elevated, which accelerates the acetylcholine breakdown process. Partial significance of the enzyme in the production of amyloid plaques as well as neurofibrillary has also been linked to Alzheimer's disease. Evidence suggests that AChE forms a compound with the expanding fibrils of β-amyloid, so promoting the aggregation of the peptide fragments. It has been established that these complexes are much more cytotoxic then β-amyloid fibrils on their own [42,43]. The periphery anionic AChE site has been characterized as a conformational region of AChE that facilitates b-amyloid polypeptide fibril production [44,45]. The proaggregating potential of AChE towards Aβ is inhibited by compounds that engage either primarily with PAS perhaps with the catalytic and peripheral AChE sites of binding. Many AChE inhibitors have been shown in tests to reduce not just cholinergic transmission but additionally the production, deposit, and accumulation of toxic Aβ. As a result, blocking AChE has been shown to be an important tool in treating AD. Hence, drugs that bind to the peripheral and catalytic sites of AChE are promising new treatment of AD. When exposed to either natural or manufactured cholinergic poisons, AChE is a vulnerable target. Plant-based carbamates as well as inhibitors of glycoalkaloid are natural examples of anti-AChEs [46]. In addition, a natural AChE inhibitor was discovered in a mollusk [47]. Anatoxins, which are found in blue-green algae, are extremely potent toxins that inhibit the enzymatic activity. The cytotoxic peptide fasciculin is present in venom of green mamba and prevents access to both the central and peripheral sites of acetylcholinesterase [48]. Hence, anti-AChEs have been used as weapons of defence and offence in nature long before they were ever employed by humans. Before to their use in agriculture, anti-AChEs were researched and produced as highly toxic organophosphate as well as carbamate neurological gases. Diseases characterised by impaired acetylcholine-associated neurotransmission have responded well to the careful administration of AChE inhibitors with in laboratory.

3. NATURALLY DERIVED ChE INHIBITORS

3.1. Huperzine (Hupe)

The alkaloid hupe comes from the lycopodium plant. The plant Huperzia serrata seems to be a source of Hup [49]. There are two distinct Hup strains in existence, designated Hupe-A as well as Hupe-B. As Hupe-natural A's homologue, the Hupe-B is employed to treat Alzheimer's disease and memory associated with age gets decline, as well as to improve learning and memory. Hupe-A is superior to rivastigmine and tacrine and galantamine [50]. Hupe-A inhibits AChE activity selectively and effectively. However, its effectiveness towards BChE is lower than its effectiveness towards AChE. Hybrids of tacrine and huperzine A (HupA) have been found to have the potential to inhibit acetylcholinesterase [51]. The ZT-1, Hup-A prodrug, is being developed for the treatment of Alzheimer's disease. Hup-A as well as -B have analogous relationships with AChE. Each Hup molecule engages in π-π stacking on the anionic sites, including CH/π-bindings or van der Waals forces with Trp84 as well as Phe330. The pyridone group of Hup binds to the AChE active site via CH/- interactions. The Carbonyl oxygen of compound Hupe is antagonistic to carbonyl oxygen of Gly117. The peptide link between Gly118 and Gly117 is flipped as a result. As an added bonus, oxygen of Gly117 forms H-bonds with the nitrogen atoms of Ala201 and Gly119, which stabilises the inverted peptide planar conformation [52]. Hup-A, on the other hand, has the potential for minor cholinergic side effects such sickness with diarrhoea [53].

3.2. Flavonoid

Because of their ability to scavenge free radicals, the flavonoids have garnered a lot of attention. In vitro tests on a number of flavonoids have demonstrated their ability to effectively suppress AChE [54]. A flavanoid, Galangin, a flavonol isolated from the rhizomes of Alpiniae officinarum's rhizomes, which demonstrated strong AChE inhibition effect [55]. Unfortunately, no preclinical nor clinical studies, nor any published human trials, had looked into the toxicity of these flavonoids.

3.3. Cardanol

The inhibitory efficacy of different non-isoprenoid polyphenol lipids derived from Anacardium occidentale was examined in year 2009 [56]. One phenolic lipid in particularly, cardanol, had demonstrated encouraging outcomes. Furthermore, cashew nut shells may be utilized to extract cardanol [57]. Experimental and clinical experiments have not yet been conducted to examine its toxicity.

4. PLANT SPECIES WITH ANTI-ACETYLCHOLINESTERASE ACTIVITY

Acetylcholine seems to be a neurotransmitter that's also destroyed by the substrate-specific enzyme acetylcholinesterase there at neural synapse. Acetylcholine is known to be crucial for memory, and anomalies in cholinergic neuronal activity have already been connected to cognitive decline and behavioural issues in people with Alzheimer's disease. As such, the most cutting-edge medications for the treatment of Alzheimer's disease come from inhibitors of cholinesterase [58]. In order to create new anti-AD medications, several plant species that generate a variety of alkaloids, coumarins, terpenes, and polyphenols have been examined for their anti-AChE action. Thirty six isolated compounds and

extracts from fifty four species across 29 plant groups were categorised and discussed for their potential anti-AChE pharmacological efficacy. Among five and four species each, Amaryllidaceae, Lycopodiaceae, and Polygonaceae were the most prevalent families [59].

Among these structurally different groups which is being thoroughly researched to find novel drug candidates to treat Alzheimer's disease is alkaloids. A family of monocotyledonous family of mostly bulbous, perennial blooming plants with a high alkaloid content is known as the Amaryllidaceae [60]. There are around 1100 perennial bulbous species in the Amaryllidaceae family, grouped into 85 genera. Each of these species has a distinctive collection of isoquinoline compounds called as Amaryllidaceae alkaloids. The Galanthus woronowii Losinsk yielded the most famous Amaryllidaceae alkaloid, galantamine, which is now used to treat mild to severe AD due to its anti-acetylcholinesterase activity. The very same family's Narcissus L. genus has also been the subject of a great deal of phytochemical research due to its broad alkaloidal spectrum. On a commercial scale, galantamine is now produced from the bulbs of the Narcissus genus [61].

Out of almost 600 identified Narcissus L. species of Amaryllidaceae alkaloids, produced more than 100 alkaloids [62]. Many Amaryllidaceae plants contain significant levels of haemantamine. Moreover, the Narcissus species are straightforward to separate for semi-synthetic procedures. In addition to having high in vitro cytotoxic action against a variety of cancer cell lines, including HepG2, MOLT-4, MCF7, HeLa, K562, and A549 and CEM, haemanthamine itself has AChE activity [63]. Conventional medicine uses the Amaryllidaceae plant Hippeastrum psittacinum as a purgative, aphrodisiac, and anti-cough agent. The Alkaloid-rich fractions (ARF) as well as ethanol extract (EE) of H. psittacinum bulbs were investigated for their ability to inhibit AChE [64]. The cytotoxicity and anti-inflammatory properties of EE, as well as the neuroprotective and genotoxic activities in SH-SY5Y cells, were all identified in RAW 264.7 cells. In the EE, 15 alkaloids were discovered utilizing gas chromatography and mass spectrometer. ARFs have been less successful at suppressing AChE than EE. There is more proof that H. psittacinum has the potential to be an AChEi, in addition to an anti-inflammatory as well as neuroprotective medication. Twenty-five alkaloidal compounds having distinctive chemical structures, lignan, and epipinoresinol and lignan were found in three different Galanthus species, including G. gracilis, G. krasnovii, and an indigenous plant, G. peshmenii, when they were examined using GC-MS [65]. The cholinesterase inhibitory ability of the plant extracts was also evaluated in vitro by Ellman's technique. Galanthus krasnovii bulb extracts were shown to have the highest levels of AChEi activity [66].

After being used for over a millennium in China to treat a wide range of cognitive and neurological disorders, Huperzia spp. (Lycopodiaceae) had already recently attracted the attention of the pharmaceutical companies due to the extraction of the alkaloid Huperzine A from H. serrata. Massive amounts of time and energy have been spent on the extraction of Lycopodium alkaloids like Huperzine A from Huperzia spp. and other Lycopodiaceae plants. In spite of this, research has uncovered five Huperzia species (H. serrata, H. squarrosa, H. brevifolia, H. compacta, and H. tetragona) that have anti-AChE action [67]. Research suggests that some Lycopodiaceae species native to Brazil's highland forests, including H. quadrifariata, H. acerosa, H. heterocarpon, L. cernua and H. reflexa, may suppress AChE and BChE activity. While commonly known Lycopodium alkaloids like huperzines don't seem to have any effect as cholinesterase inhibitors, this doesn't rule out the possibility that other alkaloids within the extracts are what actually do the trick. Hence, those plants, which represent the rich diversity of South American Pteridophyta, warrant further study as potential leads in the development of medications for the treatment of AD [68].

Two novel Lycopodium alkaloids, the huperphlegmines B and A, and five known compounds, including lycophlegmariol A, phlegmariurine B, 5-hydroxymethyl-2-furaldehyde, rhemanone C, and loliolide, were discovered in Vietnam from the aerial portions of Huperzia phlegmaria. Both Huperphlegmine A and Huperphlegmine B were shown to significantly inhibit acetylcholinesterase, with IC50 values of 25.95 0.68 and 28.14 0.778g/mL, respective [69]. Both Huperzia species native to Brazilian habitats (H. quadrifariata and H. reflexa) with established in vitro AChEi capabilities were tested for their effects on mouse brains following an one-time intraperitoneal injection. Several doses of alkaloid extracts (10, 1, and 0.5 mg/kg) were administered to mice, and acetylcholinesterase activity was measured post mortem in 2 regions of the brain using Ellman's colorimetric method. It was found to significantly suppress AChE activity in both the cortex and the hippocampus, though not as well as the reference antagonist huperzine A with concentration of 0.5 mg/kg. Consequently, alkaloid extracts from H. quadrifariata and H. reflexa, which suppress acetylcholinesterase in vitro, appeared to be have highly effective in vivo activity, suggesting that perhaps the Huperzia species may still be a potential resource of chemicals with pharmacological promise for AD [70].

Along with part of a campaign to identify naturally AChE inhibitors [71], invasion plants such as Reynoutria sachalinensis F. Schmidt ex, Polygonum cuspidatum Siebold & Zucc. (Polygonaceae), or Maxim. Based on the results of the screening, the AChEi activities can be found there in methanol extract made from B. davidii leaves [72]. The R. hastatus, a species of the Polygonaceae family, is employed to manage an array of neurological diseases. Many species have been shown to have antioxidant as well as anticholinesterase effects. The folkloric use of Rumex hastatus for neurodegenerative diseases will be researched by testing the extract, saponins, fractions, and flavonoids for acetylcholinesterase and butyrylcholinesterase suppression as well as other antioxidant properties. Polygonum sachalinensis is a widespread weed that has invaded many European countries. The chemical profiles of its several organs were studied using HPLC-UV-ESI/MS. Seven major components were isolated: quercetin-3-O-Dgalactopyranoside; lapathoside D; quercetin-3-O-arabinopyranopyranoside; N-trans-feruloyltyramine; lapathoside C; vanicoside B. hydropiperoside; It was determined whether raw MeOH extracts as well as compounds has acetylcholinesterase inhibitory activities [74].

Table 1. Active constituents of Alkaloids as cholinestaerase Inhibitors from plants.

S.No.	Active constituent	Plant name	Family	Class	References
1.	Tazettine, Lycorine, Crinine	*Galanthus ikariae*	Amaryllidacae	Alkaloid	[75]
3.	Bulbocapnin, corydaline	*Corydalis cava*	Fumariaceae	Alkaloid	[76]
2.	Conypododiol	*Asparagus adscendens*	Asparagaceae	Alkaloid	[77]
4.	N-methylasimilobine	*Nelumbo Nucifera*	Nelumbonacae	Alkaloid	[78]
	cyclanoline , Stepharanine, *N*-methyl stepholidine	*Stephania venosa*	Menispermaceae	Quaternary protoberberine alkaloids	[79]
	Juliflorine	*Prosopis juliflora*	Papilionaceae	Piperidine alkaloids	[80]
5.	Annotinine, Lycodoline, Lycofoline, Annotine, Gnidioidine N-oxide, Acrifoline Lycoposerramine	*Lycopodium annotinum*	Lycopodiaceae	Lycopodane-type alkaloid	[81]
	Isotalatizidine hydrate	*Delphinium denudatum*	Ranunculaceae	Diterpenoid alkaloids	[82]
	Dehydroevodiamine	*Evodia rutaecarpa*	Rutaceae	Quinazoline alkaloid	[83]
	Trigonelline	*Trigonella foenumgraecum L*	Leguminosae	Alkaloid	[84]
	(–)-huperzine A	*Huperzia serrata*	Lycopodiaceae	Quinolizidine alkaloid	[85]

4.1. Terpenoids

Metabolites from microorganisms have yielded novel meroterpenoid Acetylcholinesterase inhibitors. Extraction of terreulactones and then another isoterreulactone-A, polar metabolite was achieved through fermentation in solid state of fungus Aspergillus terreus. The meroterpenoid chemicals terreulactone A as well as terreulactone D have opposing biological effects. The terpenoid polyketide compounds that inhibited acetylcholinesterase (Table 2). Although though it shares the same class as isoterreulactone A, terreulactones, is ten times lower like an AChE Inhibitors [86] due to its structure that contains a near about seven-membered lactone backbone. To attach to the enzyme's peripheral location, these novel inhibitors (Table 2) feature new substituents related to the nitrogen atom N-20.

Table 2. Active constituents of Terpenoids as cholinestaerase Inhibitors from plants.

S.No.	Active constituent	Plant name	Class of compound	Family	Refno
1.	β-pinene α-pinene,	*Salvia potentillifolia*	Monoterpene	Lamiaceae	[87]
4.	(+)-limonene, (+)-sabinene	*Pimpinella anisoides*	Terpene	Apiaceae	[88]
3.	Ursolic acid	*Origanum majorana*	Pentacyclic triterpene acid	Lamiaceae	[89]
2.	α-pinen ,1,8-cineol,	*Salvia lavandulaefolia*	Monoterpene	Lamiaceae	[90]
7.	Taraxerol	*Vaccinium oldhami*	Triterpine	Ericaceae	[91]
6.	Cryptotanshin,	*Salvia miltiorhiza Bunge*	Diterpenoids	Lamiaceae	[92]

4.2. Steroids

Sarcococca saligna was shown to contain steroid hormones that inhibit cholinesterase. Several micromolar range inhibitors of AChE as well as BuChE have a steroidal backbone that includes a monomethylamino substituent at the position 3of carbon and/or C-20 positioning of the basic steroidal backbone. For salignenamide-F, axillaridine-A, salignenamide-E were the most effective of almost twenty novel steroids. As far as we can tell, every steroid we've looked at has an amino nitrogen atom at either C-3 or C-20. As such, they are crucial to the inhibitory function of these drugs [93].

Table 3. Active constituents of Steroids as cholinestaerase Inhibitors from plants.

S.No.	Active constituent	Plant name	Class	Family	References
1.	Assoanine	*Narcissus assoanus*	Steroids	Amaryllidaceae	[94]
3.	Sanguinine	*Eucharis grandiflora*	Steroids	Amaryllidaceae	[94]
2.	11-hydroxygalantamine	*Narcissus poeticus*	Steroids	Amaryllidaceae	[94]
5.	Homomoenjodaramine, moenjodaramine	*Buxus hyrcana*	Steroids	Buxaceae	[95]
4.	Epinorgalantamine	*Narcissus confuses, Narcissus leonensis, Narcissus poeticus*	Steroids	Amaryllidaceae	[94]
6.	Hookeriana (H, I) Sarcovagine C, Dictyophlebine	*Sarcococca hookeriana*	Steroids	Buxaceae	[94]
7.	Sarsalignone, Vaganine	*Sarcococca saligna*	Steroids		[96, 97]

4.3. Xanthone

Adenosine deaminase Inhibitors (Xanthine)Bellidifolin, Bellidin, Norswertianolin, and swertianoline are xanthones which have been linked to AChE inhibitory action in a methanol extracts of Gentiana campestris leaves, as described by Urbain et al. Bellidifolin's AChE inhibition is higher than that of other xanthones, maybe due to the hydrophobicity, but it's also possible that the difference is due to some other factor. The addition of a methoxy compound in position C-3 boosts its inhibition property [98].

4.4. Flavanoids

Zhang et al (2006) asserted that the catechol moiety within composition of analogues of flavonoid caused them to exhibit AChE inhibitory action [99].

Table 4. Active constituents of Flavanoids as cholinestaerase Inhibitors from Plants.

S.No.	Active constituent	Plant name	Family	Class of compound	References
1.	Isomucronulatol	*Micromeria cilicica*	Lamiaceae	Isoflavone	[100]
4.	Sophoflavescenol, icaritin, kaempferol	*Sophora flavescens*	Fabaceae	Flavonol	[101]
3.	Tiliroside, Quercetin	*Agrimonia pilosa*	Rosaceae	Flavonoid	[102]
2.	Sudachitin	*Micromerian cilicica*	Lamiaceae	Polymethoxylated flavones	[100]
6.	Naringenin	*Citrus junos*	Rutaceae	Flavanone	[103]

4.5. Shikimate Associated Compounds

Structural research reveals that most AChE-inhibiting compounds produced from shikimates include either a single phenylpropanoid unit or a combination of two or more phenylpropanoids. Esculetin as well as Daphnetin, both of which contain an O-dihy droxyl (Catechol) group, were shown to have the strongest AChE inhibitory action. Both umbelliferone has a -OH group at position number 7, but umbelliferone 6-carboxylic acid also has a carboxyl group on position number 6. Although there are structural differences between the three compounds, the latter substance has weaker inhibitory effect than Esculetin as well as Daphnetin. The isoscopoletin, scopoletin, scopolin, and 7-methoxy coumarin and scoparone all showed action; however, their inhibitory capability was diminished due to the addition of a methoxyl or glycosyl group. Having two substituents, as in 20-isopropyl psoralene, reduces its AChE inhibitory property [104].

Table 5. Active constituents of Flavanoids as cholinestaerase Inhibitors from Plants.

S.No.	Active constituent	Plant name	Family	Class	References
1.	Daphnetin, Esculetin, 7-methoxy coumarin Umbelliferone, Scopoletin,	*Angelica decursiva,* *Artemisia capillaris*	Umbelliferae	Coumarin	[104]
4.	Hainanmurpanin ,Murranganin	*Murraya paniculata*	Rutaceae	Pyrenlated coumarin	[105]
3.	Isopimipne, Xanthotoxin,	*Angelica aqutiloba*	Apiaceae	Furanocoumarins	[105]
2.	Scopolatin	*Vacinnium oldhami*	Ericaceae	Coumarin	[106]
1.	Daphnetin, Esculetin, 7-methoxy coumarin Umbelliferone, Scopoletin,	*Angelica decursiva,* *Artemisia capillaris*	Umbelliferae	Coumarin	[103]
4.	Hainanmurpanin ,Murranganin	*Murraya paniculata*	Rutaceae	Pyrenlated coumarin	[104]

4.6. Miscellaneous

The phytochemical screening of Jacaranda oxyphylla leaf extract published by Pereira et al. revealed the presence of three types of substances: fatty compounds, sterols, as well as triterpenes. Other phytochemicals that found useful in the treatment of Alzheimer have been illustrated in the table.

Table 5. Active constituents of Miscellaneous as Cholinestaerase Inhibitors from Plants.

S.No.	Active constituent	Plant name	Family	Class of compound	References
1.	Bracteosin C BracteosinA, Bracteosin B	*Ajuga bracteosa*	Labiatae	Withanolide	[105]
4.	Curcumin, demethoxycurcumi, bisdemethoxycurcmin	*Curcuma longa* L.	Zingiberaceae	Curcuminoid	[106]
2.	WithaferinA, Stioindosides,	*Withania somnifera*	Solanaceae		[107]
3.	Haloxysterols (A-Z)	*Haloxylon recurvum*	Chenopodia ceae	Sterol	[108]

CONCLUSION

In many individuals, Alzheimer's disease (AD) is the main reason for dementia. Deposits of aberrant -amyloid protein, oxidative stress, protein hyperphosphorylation and low rates of acetylcholine (ACh) appear to have an important part in the aetiology of this disease, but the exact mechanism is not fully understood. Given the multifaceted causes of Alzheimer's disease, scientists are making concerted efforts to discover and develop multi-target drugs that have at least two different biological effects. It has recently come to light that there are dual inhibitors that block the effects of both monoamine oxidase (MAO) as well as acetylcholinesterase (AChE). Cholinesterase (AChE) inhibition improves neurotransmitter release at cholinergic synapses and, consequently, temporarily mitigates the cognitive deficit. Furthermore, AChE plays a role in the formation, differentiation, adhesion, and processing of -amyloid protein in neurons. When MAOB is inhibited, cognitive decline is slowed.

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